

THE PHYSIOLOGICAL ACTION OF EPINEPHRIN ON THE BRONCHI.*

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I.

The earlier experimenters (1) in their work on the physiology of the bronchial muscles directed their attention to the effects of stimulation of the vagus. In most instances they used excised, but still living, preparations. They recorded the resulting changes in intrapulmonary pressure generally by means of a water manometer connected with the trachea. Their experiments, dating back to 1840, indicated with considerable uniformity that the result of vagus stimulation is constriction of the bronchi. While their experiments are valuable as a whole, the methods used are open to criticism.

Einthoven (2) was the first to make accurate use of a new procedure, "air perfusion," which has been the basis of the best subsequent experimentation in this direction. By rhythmically injecting air into the trachea of a living animal, he maintained a constant artificial respiration, and was able to determine variations in the size of the bronchi before and after stimulation of the vagus, through records of the changes in the maximal (inspiratory) intratracheal pressure. He found that stimulation of this nerve produced constriction of the bronchi, but he obtained no evidence of any relaxing effect. As section of the vagi produced no change in his results, he concluded that normally the bronchial muscles are not in a condition of vagus tone.

The first experiments concerning the effect of epinephrin on the bronchial muscles were conducted by Dixon and Brodie (3), though it should be remarked that their experiments with epinephrin represented only a small part of a larger work. They used living animals.

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Their method consisted in measuring variations in volume of the lobe of lung under examination by means of an oncometer, while artificial respiration was kept at a constant. Since no other variable, except possibly the pulmonary circulation, was present (any error due to this they took particular pains to exclude), they attributed the oncometric variation in the inspiratory and expiratory volumes of the lobe to changes in the size of the bronchi. They found that, although stimulation of the vagus produced bronchial constriction, stimulation of the vagus caused inhibition of the spasm, when spasm of the bronchi had been induced through pilocarpin or muscarin. This effect they interpreted as due to the presence of dilator fibers in the vagus, and they were able to demonstrate the presence of such fibers by several degeneration experiments. They got no effect on stimulation of the sympathetic (ganglion stellatum). With regard to the action of epinephrin they write:

“Suprarenal extract produces very little effect on the bronchi, small tests giving rise to neither constriction nor dilatation. With large injections, however, constriction of a temporary character has been observed in a small percentage of cases. It is possible that in this case the free movements of the air are interfered with by the great vascular engorgement which is present.”

When, therefore, epinephrin was used, the possibility of error from changes in the pulmonary circulation could not be excluded; and if any effect at all on the bronchi was produced, that effect was constriction.

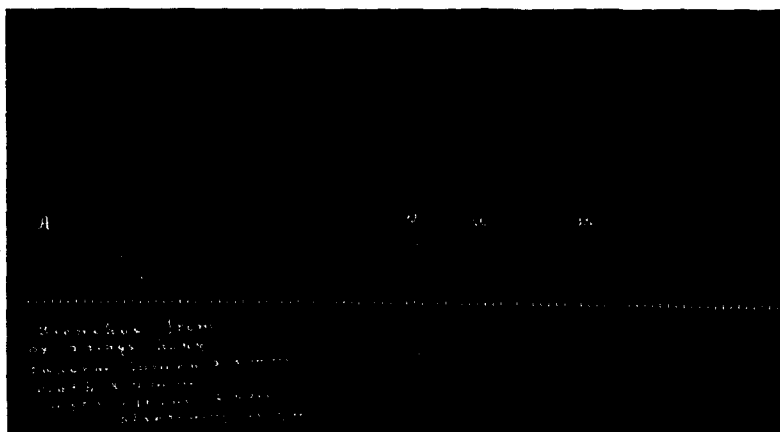
Kahn (4) in 1907 had studied the action of epinephrin on the trachea, and had learned that it exerts usually a relaxing effect. But Januschke and Pollak (5) were the first to publish a careful investigation of the physiological action of epinephrin on the bronchial muscles. Employing Dixon and Brodie's method they found that epinephrin caused a slight dilatation of the bronchi. When, however, constriction had been induced by pilocarpin, muscarin, or Witte's peptone, they observed that epinephrin caused a dilatation sufficiently pronounced to offset the former constriction. This dilatation was transient, but could be re-induced by repeating the injection of epinephrin. The dilatation from epinephrin they interpreted as proof of the sympathetic innervation of the bronchi, and suggested, in order to harmonize their view with the findings of Dixon

and Brodie of dilator fibers passing to the bronchi in the vagus trunk, that the latter had acquired sympathetic fibers in the abundant interanastomoses in neck and thorax. It might be remarked that Januschke and Pollak found it necessary to go to some length to prove that their results could not have been modified by changes in the pulmonary circulation.

The most recent publication on this subject is that of Pal (6). He produced spasm in the bronchi of guinea pigs by the use of Witte's peptone or pilocarpin. Certain drugs, as he had previously determined by experiments on other species, relax the coronary artery. He found that these same drugs injected into the guinea pigs caused inhibition of the bronchial spasm. Therefore he inferred that the bronchial and coronary musculatures were physiologically similar and were alike relaxed by epinephrin.

The experiments here reported are based on the reaction to epinephrin of excised rings of bronchi from the ox. The method is the application to the bronchi of that used by Meyer (7) for the study of the reaction of blood-vessels to epinephrin, and by von Langendorff (8) and others to the study of the coronary artery. It is a direct method for the determination of the reaction of the bronchial muscles to epinephrin. Rings of bronchi, two to three millimeters thick, were hung in series in a glass chamber; the lowest ring was fastened to the floor of the chamber, and the upper to the short arm of a lever. The long arm of this lever recorded on a drum. Constriction of these bronchial rings produced an ascent of the curve, dilatation a fall. The glass chamber containing the bronchi was kept filled with Locke's fluid at a temperature of 37° or 38° C. A constant stream of oxygen was passed through the fluid. The mode of introduction of the epinephrin was either to drop it from a pipette or to substitute the desired concentration of epinephrin in Locke's fluid. Medium sized, as well as very small bronchi were used, some so small as to require a needle to thread them. The larger bronchi were hung in pairs, the smaller in series of four, so as to increase the magnitude of the resulting curve. The epinephrin used was an especially prepared "adrenalin" of Parke, Davis and Company, free from preservatives. The maximal concentration was one in fifty thousand, the minimal one in ten million.

Epinephrin caused relaxation of the bronchi in each experiment. As might be supposed, the relaxation was more extensive when medium sized bronchi were used than when very small bronchi were tested. The degree of relaxation was found to vary also with the concentration of the epinephrin. Threshold values, one to twenty million, produced a just distinguishable relaxation of the bronchi. There was no evidence of primary constriction from exceedingly dilute solutions of epinephrin, analogous to the primary constriction which Brodie and Cullis have reported as occurring in their perfusion experiments on the coronary artery. In order to exclude error



TEXT-FIG. 1. Ox bronchus, 2 rings, lumen 2 to 3 mm. Loads: stretching, 10 gm.; lifting, 6 gm. in Locke's fluid. *A* = epinephrin (adrenalin chlorid) 1:50,000. *W* = washing with Locke's fluid; *B* = barium chlorid 2 *M*/10. Magnification, $\times 7\frac{1}{4}$ (half size reproduction).

which might be attributable to fatigue or death of the preparations, a known constrictor of living smooth muscle, barium chlorid, was substituted for the epinephrin solution, when the effect of the latter had reached its maximum. Barium chlorid produced a constriction which exceeded the relaxation previously found with epinephrin. The character of the dilatation curve is the abrupt fall which characterizes that of the ox coronary. With the bronchus, as with the coronary artery, it is useless to attempt to compute the extent of relaxation in terms of the diameter or circumference of the bron-

chus used, because this relaxation can be made to vary in the same preparation by a number of different factors (text-figures 1, 2, 3, and 4).

II.

As clearly as the empirical use of a drug in a given disease can indicate its physiological action in that disease, so the use of epinephrin in bronchial asthma has indicated that its physiological action is dilatation of the bronchi. Kaplan in America was the first to direct attention to the clinical fact that epinephrin inhibits asthmatic attacks.

In their exposition of the antagonistic relation between the

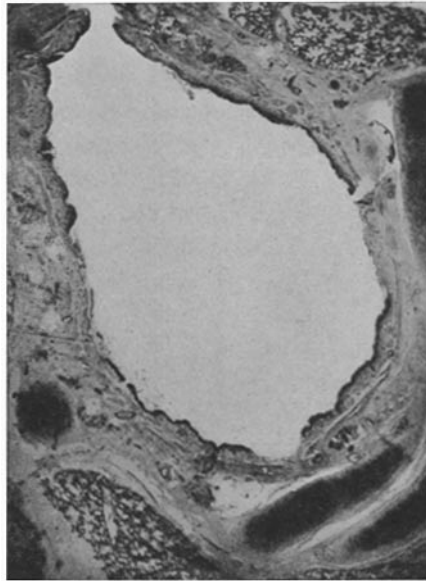


TEXT-FIG. 2. Ox bronchus, 2 rings, lumen just admitted thread. Loads: stretching, 5 gm.; lifting, 2½ gm. in Locke's fluid. *A* = epinephrin (adrenalin chlorid) 1:50,000. *W* = washing with Locke's fluid; *B* = barium chlorid 2*M*/10. Magnification, $\times 7\frac{1}{4}$ (half size reproduction).

“sympathetic” and “autonomic” (vagus) systems, Eppinger and Hess (9) class bronchial asthma in their group of *vagotonische* diseases. They make the observation, which is corroborated by Frank (10), that in bronchial asthma epinephrin fails to give much, if any, rise in blood pressure. They use this fact to illustrate their statement that epinephrin, related as it is to the sympathetic system, is ineffective in diseases in which the influence of the autonomic system (vagus) seems to predominate. Frank, however, has

demonstrated that epinephrin may cause hyperglycemia in diseases of a *vagotonische* as well as a *sympathicotonische* nature, indiscriminately; in fact, three of his best examples of hyperglycemia occurred in cases of bronchial asthma. By his experimental proof that hyperglycemia induced by epinephrin could occur outside of the *sympathicotonische* state, he deprived the Eppinger and Hess theory of one of its main supports.

Experiments performed by T. C. Janeway and the writer on surviving arteries by the excised strip method would indicate that the possible effect of epinephrin on the excised artery in a physiolog-

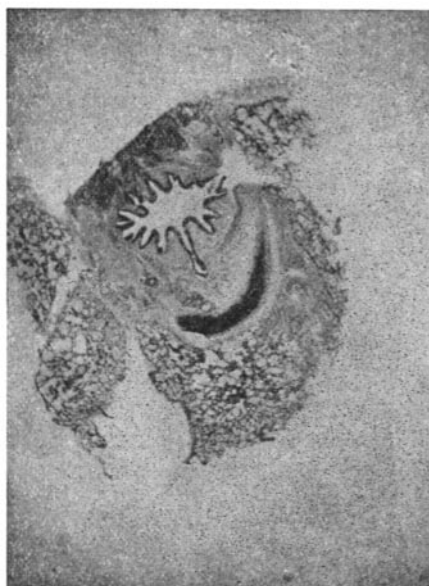


TEXT-FIG. 3. Section of the bronchus used to obtain the tracing shown in text-figure 1. Magnification, $\times 11\frac{1}{4}$ (half size reproduction).

ically inert solution is in inverse ratio to the degree of tonus possessed by that artery. By this method a peripheral artery already contracted will not be made to undergo great further contraction from epinephrin, nor will a much relaxed coronary artery show considerable further relaxation. On the other hand, epinephrin will give rise to an unusually great contraction in a much relaxed periph-

eral artery, and a correspondingly great relaxation in a constricted coronary. If the tonus of an artery, then, is optimal for the specific action of epinephrin, the response of that artery to epinephrin will be maximal.

Perhaps, then, it is not so remarkable that in bronchial asthma,



TEXT-FIG. 4. Section of the bronchus used to obtain the tracing shown in text-figure 2. Magnification, $\times 11\frac{1}{4}$ (half size reproduction).

an affection in which the bronchial musculature is presumably in a highly constricted state, this relaxing effect of epinephrin on the bronchi should be entirely out of proportion to its effect elsewhere. Indeed, it would seem probable that the effect of epinephrin on the bronchi in bronchial asthma must be due to the very fact that this disease, in so far as the bronchi are concerned, is *vagotomisch* in nature. This view is entirely in accord with those experimental findings of Januschke and Pollak which showed the relaxing action of epinephrin on the bronchi after artificially induced spasm, but it is diametrically opposed to the theory of Eppinger and Hess.

Other instances than bronchial asthma can be cited of the almost

selective action of epinephrin. In certain disturbances of the vascular system characterized by low blood pressure and relaxation of the arterial wall, for instance, in Addison's disease or in shock, the rise in blood pressure following an injection of epinephrin may be enormous. In certain forms of urticaria also, as Swann (11) has determined, an injection of epinephrin causes disappearance of the wheals in a comparatively short period. In both these instances the remarkable effect of epinephrin may be explained on the common ground of the existence of a state of tonus in the involved parts of the vascular system optimal for the action of epinephrin. In the conditions of generally deranged tonus above referred to, the effect of an injection of epinephrin is a general one and manifests itself by a maximal rise in blood pressure, since the entire arterial system, or at least the larger part of it, is in a state of tonus optimal for the action of epinephrin. In urticaria, since only isolated areas of the vascular system, namely, those situated in the wheals, are in a state of optimal tonus, the maximal effect of epinephrin is a local one and manifests itself by disappearance of the wheals, owing to the constriction in them of the arterioles and very possibly the venules also. Surely, in these instances the action of epinephrin on the vascular system, which may be thought of as being in a sensitized state, completely overshadows its action on the bronchial musculature or its action in the production of hyperglycemia; or in the case of urticaria, on the vascular system as a whole. It would be interesting to know whether epinephrin could be regarded as exhausting itself on those body mechanisms which are in a state particularly receptive or optimal for it.

The direct method for determining the reaction of the bronchial musculature to epinephrin used in these experiments is obviously superior to the method employed by Roy and Brown (12) to determine the reaction of the bronchi to stimulation of the vagus and other conditions. Their method consisted in measuring volume changes by means of a thin walled bag introduced into the interior of the bronchus. In several respects, this excised ring method offers advantages over the indirect air perfusion methods which have been described. For example, it obviates all sources of error due to vascular changes in the lungs, which should be considerable when

epinephrin is injected intravenously into a living animal. It avoids also the possibility of error due to swelling of the mucosa of the bronchi; and lastly, since excised structures were used, the action of epinephrin must be exerted directly on the bronchi, that is, on the receptive substances of their musculatures, though there is, of course, no reason to suppose that the law governing the action of epinephrin elsewhere should have an exception here.

BIBLIOGRAPHY.

1. Dixon, W. E., and Brodie, T. G., Contributions to the Physiology of the Lungs. Part I, The Bronchial Muscles, Their Innervation and the Action of Drugs upon Them, *Jour. Physiol.*, 1903, xxix, 97.
2. Einthoven, W., Über die Wirkung der Bronchialmuskeln, nach einer neuen Methode untersucht, und über Asthma nervosum, *Arch. f. d. ges. Physiol.*, 1891, li, 367.
3. Dixon, W. E., and Brodie, T. G., *Loc. cit.*
4. Kahn, R. H., Zur Physiologie der Trachea, *Arch. f. Anat. u. Physiol., Physiol. Abt.*, 1907, 398.
5. Januschke, H., and Pollak, Leo, Zur Pharmakologie der Bronchialmuskulatur, *Arch. f. exper. Path. u. Pharmakol.*, 1911, lxvi, 205.
6. Pal, J., Über toxische Reaktionen der Koronararterien und Bronchien, *Deutsch. med. Wchnschr.*, 1912, xxxviii, 5.
7. Meyer, O. B., Über einige Eigenschaften der Gefässmuskulatur, mit besonderer Berücksichtigung der Adrenalinwirkung, *Ztschr. f. Biol.*, 1906, xxx, 352.
8. von Langendorff, Über die Innervation der Coronargefäße, *Zentralbl. f. Physiol.*, 1907-08, xxi, 551.
9. Eppinger, H., and Hess, L., Zur Pathologie des vegetativen Nervensystems, *Ztschr. f. klin. Med.*, 1909, lxvii, 344.
10. Frank, E., Bestehen Beziehungen zwischen chromaffinem System und der chronischen Hypertonie des Menschen? *Deutsch. Arch. f. klin. Med.*, 1911, ciii, 397.
11. Swann, A. W., Personal communication.
12. Roy, C. S., and Brown, G., On Bronchial Constriction, *Jour. Physiol.*, 1885, vi, p. xxi.