

STUDIES ON PULMONARY EDEMA

II. THE PATHOGENESIS OF NEUROPATHIC PULMONARY EDEMA

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Studies reported in an accompanying paper have shown that severe pulmonary edema, and death, are brought about in the rabbit by bilateral cervical vagotomy. Of the several factors which are of importance in producing the pulmonary changes under the experimental conditions employed, laryngeal paralysis was excluded as an essential part of the mechanism involved. There remains for consideration, the part played by other organs deprived of vagal innervation as a result of bilateral cervical vagotomy. The heart, as will be shown, can be excluded as a primary factor. The organs supplied by the subdiaphragmatic branches of the vagus nerves can be dismissed also. Recently Beazell and Ivy (1) destroyed all branches of the vagus below the diaphragm in the rabbit in a study concerning gastric ulcer. Their animals lived from 52 to 117 days after operation, a fact which, in view of our experimental findings, immediately excludes any important effect of the subdiaphragmatic branches on the lungs. We are led, then, to an investigation of the vagal innervation of the lungs in the pathogenesis of neuropathic pulmonary edema.

Material and Methods

Guinea pigs were used in these experiments. These animals varied in weight from 250 to 700 gm. The guinea pig was selected for this portion of the study because the survival time after bilateral cervical vagotomy is short (2½ to 4 hours for guinea pigs of 250 to 700 gm. in weight (2)). Furthermore, the time of death can be predicted with great accuracy after some experience. The clinical picture and the pathologic findings are almost exactly the same as in the rabbit, so that comparisons are permissible. The operative procedures were identical with those used in the experiments performed on rabbits. With the aid of urethane anes-

thetia the vagus nerves, unless otherwise stated, were severed low in the neck. One change in experimental procedure was employed in these experiments. After insertion of a tracheal cannula of suitable size, the cannula was connected to an apparatus for artificial respiration. Suitable control observations were made on a small series of guinea pigs with vagus nerves intact until the optimum conditions of continuous artificial respiration for the guinea pig were found. Such control experiments were continued for a period of 1 hour longer than the greatest survival time noted in a guinea pig after bilateral cervical vagotomy. Postmortem examination of these animals revealed no pulmonary edema. The lungs showed slight congestion, and a moderate deepening of the normal pink color. No changes in the lungs were observed which could be confused with the pathologic picture produced by section of the vagus nerves.

EXPERIMENTS

Series 1.—Under conditions of continuous artificial respiration and urethane anesthesia (injected intraperitoneally in amounts of 1.5 mg. per kilo of body weight) guinea pigs were subjected to bilateral cervical vagotomy. At intervals the frothy serous fluid which appeared at the mouth of the tracheal cannula was withdrawn by means of a 2 cc. syringe. The smallest possible amount of pressure was used in removing the fluid, no attempt being made to withdraw fluid lower down in the trachea and bronchial tree. Death occurred usually within $3\frac{1}{2}$ to 4 hours after vagotomy. Postmortem examination revealed the usual picture of massive consolidation caused by severe pulmonary edema and congestion.

The experiments in series 1 give further proof to supplement that obtained in the rabbit, that the factor of laryngeal paralysis is not essential to the production of acute pulmonary edema following bilateral cervical vagotomy.

Series 2.—The same experimental procedures were employed as in series 1, with one addition. Before the vagus nerves were cut in the neck, the sternum was raised to permit direct inspection of the heart and lungs. Care was taken to prevent loss of blood and shock. The animals were kept warm with the aid of a heating pad, and the contents of the thoracic cavity were kept warm and moist by the application of pieces of cotton saturated with hot normal saline solution. Suitable control experiments were first carried out under these conditions on guinea pigs with intact vagus nerves. Artificial respiration was continued for 5 hours, at which time the animals were still alive. The heart was beating regularly, and the lungs showed only slight congestion. No pulmonary edema was present.

Another group of guinea pigs was subjected to bilateral cervical vagotomy after the sternum had been elevated. About 30 minutes after vagotomy red petechiae

appeared in scattered areas over the lung surfaces. These petechiae gradually enlarged and finally coalesced to form confluent areas of red discoloration, and what later proved to be consolidation. The heart continued to beat regularly and vigorously until the last few minutes, when dilatation of the right side became apparent. The heart stopped beating, usually $3\frac{1}{4}$ to $4\frac{1}{4}$ hours after the vagus nerves had been severed. Postmortem examination and histologic study revealed the usual picture of severe pulmonary edema and congestion.

The results of experiments in series 2 permit exclusion of possible alterations in the heart of any importance in the causation of acute pulmonary edema following bilateral vagotomy. These experiments also afforded an opportunity to study the gradual onset of the pulmonary edema produced under these experimental conditions.

Series 3.—The experiments in this series were designed to permit a direct approach to the rôle played by the innervation of the lungs in the production of neuropathic pulmonary edema. Exactly the same procedures were used as in series 2, with one exception. The vagus nerves were not severed. Instead, the innervation of the lungs was temporarily abolished by the application of small pieces of cotton saturated with 1 per cent novocaine solution both anteriorly and posteriorly to the roots of both lungs. Care was taken to prevent the spread of the solution to neighboring structures. The applications of novocaine were regularly renewed at intervals of $\frac{1}{2}$ to 1 hour. Weak solutions of phenol were first tried, but were found unsatisfactory because of their injurious effect upon the tissues.

Under direct observation, lesions in the lungs developed as in series 2. The heart continued to beat regularly until a rather abrupt change occurred, usually about 4 to $4\frac{1}{4}$ hours after the first application of novocaine had been made. Moderate dilatation of the right auricle and right ventricle was then observed. After a few minutes, the heart stopped, and artificial respiration was discontinued. In all important respects, both in the gross and microscopically, the lungs were duplicates of those of intact guinea pigs which died after bilateral cervical vagotomy. Severe pulmonary edema and congestion were the main features.

We may conclude from the experiments in series 3, that the loss of the innervation of the lungs is the essential factor brought about by bilateral cervical vagotomy in regard to the production of neuropathic pulmonary edema in the guinea pig. It is obvious that both the sympathetic and the vagal fibers are temporarily abolished by the experimental procedure employed in series 3. No attempt is made at this time to separate the action of the two types of pulmonary nerves.

DISCUSSION

The results of these experiments depend for explanation upon the innervation of the lungs. The branches to the bronchi may be dismissed from consideration, since no evidence of bronchoconstriction was found. The effects of vagotomy on the trachea and bronchi lie rather in the opposite direction, dilatation. The histologic picture emphasizes the dilatation and engorgement of the pulmonary vessels, particularly the veins and capillaries. Attention is therefore directed to the vasomotor control of the pulmonary vessels. It is now generally agreed that such a vasomotor control does exist.

Adequate anatomic proof of the existence of nerve endings in the pulmonary vessels has been given by Karsner (3) and by Larsell (4). Important contributions and critical summaries of the literature concerning the vasomotor control of the pulmonary vessels may be found in the writings of Luckhardt and Carlson (5), Wiggers (6), and Daly (7). Luckhardt and Carlson not only demonstrated vagal vasoconstrictor fibers to the pulmonary arteries in the frog and the turtle, but observed that section of the vagosympathetic nerves leads to dilatation of the lung arteries on the same side. These authors pointed out also that the injudicious use of atropine in the preparation of experimental animals was responsible for inconclusive or negative results of many previous workers. We are indebted to Daly and his colleagues for most of the recent information concerning the vasomotor control of the pulmonary vessels. Their experimental technique has been so perfected that many objections to the use of artificial preparations (perfused organ experiments) have been overcome (8-10).

Of direct bearing on the problem presented in this paper, is the status of the vasomotor control of the pulmonary vessels in the rabbit. No references to the condition in the guinea pig are at hand. Cavazzani, 1891 (11), noted a rise in pulmonary arterial pressure on stimulation of the cervical vagus nerves. This was confirmed by von Euler, 1932 (12), who demonstrated, in addition, that such constriction was enhanced by eserine and suppressed by atropine. von Euler found also that adrenalin (0.01 to 0.2 mg.) causes vasoconstriction in the rabbit lung. This effect is opposed by ergotamine.

Ettinger and Hall (13) found that acetylcholine caused vasoconstriction in the rabbit lung. This effect was prevented by atropine and increased by eserine. They also noted that a greater constrictor action could be effected by acetylcholine if the vessels were previously potentiated by adrenalin, barium chloride, or histamine. Since there is only a feeble reaction of the pulmonary artery of the rabbit to adrenalin and to sympathetic stimulants, Ettinger and Hall suggest that the vagus or other parasympathetic fibers are mainly responsible for vasoconstriction. They propose the hypothesis that parasympathetic fibers, probably vagal, are chiefly responsible for the degree of constriction of the pulmonary artery repre-

senting the ordinary activity of the rabbit, but that the parasympathetic acts synergically with the sympathetic, in that the latter must produce a certain grade of tonus before the former can act.

Sufficient evidence points to the existence of strong parasympathetic vasoconstrictor fibers and weak sympathetic vasoconstrictor fibers in the lung of the rabbit. The application of this conclusion to our problem is evident: Loss of the power of pulmonary vasoconstriction by section of the cervical vagus nerves deprives the pulmonary vessels of a mechanism necessary in the adjustment of pulmonary vascular dynamics. Assuming that some sympathetic vasoconstrictor control is left intact under these experimental conditions, only a weak degree of tone can be present, and apparently in an amount insufficient to meet the needs of altered, or even normal, pulmonary vascular dynamics.

It is interesting to recall here that the vascular changes secondary to loss of vagal vasomotor control of the pulmonary vessels (bilateral vagotomy) were termed neuroparalytic hyperemia of the lungs by Schiff (14) in 1847, a few years before the first demonstration of vasoconstrictor nerves in the cervical sympathetic. Schiff was anticipated in some ways by Legallois, 1812 (15), who stated that "there occurs without doubt a loss of tone within the lungs, a sort of paralysis since the various tissues supplied by the vagus are engorged with blood."

It is impossible to conclude from the literature on the vasomotor control of the pulmonary vessels what the status is in man. Nor is it possible to conclude with certainty, the exact status in the intact rabbit or guinea pig, since the best information has come from perfused organ or isolated vessel preparations. It does appear, however, from available evidence, that both the sympathetic and the vagal systems exert a control over the pulmonary and bronchial vessels. Section of the vagus nerves (which contain some sympathetic fibers) in the rabbit and guinea pig, or destruction of the vagal and sympathetic fibers supplying the lungs in the guinea pig does disturb that control to a serious extent, as is demonstrated in our experiments by the production of severe pulmonary edema which leads to death, when those experimental procedures are carried out. No attempt will be made at this time to define that disturbance of control more closely in terms of the exact inbalance of the pulmonary nerves effected by

our experimental methods. Further investigation of these problems is indicated, and is being carried out.

Sufficient evidence from the experiments reported here, and from the literature in the related problem of the vasomotor control of the pulmonary vessels, is at hand to indicate that disturbances to the vasomotor control of the pulmonary vessels cause serious alterations in the dynamics of the pulmonary circulation, and in the integrity of the walls of the pulmonary vessels. These alterations lead to the production of severe pulmonary edema and congestion, which are the immediate causes of death. Preliminary studies in man indicate that in a number of conditions, the vasomotor control of the pulmonary vessels may be disturbed, either by central or peripheral disease, and that acute pulmonary edema is dependent upon such a disturbance. These studies suggest the pathogenesis of one type of acute pulmonary edema in man which we have termed neuropathic pulmonary edema.

CONCLUSIONS

1. Guinea pigs die shortly after bilateral cervical vagotomy, even when continuous artificial respiration effected through a tracheal cannula is carried out. Death is caused by severe pulmonary edema and congestion.

2. Direct observation of the lungs after bilateral vagotomy demonstrates that pulmonary edema develops gradually and increases slowly in amount and severity. Congestion precedes and accompanies the development of the edema.

3. Neuropathic pulmonary edema in the guinea pig is caused by disturbance to or abolition of the pulmonary vasomotor nerves.

4. The evidence obtained by experiments on animals suggests that neuropathic pulmonary edema in man is caused by disturbances, either central or peripheral, to the vasomotor control of the pulmonary vessels.

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BIBLIOGRAPHY

1. Beazell, J. M., and Ivy, A. C., *Arch. Path.*, 1936, **22**, 213.
2. Farber, S., and Handovsky, H., to be published.

3. Karsner, H. T., *J. Exp. Med.*, 1911, **14**, 322.
4. Larsell, O., *J. Comp. Neurol. and Psychol.*, 1921, **33**, 105.
5. Luckhardt, A. B., and Carlson, A. J., *Am. J. Physiol.*, 1921, **56**, 72.
6. Wiggers, C. J., *Physiol. Rev.*, 1921, **1**, 239.
7. Daly, I. de B., *Physiol. Rev.*, 1933, **13**, 149.
8. Alcock, P., Berry, J. L., and Daly, I. de B., *Quart. J. Exp. Physiol.*, 1935, **25**, 369.
9. Alcock, P., Daly, I. de B., and Narayana, B., *Quart. J. Exp. Physiol.*, 1936, **26**, 13.
10. Daly, I. de B., and von Euler, U. S., *Proc. Roy. Soc. Biol.*, 1932, **110**, 92.
11. Cavazzani, E., *Arch. ital. biol.*, 1891, **16**, 32.
12. von Euler, U. S., *J. Physiol.*, 1932, **74**, 271.
13. Ettinger, G. H., and Hall, G. E., *Quart. J. Exp. Physiol.*, 1935, **25**, 259.
14. Schiff, M., *Gesammelte Beitræge zur Physiologie*, Lausanne, B. Benda, 1894, **1**.
15. Legallois, M., *Experiments on the principle of life*, Philadelphia, M. Thomas, 1813.