

A STUDY OF THE MECHANICAL FACTORS IN EXPERIMENTAL ACUTE PULMONARY EDEMA *

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During recent years the rôle of chemical agents in the development of edema has received considerable attention and several theories have been propounded with a view of explaining all forms of edema on a chemical basis. As a consequence the importance of mechanical factors has been somewhat discredited. Previous studies of the mechanical agents in acute pulmonary edema would indicate that here the phenomena may be explained on a mechanical basis. A continuance of these studies might, therefore, be of interest in order to determine whether pulmonary edema the result of other means than those previously employed could be explained without the aid of chemical agents.

In an exhaustive article published in 1878, William H. Welch¹ made the first attempt to explain, on an experimental basis, the phenomena of acute pulmonary edema. Working with rabbits he determined that ligation of the thoracic aorta, in such a manner that the only outlet was the left carotid and left subclavian, produced uniformly in animals with strong hearts a marked pulmonary edema. In animals with presumably weak hearts, as shown by the failure to respond to a rise in the pulmonary blood pressure, edema did not occur. He also determined that pulmonary edema could be produced by marked constriction of the pulmonary vein or compression of the left ventricle to the extent that its capacity was reduced 75 per cent. He noted that all of these procedures caused a marked rise in pressure in the pulmonary artery, which he considered a very important factor in the development of edema. Welch formulated the results of his experimental work in the following words: "Mechanical edema is the result of a disproportion between the working power of the left ventricle and the right ventricle of such a character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." This explanation of pulmonary edema gave as the important factor passive congestion in the pulmonary artery. Welch's theory called forth consid-

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1. Welch, W. H.: Zur Pathologie des Lungenödems. Virchow's Arch. f. path. Anat., 1878, lxxii, 375.

erable criticism, especially from clinicians who attempted to apply this explanation to acute pulmonary edema in man. Sahli called attention to the absence of evidence of intense hyperemia in pulmonary edema, especially in nephritic and cachectic conditions. Welch answers this criticism by saying that the color of dropsical tissues is an unsafe guide as to their blood content, as a pale dropsical lung may be markedly hyperemic. Especial stress has been laid on the character of the pulse during an attack. While usually small and rapid, it is at times normal or even of high tension (Sahli,² Hewlett,³ Riesman,⁴ Crummer⁵). The presence of high pressure has been used as an argument against impaired activity of the left ventricle. Welch's reply to this criticism was that complete paralysis of the left ventricle is not necessary to cause a disproportion between the working power of the two ventricles.

Welch's experiments were repeated by Mayer,⁶ Sahli² and Löwit.⁷ Mayer obtained the same results, but considered the rise in systemic pressure to be due to vascular spasm excited by the cerebral anemia. Sahli, working with dogs instead of rabbits, was able only infrequently to produce edema, which he explained by the greater permeability of the vessel walls in rabbits, and this factor rather than mechanical agents he considers responsible for the edema. Löwit, in repeating the experiments, obtained the same results, but considers overfilling of the pulmonary vessels as an important element. By taking the pressure in the left auricle and at the same time in the pulmonary and systemic circulation, he made the interesting observation that an increase in the pulmonary artery may be associated with lessened pressure in the left auricle or *vice versa*; that is, that direct transmission of pressure through the pulmonary artery to the pulmonary vein does not necessarily occur.

Both Löwit and Bettelheim⁸ were able to produce pulmonary edema by ligating the left coronary artery, the edema being associated with a fall in the systemic and a rise in the pulmonary pressure.

2. Sahli, H.: Zur Pathologie und Therapie des Lungenödems. Arch. f. exper. Path. u. Pharmacol., 1885, xix, 431.

3. Hewlett, H. M.: Four cases of acute suffocative pulmonary edema. Intercolonial Med. Jour., Australasia, 1903, viii, 611.

4. Riesman, D.: Acute pulmonary edema, with special reference to a recurrent form. Tr. Assn. Am. Phys., 1906, xxi, 155.

5. Crummer, L.: Acute suffocative pulmonary edema. Northwestern Lancet, 1902, xxii, 203.

6. Mayer, S.: Verhandl. d. Akad. d. Wissensch, Wien., 1878, lxxvii, 266.

7. Löwit, M.: Ueber die Entstehung des Lungenödems. Beitr. z. path. Anat. u. z. allg. Path., 1893, xiv, 401.

8. Bettelheim, J.: Ueber die Störungen der Herzmechanik nach Kompression der Arteria Coronaria sinistra des Lungenödems. Ztschr. f. klin. Med., 1887, xii, 550.

Grossman⁹ and Löwit produced pulmonary edema in dogs by intravenous injection of muscarin nitrate. Grossman reported a fall in the systemic pressure, with a temporary fall followed by a rise in the pulmonary artery. He explains these blood-pressure changes by a selective action of the drug causing spasm of the left ventricle. He calls attention, however, to a few instances in which the rise appeared earlier in the pulmonary artery than in the left auricle, a phenomenon which could not be explained by stasis in the left heart. As Brunton had stated that muscarin may constrict the pulmonary artery, Grossman cut the cord, but found that this did not interfere with the primary rise in the pulmonary artery. Brodie and Dixon¹⁰ have recently shown that muscarin dilates rather than constricts the pulmonary artery. Löwit was able to produce pulmonary edema with muscarin. His results differ from Grossman in that almost invariably the rise in pressure appeared earlier in the pulmonary artery than in the left auricle and, therefore, stasis arising from spasm of the left ventricle could not be the cause. Grossman and Löwit agree that evidence of disproportion between the working power of the two sides of the heart develops, but that the cause of this disproportion is still undetermined. Muscarin edema has a direct clinical bearing as in poisoning with toadstools (*Agaricus muscarinus*) pulmonary edema is a prominent symptom. Pilocarpin, which resembles muscarin in its action, has probably been responsible for many attacks of pulmonary edema in nephritics. Tyson¹¹ refers to the frequency with which pulmonary edema appeared at the time it was customary to administer large doses of pilocarpin in kidney cases.

Löwit has studied very carefully the blood-pressure changes associated with acute pulmonary edema produced by acetic ether. He found, immediately after the intravenous injection of a small amount, a decided fall in the systemic blood pressure and simultaneously with this a rapid fall in the pressure in the pulmonary artery followed by cardiac standstill. Since these pressure changes do not show any evidence of stasis, Löwit considered that he had demonstrated that acute experimental pulmonary edema could be produced independently of mechanical agents. As supporting this view, he has been able to cause quite extensive transudation into the peritoneal cavity by the intraperitoneal injection of butyric ether.

9. Grossman, M.: Das Muscarin-Lungenödem. Ein Beitrag zur Lehre von der Entstehung des acuten Allgemeinen Lungenödems. Ztschr. f. klin. Med., 1887, xii, 550.

10. Brodie, T. G., and Dixon, W. E.: Contributions to the physiology of the lungs. Jour. Physiol., London, 1904, xxx, 476.

11. Tyson, J.: A discussion of Riesman's paper on acute pulmonary edema. Tr. Assn. Am. Phys., 1906, xxi, 175.

Guinard and Teisser¹² demonstrated typical pulmonary edema in rabbits after the intravenous injection of 30 mg. of methyl salicylate, the observed pressure changes corresponding to those seen after the use of muscarin.

Von Zeissl¹³ by intravenous injection of Lugol's solution into dogs was able to produce very extensive pulmonary edema. During the development of the edema the pulmonary pressure always rose, the systemic pressure varied, at times a rise, at other times a fall, and, as had been observed with acetic ether, pressure changes in the left auricle that were apparently independent of that in the pulmonary artery. The right ventricle dilated, the left remained normal or became contracted. Although these pressure phenomena showed the presence of stasis, he considers changes in the vessel walls as probably an important factor in the development of the edema.

Finally, there is the experimental work of Powkuský¹⁴ with carbonic oxid. He was able to cause extensive edema in dogs and rabbits by this means. Blood-pressure measurements were not made, but he reports that during the experiment the left side of the heart appeared empty and contracted, the right heart full and dilated and the pulmonary arteries distended with blood—precisely the appearance that had been noted after acetic ether and iodid.

Summarizing the cardiovascular changes observed in the pulmonary edema produced by these various chemical agents, we notice a striking similarity. Generally there is a fall in the systemic pressure and a rise in pressure in the pulmonary artery. At the same time the right side of the heart becomes dilated, the left remains normal in size or, as some have maintained, contracted. Pressure changes in the pulmonary artery are not necessarily associated with corresponding changes in the left auricle, since a rise in pressure in the pulmonary artery may be associated with a fall in pressure in the left auricle or *vice versa*.

EXPERIMENTAL OBSERVATIONS

Our experimental work was undertaken with a view of determining the following questions: first, whether acute pulmonary edema, produced by other agents than those already tried, is associated with a rise in

12. Guinard, S., and Teisser, J.: Nouvelles recherches expérimentales sur la pathogénie de l'œdème aigu du poumon. Jour. de physiol. et de path. gén., 1901, iii, 42.

13. Van Zeissl, M.: Ueber Lungenödem in Folge von Jodintoxication. Ztschr. f. klin. Med., 1895, xxvii, 363.

14. Powkuský, W.: Ueber die Vergiftung mit Kohlenoxydgas. Virchow's Arch. f. path. Anat., 1869, xxx, 524.

pressure in the pulmonary artery; second, to repeat the experiments with acetic ether, since in the previous work the acetic ether had been an exception, inasmuch as it produced pulmonary edema without an increase in pressure in the pulmonary artery; third, the value of various agents in controlling the development of modifying the course of acute experimental pulmonary edema.

Nitric oxid, ammonia vapors and illuminating gas are all recognized as causing acute pulmonary edema in man. Hall¹⁵ reports three cases of edema in firemen exposed to the fumes of nitric oxid, and pulmonary edema under similar circumstances¹⁶ has been noted with ammonia vapors. Adrenalin often produces a pulmonary edema in rabbits, and Sahli refers to the frequency with which pulmonary edema occurs in dogs poisoned by hydrocyanic acid. These various agents were employed in our work and, in addition, the effect of artificial mitral stenosis on the pulmonary circulation. Dogs were used in most of our experimental work. In a few cases rabbits were utilized instead. Ether was used as an anesthetic. Artificial respiration was maintained by a bellows and motor. The pressure in the pulmonary artery was determined by a mercury manometer, the descending arm of which had twice the diameter of the ascending arm; in this way slight changes in pressure could be more readily detected. The cannula was tied in the branch of the left pulmonary artery supplying the upper or middle lobe. The systemic pressure was taken from the right carotid. Pulmonary edema was considered present when froth either issued from the trachea or could be expressed freely from the large bronchi by moderate compression of the lung.

Nitric Oxid.—Nitric oxid was generated from a mixture of metallic copper and nitric acid. The fumes were forced from the flask in which they were generated into the tracheal tube, where they became mixed with the ether vapor. As soon as a small amount of the gas had been inhaled, there was a very decided fall in the carotid pressure with a very slight fall in pressure in the pulmonary artery. The carotid pressure soon reached a level at which it remained stationary, but the pressure in the pulmonary artery steadily continued to fall. If the amount of gas was suddenly increased, there was at once a fall in pressure in both arteries. Eight minutes after beginning the gas, bradycardia and arrhythmia were noted, followed by cardiac standstill. There was no evidence of unilateral dilatation of the heart at any time. The lungs

15. Hall, J. M., and Cooper, C. E.: The effects of inhalations of the fumes of nitric acid, with report of cases. *Jour. Am. Med. Assn.*, 1905, xlv, 396.

16. Several cases of this character occurred in firemen fighting the flames in a refrigerator plant at the stockyards in Chicago.

showed very marked hemorrhagic edema; blood-tinged froth issued from the trachea. Here, as in all other edemas, the lower lobes were most extensively involved, the posterior median portion of the middle lobe less edematous, the remainder of the middle lobe still less involved. The upper lobes usually showed a slight patch in the posterior median portion. The lobe supplied by the branch of the pulmonary artery which contained the cannula was always free from edema.

The changes in blood pressure are shown in Table 1.

TABLE 1.—CHANGES IN BLOOD PRESSURE WITH NITRIC OXID

Time.	Carotid Pressure.	Pulmonary Artery Pressure.	Remarks.
	110	13.5	Before giving nitric oxid.
36 seconds	66	11.0	After beginning nitric oxid.
72 seconds	60	9.0	Inhaling nitric oxid continuously
250 seconds	56	8.0	Inhaling nitric oxid continuously.
300 seconds	32	6.0	Amount of nitric oxid increased.
480 seconds	0	0.0	Very marked pulmonary edema.

At no time throughout the course of this experiment was there an increase in pressure in the pulmonary artery. To consider a disturbance in the ratio between the two pressures as of importance in supporting Welch's theory is more or less fallacious, as drugs like nitroglycerin cause a very marked fall in the carotid pressure without affecting the pressure in the pulmonary artery. If mere disturbance of the ratio was an important factor, pulmonary edema would develop under these circumstances. In this experiment of producing acute pulmonary edema by means of nitric oxid, we were unable to detect any evidence of disproportion in the work of the two sides of the heart. The pulmonary pressure steadily fell. There were no signs of overdistention of any single cardiac chamber, or of one side of the heart. For this reason it would be impossible to apply Welch's theory to explain the development of the edema. It would appear that irritation of the bronchial or alveolar epithelium or the underlying vessels was an important factor. Cohnheim and Lichtheim demonstrated that in animals in which they had produced a hydremic plethora by transfusion, irritation of the skin with iodine or exposure to the sun was sufficient to produce a local edema. We must bear in mind that in Cohnheim's experiments a predisposition to edema was present. Whether such a predisposing factor is essential in the lungs, it would be impossible to say. There is no evidence in any case that this predisposing factor is a disproportion in work of the two ventricles.

Ammonia Vapor.—The results obtained by inhalation of ammonia vapors were similar to those produced by the nitric oxid. It was neces-

sary, however, to expose the animal for a much longer period of time; the edema was less marked and of the pale type.

Carbon Monoxid.—When the gas was administered slowly the carotid pressure was very slightly lowered; the pressure in the pulmonary artery unchanged or at times showed a very slight rise. When the gas was administered more freely, a point was reached where the systemic pressure dropped suddenly to zero, with extreme slowing followed promptly by cardiac standstill. During this time the pressure in the pulmonary artery rapidly fell, standstill of both ventricles occurring at the same time. If the flow of gas was stopped, the heart gradually returned to normal. In none of our attempts, either by prolonged slow administration or the free use of the gas, were we able to produce a pulmonary edema, although, following Powkowsky's advice, young dogs were used. The experiment was repeated on rabbits; they appeared much more tolerant of the gas than dogs; prolonged free inhalation was required to bring about cardiac standstill and the lungs were free from involvement.

Hydrocyanic Acid.—Sahli referred to the frequency of pulmonary edema in dogs after poisoning with hydrocyanic acid. In Germany it is apparently a practice among veterinarians to kill incurable or suffering dogs in this way. Sahli unsuccessfully attempted to produce pulmonary edema in rabbits with the hydrocyanic acid. We used the dilute acid of the U. S. Pharmacopeia. This we administered in various ways by mouth, directly into the stomach, subcutaneously and intravenously, but were unable to produce even a moderate pulmonary edema. There was a slight fall in the carotid pressure, the pulmonary pressure remaining unchanged or showing a very gradual lowering, except in one animal in which we obtained a drop of 30 mm. Hg. in the carotid pressure with a rise of 3 mm. Hg. in the pulmonary artery, independent of any struggling, without, however, producing an edema. This single case is suggestive on account of the evidence of disproportion of work between the two sides of the heart. With stronger solutions or in certain animals this difference in pressure might reach a sufficient degree to give rise to a pulmonary edema.

Iodids.—Lugol's solution was used in these experiments; in the first series of 10 per cent., in the second series a 50 per cent., and in the third series the undiluted solution. In Series 1 the animal received intravenously 200 c.c. of the 10 per cent. solution within a period of twenty minutes. There was a sharp rise in the carotid pressure immediately after the injection was begun, this high pressure being maintained until about 180 c.c. had been injected; following this there was a rapid fall and cardiac standstill. Toward the end the heart became irregular; long

vagus strokes appeared and continued until the end. After the injection of 100 c.c. there was a gradual rise in pressure in the pulmonary artery, which was maintained during the beginning of the fall in the carotid pressure (Table 2).

TABLE 2.—CHANGES IN BLOOD PRESSURE WITH 10 PER CENT. LUGOL'S SOLUTION

Time.	Carotid Pressure.	Pulmonary Pressure.	Remarks.
	130	30	Previous to giving Lugol's sol.
30 seconds	150	32	Transfusion with 10% Lugol's sol.
270 seconds	175	40	Had received 100 c.c. Lugol's sol.
900 seconds	180	44	Had received 150 c.c. Lugol's sol.
1200 seconds	50	40	Had received 180 c.c. Lugol's sol.
1320 seconds	0	0	Very slight pulmonary edema.

During the rise in pulmonary pressure the right ventricle and right auricle dilated, the left ventricle and auricle remained normal in size throughout the experiment. The lungs showed a moderate degree of hemorrhagic edema.

In the second series the animal received 60 c.c. of a 50 per cent. Lugol's solution, in doses of 20 c.c. each, extending over a period of eleven minutes. The animal was a young dog weighing 5 kilos. During the preparation the blood pressure became very low. After the first dose of Lugol's solution there was a distinct rise in the carotid pressure, which was maintained until the animal had received 60 c.c., then the long vagus stroke appeared and the blood pressure fell rapidly. This was associated with a distinct rise in the pressure in the pulmonary artery, which was maintained until the end (Table 3).

TABLE 3.—BLOOD PRESSURE WITH 50 PER CENT. LUGOL'S SOLUTION

Time.	Carotid Pressure.	Pulmonary Pressure.	Remarks.
	36	8	Previous to giving Lugol's sol.
30 seconds	40	10	After 20 c.c. 50% Lugol's sol.
300 seconds	48	11	After 20 c.c. 50% Lugol's sol.
720 seconds	0	0	After 20 c.c. 50% Lugol's sol.

The condition of the heart was the same as in the preceding experiment. Pulmonary edema was much more marked than in the first experiment.

In the third experiment the animal received three intravenous injections of 25 c.c., each of undiluted Lugol's solution. Immediately following the first injection there was a marked rise in the carotid pressure and at the same time a gradual rise in pressure in the pulmonary artery (Table 4 and Tracing 1).

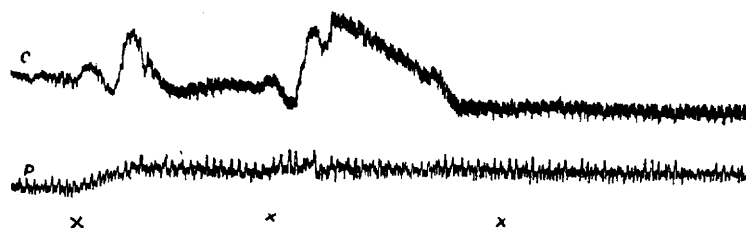
The carotid pressure quickly returned to the normal level to mount up again after the second injection; the pulmonary pressure, however, remaining high until just before death. The carotid pressure following

the third injection remained unchanged, gradually falling later. The heart was the same as in the preceding series, but the pulmonary edema was much more marked.

TABLE 4.—BLOOD PRESSURE WITH UNDILUTED LUGOL'S SOLUTION

Time.	Carotid Pressure.	Pulmonary Pressure.	Remarks.
	90	10	Previous to giving Lugol's sol.
30 seconds	110	34	After 25 c.c. Lugol's sol.
180 seconds	120	36	After 25 c.c. Lugol's sol.
300 seconds	70	36	After 25 c.c. Lugol's sol.
540 seconds	52	32	
660 seconds	0	0	Very decided lung edema.

These results are fully in accord with those of Van Zeissl. Attention is called especially to the appearance of the heart: dilatation of the right auricle and ventricle, the left auricle and ventricle normal. Van Zeissl reported the left side of the heart contracted; with this we can



Tracing 1.—Showing effect on the carotid and pulmonary arterial pressure of the intravenous injection of undiluted Lugol's solution. P, pulmonary; C, carotid; X, 25 c.c. of Lugol's solution injected.

not agree; while compared with the right side it appeared small, the size of the chambers corresponded closely to that preceding the injection. As Van Zeissl suggested that the rise in pulmonary pressure was due to constriction of the pulmonary artery, we used the various vasodilators without being able to lower the pulmonary arterial pressure. In another animal the cervical cord and vagi were cut before giving the iodid, but the rise in pulmonary pressure occurred the same as in the untreated animal. As our experience with acetic ether had shown that occasionally very large doses produced edema without a rise in pressure in the pulmonary artery, attempts were made to bring about the same results by using a very strong solution of iodine and potassium iodid. In every instance, however, a rise in the pulmonary pressure was observed. The mechanical factors favoring the development of edema were present; whether, however, they were responsible for the edema is questionable. This matter will be considered more in detail in discussing the effects of acetic ether.

Acetic Ether.—The inhalation or intravenous injection of a small amount of acetic ether invariably produces in dogs a typical pulmonary edema. The acetic ether was administered either by inhalation or intravenous injection to 17 dogs and produced an extensive hemorrhagic edema in every animal. In our early experiments doses of 2 to 3 c.c. were injected into the femoral vein; later smaller doses of 0.5 to 1 c.c. were used. Even with the smaller dose there is a distinct fall in the carotid pressure followed by a prompt partial recovery. Each succeeding dose produces a similar effect until, finally, the heart stops suddenly. With the very large doses occasionally death occurs without any rise in pressure in the pulmonary artery. More frequently, however, and invariably with the smaller doses, a very decided rise in pressure was observed. During the rise in the pulmonary arterial pressure, the right ventricle and auricle became much dilated, but we were never able to observe any dilatation of the left auricle or left ventricle. Preceding the cardiac standstill there was marked bradycardia. The left ventricle stopped first; quite regular pulsation of the right ventricle could often be observed one or two minutes after the left ventricle had ceased beating. In those animals also in which a rise in pulmonary arterial pressure did not occur, a very extensive edema was found, apparently as extensive as in those cases in which the pulmonary pressure was increased, thus showing that an increase in the pulmonary pressure is not essential for the production of edema. When the acetic ether was inhaled the same phenomena were observed, with the exception that a rise in pulmonary arterial pressure always occurred. Tables 5, 6 and 7 show the blood pressure changes and the ratio between the carotid and pulmonary pressure.

TABLE 5.—EFFECT OF LARGE DOSES OF ACETIC ETHER

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Ratio Between Carotid and Pulm.	Remarks.
	80	14	5.7	Beginning ether.
60 seconds	44	9	4.9	After 2 c.c. acetic ether.
150 seconds	30	6	5.0	
270 seconds	14	3	4.6	After 1 c.c. acetic ether.
450 seconds	42	12	3.5	
660 seconds	56	10	5.6	
720 seconds	11	3	3.6	After 2 c.c. acetic ether.
750 seconds	0	0		Very marked edema.

In the experiment shown in Table 5 we see the pulmonary pressure never reached the height it obtained before treatment was instituted, though after the second injection of acetic ether there was a sharp rise in the pulmonary arterial pressure, at which time it approached the original level. The ratio between the blood pressure in the two ventricles

shows that, following the second injection of acetic ether, the right ventricle was doing about one-third the amount of work done by the left ventricle, while, preceding the first injection, it was only doing about one-sixth as much work as the left ventricle. Too much stress, however, should not be placed on a disturbance in the ratio as a factor in the development of pulmonary edema. Apparently an actual rise in the pulmonary pressure is essential rather than a disturbance in the relative amount of work done by the two chambers. Whether a rise in the pulmonary pressure, which follows a fall and which does not reach the original level, as in the above table, can be looked on in the same light as an actual rise in pulmonary pressure appears to the writers very doubtful.

TABLE 6.—ACETIC ETHER IN SMALL DOSES INTRAVENOUSLY

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Ratio Between Carotid and Pulm.	Remarks.
	84	9.0	9.2	Before receiving ether.
20 seconds	64	10.5	6.3	After 1 c.c. acetic ether.
60 seconds	68	13.5	5.0	
220 seconds	80	17.5	4.6	
300 seconds	70	15.0	4.6	20 s. after 1 c.c. acet. eth.
480 seconds	36	12.0	3.0	30 s. after 1 c.c. acet. eth.
540 seconds	0	0.0	..	Very marked edema.

A very marked pulmonary edema was produced by the inhalation of acetic ether. The rise and absolute height of the pressure in the pulmonary artery was greater than we have been able to produce by any other means. Another peculiarity of this test was a decided gradual rise in the pulmonary pressure without a fall in the carotid pressure. Later, when the amount of ether was increased, a very marked fall in carotid pressure took place.

TABLE 7.—INHALATION OF ACETIC ETHER

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Ratio Between Carotid Pressure.	Remarks.
	108	24	4.5	Before acetic ether.
120 seconds	108	32	3.5	2 min. after beginning inhalation.
240 seconds	40	32	1.2	4 min. after beginning inhalation.
360 seconds	80	40	2.0	6 min. after beginning inhalation.
480 seconds	54	44	1.2	8 min. after beginning inhalation.
600 seconds	104	48	2.1	Ether discontinued for one minute.

As we had determined that pulmonary edema could be produced with large doses of acetic ether, without an increase in the pulmonary pres-

sure, it was important to determine whether with the small doses a rise in the pulmonary pressure was essential for its development. Auscultation over the lungs revealed the presence of numerous râles following the injection of small doses, and before a rise in pressure in the pulmonary artery took place. As a further test the heart and lungs were quickly removed just at the moment a rise in the pulmonary pressure was observed, in one instance within two seconds. Under these circumstances marked pulmonary edema had already developed. This experiment was repeated several times with always the same result. We must, therefore, conclude that the rise in pressure in the pulmonary artery really took place after the edema had appeared.

In endeavoring to explain the increase in the pulmonary arterial pressure, without evidence of stasis in the left heart, the possibility that the edema might cause the rise in pressure was considered. It is con-



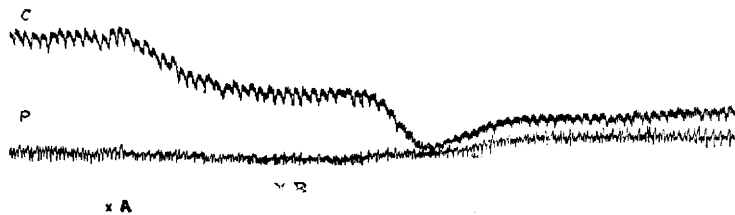
Tracing 2.—Effect on the blood pressure of small doses of acetic ether injected intravenously. P, pulmonary artery; C, carotid; X, 1 c.c. of acetic ether injected into the femoral vein. Very marked pulmonary edema.

ceivable that the pressure exerted on the arterioles of the pulmonary artery by the distended alveoli might increase the resistance sufficiently to cause such a rise in pressure. The effect on the blood pressure of overdistention of the lung with air was first tested. We were unable, however, even after prolonged distention, to produce a rise in the pulmonary blood pressure. An attempt was then made to distend the alveoli by allowing water to flow slowly down the trachea. An 8-kilo dog received in this way 250 c.c. of water in a period of 10 minutes. After the instillation of 100 c.c. a gradual rise in the carotid pressure was noted, which slowly increased until 175 c.c. had been given, when a gradual fall set in, which continued as long as the instillation of water was kept up. With the beginning of the rise in the carotid pressure, there was a gradual increase in pressure in the pulmonary artery, which reached its maximum much later than the maximum rise in the carotid. Following this there was a slight fall in pressure not commensurate, however, with the fall in the carotid. These blood-pressure changes are shown in Table 8. The lungs of this animal had the same appearance as those with pul-

monary edema. Abundance of bloody froth could be expressed from the large bronchi, and red blood corpuscles and granular material were found in the alveoli on microscopic examination. Apparently the instillation of water produced a pulmonary edema, and, therefore, the rise in pressure in the pulmonary artery was not necessarily due directly to the instillation of the water.

TABLE 8.—EFFECT ON CAROTID AND PULMONARY PRESSURE OF INSTILLATION OF WATER INTO THE TRACHEA

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Remarks.
	130	19.0	Before instillation began.
200 seconds	156	22.0	After 125 c.c. of water.
240 seconds	170	23.5	After 175 c.c. of water.
330 seconds	90	26.0	After 200 c.c. of water.
450 seconds	68	21.0	After 220 c.c. of water.
600 seconds	10	17.0	After 250 c.c. of water.

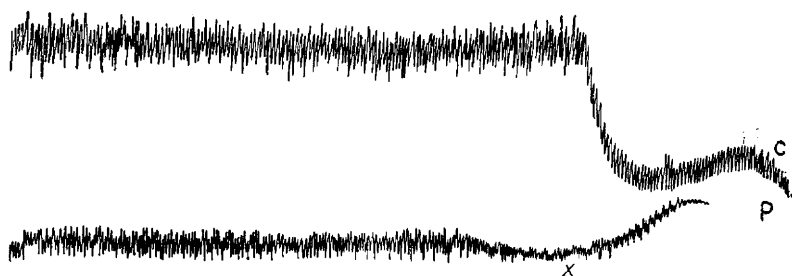


Tracing 3.—Showing the effect of acetic ether after section of the cord in the mid-cervical region. A, cord cut; b, 1 c.c. acetic ether intravenously.

From a study of the edema produced by iodids, we must conclude that with this agent, at least, the edema is not the cause of the rise in pressure in the pulmonary artery, as Van Zeissl determined that animals killed a few seconds after the increase in pulmonary pressure began did not show edema, but that prolonged increase in pressure was essential for its development. The rise in pressure in the pulmonary artery after acetic ether could not be prevented or modified by large doses of nitroglycerin. Combined section of the cord in the mid-cervical region and of the vagi also failed to prevent or modify it. The effect of section of the cord is shown in Tracing 3. It would, therefore, appear that the rise in pressure in the pulmonary artery is not of nerve origin. A close study of Tracing 4 would certainly give the impression that stasis from the left heart was a factor, as we note in the tracing that the increase in pressure in the pulmonary artery begins during the period of sudden drop in the carotid pressure, exactly what could be expected if stasis were the cause. If we could accept Löwit's explanation that direct transmission of pressure from the left auricle through the pulmonary veins to the pulmonary artery does not necessarily occur, and that increased

pressure in the pulmonary artery is not necessarily transmitted to the pulmonary veins, stasis could still explain this phenomenon.

In seeking for an explanation of the rise in the pulmonary arterial pressure without corresponding increase in pressure in the left auricle, it was suggested that capillary thrombosis might be responsible. We can readily see that a plugging of the terminal branches of the pulmonary artery would be followed by the above pressure changes. Silbermann¹⁷ has shown that capillary thrombosis may be readily induced by various toxic agents, including carbon monoxid and ether, and that the capillaries of the lungs, on account of their exceedingly small caliber and low blood pressure, are especially prone to thrombosis. To demonstrate that such thrombosis was antemortem, Silbermann injected 400 to 500 c.c. of a saturated watery solution of indigo-carmin into a vein of the living animal. The areas of tissue in which the capillaries were plugged



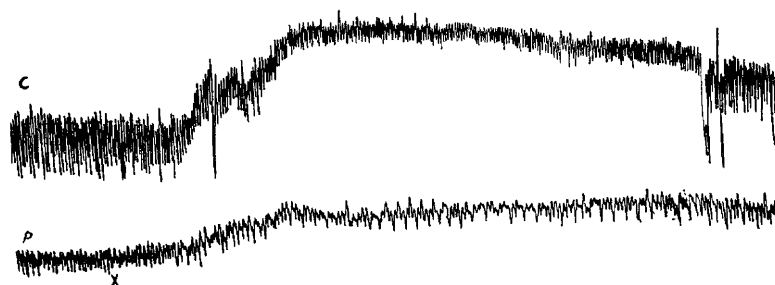
Tracing 4.—Showing the simultaneous changes taking place in the carotid and pulmonary pressure after acetic ether. C, carotid; P, pulmonary artery; X, 0.5 c.c. acetic ether intravenously.

would not be colored, while tissues with patulous vessels would take the stain. We resorted to this test in animals that had previously received iodid or acetic ether in sufficient amounts to cause pulmonary edema, but were unable to demonstrate the presence of capillary thrombosis. Microscopic examination of sections of the lung also gave negative results.

Adrenalin Chlorid.—On account of the occasional recurrence of pulmonary edema in rabbits after the intravenous injection of adrenalin chlorid, an attempt was made to study the blood-pressure changes during the development of such an edema. With cannulas in the carotid and pulmonary arteries efforts were made to produce a pulmonary edema by intravenous injection of 0.5 to 2 c.c. of a 1:1,000 solution of adrenalin

17. Silbermann, O.: Ueber das Austreten multiples intravitalen Blutgerinnungen nach acuter Intoxication durch Chlorsäure Salze-Arsen, Phosphor und einige andre Blutgifte. Virchow's Arch. f. path. Anat., 1889, cxvii, 288.

chlorid. Although the experiment was repeated on a considerable number of rabbits, we were never able to obtain one in which a pulmonary edema could be produced by this measure. The experiment was then modified by cutting off part of the circulation. The descending portion of the thoracic aorta was ligated, beyond where the large trunks are given off to the head and upper extremities. This ligation was followed by a very marked rise in the carotid pressure; the pressure in the pulmonary artery, however, was not affected; nor did pulmonary edema develop. The animal then received 0.5 c.c. of a solution of adrenalin chlorid, which caused a still further rise in the carotid pressure in the pulmonary artery, and the development of a marked pulmonary edema. This same experiment was repeated on dogs with similar results. These pressure changes are shown in Table 9 and also in Tracing 5.



Tracing 5.—Effect of adrenalin after ligation of the thoracic aorta. C, carotid; P, pulmonary artery; X, 1 c.c. adrenalin chlorid 1:1,000.

TABLE 9.—EFFECT OF ADRENALIN AFTER LIGATION OF THE THORACIC AORTA

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Remarks.
	106	9	Before ligation of aorta.
	146	7	After ligation of aorta.
30 seconds	210	19	After 1 c.c. adrenalin chlorid 1:1000.
120 seconds	204	18	Animal killed; pulmonary edema.

The development of pulmonary edema in these animals can best be explained by the vasoconstrictor action of the adrenalin raising the pressure in the systemic circulation to such a degree that the left ventricle is unable to empty itself completely. Stasis in the left auricle, pulmonary vein and pulmonary artery then follows with a consequent rise in pressure in the pulmonary artery and the development of edema. This is quite in accord with the theory advanced by Meltzer to explain the pulmonary edema following the use of adrenalin. By slow transfusion with a solution of adrenalin chlorid, 1:1,000,000, we were able to maintain a very high carotid pressure for twenty minutes, the pulmonary pressure

also showing a decided rise in case the thoracic artery had been previously constricted. Edema under these circumstances is of especial interest, as its development is associated with high pressure in the systemic circulation. One of the strongest arguments against the clinical application of Welch's theory is that it did not account for the high tension pulse often seen during an attack. In nephritis with extremely high blood pressure, the failure of the left ventricle to empty itself completely, with resulting stasis, increase in pressure in the pulmonary artery, and development of acute pulmonary edema, with high tension pulse, may occur exactly as it does in the rabbit after the use of adrenalin. It is well understood that high systolic pressure may be associated with small systolic output provided the pulse pressure, i. e., the difference between the systolic and diastolic pressure, is reduced. A high-tension pulse does not necessarily imply normal systolic output.



Tracing 6.—Effect of bleeding, after artificial mitral stenosis. X', 15 c.c. of blood withdrawn from the jugular. 15 c.c. withdrawn at X'' X''' X''''; C, carotid; P, pulmonary.

Artificial Mitral Stenosis.—The effect on the pulmonary pressure and the development of pulmonary edema was studied in dogs in which an artificial stenosis had been produced. With a little practice a ligature may be passed through the auriculoventricular groove in such a manner that on tightening it any degree of mitral stenosis may be produced. The first effect of narrowing the orifice is a fall in the carotid pressure. This occurs only after a considerable degree of constriction. In one animal the orifice was reduced one-half in size with only slight effect on the carotid pressure. When the constriction is carried still further, a rise in pressure in the pulmonary artery takes place. This rise may be slight or very marked, depending on the degree of obstruction induced. Table 10 shows the changes of blood pressure after constriction of the orifice from 8 to 3 mm. All of these animals when a satisfactory constriction of the orifice was obtained developed a decided pulmonary edema of the hyperemic type. After the constriction had reached a moderate degree, dilatation of the left auricle occurred followed by dilatation of the right auricle and right ventricle. The development of edema under these circumstances is best explained by Welch's theory.

TABLE 10.—PULMONARY AND CAROTID PRESSURE FOLLOWING MITRAL STENOSIS

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Remarks.
	100	9	Before production of stenosis.
60 seconds	50	9	Slight constriction mitral orifice.
300 seconds	84	14	Orifice constricted from 8 to 3 mm.
420 seconds	80	18	Showing increase in pulmonary pressure although no change in constriction since previous reading.

EXPERIMENTAL THERAPEUTIC AGENTS

In applying therapeutic agents to the treatment of experimental edema, it can readily be seen that no single remedy would be indicated in all instances. While the pulmonary arterial pressure was increased in most forms of experimental edema, the systemic blood pressure varied, low in some instances, high, however, in that type produced by adrenalin. Assuming that mechanical factors are important, a drug or method of treatment, in order to be considered beneficial, should tend to equalize the work of the cardiac chambers. The only form of experimental edema that yields readily to treatment is that produced by muscarin. Atropin has here a physiologic antagonistic action, and under its use the left ventricle assumes its normal working power, the blood pressure becomes equalized and the edema gradually subsides. Atropin, however, in pulmonary edema from other causes was without beneficial effect. When used in the edema produced by acetic ether or iodids the pressure in both carotid and pulmonary artery was increased, the developing edema was not checked nor was the life of the animal prolonged.

Nitroglycerin was also tried in the edema produced by acetic ether and iodids with the idea that perhaps the rise in pressure in the pulmonary artery was in part due to a vasoconstrictor action. As previously mentioned, however, large doses of nitroglycerin under these circumstances did not reduce the pulmonary arterial pressure. In the edema induced by adrenalin with high systemic pressure, the nitroglycerin was ineffectual on account of its action being interfered with by the more powerful adrenalin. This does not mean, however, that in pulmonary edema of this type in man nitroglycerin might not be beneficial, as the high tension in the systemic circulation may be due to other agents than adrenalin, which yield, slightly at least, to the vasodilators.

Barium chlorid, on account of its constriction of the pulmonary artery, due to its action directly on the unstriated muscle, was tried both for the prevention and alleviation of experimental pulmonary edema. As there is hyperemia of the lung with the edema, and the theory has been advanced that pulmonary edema is due to vasomotor paresis of the

pulmonary artery, it was thought that barium chlorid might exert a desirable influence. The results, however, were entirely negative either as regards preventing the edema or modifying its course. Changes in pressure in the carotid and pulmonary artery occurred as in the untreated animals.

Digitalis was also tried, both in preventing and alleviating developed edema. The only form of edema in which it appeared to have any beneficial action was that due to artificial mitral stenosis. Here in conjunction with venesection it contributed to the equalization of the circulation.

The effect of venesection was noted in animals with acute pulmonary edema from the various causes. The results on the whole were quite disappointing. Before any effect could be seen on the pressure in the pulmonary artery, it was necessary to withdraw a sufficient amount of blood to lower the general blood pressure materially. Rapid withdrawal of 10 to 20 c.c. of blood from the jugular vein of a 12-kilo dog would lower the pressure in the pulmonary artery momentarily, but it would promptly return to the previous level (see Curve 5). The withdrawal of 100 c.c. within two minutes in an 8-kilo dog would cause a permanent fall in both carotid and pulmonary artery, which, however, could not be considered as beneficial. When digitalis was given in conjunction with moderate bleeding, in the edema due to mitral stenosis, the pulmonary pressure could be lowered slightly and the carotid pressure raised to its previous level. It was not determined whether this increase in pressure in the systemic circulation was due to increased systolic output or to general vasomotor constrictions; however, as there was a slight fall in pressure in the pulmonary artery apparently the systolic output of the left ventricle was somewhat increased. With the adrenalin edema better results were obtained by bleeding from an artery than from a vein.

Although our therapeutic results in the treatment of experimental edema were so unsatisfactory, a knowledge of the factors at work in producing an edema should be of assistance in its intelligent treatment. We must remember that many attacks of acute pulmonary edema in man subside without treatment and, for this reason, clinical experience in the value of therapeutic agents must be accepted with considerable reserve. Considering marked disturbance of the circulation as the chief underlying cause of the trouble, intelligent rather than empirical treatment should be instituted. To give adrenalin, digitalis or caffein in a case of edema associated with high arterial tension might hasten a fatal termination. Atropin under these conditions, on account of its raising the blood pressure by quickening the heart action, would not be indicated. In this type of edema efforts should be directed toward lowering the

arterial tension, by the vasodilators or counter-irritation to the surface of the body or by bleeding with the type of edema associated with low-tension pulse, this form of treatment might be injurious. Here digitalis and caffeine would be indicated. It is interesting to note the frequency with which atropin is recommended in the treatment of acute pulmonary edema. The foundation of this treatment is apparently its beneficial results in the edema due to poisoning with toadstools and pilocarpin. The pulmonary edema developing in nephritics after the use of pilocarpin is often due in reality to the drug, as it produces edema in the same manner as muscarin, and atropin is the physiologic antidote. The second reason for its general use is based on its power to lessen glandular secretion. It is unnecessary to state that in acute pulmonary edema we are not dealing with a glandular secretion, but a transudation. The use of adrenalin is to be discouraged as being, under certain conditions, very dangerous and probably always valueless. Oxygen inhalations are harmless and give some temporary relief and may assist in tiding the patient over. Morphine, by allaying the patient's fears, is decidedly beneficial in its effects and could be safely used in small doses in any type of acute pulmonary edema. Venesection is another measure which is probably safe if practiced on individuals not already decidedly anemic. Its real value, however, can only be determined by extensive clinical observations. Unfortunately for the science of medicine, no one physician is able to see a sufficient number of cases of acute pulmonary edema during his lifetime to make a careful comparative study of the value of the various forms of treatment.

CONCLUSIONS

1. When pulmonary edema develops after exposure to nitric oxid or ammonia, there is no evidence that mechanical factors play a rôle; i. e., we are unable to detect any evidence of disproportion between the working power of the two sides of the heart.

2. The acute pulmonary edema following inhalation or intravenous injection of acetic ether is usually associated with evidence of disproportion in the working power of the two sides of the heart, as there is a fall in the systemic and a corresponding rise in pressure in the pulmonary artery. When large doses of acetic ether are injected intravenously, pulmonary edema may occur without evidence of disproportion in the working power of the two sides of the heart, thus showing that such changes are not essential for its appearance. It would appear, therefore, that mechanical factors are not responsible for the edema.

3. In the acute pulmonary edema produced by iodids, there is in the beginning a marked rise in pressure in both the systemic and pulmo-

nary circulation; later the systemic blood pressure falls, but the pressure in the pulmonary artery remains high. This disproportion in the working power of the two ventricles was present in every instance; it would, therefore, appear from our experiments that the edema might be explained by mechanical agents, although not necessarily so.

4. The intravenous injection of adrenalin chlorid, when preceded by ligation of the thoracic aorta, causes pulmonary edema. Apparently as a result of the great increase in the systemic blood pressure after such a procedure, the left ventricle is unable to empty itself completely; stasis and rise in pressure in the pulmonary artery follows. This is perhaps the mechanism of acute pulmonary edema in nephritics with hypertension.

5. In the mechanical edemas, therapeutic measures to be of value should tend to equalize the work of the cardiac chambers. This may mean the use of vasodilators in some instances, in others the use of drugs that stimulate the heart activity.

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