

EXPERIMENTS ON THE CAUSATION AND AMELIORATION OF ADRENALIN PULMONARY EDEMA.

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PLATES 14 TO 16.

(Received for publication, March 21, 1917.)

During an investigation of the absorption of drugs¹ by the pulmonary air passages of the rabbit we observed that an intratracheal injection of adrenalin, after a double vagotomy, apparently produced a fulminant pulmonary edema much more readily than when the vagi were intact. In the present paper we shall report a study of this subject, together with other series of experiments, which finally led to the recognition of a practically ignored respiratory factor in the production of adrenalin pulmonary edema.

That adrenalin may cause pulmonary edema in the normal rabbit was noted early in the experimental investigation of this substance. Bouchard and Claude² in 1902 observed pulmonary edema and death in the normal rabbit after the intravenous injection of adrenalin, an observation abundantly corroborated. Pulmonary edema in the rabbit may also be obtained when the adrenalin is injected subcutaneously, though tremendous doses are then necessary; thus Battelli and Taramasio³ produced this effect with the subcutaneous injection of 10 mg. of adrenalin per kilo.

The facilitating action of vagus section upon the occurrence of adrenalin pulmonary edema in the rabbit has not to our knowledge been observed before. In artificially induced hydremic plethora, however, the vagi, according to Kraus,⁴ play in this respect a decisive part.

¹ Auer, J., and Gates, F. L., *J. Exp. Med.*, 1916, xxiii, 757.

² Bouchard, C., and Claude, H., *Compt. rend. Acad.*, 1902, cxxv, 928.

³ Battelli, F., and Taramasio, P., *Compt. rend. Soc. biol.*, 1902, liv, 815.

⁴ Kraus, F., *Z. exp. Path. u. Therap.*, 1913, xiv, 402.

EXPERIMENTAL.

Methods.

Rabbits only were used in this investigation. The animals were placed on an electric warming pad and ether anesthesia was employed for operative procedures. A wide glass tube about 2 cm. long was tied into the trachea. When blood pressure was recorded the right carotid artery was connected to the mercury manometer by tubing filled with half saturated sodium sulfate. When the lungs and heart were inspected the sternum was split longitudinally; usually both pleural sacs were opened. Intratracheal insufflation was then started so that the lungs were always moderately distended. The vagi, when sectioned, were divided in the neck.

The adrenalin employed was the ordinary commercial product obtained in the market, and was slowly injected by syringe through the tracheal tube. The dose was usually 0.25 cc. per kilo of body weight; occasionally more or less was used.

When atropine was administered, this drug was usually injected intratracheally; in a few instances the atropine was injected intramuscularly.

As criteria for the presence of pulmonary edema we utilized the appearance of foam in the trachea and the autopsy findings. As a rule, the medulla was punctured in the survivors 30 minutes after the injection; in some instances 1 to 3 hours were allowed to elapse.

Although the appearance of the typical tracheal foam is positive proof of the existence of pulmonary edema, yet its absence by no means indicates the absence of pulmonary edema. Râles may be audible to the unaided ear and easily felt by the fingers and yet the trachea may remain perfectly clear of foam. This happens especially when the injected animals do not struggle; there is then no mechanical compression of the lungs and the foam and fluid remain in the lower air passages. For this reason we killed the surviving animals after a period of time by medullary puncture and at once examined the lungs.

Several series of experiments were carried out. In the first series both vagi were divided and after not less than 10 minutes the adrenalin was injected. The controls for this series were normal animals with intact vagi, but in many of them the adrenalin was injected repeatedly, thus rendering the control test especially severe.

In another series with divided vagi, the behavior of the heart was examined by inspection, the sternum being split lengthwise and the pericardial sac opened. Artificial respiration was instituted before the lungs were exposed. The adrenalin was always administered repeatedly. In a subsidiary series artificial respiration, with and

without ether, was given to rabbits with chests intact but with vagi divided.

In still another series the vagi were again divided, but atropine was administered before the injection of adrenalin.

In a final series the effect of tracheal stenosis upon the production of pulmonary edema in normal rabbits (vagi intact) was tested.

Results in Series with Divided Vagi.

The vagi were divided before the adrenalin was injected. The average dose was 0.25 cc. per kilo, and as a rule only one injection was given. The following protocol will give a clear picture of a typical experiment.

Rabbit 1.—Gray male; weight 1,740 gm.

10.45. On electric pad at medium.

10.58. Start ether.

11.02. Operation completed; both vagi divided, cannula in trachea. Stop ether.

11.08. Respiration rapid, easy. No inspiratory stoppage. Heart moderately rapid, regular, good strength.

11.10. Change pad to low.

+11.12. 0.52 cc. adrenalin into trachea (0.3 cc. per kilo); no loss.

11.13. Respiration more shallow and more rapid.

11.13½. Respiration slowed, deeper, with retraction of costal margin; respiration stopped.

11.14½. Respiration starts, slow, deep, with retraction of costal margins. Heart very rapid, apparently regular, good strength.

11.15. Struggle; pink foam in tracheal tube.

11.15½. Pink foam pouring from tracheal tube.

11.16. Struggle, marked outflow of pink foam. Heart apparently regular, rapid (palpation).

11.17. Respiration rapid; strong retraction of costal margin.

11.18. Convulsive struggles; pink foam and fluid pouring from tracheal tube. No heart palpable. Occasional gasp. Pupils wide.

11.19. No respiration. No heart palpable.

Autopsy at once. No excess fluid in peritoneal cavity. Well marked peristalsis of small gut and cecum; cecum full of gas. Spleen and liver congested. Kidneys apparently normal. No hemorrhages in diaphragm. Lungs do not collapse. Heart large, fills entire pericardial sac. Auricles and ventricles dilated. Heart flabby, large, with no hemorrhages on pericardial or endocardial surfaces. No clot in pulmonary artery or aorta. Lung and trachea excised;

lungs large, erect, heavy, surfaces covered with many small hemorrhages, often confluent. Lower lobes show most hemorrhages; bluish black-red color; upper lobes pink. In trachea pink foam and white foam, alternately in layers. On section, lower lobes extremely juicy, like a wet sponge; not much air, chiefly red fluid with some foam. Upper lobes contain a large amount of white foam, not much fluid; not heavy like lower lobes (Fig. 2).

Of 27 rabbits whose vagi had been divided, 21 showed on autopsy a marked pulmonary edema of the general type described in the preceding protocol. 14 died within 20 minutes of the single intratracheal injection of adrenalin, and of these 10 died within 10 minutes, showing the general symptoms noted above. In only 6 did the autopsy show slight or no edema. Thus in about 78 per cent (21 out of 27) of the animals a single intratracheal injection of a moderate dose of adrenalin caused a marked pulmonary edema.

Control Series with Vagi Intact.

In this group of sixteen animals the adrenalin was usually injected repeatedly into the trachea, the time interval varying between 4 to 20 minutes. The dosage was usually 0.25 cc. per kilo. In addition to the intratracheal injection a number of the rabbits received intramuscular injections of adrenalin.⁵ This series therefore forms a severe control for the group with divided vagi.

The results are briefly as follows: None of the rabbits, in spite of the repeated injections, died within 20 minutes; 3 succumbed after 40 to 45 minutes. The survivors (13) were either killed by medullary puncture 15 to 60 minutes after the first dose of adrenalin or were etherized after 15 minutes and the heart was clamped off. Autopsy revealed in no instance a pulmonary edema of the degree which was found in the series with divided vagi. Pulmonary edema, however, was present to some degree in the lungs of most of the animals; in 6 rabbits the edema was moderate, in the remaining 6 it was slight; one autopsy record was lost.

A comparison of the two series shows clearly that the intratracheal injection of adrenalin exerts a much severer effect in vagotomized

⁵ Specimen protocols in tabular form will be found in our previous article, Auer and Gates,¹ pp. 760-761.

than in normal animals. Thus 14 out of 21 vagotomized animals died acutely in 20 minutes after a single intratracheal injection of about 0.25 cc. of adrenalin per kilo, while only 3 out of 16 normal animals succumbed within 40 minutes, although the normal animals received the adrenalin repeatedly. In addition it must be emphasized that the degree of pulmonary edema was much greater in the vagotomized series than in the control series whose vagi were intact.

Behavior of the Heart.—In a number of experiments where the blood pressure was recorded, it was observed repeatedly that the blood pressure at one time or another after the adrenalin injection showed sudden, profound drops varying in duration from 10 seconds to 3 minutes associated usually with convulsions after the low pressure level had been attained. Foam in the trachea was noted in some cases, especially those in which the low pressure level was maintained for some time. In Fig. 1, for example, foam first appeared in the trachea after the second series of convulsions following the second abrupt drop of blood pressure.

These abrupt drops of blood pressure were obtained not only in animals with intact vagi, but also in those whose vagi had been sectioned. The cause of these drops was therefore peripheral and probably located in the heart itself. In order to gain information on this point the heart was exposed in a series of seven etherized animals by splitting the sternum and opening the pericardial sac. Usually both pleural sacs were also opened, the respiration being maintained by intratracheal insufflation. In all except one animal the vagi were severed. A specimen protocol will illustrate the observations made and their time relations.

Rabbit 2.—Gray female; weight 1,885 gm.

10.20. On pad at low. Ether.

10.46. Operation finished: both vagi divided; cannula in trachea; chest split longitudinally to expose heart. Insufflation of air-ether with remissions; air catheter through tracheal cannula.

Change pad to medium. Heart beats regular, rapid after opening pericardium. Both pleural cavities open; lungs pink, good distension; spontaneous respiration present.

+10.50. 0.47 cc. of adrenalin into tracheal cannula (air catheter temporarily withdrawn), 0.25 cc. per kilo.

10.51. Left ventricle beats half as fast as right ventricle, right auricle, and left auricle. Left ventricular contractions weaker than those of right.

10.54. Both ventricles beat synchronously, following auricles; left ventricle stronger beat than before. No foam in trachea.

11.01. Chambers beat synchronously; good strength.

+11.03½. 0.47 cc. of adrenalin, into trachea.

11.04. Left ventricle half as fast as right ventricle; left auricle very large now; both auricles and right ventricle beat at same rate; left ventricle at half that rate and contractions weak.

11.06. As before, but left ventricle beats more strongly.

11.06½. Left ventricle shows strong and weak beat alternately.

11.08. Left ventricle now beats at same rate as right ventricle; left auricle much smaller now.

Animal killed by clamping the heart. On excising the lungs, the right side is large, full, rounded, with no emphysematous blebs on surfaces; the left side collapses fully. Right lung shows a good amount of foam in the alveoli and large bronchi; the left lung exhibits only slight edema. The surfaces show a moderate number of pin-point hemorrhages. Heart beats vigorously after excision; there are numerous hemorrhages over the left and right ventricles. Left auricle shows extensive hemorrhage on inner surface. Right ventricular endocardium shows a fair number of hemorrhages, only a few in left ventricle. Heart swiftly passes into rigor.

The protocol given above does not, however, show all the gross changes which may be observed in a series of experiments by inspection of the heart. The change of the left ventricular rate to half of that of the right ventricle is usually preceded by a stage in which the left ventricle shows an alternation of a weak and a strong beat. Then the weak beat becomes no longer detectable to the eye and the left ventricle apparently beats at half the right ventricular rate. The left auricle usually beats at the same rate as the right half of the heart, but in one instance its rate was that of the left ventricle; the right half of the heart thus contracted twice to one contraction of the left half. This alteration in the functional activity of the left ventricle was noted in six of the seven experiments. The duration varied from a few seconds to 3 minutes.

In a few instances the entire heart stopped for the length of a beat or two, which accounts for the abrupt blood pressure drops mentioned previously. The dilatation of the left auricle was often tremendous, and made this structure look like a bright red blister. This dilatation is not dependent upon section of the vagi, for a sim-

ilar large dilatation of the left auricle with marked swelling of the aorta and pulmonary artery was also noted in the single experiment of this series in which the vagi were intact.

The pulmonary artery may dilate tremendously after the intratracheal injection of adrenalin; the dilatation develops shortly after the injection and may last 7 minutes. This dilatation is just as marked during diastole of the right ventricle as during its systole. Dilatation of the pulmonary artery was noted in three experiments, not looked for in three, and not seen, though sought for, in one experiment.

The aorta dilated markedly shortly after the adrenalin injection in five experiments and its condition was not observed in two.

In two experiments the adrenalin seemed to exert a locally inhibiting effect upon the muscle of the ventricle. In one instance the upper half only of the right ventricle contracted during systole, the lower half dilating. In this experiment the state of the aorta and pulmonary arteries unfortunately was not observed, but the left auricle dilated enormously and the left ventricle showed the changes in beat already described.

In the second instance the musculature of the left ventricle was affected locally, and with each systole a prominent though small, bright red bulging appeared near the apex. In this animal the aorta and left auricle were strongly dilated; the left ventricle showed the changes in character and rate of beat described previously; the pulmonary artery was not observed. The pulmonary edema obtained in this animal was only slight.

In this series of experiments with double vagotomy and exposure of the heart under artificial respiration none of the animals died acutely, but all were killed after at least 20 minutes had elapsed, by clamping the heart or by medullary puncture. Moreover, the pulmonary edema observed in the excised lungs was only slight in four, and fair to moderate in the other three experiments.

In these experiments the right auricle and right ventricle showed no marked dilatation at any time, nor was any dilatation of the left ventricle observed which could account for the swelling of the left auricle by regurgitation through the mitral valves. On the contrary, the left ventricle was in a state of greater tone with small systolic and diastolic excursions, so that the distension of the left auricle was caused by the inability of this chamber to empty all the blood it received from the lungs into the tonically contracted left ventricle.

Although these experiments yielded interesting information concerning the activity of the heart after the repeated administration of adrenalin in vagotomized animals, the main result is the suggestive absence of any considerable pulmonary edema. This is the more interesting because all the conditions apparently favored the production of pulmonary edema: pressure in the pulmonary veins was surely raised because the dilatation of the left auricle shows that it received more blood than it could handle, so that back pressure resulted; the pressure in the pulmonary artery was also raised as shown by its dilatation; and still further proof of increased pressure in the pulmonary circulation is furnished by the development of hemorrhages during inspection of the lung.

As these experiments were necessarily carried out under artificial respiration, a small series of tests was made to study the effect of artificial respiration upon the production of pulmonary edema when the chest was intact. Four rabbits were utilized; their vagi were divided and intratracheal insufflation started with air-ether in various proportions; in one animal air only was given after the operation had been completed. The adrenalin dose was 0.25 cc. per kilo intratracheally, administered once. In this series one animal died 17 minutes after the injection without any convulsions or foam in the trachea. Death was due to too much ether; autopsy showed pregnancy and only a slight degree of pulmonary edema. The other three animals were killed by medullary puncture 25 minutes after the adrenalin was injected, and the lungs were examined at once. None of them showed a marked degree of pulmonary edema, but some was present in all, especially in the lower lobes.

These results thus indicate that artificial respiration has a restraining effect upon the formation of pulmonary edema, and corroborate a similar observation made by Emerson.⁶ How this protection is possibly exerted will be discussed later.

Tracheal Stenosis.

In another set of experiments the effect of an inspiratory decrease of pressure in the lung alveoli upon the production of pulmonary

⁶ Emerson, H., *Arch. Int. Med.*, 1909, iii, 368.

edema in animals with vagi intact was tested. This was accomplished by compressing the trachea with a clamp. The air now entered so slowly during inspiration that a rarefaction of the intrapulmonic air occurred, as was evidenced by the sinking in of the costal margins and of the lower part of the sternum. The lung alveoli thus must exert some suction during inspiration upon the capillaries in their walls, and this should aid in the production of an adrenalin pulmonary edema in normal rabbits (vagi intact).

Fifteen experiments were made, of which ten were controls. The adrenalin animals received 0.3 cc. of adrenalin per kilo intratracheally; after about 2 minutes the trachea was stenosed. About 15 minutes after the injection the animals were killed and the lungs examined at once.

In 5 rabbits where adrenalin had been injected intratracheally and the trachea stenosed, 4 exhibited a good or well marked pulmonary edema; in 1 the edema was slight. The edema, however, was never as great as that seen in vagotomized animals.

In 5 controls, adrenalin was injected in the same dosage, but the trachea was merely exposed, but not constricted. 4 of these rabbits showed slight or no edema, but the fifth exhibited a well marked pulmonary edema. This latter animal, however, was abnormal, for both peritoneal and pleural cavities contained a large amount of clear straw-colored fluid.

In the second set of controls no adrenalin was injected but the trachea was constricted and the animal killed by asphyxia 15 minutes after beginning the stenosis. Of these five animals, all showed either slight or no edema of the lungs. It is seen that stenosis of the trachea and final asphyxia do not suffice in the normal rabbit to bring about pulmonary edema.

This series of experiments thus shows clearly that the cupping action of the lung alveoli on the pulmonary capillaries during inspiration plays a part in the production of adrenalin pulmonary edema.

Distribution of the Pulmonary Edema.

The edema obtained after vagus section was not uniform in its distribution throughout the lung. Invariably the lower lobes were much juicier and more hemorrhagic than the middle and upper lobes. On section the heavy, lower

lobes resembled sponges soaked to saturation with a pink fluid; squeezing usually yielded little foam but much fluid. The middle and upper lobes showed chiefly white foam with little fluid; occasionally, however, the middle and upper lobes also contained much fluid.

Hemorrhages also were much more extensive over the surfaces of the lower lobes than over the upper lobes (Fig. 2). The outer third of the upper lobes was usually free from hemorrhages.

As a rule, the right and left halves of the lungs were equal in size, but in a number of instances the right side was appreciably larger than the left, and in some of these cases the pulmonary edema was also greater in the larger half.

Atropine Series.

This series of experiments was undertaken in order to test the effect of adrenalin after paralysis of the motor vagus endings. The animals were tracheotomized, the vagi divided, and atropine sulfate was injected in 1 per cent solution about 5 minutes before the adrenalin. In some cases the blood pressure was recorded. The thorax was intact, and no artificial respiration was given. The dose of atropine varied between 1 and 2 mg. per kilo; the amount of adrenalin was always 0.25 cc. per kilo, injected intratracheally. The atropine was injected intramuscularly in the first three animals but in the remaining seven it was administered intratracheally.

Of 3 animals which received atropine intramuscularly, 2 died acutely in 10 to 14 minutes after a single injection of adrenalin showing typical symptoms of pulmonary edema. The other rabbit, however, gave no clinical signs of pulmonary edema within 1 hour, during which he received not one but three doses of adrenalin, each 0.25 cc. per kilo, at 15 to 20 minute intervals. Death occurred after 2½ hours and the lungs exhibited a marked pulmonary edema. This last animal received a larger dose of atropine than the two preceding ones; the first two received 1 and 1.25 mg. respectively per kilo, while the third rabbit was injected with 1.5 mg. per kilo.

In the other seven experiments the atropine was injected intratracheally, the first dose tested being 1.25 mg. per kilo. This amount, in subsequent tests, was increased until 2 mg. per kilo were given. In this series the results were encouraging. 1 animal showed foam and fluid in the trachea, but was in fair condition 35 minutes after the adrenalin injection. The other 6 showed no clinical sign of edema,

the respiration was easy, no râles were palpable or audible, and no foam or fluid was ever seen during the 30 to 40 minutes of observation. All the animals were then killed by medullary puncture and the lungs examined: 5 animals showed slight or no edema, 1 showed moderate edema, and 1 exhibited a marked degree of pulmonary edema. This animal was the one in which foam and fluid issued from the trachea 15 minutes after the adrenalin injection.

Five control experiments without atropine were made with animals from the same lot. Of the 5, 2 died within 10 minutes and the remaining 3 succumbed within 20 minutes after the adrenalin injection. The lungs of all showed a marked degree of pulmonary edema. The differences between lungs of these two series is well brought out by Figs. 2 and 3.

The following table summarizes the results of the atropine series and its controls.

Atropine Series. Vagi Divided. All Injections Intratracheal.

No. of animals used.	Atropine per kilo.	Adrenalin per kilo.	Death in 10 min.	Death in 20 min.	Autopsy.
7	<i>mg.</i> 1.25-2.00	<i>cc.</i> 0.25	0	0	Slight or no pulmonary edema in 5 animals; moderate pulmonary edema in 1; marked pulmonary edema in 1.
5	None given..	0.25	2	3	Marked pulmonary edema in all.

The protective action of atropine against adrenalin pulmonary edema in normal animals has been noted by Biedl.⁷

DISCUSSION.

In the previous pages we have shown that adrenalin pulmonary edema occurs more frequently, in a more severe form, and after a smaller dose in rabbits if the vagi are sectioned previous to the intratracheal administration of the drug, than when the adrenalin is given in the same way to rabbits with vagi intact. It has been pointed

⁷ Biedl, A., *Innere Sekretion*, Berlin, 2nd edition, 1913, i, 522.

out that artificial respiration strongly reduces the degree of pulmonary edema after adrenalin when the vagi have been divided, and this result is obtained both with opened and intact chests. Data have been furnished which indicate that after adrenalin administered intratracheally the heart ventricles temporarily deliver unequal amounts of blood with each systole, the right ventricle delivering more blood than the left, shown by the tremendous dilatation of the left auricle and by the marked swelling of the pulmonary artery, which remained distended during diastole as well as systole; it has also been shown that adrenalin produces a temporary incoordination of the heart so that the left ventricle beats at one-half the rate of the right auricle and ventricle. Finally we have demonstrated that atropine markedly reduces the occurrence of pulmonary edema after vagus section and adrenalin.

What bearing do these facts have on the production of pulmonary edema? Leaving aside for the moment the striking adjuvant action of vagus section in the formation of pulmonary edema, it will be noted in the first place that the cardiac changes observed by us after the administration of adrenalin are in full accord with the fundamental postulate of Welch's theory⁸ for the production of a general acute pulmonary edema. It will be remembered that this is a disproportion between the ventricular outputs of such a character that the left ventricle expels less blood per systole than the right, thus producing an acute venous hyperemia of the lungs. In our experiments on rabbits whose hearts were exposed for inspection (artificial respiration) we saw this demand fulfilled: shortly after the intratracheal injection of adrenalin the pulmonary artery dilated widely and remained dilated during each diastole of the heart; at the same time the left auricle swelled tremendously and sooner or later the left ventricle showed a rate which was only half that of the right side of the heart, and its amplitude of contraction was small. These facts indicate unquestionably that the right heart is acting vigorously, that the arterial and venous pressures in the lung are

⁸ Welch, W. H., *Virchows Arch. path. Anat.*, 1878, lxxii, 375. See also his later presentation in S. J. Meltzer's Harrington Lectures on Edema, *Am. Med.*, 1904, viii, 37 of reprint.

raised, and finally that the left heart is surely expelling less blood per systole than the right.⁹

The physical conditions for the production of pulmonary edema demanded by Welch are therefore present, and yet the pulmonary edema which we obtained in this series with vagi divided, where the heart was exposed under artificial respiration, was slight and even negligible when compared with the tremendous edema which resulted when the same dose of adrenalin was injected into animals (vagi divided) whose thorax was intact and which were breathing in the normal way. Artificial respiration thus seemed to be an inhibitory factor, a supposition which was strengthened by the results of another series of experiments with chest intact, where the vagi were divided and intratracheal air insufflation with rhythmical remissions of the pressure was given throughout. Here again no marked degree of pulmonary edema was observed after the injection of adrenalin, either clinically, or after killing the animal and examining the lungs. Moreover, there are statements in the literature which furnish direct and indirect evidence regarding the effect of artificial respiration on pulmonary edema.

Emerson⁶ in a brief note reports that gentle artificial respiration, with or without suction, produces an amelioration of the pulmonary edema in cats, caused by the intravenous injection of massive doses of adrenalin. That artificial respiration may even prevent adrenalin pulmonary edema in rabbits follows directly from a statement of Miller and Matthews¹⁰ that they were never able to obtain pulmonary edema in a considerable number of rabbits by injecting intravenously 0.5 to 2 cc. of 1:1,000 adrenalin. Now, 1 to 2 cc. of adrenalin, intravenously administered, are sure to cause pulmonary edema in a percentage of normal animals provided that the number tested is not too small, and Miller

⁹ While our experiments show only that a rise of pressure undoubtedly exists in the pulmonary circulation, it might be assumed that it is due solely to back pressure from the left auricle. There is, however, good evidence to show that adrenalin contracts the pulmonary blood vessels, and without entering into the question of pulmonary vasomotors, the following observers, who have noted a rise of pressure in the pulmonary artery or a constriction of the pulmonary vessels after adrenalin, may be mentioned: Weber, E., *Arch. Physiol.*, 1910, Suppl., 410; 1912, 383; 1914, 535. Fühner, H., and Starling, E. H., *J. Physiol.*, 1913-14, xlvii, 301. Tribe, E. M., *ibid.*, 1914, xlviii, 154.

¹⁰ Miller, J. L., and Matthews, S. A., *J. Physiol.*, 1909, iv, 370.

and Matthews state that they used a "considerable number." But artificial respiration was necessary in their experiments to record the pressure in the pulmonary artery, and in view of the statements already made regarding the action of this procedure on the production of pulmonary edema, their failure to obtain edema is readily explained. Hallion and Nepper¹¹ also give as an impression that acute pulmonary edema in rabbits after the intravenous injection of large doses of adrenalin occurred apparently less readily when the thorax was open than when the chest was intact. They are inclined to attribute this action to mechanical conditions of the experiment, circulatory changes in the lung, and they also mention as a factor the positive intraalveolar pressure produced by artificial respiration.

The question now arises how artificial respiration reduces or prevents the pulmonary edema called forth by adrenalin in rabbits.

Artificial respiration does not prevent cardiac changes resulting in an acute congestion of the lungs, for we have observed, as described previously, such cardiac changes in rabbits when the chest was open. Emerson's tentative explanation¹² that the distension of the lung by artificial respiration drives a considerable amount of blood into the left auricle thus relieving the pulmonary congestion, is unsatisfactory even for the conditions theoretically deduced or experimentally observed by him, for he states that the adrenalin causes acute dilatation of the left ventricle with consequent mitral regurgitation, acute congestion of the lungs, and a dilatation and failure of the right heart; edema results due to the back pressure from the left ventricle. On the basis of this conception it is impossible for us to see how the massage of blood by artificial respiration from the lung into an acutely dilated left ventricle with incompetency of the mitral valves, could reduce the back pressure which, according to Emerson, causes the edema. In this connection we may say that we did not observe any acute dilatation of the left ventricle or regurgitation into the left auricle, nor have we seen any marked dilatation of the right ventricle during the cycle of cardiac changes induced by adrenalin. The left ventricle in the rabbit after adrenalin always seemed in a state of greater tone than normal. A few times the entire heart apparently stopped for a few beats in diastole but without any resulting marked dilatation. We are inclined therefore to believe that

¹¹ Hallion and Nepper, *J. physiol. et path. gén.*, 1911, xiii, 893.

¹² Emerson,¹ p. 370.

artificial respiration with positive pressure does not exert its inhibitory action on pulmonary edema through an action on the heart itself.

There is a factor, however, in the production of pulmonary edema, which is abolished by ordinary artificial respiration, that has received practically no consideration so far as we know. That factor is the aspirating action of the lung alveoli under certain conditions during inspiration. When the diaphragm descends, the negative pressure in the thorax increases, and air enters freely into the alveoli through the trachea and bronchi. The air pressure in the alveoli and consequently upon the capillaries in the alveolar walls remains at atmospheric level. If, however, there is a partial or even complete obstruction in the bronchioles, for example, by contraction of the bronchial muscles, hindering or preventing the entrance of air, then during each inspiration every alveolus connected with such a constricted bronchiole must act like a miniature dry cup, for the pressure in the alveoli and on the capillaries in their walls must decrease as these elastic chambers expand due to the disproportion between intra-alveolar and intrathoracic pressures. If in addition there is a congestion in the pulmonary circulation the passage of a transudate into the alveoli is surely facilitated if not even initiated by this pressure decrease in the alveoli. Experimental support for this view is given by the series of experiments where adrenalin was injected in rabbits whose tracheæ were stenosed.

This conception that the lung alveoli may act like dry cups, has been mentioned as early as 1845 by Mendelsohn.¹³ It must be added, however, that this action of the pulmonary air cells occupies but a subsidiary part in Mendelsohn's elaborate development of the thesis that lung hyperemia in general depends upon diminished expansion and contraction of the lungs during respiration. For, according to Mendelsohn, distension of the lungs stretches the pulmonary artery and its capillaries, increasing their volume capacity and thus aspirating blood; any diminution of the expansion and contraction diminishes this aspiration and reduces the pulmonary circulation which now depends solely upon the propulsive power of the right ventricle, so that stasis occurs.¹⁴

¹³ Mendelsohn, *Arch. physiol. Heilk.*, 1845, iv, 277.

¹⁴ See also Mendelsohn's final publication, *Der Mechanismus der Respiration und Cirkulation, oder das explicierte Wesen der Lungenhyperämien*, Berlin, 1845.

Is there any evidence that such a constriction of the bronchioles occurs after the injection of adrenalin? Since the publication of Kaplan's¹⁵ observation that adrenalin relieves bronchial asthma, most of the investigators describe a relaxation of the bronchial muscles as the result of an adrenalin injection,¹⁶ yet bronchial constriction by the same substance has also been noted. Golla and Symes¹⁷ with a new method of artificial respiration obtained constriction of the bronchioles in decerebrate cats and rabbits after adrenalin unless the bronchioles were initially constricted by other drugs, under which condition a relaxation was obtained. One of us, in some unpublished work, has also observed oncometrically a definite decrease in the amplitude of the lungs in rabbits after the intravenous injection of adrenalin, and it has already been stated that we have often seen a distension of the excised rabbit lung after adrenalin which was not accounted for by the degree of pulmonary edema present.

There is thus sufficient experimental proof that adrenalin may cause a constriction of the bronchial muscles and it is evident that as soon as this occurs the cupping action of the alveoli during inspiration can take place, thus aiding the passage of fluid from the gorged capillaries into the alveoli.

On the basis of this action of adrenalin, the protective action of artificial respiration may be explained; the positive pressure which artificial respiration produces in the lung reduces or overcomes the bronchial constriction due to the adrenalin and thus prevents the intraalveolar pressure from becoming negative during inspiration. Consequently the cupping action on the pulmonary capillaries does not occur. Thus one link in the chain of conditions which are more or less necessary for the production of pulmonary edema is broken, and edema is then produced with greater difficulty and to a less extent.

The protective action of atropine against pulmonary edema from adrenalin after vagus section may also be explained by paralysis of the bronchomotor endings of the vagus, and the consequent inability

¹⁵ Kaplan, D. M., *Med. News*, 1905, lxxxvi, 871.

¹⁶ Januschke, H., and Pollak, L., *Arch. exp. Path. u. Pharm.*, 1911, lxvi, 206-214. Trendelenburg, P., *ibid.*, 1912, lxix, 104. Jackson, D. E., *J. Pharm. and Exp. Therap.*, 1912-13, iv, 74, 291; 1913-14, v, 509. Baehr, G., and Pick, E. P., *Arch. exp. Path. u. Pharm.*, 1913, lxxiv, 62, 71. Dixon, W. E., and Ransom, F., *J. Physiol.*, 1912-13, xlv, 413.

¹⁷ Golla, F. L., and Symes, W. L., *J. Pharm. and Exp. Therap.*, 1913-14, v, 88.

of adrenalin to bring about constriction of the bronchioles, thus preventing the aspirating action of the alveoli. This is in accord with the prevailing view concerning the point of attack of both atropine and adrenalin. It must be mentioned, however, that Golla and Symes¹⁸ report that 10 mg. of atropine in a rabbit failed to relieve the bronchoconstriction caused by adrenalin. It is of course obvious that atropine may also affect the heart or the lung vessels and endothelia in such a way as to prevent or reduce pulmonary edema. But as we have no direct experimental evidence of our own we shall not enter into a discussion of these possibilities.

The aspirating action of the lung alveoli during coexisting pulmonary congestion also explains why the edema is always greater in the lower lobes than in the middle and upper lobes. This is due to the fact that the negative pressure is greater in the lower lobes than in the others. Experimental evidence for this is furnished by the work of Meltzer¹⁹ and Meltzer and Auer,²⁰ which indicates that the negative pressure in the chest is not the same at all levels but is greatest in the lower portion of the thoracic cavity. If a bronchiolar constriction occurs during a marked hyperemia of the lungs it follows that the cupping action of the alveoli during inspiration must be most effective where the negative pressure variation is greatest, provided that the hyperemia and endothelial permeability are the same throughout the lung.

We come now to a consideration of the remarkable accelerating effect which vagus section exerts upon the production of adrenalin pulmonary edema, and it may be stated at once that we cannot offer a full analysis because the experimental test of the various possibilities is incomplete. It may be said, however, that this difference in action is apparently a quantitative one, for pulmonary edema can usually be obtained in the normal rabbit provided that sufficient adrenalin is administered without causing cardiac death. The optimum state for the occurrence of a strong pulmonary edema develops more slowly in a rabbit with vagi intact than in one with vagi sectioned. This suggests that the structure primarily responsible for

¹⁸ Golla and Symes,¹⁷ p. 93.

¹⁹ Meltzer, S. J., *J. Physiol.*, 1892, xiii, 218.

²⁰ Meltzer, S. J., and Auer, J., *J. Exp. Med.*, 1910, xii, 34.

the fulminant onset of edema is the heart. By vagus section the heart is deprived of important regulating influences, and incoordination of the two sides of the heart perhaps then results more readily under stress; that such an incoordination does take place promptly when the vagi are divided and adrenalin is administered, we have already shown. Our experiments on the action of adrenalin on the fully innervated exposed heart of the rabbit are too few to permit any conclusion. The electrocardiographic studies on the action of adrenalin in the dog made by Kahn²¹ and by Rothberger and Winterberg²² which showed no incoordination of the heart after the vagi were sectioned (Kahn), but elicited changes in the form of waves very similar to those obtained by faradic stimulation of the accelerators (Rothberger and Winterberg), tend to support our view because the dog after vagus section tolerates large doses of adrenalin without developing pulmonary edema.

Another action which vagus section may facilitate is the production of bronchial constriction by adrenalin. After vagus section the bronchial muscles are relaxed and thus in the optimum state for contraction as demanded by Golla and Symes. The adjuvant action of bronchial constriction in the production of pulmonary edema has already been discussed.

Vagus section not only facilitates the formation of pulmonary edema after adrenalin, but it is an indispensable preliminary for obtaining pulmonary edema in experimental hydremic plethora.

Kraus²³ reports that the infusion of large quantities of salt solution in cats and rabbits only caused pulmonary edema when the vagi were sectioned. He also observed that adrenalin aided in the production of this edema; that open or closed thorax exerted no influence; and that atropine did not prevent this form of edema. Kraus assumes tentatively that section of centripetal vagus fibers, which govern reflexly the lung vasomotors, causes a disturbance in the regulation of the blood supply to the lung leading indirectly to edema.

Although Kraus' experiments and our own were carried out under widely different conditions so that a comparison cannot be made,

²¹ Kahn, R. H., *Arch. ges. Physiol.*, 1909, cxxix, 379.

²² Rothberger, J., and Winterberg, H., *Arch. ges. Physiol.*, 1910, cxxxv, 531.

²³ Kraus, F., *Z. exp. Path. u. Therap.*, 1913, xiv, 402.

it is nevertheless highly suggestive to note than in both sets of experiments *vagus* section exerted a profound influence. The nature of this influence cannot be stated with certainty at the present time.

In the preceding pages we have made no attempt to give a complete presentation of the problem of pulmonary edema but have limited ourselves largely to those facts which follow directly from our experiments. Necessarily, therefore, numbers of factors have been touched only lightly or not at all in the discussion.

SUMMARY.

The intratracheal injection of one moderate dose of adrenalin in rabbits whose vagi are divided produces a marked pulmonary edema in a large percentage of cases. The same dose in normal animals causes only slight effects.

Artificial respiration greatly reduces the production of pulmonary edema in vagotomized rabbits after adrenalin.

As adrenalin can exert a bronchoconstrictor effect, evidence is submitted to show that the aspirating action of the lung alveoli under this condition apparently plays an important part in the production of adrenalin pulmonary edema. On the basis of this mechanism the protective action of artificial respiration is explained.

Stenosis of the trachea facilitates the production of adrenalin pulmonary edema in rabbits whose vagi are intact.

The intratracheal injection of adrenalin in vagotomized rabbits produces a temporary incoordination between the heart ventricles, visible on inspection, so that the left ventricle beats apparently half as fast as the right, causing hyperemia of the lungs and hemorrhages.

Atropine injected intratracheally in vagotomized rabbits exerts a protective action against adrenalin pulmonary edema.

EXPLANATION OF PLATES.

PLATE 14.

FIG. 1. Blood pressure record. Rabbit 3; black female. Weight 1,980 gm. Both vagi were divided. The time is marked in 4 second intervals. The time line is also the zero pressure level. 0.5 cc. of adrenalin (0.25 cc. per kilo) was injected into the tracheal glass cannula. Note the three abrupt drops in the blood pres-

sure with prompt recovery. The low level (25 to 50 mm. of mercury) was maintained for 20 to 60 seconds, and convulsions appeared during this time. The typical foam of pulmonary edema appeared in the trachea after the second fall, and pink fluid during the terminal descent of the blood pressure. The terminal fall was slowed by a partial clot. These abrupt pressure drops are possibly caused by a complete cardiac stoppage such as was observed when the heart was exposed for inspection.

PLATE 15.

Figs. 2 and 3 show the protective effect of atropine. In both rabbits the vagi were divided and both received 0.25 cc. of adrenalin per kilo intratracheally. Rabbit 5, however, was injected with 1.75 mg. of atropine sulfate per kilo intratracheally before the adrenalin was administered.

FIG. 2. Rabbit 4, adrenalin alone. Typical pulmonary edema developed, with death in 18 minutes. The lungs were large, heavy, erect, hemorrhagic, with foam and fluid in the tracheal cannula.

PLATE 16.

FIG. 3. Rabbit 5, which received atropine before the adrenalin, showed no symptoms of pulmonary edema, and was killed after 45 minutes. The lungs collapsed practically normally, but the surfaces were peppered with small hemorrhages. The trachea showed no foam or fluid.

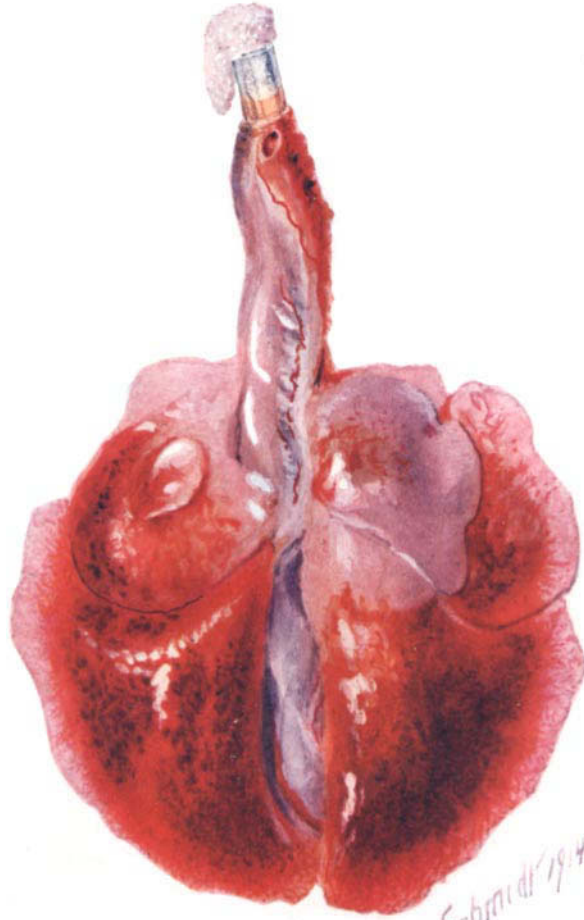


FIG. 2.

(Auer and Gates: Adrenalin pulmonary edema.)



FIG. 3.

(Auer and Gates: Adrenalin pulmonary edema.)