

EXPERIMENTAL PULMONARY EDEMA *

BENJ. H. SCHLOMOVITZ, M.D.

MADISON, WIS.

The following summary of the literature on pulmonary edema is to serve as a background for the present great interest in pulmonary edema stimulated by the work done on gas poisoning in the battle areas and in the laboratories. It was decided that the purpose of our work could be best fulfilled if an accurate recital of the experiments and data on experimental lung edema were chronologically arranged. The interjection of personal opinion and interpretation, therefore, is reserved until after the recital of the data.

In a study of the papers which might give information concerning the cause of pulmonary edema, it was found that the results could be grouped in the following order: (1) Lung edema occurring as an incident in an experiment; (2) lung edema produced for study; (3) lung edema recognized as a feature in an experiment, but its immediate cause overlooked or neglected. For this review, the second group is, of course, the most instructive and most deserving of attention, while the other two groups are suggestive.

HISTORICAL REVIEW

Virchow,¹ in 1853, produced pulmonary edema by injecting fat into a jugular vein. The mechanism was not investigated.

Pokrowsky,² while studying carbon monoxid poisoning in cats, dogs, rabbits and frogs, occasionally obtained lung edema. He was confirmed by Friedländer and Herter.³

Falk⁴ studied the effect of gases and poisons on the glottis primarily. He was interested in the occurrence of spasm, and observed lung edema in mammals during chlorin gas poisoning.

*From the Department of Physiology, University of Wisconsin Medical School.

*The data in this paper were prepared originally for the Chemical Warfare Service as confidential matter in furthering the study of toxic war gases. Permission to publish has been granted.

1. Virchow: Virchows Arch. **5**:308, 1853.

2. Pokrowsky: Carbon Monoxid Poisoning, Virchows Arch. **30**:525, 1864.

3. Pokrowsky, Friedländer and Herter: Carbon Dioxid Rich Atmosphere to Rabbits Get Various Grades of Pulmonary Edema, Cohnheim's Allg. Path., Ed. 2, **1**:502; **2**:273, 1882.

4. Falk: Spasmus glottidis bei gewaltsamen Todesarten, Viertelj. gericht. med. **16**:6, 1872.

Friedländer⁵ ligated the ascending aorta proximal to the innominate artery in the rabbit. The animal died in a short time and postmortem examination showed lung edema.

Longet⁶ (from Chemery) noted the occurrence of lung edema after vagal section. (See also von Frey.⁷)

Schweninger⁸ noted that fat emboli led to acute lung edema. This was confirmatory of Virchow's work.

Lassar⁹ studied the effects of acid vapors, nitric, sulphuric and hydrochloric, and of iodine on dogs and rabbits. The vapors rarely induced a bronchitis or a bronchopneumonia when sufficient air was mixed with them. In a few instances, lung edema occurred after asphyxia. He noted the nonappearance of acids in the urine, and stated that either the acids do not diffuse through the alveolar walls, or they are precipitated higher up in the respiratory passages, in which case they may unite with the lung epithelium before they can get through. Their danger lies in the fact that they lower the oxygen percentage of the inspired air, producing asphyxial symptoms.

Cohnheim and Lichtheim,¹⁰ morphinized or curarized dogs and rabbits, and then injected enormous quantities (from 64 to 92 per cent. of the body weight) of a 0.6 per cent. solution of sodium chlorid at body temperature intravenously. In several cases, exitus occurred in a few hours with symptoms of acute pulmonary edema. The dogs had a decreased dry weight of the blood. Arterial pressure was increased temporarily or not at all, while the venous pressure rose slightly or not at all, but never came back to zero if it did rise. The pulse frequency was not increased. There was an increased velocity in the blood stream, and an increased lymphatic flow. There was a marked outpouring of fluid in the glandular organs, although none in the skin, central nervous system, or thoracic cavity. The blood count was uniform in the portal, jugular and femoral vessels. They say that venous stasis is not responsible for the edema. They also injected distilled water, a 3 per cent. glucose solution, various salt solutions and diluted blood serum, and obtained similar results. Merely replacing the blood was negative. Their view is that the capillaries vary in permeability, and they felt that this was proven by obtaining skin edema in these animals after wounding the skin, or painting it with iodine, or exposing the shaved abdomen to the sun's rays.

5. Friedländer: Untersuchungen über die Lungenentzündung, Berlin, 1873.

6. Longet: Physiologie, Ed. 3, 2:507, 1873 (see Chemery).

7. Von Frey: Die Pathologischen Lungen-Veränderungen nach Lähmung der nervi vagi, Leipzig, 1877.

8. Schweninger: Aertztliches Intellig. Blatt, 1876.

9. Lassar, O.: Ueber irrespirable Gase, Ztschr. f. Physik. Chem. 1:165, 1877.

10. Cohnheim and Lichtheim: Ueber Hydrämie, Virchows Arch. 69:106, 1877.

Welch,¹¹ in the *first extensive research on pulmonary edema* per se, raised issues which challenged the attention of many workers. He reviews the causes of pulmonary edema postulated by others, such as increased heart activity, direct irritants, collateral hyperemia, thinning of the alveolar air, effect of cold drinks, inflammatory conditions, stasis—pulmonary vein obstruction or weakened heart action with both chambers equally weak. He says that the mechanical factors have not been exhausted, and that a stasis edema is possible by the production of obstructions in the lung veins, left auricle, left ventricle and aorta. He produced lung edema in dogs and rabbits, more easily in the latter. Tying the aortic arch between the innominate and left subclavian arteries produced lung edema in only one rabbit, while tying two additional branches of the innominate artery resulted every time in lung edema accompanied by asphyxial phenomena. It requires almost complete occlusion of the aorta between the heart and the innominate artery to get an edema. Lung edema occurred when the pulmonary artery pressure rose. The carotid pressure usually rose. The stasis occurs because more blood goes to the heart than comes away, and the stasis is not due to weakness of the right ventricle. These methods, however, he says, are not applicable to human cases, nor are they comparable to what occurs in the human being. Ligation of pulmonary veins must be extensive before edema occurs, while pulmonary artery pressure rises slightly until the onset. Welch emphasized the fact that marked pressure on the left auricle and left ventricle produced lung edema in the rabbit. The microscopic picture resembles that found in man. Welch postulated a disproportion between the working power of the ventricles with the left less efficient than the right. He attempted to produce a onesided cardiac paralysis by the use of potassium, iodine, salts, carbon monoxide and strychnine internally, while potassium salts, chloroform, ice and heat were applied externally. At last, he succeeded in producing such a paralysis by squeezing the left ventricle of rabbits with his fingers. He never obtained edema by pressure on the right ventricle alone, or by pressure on the right and left ventricles. He believes that the increased capillary pressure in the lung vessels is added on to the greater permeability of the lung capillaries. Too much emphasis should not be laid on the fact that the pulse is weak in some human cases. Microscopic section showed distended capillaries filled with red blood corpuscles. Red blood cells were also found in the interstitial tissue.

Rosenbach,¹² while studying artificially produced valvular insufficiency, obtained pulmonary edema in two cases. His postmortem

11. Welch: Zur Pathologie des Lungenödems, Virchows Arch. 72:375, 1878.

12. Rosenbach, O.: Ueber Artificielle Herzklappenfehler, Arch. f. Exp. Path. u. Pharm. 9:1, 1878.

examination findings inclined him to accept Welch's view of unequal activity of the ventricles.

Lichtheim¹³ produced pulmonary edema in rabbits by ligation of the artery and veins at the hilus. This occurred when the ligation was done unequally, by which he meant that the inflow had not ceased while the venous outflow had. These lungs had the same appearance as in those experiments in which only the pulmonary veins were tied.

Mayer¹⁴ confirmed Welch's findings. Ligation of the innominate and left subclavian arteries in noncurarized animals leads in most cases to marked edema with strong convulsions. In curarized animals no such results follow. He quotes Kussmaul and Teuner who produced pulmonary edema by ligating the arteries going to the head as indicating the importance of asphyxia as a cause of edema. Mayer obtained some results by ligating four main aortic branches. He believes that the variation in intensity of edema is due to (1) increased vascular tension, (2) vessel tonus, and (3) the milking effect of the right ventricle; and that these factors are especially present when asphyxial convulsions occur. Opening the abdomen and combining vessel ligation with the production of a double pneumothorax, so as to eliminate the mechanical effects of convulsions, prevented the occurrence of edema.

Sahli¹⁵ endeavored to repeat Welch's results, but failed in most cases. In some cases, ligation of the aorta and pressure on the left auricle produced a rise in pulmonary artery pressure, followed by a lung edema in dogs and rabbits. He says, however, that such methods are crude and not applicable to human conditions. He minimizes convulsive factors on the basis of strychnin experiments in which he got high lung artery pressures. Even when the pulmonary artery pressure is high and the carotid pressure is low, no edema need result. Cohnheim, in 1876, showed that marked changes in the systemic circulation have little effect on the pulmonary circulation. A paralysis of the left ventricle need not produce lung edema in dogs. Pressure, clamping, isolated faradization, narrowing of coronary vessels and injection of cardiac poisons were all negative. In man, he reiterates, lung edema is possible where *both* ventricles are *weak*, as in a case of combined aortic and mitral insufficiency. Then, again, a majority of the lung edemas in man are of inflammatory origin in the lung itself. His experiments with hydrocyanic acid were negative.

13. Lichtheim: Versuche über Lungenatektäse, Arch. f. Exp. Path. u. Pharm. **10**:71, 1879.

14. Mayer, Sigmund: Experimentale Pathologie des Lungenödems, Sitz. Berichte d. k. Akad. d. Wissensch. Wien. **77**: Part 3.

15. Sahli: Zur Pathologie und Therapie des Lungenödems, Arch. f. Exp. Path. u. Pharm. **19**:433, 1885.

Martin,¹⁶ perfusing the mammalian heart with defibrinated blood, notes the frequent, unfortunate interruption of the experiments by the onset of lung edema. He was primarily interested in the activity of the heart itself.

Tigerstedt and Santesson¹⁷ filled freshly removed frog's lungs with 0.6 per cent. sodium chlorid solution and found that they withstood a pressure of 14 mm. Hg for several hours, whereas, if the lungs were injured by heat, or by pouring into them distilled water or frog's bile, filtration is obtained at once.

Lehmann¹⁸ obtained lung edema by exposing cats, rabbits and guinea-pigs to hydrochloric acid and ammonia vapors. He includes a microscopic description of the lungs. Lehmann probably deserves credit for his prophetic insistence that poisonous (irrespirable) gases deserve and require intensive experimental study with the development of proper technic. He quotes and criticizes Eulenberg,¹⁹ Lewin²⁰ and Hirt.²¹ The work of Hirt is discredited by him, even though Hirt was widely quoted as an authority at the time. Eulenberg studied a number of irritating gases somewhat superficially, he says, and without proper attention to oxygen supply and carbon dioxid removal. Lewin is at fault because he uses Hirt's data. Lehmann experimented with a gas mask in a gas-filled room. His experimental method provided oxygen supply and carbon dioxid removal by means of a modified Pettenkofer-Voit respiration chamber. It may here be stated, that many of his reports on gas effects state the mere fact that a lung edema occurred, but there is little attempt to study the sequence of symptoms, their interrelation, significance and cause singly.

Pettenkofer²² reported the studies on irrespirable gases of his pupils (Gruber, Ogata, Lehmann, Nakahama and Mori) to the Munich Academy of Scientists. He emphasized Lehmann's results on guinea-pigs, cats, rabbits and man. Lung edema appeared with toxic doses of hydrochloric acid, ammonia, chlorin, bromin, hydrogen sulphid, carbon disulphid and anilin. Nitrobenzol was negative. The toxicity of all

16. Martin: A New Method of Studying the Mammalian Heart, Studies from Biological Laboratory, Johns Hopkins University 2:118, 1882.

17. Tigerstedt and Santesson: Bignang. till. K. Svensk. Vet. Akad. 11: No. 2, 1886.

18. Lehmann, K. B.: Experimentelle Studien über den Einfluss technisch und hygienisch wichtiger Gase und Dämpfe auf den Organismus (Ammoniak und Salzsäuregas), Arch. f. Hygiene 5:1, 1886.

19. Eulenberg: Die Lehre von den Schädlichen und giftigen Gasen, Braunschweig, 1865; Gewerbe Hygiene, Berlin, 1876. See Reference 18.

20. Lewin: Lehrbuch der Toxicologie. See Reference 18.

21. Hirt: Die Gasinhalations Krankheiten, Breslau, 1873. See Reference 18.

22. Pettenkofer: Ueber Gesundheitschädlichkeit mehrerer hygienisch u. technisch wichtiger Gase und Dämpfe, Sitz. berichte d. k. bayer. Akad. d. Wissensch. zu München. 17:179, 1887.

the substances was determined. Hydrochloric acid was toxic to mammals in 1:10,000, a figure markedly different from those previously reported. Chlorin poisoning was followed by a narcotic effect.

Grossmann²³ noted the appearance of lung edema following muscarin injection. Curarized dogs were used. Lung capacity, venous, carotid, pulmonary artery and left auricle pressures were recorded. He gives credit to von Basch for observing this type of edema first. After muscarin injection he claimed that there was a rise in venous pressure, right auricle pressure and left auricle pressure, and a fall in aortic pressure. Atropin administration and accelerator stimulation was followed by a disappearance of the muscarin induced lung edema. The blood flows slowly through the lung capillaries and under a high pressure. Section of the splanchnics or cervical cord did not prevent lung edema occasioned by muscarin. Strychnin was ineffective. Decreasing the amount of blood from the right ventricle prevented the appearance of the edema. Intravenous (jugular) injection of physiologic sodium chlorid solution caused signs of edema to disappear. Muscarin produced a decrease in the size of the left ventricle, and an increase in size of the right ventricle. Vagal stimulation dilated both ventricles. Muscarin probably produces a spasm of the left ventricle. Grossmann obtained stasis edema in eighty-five dogs with intact cardiac valves and strong pulses.

Grossmann, von Zeissl (*vide infra*) and Winkler (*vide infra*) are pupils of von Basch who claimed that (a) increased lung volume and (b) diminished expansibility of the lungs followed after increased filling of the lung vessels. They used special apparatus to record lung volume changes. The von Basch theory, if not discredited, at least is not accepted at present.²⁴ His pupils go a step further in postulating the occurrence of lung edema if (a) and (b) persisted as shown in their tracing without verification very often of the presence of an edema by direct examination of the tissues.

Sahli,²⁵ in a polemic against Grossmann, reiterates his criticism of Welch as the proponent of the left ventricle weakness theory of lung edema which Grossmann supports, in the main. He states also that spasm of the left ventricle and low blood pressure should be accompanied by signs of arterial anemia. Of course, clinically they are not. Therefore, Grossmann's low blood pressure data and other factors are at variance with clinical facts. The von Basch theory is completely thrown out of court. Sahli says that he obtained high pulmonary

23. Grossmann: A Study of Acute General Lung Edema. Muscarin lung edema, *Ztschr. f. klin. Med.* **12**:559, 1887.

24. Heinz: *Handb. d. Experimentellen Pathologie und Pharmakologie* **2**:514, 1906.

25. Sahli: Pathologic Lung Edema, *Ztschr. f. klin. Med.* **13**:482, 1888.

artery pressures for hours and still got no edema, therefore he doubts whether Grossmann could get any edema during a short period of high pressure.

Grossmann²⁶ describes the microscopic and gross changes in the lungs of cases of muscarin edema. The carotid pressure served as an index of what was occurring in the pulmonary artery. He dilates further on the von Basch theory that a more than normal filling of the blood vessels is followed by an increase in the alveolar space. He does not believe that muscarin narrows the bronchioles. The intrapulmonic air space decreases before there is cardiac slowing; then it increases. With carotid bleeding, the diminished expansibility of the lungs is reduced. In one series he put physiologic sodium chlorid solution into the trachea, as much as 600 c.c. in one experiment, without changing the lung capacity. He answers Sahli by saying that lung edema can be produced in dogs by compression of the left ventricles.

Grossmann²⁷ later returned to the von Basch theory with a study of obturation of the right auricle and left ventricle.

Löwit²⁸ criticizes Grossmann for postulating pulmonary artery pressure from carotid pressure when neither Knoll nor Löwit find constant effects in the pulmonary artery pressure by asphyxiation or aortic compression. Cats and rabbits were used after receiving hirudin. Marked compression of the aorta can produce simultaneous pressure rises in the pulmonary artery or in the left ventricle, or in one alone, or no rise at all. Therefore, the condition of the pulmonary artery pressure cannot be postulated from an examination of the left auricle pressure. He criticizes Grossmann's method of diagnosing lung edema. The best test is the transudate. Compression of the aortic root also produces varying results. Narrowing the tricuspid lumen to one third of the original opening hinders the outflow of blood to the right heart, resulting in a fall in pulmonary artery pressure. A large amount of blood can be accommodated by the pulmonary circuit without producing edema. Salt injection in the jugular, plus aortic root clamping, always resulted in lung edema. With an obstructed outflow of pulmonary blood, and an increased inflow of pulmonary blood lasting for some time, a stasis edema results in curarized or noncurarized animal, although sooner in the latter. He agrees with Mayer as to the importance of accessory factors. Marked compression of the left ventricle resulted in edema only when the pulmonary artery pressure rose;

26. Grossmann: Acute General Edema, *Ztschr. f. klin. Med.* **16**:161, 183, 270, 310, 1889.

27. Grossmann: Lungenschwellung u. Lungenstarrheit, *Ztschr. f. klin. Med.* **20**:397, 1892.

28. Löwit: Ueber die Entstehung des Lungenödems, *Beitr. z. Path. anat. u. z. allg. Path.* **14**:401, 1893.

therefore, he disclaims left ventricle weakening as the cause. He maintains that Welch obtained his edema following asphyxia. He has often noted no volume increase in lungs with edema, and often marked volume increase in lungs after muscarin with no lung edema. Double vagotomy results in inflammatory edema after from one to two hours, because Knoll showed that vagotomy produces no change in the small circulation. The pressure changes are negative.

Toxic lung edema was next considered by him. His studies with muscarin led to different results than Grossmann's. The pulmonary artery pressure rises, while the left auricle pressure rise is only temporary and coincident with the cardiac slowing. Löwit never got a lung edema with muscarin. Intravenous injection of acetic ether produced lung edema and transudation in other parts of the body. Löwit postulates vascular wall changes. Sulphuric and butyric ether act similarly. These types resemble the following in man: (1) Acute general edema; (2) inflammatory; (3) agonal, and (4) direct irritants of the lungs. Lung edema can be produced experimentally by excessive artificial ventilation. This is not accompanied by any pressure changes as a rule, therefore, it is not of stasis origin. Von Kahldeen (1895) abstracted his article.

Alexandrow,²⁹ in the main, confirms Welch, but in addition introduces nerve section and infusion experiments. Vagotomy is followed by edema. Lung capacity is lessened when there is blood stasis in the lung vessels. Artificial respiration delays the onset of lung edema. Section of recurrent nerves and accessories, or section plus hindrance to ingoing air is followed by lung edema. He worked with dogs, cats and rabbits.

Von Zeissl³⁰ produced lung edema in dogs by intravenous injections of iodine solution. He follows von Basch in his interpretations, and gets practically the same changes as Grossmann does with muscarin. In one experiment the lung edema was accompanied by a fall in the left auricle pressure. Morphinized and nonmorphinized animals were used with thorax both intact and open.

Jacobj³¹ discusses the technic of perfusing surviving lungs while under artificial respiration. The onset of edema is earlier the more dilute the blood is made. In these isolated lungs, with edema present, he hypothecates a disturbance of the gas exchange mechanism.

29. Alexandrow: Ueber Die Entstehungsweise des Stauungsödems in den Lungen, Diss. Moskau, 1892; Abstr. *Centralbl. f. allg. Path. u. path. Anat.* **4**: 691, 1893.

30. Zeissl: Ueber Toxisches Lungenödem, *Centralbl. f. Physiol.* **7**:702, 1893; *Ztschr. f. klin. Med.* **27**:363, 1895.

31. Jacobj, C: Ein Beitrag zur Technik der Künstlichen Durchblutung überlebender Organe, *Arch. f. Exp. Path. u. Pharm.* **36**:530, 1895.

Grossmann³² returns to the further elucidation of the von Basch idea. He claims that pulmonary artery pressure and left auricle pressure need not be registered simultaneously. Obturation of the left auricle produces a fall in carotid and venous pressures, accompanied by a marked rise in pulmonary artery pressure. The fall in venous pressure is interpreted as being due to the diminished amount of blood coming to the right heart. In this set of experiments Grossmann postulates that swelling of the lungs and their diminished expansibility is an invariable accompaniment of increased lung artery pressure, on the basis of his previous experiments. Compression of the root of the aorta causes a fall in carotid, and a rise in pulmonary artery and left auricle pressures. Fluid injected into a pulmonary vein produces the same result. In a polemic against Löwit, he believes that Löwit had clots in the blood vessels in spite of using leech extract, and that Löwit included the pulmonary artery often on aortic compression. He states, again, that the left auricular pressure rise is not directly related to the muscarin heart slowing. This rise is caused by the left ventricle spasm, and is followed by stasis hyperemia, which, in turn, are succeeded by lung swelling and diminished expansibility.

Löwit³³ answered Grossmann's critique.

Benedicenti³⁴ reported the occurrence of lung edema in mammals following inhalation of 25 to 30 per cent. carbon dioxid.

Winkler,³⁵ in administering amyl nitrite to curarized and morphinized animals, obtained lung edema with the typical carotid fall by nitrites. He is a pupil of von Basch, and used Grossmann's methods. Tigerstedt³⁶ cited the work of Bradford and Dean that a carotid pressure fall is accompanied by a pulmonary artery pressure rise. Tigerstedt states that amyl nitrite weakens the left heart.

Kockel³⁷ incorporates Weltzel's data with his own on the effect of nitric and nitrous acids on man and animal (rabbits, mice, guinea-pigs). He cites Bauer³⁸ as having the same results. After gassing, there is a period of relatively good health before untoward symptoms

32. Grossmann: Stauungshyperämie in den Lungen, *Ztschr. f. klin. Med.* **27**:151, 1895.

33. Löwit: Polemic vs. Grossmann, *Centralbl. f. allg. Path. u. path. Anat.* **6**:97, 1895.

34. Benedicenti: Die Wirkung der Kohlensäure auf die Atmung, *Dubois Arch.*, 1896.

35. Winkler: Neue beiträge zur Kenntniss des Amylnitrits, *Ztschr. f. klin. Med.* **35**:213, 1898.

36. Tigerstedt: *Ergebn. d. Physiol.* **2**:581, 1903.

37. Kockel: Ueber das Verhalten des menschlichen und thierischen Organismus gegen die Dämpfe der Salpetrigen und Untersalpetersäure, *Viertelj. f. gericht. Med.* **15**:1, 1898.

38. Bauer: Festschrift zur Feier der 50 Conf. des Vereins d. Medicinalbeamten d. Kg.-Bez., Düsseldorf, 1895.

occur. Lung edema and inflammation of the respiratory passages are the most prominent symptoms. Microscopic sections show multiple hyalin thrombi in lung vessels. The injured regions become foci for bacterial invasion. The respiratory epithelium is desquamated. The heart is weakened and this adds to the initial lung edema. The decreased gas exchange yields a third factor conducive to the production of edema. Death is by asphyxiation. There is a direct local effect on the lungs.

Kunkel³⁹ presents a general discussion of "gaseous" poisons, symptoms and pathology, and refers in general terms to his own experiments. He outlines the following problem as to the distribution of the gas or vapor: (1) the part bound to the tissue; (2) the portion absorbed, changed or unchanged; (3) the portion resorbed, and (4) the amount excreted again via the lungs.

Magnus⁴⁰ reviews Cohnheim and Lichtheim's work, confirms it, and cites Fleischer, Dembrowski, Dastre and Loye, and Knoll as having confirmed it. He also reports on his experiments with arsenic in producing pulmonary edema.

Fouineau's thesis⁴¹ contains no original experimental work.

Carrion and Hallion⁴² injected salt solutions of various concentrations intravenously, and noted the occurrence of acute pulmonary edema. They give no tracings or records of their experiments.

Chatin and Guinard⁴³ record the occurrence of lung edema after the injection of methyl salicylate.

Miecamp⁴⁴ follows Teissier, his teacher, with emphasis on theory. He presents no original work.

Chanoz and Doyon⁴⁵ showed lung edema after injecting amylsalicylic ether intraperitoneally or intravenously. Death resulted from arrest of respiration. There were convulsions.

Winterstein⁴⁶ records lung edema and increased mucosal secretions in animals after carbon dioxid inhalation.

D'Achard and Loeper⁴⁷ confirm Carrion and Hallion.

39. Kunkel: *Handb. d. Toxikologie* 1:38, 1899.

40. Magnus: *Die Entstehung der Hautödeme bei experimenteller hydrämischer Plethora*, *Arch. f. exper. Path. u. Pharmakol.* 40:252, 1899.

41. Fouineau: *De l'œdème aigu du pœmon*, These, Paris, 1898.

42. Carrion and Hallion: *Contributions experimentales à la pathologie des œdèmes*, *Compt. rend. de la Soc. de Biol.* 51:156, 1899.

43. Chatin and Guinard: *Recherches pharmacodynamiques sur le salicylate de méthyle*, *Ibid.*, 52:669, 1900.

44. Miecamp: *Pathogenie de l'œdème aigu du pœmon*, These, Lyon, 1900.

45. Chanoz and Doyon: *Compt. rend. Soc. de Biol.* 52:716, 1900.

46. Winterstein: *Engelmann's Arch., Suppl.*, 1900.

47. D'Achard and Loeper: *Sur la retention des chlorures dans les tissus au cours de certains états morbides*, *Compt. rend. Soc. de Biol.* 53:346, 1901.

Teissier and Guinard⁴⁸ used methyl salicylate to produce edema. After curarization, artificial respiration was instituted following tracheotomy. A window in the left thorax permitted them to get the pulmonary artery pressure. Compression of the aorta was negative, except for a temporary rise in pulmonary pressure and a fall in carotid pressure. Injection of methyl salicylate produced no effect or only a slight rise in the pulmonary artery pressure. Stimulation of vagi, plus the drug, produced lung edema, but edema was not marked when the heart was irregular. They also recorded left auricular pressure. There is no need, they say, to produce a rise in the latter pressure in order to get lung edema. The left auricle pressure does not change at all after the drug is injected, while the carotid pressure gradually falls. They propose a mixed theory. First, mechanical difficulties are of themselves insufficient; second, nervous effects, such as vasodilation, plus the first, facilitate an occurrence of lung edema, but third, an intoxication is necessary to produce an edema.

Bouchard and Claude⁴⁹ confirm Josue⁵⁰ (not known to me) on the production of lung edema after intravenous epinephrin injections in rabbits. They performed six experiments, and show no records of pressure changes.

Berge⁵¹ noted repeated pulmonary edema crises following subcutaneous injection of physiologic sodium chlorid solution in an arteriosclerotic individual who was afflicted with Bright's disease and an aortic insufficiency. There was no cutaneous edema at any time. Death occurred some time later in uremic coma with Cheyne-Stokes respiration.

Hamburger,⁵² took the ascitic fluid from a patient, aged 9 years, and injected it into a calf. There was a marked increase in the lymph flow. On heating the fluid two hours at 56 C. this lymphagogenic action was destroyed. The micrococci isolated from the fluid also had a lymphagogenic action. Fluid flowed from the nose of the calf, and there was an hydropic swelling of the interstitial tissue of the lung. He cites the presence of lymphagogues in cases of cardiac dropsy (Lepine), inflammatory hydrops (Talma), uremics (Starling), and in chronic hemorrhagic nephritics with edema. His view is that with hindrance of outflow of blood certain products accumulate in the capillaries and

48. Teissier and Guinard: *Nouvelles recherches experiment. sur la pathogen. de l'oedeme aigu du poumon*, J. de Physiol. et de path. gener. **3**:42, 1901.

49. Bouchard and Claude: *Recherches exp. sur l'adrenaline*, *Compt. rend. de seances de l'Acad. D. S.* **135**:928, 1902.

50. Josue: Not located.

51. Berge: *Oedeme pulmonaire provoque par l'injection souscutanee de serum artificiel*, *Bull. et Mem. de la Soc. med. d. hôp. de Par.*, 3d Series **20**:1349, 1903.

52. Hamburger: *Osmotischer Druck und Ionenlehre* **2**:67, 1904.

stimulate the capillary endothelium to greater lymph production. He speaks of autogenous lymphagogues. The vessel walls may also have an increased permeability.

Meltzer⁵³ observed pulmonary edema in rabbits after a large dose of epinephrin. The left ventricle cannot force out all of its blood because the systemic vessels are constricted. The right ventricle, stimulated by the epinephrin, unloads with increased energy the blood which the contracting vessels drove into it. The combination produces lung edema.

Welch,⁵⁴ at Meltzer's request, restates his views on lung edema, twenty-five years after his original contribution. Welch reiterates that lung edema occurs following a passive hyperemia, and that the important factor is passive congestion in the pulmonary artery. This is obtained by producing "a disproportion between the working power of the left ventricle and of 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." He maintains that Mayer, Grossmann and Löwit have confirmed his work. A weak pulse is not necessary. The relation between the forces of each ventricle is the essential thing. An edematous lung can be pale. Osmotic pressure, alterations in capillary endothelium and interference with lymph absorption are conceivably not sufficient factors alone to be primary causes of acute general edema of the lungs. He agrees with Sahli in that "a larger number of cases of pulmonary edema are referable to inflammatory changes in the vascular walls than is generally supposed." His opinion is based on systematic bacteriologic examinations at the Johns Hopkins Hospital necropsies.

Sahli,⁵⁵ also at Meltzer's request, still states that Welch's theory is untenable, and underscores the inflammatory type as the main one met in practice.

Jores⁵⁶ produced lung edema in four minutes in one lobe of a dog's lung by letting that lobe inhale carbonic acid through a tube. The localized effect rules out circulatory disturbance due to the heart. He quotes Mares as saying that the edema is not due to the acid but to the mechanical asphyxia which disturbs the vessel walls. A tube without gas in it produces the same effect. If a large tube is used no edema results. It is easy to obtain edema, a localized edema, if a tube is inserted into a bronchiole. Reflex respiratory standstills or ballooning a bronchus were negative. Jores concludes that the presence of an

53. Meltzer: *Edema*, *Am. Med.* **8**:195, 1904.

54. Welch: See Ref. 11; also Ref. 53.

55. Sahli: See Ref. 15; also Ref. 53.

56. Jores: *Ueber experimentelles, neurotisches Lungenödem.*, *Deutsch. Arch. f. klin. Med.* **87**:389, 1906.

irritating foreign body to the mucous membrane of the smaller bronchioles is the cause of a sharply localized lung edema in a very short time. It is not a stasis edema, nor is it toxic or infectious, therefore it must be of neuropathic origin. He stimulated the external surface of the lung faradically for ten minutes. The rabbit remained quiet. Edema followed. Similar results were obtained with dogs. He believes that the electrical stimulation produces a local vasodilation. With the same technic, including section of the right vagus, done three weeks before the experiment, an edema was obtained. Section of the sympathetics and right vagus was attempted, but the animals died of pneumonia in five days. He concludes that disturbance of the gas exchange per second has no influence on the origin of lung edema.

Heinz,⁵⁷ in a general discussion of lung edema, notes its occurrence especially with cardiac poisons. The type found is an acute, general, pulmonary edema. He directs attention to the fact that lung edema may easily be simulated by excess secretion of the bronchotracheal system. Therefore, one must be cautious when making a diagnosis by a transudate emanating either from a tracheotomy opening or the mouth. He found that perfusion of a heart-lung preparation (rabbit) with a solution containing three parts Ringer's solution and one part blood usually resulted in acute, general edema in thirty minutes. Heinz also produced an epinephrin pulmonary edema. In gassing with chlorin, bromin, ammonia, hydrochloric acid, hydrobromic acid, hydrofluoric acid and nitric acid there is a preliminary expiratory standstill.

Josue and Bloch,⁵⁸ showed lung edema in rabbits after intravenous injections of epinephrin. They were confirmed by Bouchard and Claude.

Chemery⁵⁹ reviewed the subject of lung edema in his thesis, but presented no original experiments. He favors a mixed theory of lung edema causation; first, hypertension; second, chlorin retention and third, a nervous element.

Emerson⁶⁰ gave epinephrin intravenously to cats. This produced left ventricular dilatation, which is accompanied by mitral regurgitation. This in turn leads to acute congestion of the lungs, dilatation and failure of the right heart. Stagnation in the small circulation produces edema. Artificial respiration in an advanced stage of edema is of benefit.

57. Heinz: *Handb. d. exper. Path. u. Pharmakol.* 2:525, 1906.

58. Josue and Bloch: *Action hypertensive de la couche corticale des capsules surrenales*, *Semaine méd.* 1907, No. 25.

59. Chemery: *Contribut. a l'etude de l'oedeme aigu du poumon et de sa pathogenie en particulier*, These, Paris, 1908.

60. Emerson: *Artificial Respiration in the Treatment of Lung Edema*, *Arch. Int. Med.* 3:368 (March) 1909.

Miller and Matthews⁶¹ studied the effects of nitric oxid, ammonia, illuminating gas, epinephrin and hydrocyanic acid. They also produced artificial mitral stenosis. Dogs and rabbits were given ether under artificial respiration. Carotid and pulmonary artery pressures were taken. Edema was obtained with nitric oxid. Both pressures fell. Irritation of the epithelium or underlying vessels is the important factor. Ammonia vapor produced the same results as nitric oxid. Carbon monoxid produced no pulmonary edema. A slight fall in carotid pressure was accompanied by a slight rise or stationary pulmonary artery pressure. No edema was obtained with hydrocyanic acid. The lung artery pressure was unchanged or lowered gradually. Lugol's solution produced a temporary rise in the carotid, then a fall, while the pulmonary artery pressure rose. The right heart was dilated, while the left heart was unchanged. Edema was produced. They confirm Löwit's observation that acetic ether, given intravenously, results in pulmonary edema in dogs. This substance produces a temporary fall in the carotid pressure. The right heart is dilated, while the left heart never is dilated. A marked bradycardia precedes cardiac standstill. A small dose always gave a decided rise in the pulmonary artery pressure, while a large dose occasionally was negative on the latter pressure, although edema was present. They say a rise in the latter pressure occurs after the edema appears. They call attention to Silbermann's work^{61a} that capillary thrombosis may readily be induced by toxic agents, and that the lung capillaries, because of small caliber and low blood pressure may be especially prone to thrombosis, which may be responsible for the rise in the pressure of the lung artery. Intravenous injections of epinephrin were negative unless the thoracic aorta was ligated. Then a marked pulmonary edema followed. Stasis results because the left ventricle is unable to empty itself completely. If a marked mitral stenosis is produced, an edema follows. Acetic ether edema is usually associated with evidence of disproportion between the two sides of the heart, but they feel that the mechanical factors are not responsible for the edema.

Bokarius⁶² reviews the subject briefly, and supports Welch on the basis of pathologic diagnoses in selected clinical cases out of 1,200 submitted. He chose clearly cut cases of lung edema with cardiac weakness but not valvular disease or lung changes other than the edema.

61. Miller and Matthews: A Study of the Mechanical Factors in Experimental Acute Pulmonary Edema, *Arch. Int. Med.* **4**:356 (Sept.) 1909.

61a. Silbermann: *Virchows Arch.* **117**:288, 1889.

62. Bokarius: Zur Entstehung des Lungenödems, *Viertelj. f. g. Med.* **41**:307, 1911.

Knowlton and Starling,⁶³ in revising the technic of the isolated mammalian heart-lung preparation method, eliminate the mercury because enough of it is taken up by the perfusion fluid to have a deleterious effect. The lung capillaries suffer first, and after a somewhat variable period pulmonary edema usually terminates the experiment. With this defect corrected, they noted that when the point of maximum cardiac output is reached the venous pressure rises rapidly, and that if it is maintained pulmonary edema always appears.

Klemensiewicz⁶⁴ noted that with fresh serum no edema occurs in the isolated heart-lung preparation. If old serum, or too dilute serum, or isotonic solutions are used, then lung edema occurs easily, whether the lungs are artificially respired or not. Ligation of vessels at the hilus injures the vessels, and on release of the ligature edema sets in regularly (rabbit).

Kotowschtschikow⁶⁵ reviews lung edema in a very able manner. He performed about seventy-seven experiments on dogs. They were given morphin and chloroform. If an open thorax operation was performed, curare was given. He obturated the heart chambers; infused; ligated the aorta; and sent emboli into the lung capillaries. Obturation of the left auricle was the most successful procedure in producing edema. The pulmonary artery pressure rose, the carotid pressure fell, the pulse remained about constant, while the right ventricular pressure rose markedly. A lycopodium seed suspension as emboli produced edema in two experiments. A marked hydremia usually produced edema. Hindrance of pulmonary outflow is essential. Silver nitrate was given in thirty-six experiments. Thirty-four of the animals showed lung edema. These could be divided into two groups: First, those in which mechanical factors helped produce stasis; second, those in which no such factors appeared. In most cases, the right ventricular pressure rose, the left auricular and aortic pressures fell. There was usually asynergy of the cardiac chambers, with the left heart weaker. Ether injection produced lung edema. No mechanical changes appeared; therefore vessel wall injury is hypothecated by the author. Methyl salicylate produced lung edema in each of six experiments. The right ventricular pressure can be high but need not be. There is no change in the carotid pressure. Muscarin produced no changes. Lugol's solution was used, but the author does not draw any conclu-

63. Knowlton and Starling: Temperature and Blood Pressure Variations on Isolated Mammalian Heart-Lung Preparation, *J. Physiol.* **44**:207, 1912.

64. Klemensiewicz: Das Lungenödem, Krehl and Marchand's Handb. d. Allg. Pathologie, Part 1 **2**:424, 1912.

65. Kotowschtschikow: Zur Frage nach den Veränderungen der Herzthätigkeit und des Blutkreislaufs bei acutem Lungenödem, *Ztschr. f. exper. Path. u. Therap.* **13**:400, 1913.

sions from a few experiments. He attempted to confirm Jores, but was unable to do so. He believes that the most common cause of lung edema is a toxic one, and that less often mechanical factors are operative. In the latter cases the pulmonary artery pressure is higher, the right ventricle works better and the systemic blood pressure is lower. The mechanism of toxic edema experimentally induced may be increased permeability of the lung capillary walls, or capillary thrombosis.

Biedl⁶⁶ notes that an intravenous lethal dose of epinephrin causes a lung edema in rabbits which is a stasis edema.

Kraus⁶⁷ performed his experiments on intact rabbits and on cats with open thorax. The latter had their lung volume, pulmonary artery, venous and carotid pressures recorded. Urethane was given, but no morphin. The roentgen ray shows a larger heart after salt is injected intravenously in rabbits. The carotid pressure rises, the lung volume increases, then decreases. A second injection produces no increase in the size of the heart. Injection of salt solution plus double vagotomy produced an acute pulmonary edema immediately. This occurs in cats and rabbits, whether the thorax is open or not. Epinephrin aids the onset. His electrocardiographic findings are recorded elsewhere, he says, in a journal not stated. He interprets the roentgenograms as showing a diminished air capacity and hyperemia in the edematous lungs.

Evans and Starling⁶⁸ used a method in their isolated heart-lung preparations which diminished the tendency for pulmonary edema occurring so often. After some hours there is always more or less edema. Fühner and Starling,⁶⁹ using the same method, showed that with a rise in venous pressure, the heart volume increases, and there is a rise in the lung artery, left auricle and aortic pressures. On the other hand, the venous pressure shows only small differences during wide alterations in the aortic pressure. If the left ventricle fails, and the right heart beats strongly, then the pulmonary pressure rises. Patterson and Starling⁷⁰ state that accumulation of blood in the right heart, with fair response of the latter, may cause pulmonary edema. Maximum cardiac efficiency, persisted in too long, tends to give rise to pulmonary edema. Patterson, Piper and Starling⁷¹ conclude that within wide limits cardiac output is determined by and equal to the

66. Biedl: *Innere Sekretion*, Berlin, Ed. 2, 1:522, 1913.

67. Kraus: *Ueber Lungenödem*, *Ztschr. f. exper. Path. u. Therap.* **14**: 402, 1913.

68. Evans and Starling: *Oxidation in Lungs and Isolated Heart-Lung Preparation*, *J. Physiol.* **46**:415, 1913.

69. Fühner and Starling: *Pulmonary Circulation*, *J. Physiol.* **47**:290, 1913.

70. Patterson and Starling: *J. Physiol.* **48**:357, 1914.

71. Patterson, Piper and Starling: *J. Physiol.* **48**:497, 1914.

inflow into the right auricle. A heart weighing 50 gm. puts out as much blood as it receives, whether this be 200 c.c. or 2,000 c.c. per minute.

Weber⁷² criticizes Grossmann's data obtained with muscarin. Weber studied experimental asthma and innervation of the bronchial muscles. No mention is made of edema onset in his experimental lungs.

Magnus, Sorgdrager and Storm van Leeuwen⁷³ return to Magnus' problem of 1902, concerning the impermeability of the alveolar epithelium to ammonia gas. Höber, 1912, showed the appearance of ammonium hydroxid in the lungs, after ammonia was put into the pulmonary artery, and when pulmonary edema was present. Magnus⁷⁴ never obtained lung edema when ammonia was put into the circulation. Magnus et al repeated and confirmed Magnus' 1902 experiments. They showed that with ammonia inhalation the greatest absorption and injury takes place via the tracheal and bronchial mucous membranes, and that the alveolar epithelium is relatively impermeable in rabbits even with ammonia percentages of 5.8 to 8.5. They also used the isolated lung preparation (Brodie's method). Cats and rabbits were etherized. An arterial pressure of from 35 to 38 mm. was maintained. No lung edema appeared in normal lungs during the duration of the experiments—three hours. In eleven experiments, from 0.015 to 0.017 per cent. of ammonia was placed in the blood. The drug seeps through the pleura but does not appear in the expired air. In one experiment the lung was kept bloodless a short time, while in another chloroform had been administered and fluid appeared in the trachea. The expired air contained ammonia in both experiments. The plethysmograph showed absence of bronchial spasm. Five experiments were done with increased amounts of ammonia in the blood, from 0.027 to 0.045 per cent. Lung edema followed and ammonia appeared in the expired air. Therefore, they say, the alveolar epithelium is injured. With the onset of lung edema, the respiratory excursions become smaller and finally stop. The normal alveolar epithelium is impermeable to ammonia, while that of the pathologic lung is not. McGuigan's paper⁷⁵ contains references on ammonia absorption by the lungs. A few of the experiments that he cites seem to have caused pulmonary edema.

72. Weber: *Experimental Asthma and Innervation of the Bronchial Muscles*, Arch. f. Anat. u. Physiol., 1914, p. 63.

73. Magnus, Sorgdrager, and Storm van Leeuwen: *Ueber die Undurchgängigkeit der Lunge für Ammoniak*, Arch. f. g. Physiol. **155**:275, 1914.

74. Magnus: *Schmiedeburg's Arch.* **48**:100, 1902.

75. McGuigan: *The Absorption and Excretion of Ammonia by the Lungs*, J. Pharm. & Exper. Therap. **4**:453, 1913.

Modrakowski⁷⁶ is the first investigator of experimental lung edema per se in surviving mammalian lungs. He employed the Brodie apparatus. More than fifty cat preparations were perfused with defibrinated blood or physiologic sodium chlorid solution containing from two thirds to three fourths defibrinated blood. He postulated the presence of edema when the following combination was present: a transudate in the trachea, no maximal pulmonary expansion, and when the lung did not readily collapse. He produced an acute lung edema in five minutes, and thereupon the experiment was stopped at once. In his first series, the pulmonary artery pressure was raised above normal, and considerably above, while the venous outflow was unhindered. Edema did not occur in this series. In the second series, the lung outflow was hindered by raising the pulmonary vein pressure. Lung edema was produced when the pulmonary artery and pulmonary vein pressures were raised high enough. Venous stasis alone, with venous pressure below 35 mm., is negative. Lung edema arises when with a pulmonary artery pressure of not less than 35 mm. Hg the venous outflow is so obstructed that their difference drops to 8 mm. If the epithelium or vessel walls are injured, then the permeability of the lung tissue becomes greater. In a hepatized lung (right lower) with the other lobes postpneumonic, edema was produced by only increasing the pulmonary artery pressure. In this experiment there was no venous stasis present. Ammonia in the blood produces edema with either normal or high pulmonary artery pressure, and when there is no obstruction to pulmonary vein outflow.

Staehelin⁷⁷ reported seeing many cases of phosgene poisoning all of which showed a general bronchitis and bronchiolitis with lung edema. Fever was present in all the cases. Microscopic examination of one case gave the following data—inflammation of bronchi, marked desquamation of alveolar epithelium, numerous alveoli filled with fluid, and thrombi in many pulmonary arterioles. He believes that there need be no assumption of bacterial invasion to explain the phosgene effects. Hydrochloric acid arises from carbonyl chlorid in a moist environment, and injures the epithelium.

Roos⁷⁸ presents five cases of phosgene poisoning, some covering a period of six years, with detailed description of signs, diagnosis, treatment and postmortem examination. This report is unique in that a real attempt was made to centralize attention on cause and result. At venesection it was noticed that the blood coagulated very quickly. Notable observations by Roos are the decreased cardiac energy in all

76. Modrakowski: Experimental Lung Edema in Surviving Mammalian Lungs, *Arch. f. d. g. Physiol.* **158**:527, 1914.

77. Staehelin: *Contrib. Ed. Handb. d. Inn. Med.* **2**:287, 302, 315, 1914.

78. Roos: Phosgenvergiftungen, *Thesis in Viertelj. f. ger Med.* **47**:67, 1914.

the cases, the lung changes, the heart picture and the negative spectroscopic and chemical examinations of the blood. The roentgenogram showed cardiac dilatation in two cases. Summarizing his data, we have acute dilatation; severe cough; after a few hours marked dyspnea, nearly asphyxial; albuminuria; stasis polycythemia and a marked leukocytosis; pneumonic foci, with desquamation of alveolar epithelium and leukocytic infiltration; subpleural petechial hemorrhages; acute bronchiolitis; multiple thrombi of lung arteries; increase in the amount of fibrin and multiple thrombi in brain, lungs and intestinal vessels.

Kuno⁷⁹ studied the dog's heart-lung preparation. The pressure in the left auricle rises steadily with increase in venous inflow. The pulmonary artery pressure always rises when there is increase in the venous inflow beyond a certain point.

Evans and Matsuoka⁸⁰ deduct from their isolated heart-lung preparation experiments, that lung edema comes on with ease at high pressures (apparently above 170 mm.) in the aorta. Knowlton and Starling⁸¹ state that increase in cardiac output runs parallel with increased aortic pressure until a maximum output is reached. Then the output falls rapidly. The venous pressure rises before there is any falling off in total output of the heart. Markwalder and Starling⁸² find that the cardiac output is markedly independent of other factors. The previous data did not consider the coronary circulation, they insist.

Matsuoka⁸³ discusses the pathology of obstructive lung edema as obtained in the Starling heart-lung preparation. His English is ambiguous, and there seem to be too many conclusions for the amount of data presented. Defibrinated blood with leech extract was the perfusing fluid used. The cardiac output was taken as a measure of venous inflow. When there is a relatively low arterial pressure, a very large venous inflow must be maintained for some time to produce edema. It is possible to increase the venous inflow without causing edema when a high arterial pressure prevails. Obstruction of the aortic root produces an edema with a relatively small venous inflow. The pulmonary artery pressure is raised in such a case. The blood pressure in the pulmonary artery rises with a coordinate rise of the inferior vena cava. During edema, the heart output may be reduced to a minimum, the blood content of the heart may be increased to a maximum, the pressures of the pulmonary artery, inferior vena cava, and right auricle may be increased to a maximum, all quite indepen-

79. Kuno: Pulmonary Circulation, *J. Physiol.* **50**:140, 1915.

80. Evans and Matsuoka: Gaseous Metabolism and Efficiency of the Mammalian Heart, *J. Physiol.* **49**:378, 1915.

81. Knowlton and Starling: *J. Physiol.* **44**:206, 1912.

82. Markwalder and Starling: *J. Physiol.* **48**:348, 1914.

83. Matsuoka: Pathology of Obstructive Edema of the Lung. Heart-Lung Preparation, *J. Path. & Bact.* **20**:53, 1915.

dently of the height of arterial pressure and amount of venous inflow. With a heart weighing 45 gm. the pulmonary artery pressure must be over 40 mm. Hg and be accompanied by venous obstruction so that lung edema may arise. Edema never occurs in healthy dogs' lungs when the pulmonary artery pressure is lower than 40 mm. Hg. The principal factors in transudation are the high pressure in the pulmonary circuit and the excessive passive dilatation of the lung capillaries. The gaseous metabolism and the energy consumption of the heart decrease in obstructive lung edema. The heart always dilates before the occurrence of edema.

Martin Fischer⁸⁴ discusses lung edema briefly in his thesis, and mentions a few experiments of his own. An edema results whenever the oxygen supply to the lung parenchyma is interfered with sufficiently. This can be done effectively by ligation of nutrient vessels, directly or indirectly, via interference in the systemic circulation, such as compression of left ventricle or aortic root. Ligations to a point immediately below the subclavian artery lead to edema, because the bronchial arteries leave the aorta just below the left subclavian. Ligation below the bronchial arteries is negative. The lack of oxygen leads to accumulation of acids in the tissues. Clinically, pulmonary edema occurs more frequently in nephritis than in heart disease because toxic bodies injure the lung parenchyma as well as other tissue. It is easy to produce edema in the excised lung because there is an interference with the normal oxygen supply. Fisher took sheep's lungs and permitted water or M/6 (0.975 per cent.) sodium chlorid solution to trickle into the pulmonary arteries, producing an intense edema. A lung weighing 500 gm. will take up several liters in an hour. Two periods can be designated. During the first period there is no fluid in the trachea. Later, the pleural surface is moist, and a bloody, frothy fluid emerges from the trachea. Although the veins are not ligated, no fluid emerges. The longer the lungs have been out of the animal the more quickly do these signs of pulmonary edema appear. Sodium citrate and sodium sulphate are more effective than sodium chlorid. In other words, the salts which dehydrate various protein colloids best are most effective, and therefore, the colloid theory of water absorption applies here. More water is held because acids are produced in the tissues. The tissue colloids have their capacity for water increased by the acids present.

Schäfer⁸⁵ gives an excellent report on chlorin gas poisoning. He commends Lehmann's work. Cats, rabbits and dogs were anesthetized, and then gassed. Ringer's solution saturated with chlorin injected

84. Fischer: *Edema and Nephritis*, Ed. 2, 1915, p. 233.

85. Schäfer: *On the Immediate Effects of the Inhalation of Chlorin Gas*, Brit. M. J. 2:245, 1915.

intravenously produced a slight fall in blood pressure and a slight increase in the depth of respiration. Inhalation (1 per cent. chlorin) had no immediate special effect on blood pressure or respiration, but ultimately the blood pressure fell, the respirations became deep and convulsive prior to complete arrest, and the pulse was slowed. Substitution of air produced recovery with higher blood pressure. The chlorin cannot be carried to the tissues in a free state. The short exposures show changes only in the lungs. They are congested, more solid and are slightly crepitant. He believes that fatality may be due to obstruction of pulmonary vessels. Experiments with surviving lungs and with lungs in the intact animal show a bronchiolar dilatation during gassing. This was done by catching the air escaping from the lung surface through needle holes. Chlorinated Ringer's solution perfused into the pulmonary artery produces marked constriction. Schäfer presents microscopic plates of edema, interstitial and alveolar, and of capillary engorgement. Presumably, the edema is secondary to the vascular obstruction. Mucus does not play an important part (excluded by atropin). Bromin vapor is less deleterious.

Hill⁸⁶ discusses gas poisoning especially with chlorin. The respiratory epithelium and pulmonary capillaries are injured, and the osmotic pressure of the damaged tissue is raised, producing the edema. Albuminuria is conceivably due to decreased oxygen supply to the kidney. Barcroft, he says, has shown the presence of an increased acidity of the blood. The edematous fluid produced may drown the animal. In weak concentrations, chlorin does not produce death by stasis in pulmonary vessels. When lungs were artificially respired and manipulated so that a chlorin-air mixture could be sent into one lung leaving the other airless, then an edema arose in the first lung, followed by asphyxia and failure of circulation. Recovery was rapid if air was sent into the normal lung. Kuno and Hill, he reports, administered chlorin in heart-lung preparations. They obtained congestion and edema, while the blood became more and more venous. The cardiac output was diminished. A microscopic description is given. Strong concentrations of chlorin gas causes contraction of the bronchiolar musculature. Pneumonia and bronchitis are almost invariable sequels.

Matsuoka⁸⁷ believes that the lung edema of beri beri is a characteristic feature of the disease, and is essentially an obstructive edema. This citation is of value in that Yamagiva, the noted pathologist, says that this lung edema is due to the contraction of pulmonary arterioles and bronchioles.

86. Hill: Gas Poisoning, *Brit. M. J.* **2**:801, 1915.

87. Matsuoka: Lung Edema in Beriberi, *J. Path. & Bact.* **20**:191, 1916.

Slovitzov, Chernewski and Xenophontov,⁸⁸ in a study on the chlorin content of the air as affecting oxidative functions and gaseous exchange, state that there is a diminished oxidation lasting for some hours.

Slovitzov⁸⁹ finds that in rabbits chlorin inhalation increases the coagulation time, diminishes the alkalinity, destroys the leukocytes, increases the red blood corpuscles, and increases the thrombin content in pulmonary tissue.

Slovitzov⁹⁰ describes the clinical signs, pathology and physical findings in cases of phosgene poisoning in man, horses, guinea-pigs, rats and dogs. The acute poisoning resembles that induced by chlorin, although it is milder. Most noticeable are the lung changes, myocarditis, nervous depression and alterations in the blood. The red cells are disrupted, there is increased coagulation and viscosity and decreased alkalinity.

Lucherini⁹¹ gives a graphic account of gas poisoning from the war zone.

Auer and Gates⁹² continue their study of fulminant pulmonary edema induced by intratracheal administration of epinephrin. They had previously found the onset more rapid in the vagotomized rabbit. Intratracheal administration of epinephrin in this series of rabbits gave them the following results: In twenty-seven experiments, marked edema occurred in twenty-one with vagi cut. In sixteen with vagi intact, slight edema was present. Direct observation (six out of seven experiments) of the heart showed that epinephrin induced alternating strong and weak beats of the left ventricle with halving of its rate. The dilatation of the left auricle was often tremendous. Artificial respiration has a restraining influence on the onset of lung edema. Tracheal stenosis facilitates edema production. Atropin exerts a protective action. Auer and Gates favor Welch's view of the disproportionate activity of the ventricles which in their experiments is induced by adrenalin.

Kuno⁹³ observes that when the blood used for the heart-lung preparation (dogs) is somewhat old, then the lungs gradually pass into an edematous condition. Postulating that the pulmonary circulation in

88. Slovtzov, Chernewski and Xenophontov: Chlorin on Oxidative Functions and Gas Exchange, *Vratshebnaya Gaz.*, 1916, p. 23; also *Physiol. Abstr.* **2**: 621, 1917.

89. Slovtzov: Chlorin on Animals, *Arch. d. Sc. Veterinaires*, 1916, p. 3; also *Physiol. Abstr.* **2**:621, 1917.

90. Slovtzov: Phosgene Poisoning, *Russk. Vrach* **15**:649, 1916.

91. Lucherini: Asphyxiating Gases, *Arch. farm. sper.* **22**:429, 1916; also *Chem. Abstr.* **11**:995, 1917.

92. Auer and Gates: Adrenalin Pulmonary Edema, *J. Exper. M.* **26**:201, 1917; *Ibid.* **23**:755, 1916.

93. Kuno: Amount of Blood in the Lungs, *J Physiol.* **51**:154, 1917.

edema is very slow, he kept the venous supply to the heart very low in two experiments in which he determined the amount of blood present in the lungs in edema. In normal lungs, the blood was from 8.8 to 19.4 per cent. of the total blood (equal to 7 per cent. of body weight), depending on the velocity of the blood. The edematous lungs contained 23.4 and 26.2 per cent. of the total blood.

Pellegrino⁹⁴ reports histologic researches on the pulmonary alterations following inhalation of bromin.

Kramer⁹⁵ describes the effect of chlorin on the lungs, noting among other things thrombosis in lung and heart vessels.

Klotz⁹⁶ describes acute death from chlorin poisoning in mice, guinea-pigs and rabbits. Concentrations of from 1:1,000 to 1:10,000 are lethal in from three minutes to one half hour usually. A post-mortem examination shows hyperemic lungs, with little fluid blood in congested areas. The blood coagulates within the dilated pulmonary capillaries. The unusually rapid coagulation may be the result of the intense edema whereby the blood constituents within the vessels are greatly altered. Human blood in 1:1,000 concentration coagulates in fifteen seconds, while stronger concentrations reduce this time. Hake⁹⁷ found that diluted blood yielded a colorless filtrate after chlorin gas was bubbled through it. A practically colorless precipitate was formed at the same time. The iron found gave the tests for the ferric salts.

Kruglevsky, Boldereff, Neporsky, Neiding, Sereisky and Gokh⁹⁸ present a series of papers on acute edema produced in gas poisoning. They discuss treatment, effect on vegetative nervous system, nervous symptoms, psychic symptoms and the intravenous oxygen treatment.

Meek⁹⁹ produced lung edema by intravenous injection of collargol. The fluid practically poured from the trachea. A microscopic study showed that it was purely an obstructive edema, with emboli in the pulmonary and coronary circulations.

General treatises on lung edema of importance are those by Ziegler,¹⁰⁰ Staehelin,⁷⁷ Heinz,⁵⁷ Kunkel³⁹ and Klemensiewicz.⁶⁴

94. Pellegrino: Histological Researches on the Pulmonary Alterations Following the Inhalation of Bromine, *Arch. farm. sper.* **24**:58, 1917.

95. Kramer: Chlorin Poisoning, *Viertelj. f. ger Med.* **53**:181, 1917; also *Chem. Abstr.* **12**: 1918; also *Physiol. Abstr.* **2**:528, 1917.

96. Klotz: Acute Death from Chlorin Poisoning, *J. Lab. & Clin. Med.* **2**:889, 1917.

97. Hake: Chlorin on the Blood, *Lancet* **2**:86, 1915.

98. Kruglevsky, Boldereff, Neporsky, Neiding, Sereisky and Gokh: Acute Edema of the Lungs and Various Phases of Gas Poisoning, *Russk. Vrach* **16**: 385, 1917; also *Physiol. Abstr.* **3**:61, 1918.

99. Meek: Personal Communication, 1918.

100. Ziegler: *Lehrb. d. allg. Path.* **2**:765, 1906.

Cushny¹⁰¹ notes the frequent occurrence of lung edema in cats and rabbits after poisoning with pilocarpin. This has also occurred in man. Pilocarpin, in toxic amounts, contracts the bronchi, retarding the movement of the air, retards the heart, slowing the circulation through the lungs, and has a tendency to cause convulsive movements, accompanied by rapid and labored respiration, which eventually becomes slow and weak. Asphyxia follows.

STATUS OF THE PROBLEM AFTER NOVEMBER, 1918

Shortly after the armistice was signed November 11, permission to various war department groups of investigators was granted allowing them to publish their observations on experimentally induced conditions in which pulmonary edema occurred as a prominent symptom. However, there has as yet been no comprehensive experimental study submitted concerning the cause and treatment of the edema. Barbour and Williams¹⁰² report the effects of chlorin on isolated bronchi and pulmonary vessels. Winternitz and Lambert¹⁰³ discuss the pathology of lungs obtained from gassed dogs, with emphasis on the edema as a cause of death. Underhill¹⁰⁴ delivered an excellent Harvey lecture on the physiology and experimental treatment of poisoning with the lethal war gases in which considerable experimental data were summarized, but the data were not submitted.

SUGGESTIVE METHODS FOR THE STUDY OF EXPERIMENTAL LUNG EDEMA

The detailed investigation of lung edema caused by toxic gases in the medical section of the Chemical Warfare Service directed the attention of the group at the University of Wisconsin Medical School laboratories to the following points in relation to the onset and cause of the edema. Whether there is an increase or decrease or both in (1) the blood volume, (2) red and white cell count, (3) hemoglobin percentage, (4) amount of fibrin, (5) thrombin, (6) freezing point of blood, (7) presence of lymphagogues in the blood stream, (8) spectroscopic examination of the blood, (9) chemical examination of the blood, (10) agglutination, (11) viscosity of the blood, (12) coagulation time, (13) blood counts from the right and left hearts, (14) the alkali reserve, (15) the p_H value of the blood, (16) histologic changes

101. Cushny: Textbook on Pharmacology, 1918.

102. Barbour and Williams: The Effects of Chlorin on Isolated Bronchi and Pulmonary Vessels, *J. Pharmacol. & Exper. Therap.* **14**:47, 1919.

103. Winternitz and Lambert: Edema of the Lungs as a Cause of Death, *J. Exper. M.* **29**:537, 1919.

104. Underhill: The Physiology and Experimental Treatment of Poisoning with the Lethal War Gases, *Arch. Int. Med.* **23**:753 (June) 1919.

in the bone marrow. In addition to these, the following topics require investigation: (17) the cause of polycythemia, whether it is due to decreased blood volume or to decreased oxygen supply; (18) roentgen-ray studies of the heart and lungs; (19) the first sign of the onset of edema, or a simultaneous factor occurring at the time of edema onset; (20) the pathology at various stages up to the time of death; (21) the vital capacity of the lungs; (22) wet and dry weights of the lungs; (23) response to increased oxygen or carbon dioxide administration, especially from time of gassing up to the onset of edema; (24) pressures in the following vessels and heart chambers—carotid, aorta, pulmonary vein, pulmonary artery, jugular vein, right ventricle, left ventricle, brachial artery; (25) wet and dry weights of tissues other than the lungs, as, for instance, muscle, to account partially for loss in blood volume; (26) direct effect of toxic substance as gas or chemical on the isolated or excised heart by perfusion; (27) direct effect on a surviving lung and such isolated pulmonary structures as arteries, veins and bronchi; (28) the cause of dyspnea; (29) the respiratory quotient; (30) the respiratory minute volume; (31) the picture produced by gassing one lung or lobe; (32) the presence of bronchiolar spasm.

Following the discovery of the cause of edema, one expects that the treatment of the condition could be followed out along suggestive leads. However, under the stress of the war situation, the study of treatment was instituted practically simultaneously with the study of the cause of toxic gas edema. These measures, briefly summarized were: the effect of (1) bleeding; (2) infusions of physiologic sodium chlorid solution, glucose, acacia and mixtures of these; (3) morphin; (4) atropin; (5) the digitalis series and other cardiac drugs; (6) oxygen—by vein, abdomen, etc., attempts at extrapulmonic respiration; (7) neutralization of chemical inhalants in the first stage of poisoning; (8) neutralization of gas products in the respiratory epithelium before injury to the cell has advanced very much; (9) possibility of regeneration of respiratory epithelium by drugs or chemicals; (10) changing the content of the blood so as to overcome the biochemic changes extravascular to the lung capillaries; (11) control of the alkali reserve; (12) maintenance of normal body temperature, etc., etc.

SUMMARY

A survey of the literature shows that the methods for production of edema fall into a few categories. The first method tried was the experimental production of pulmonary emboli by the use of fat droplets, lycopodium seeds, etc. (Virchow, Klotz). The edema resulting from pulmonary emboli may be explained in several ways. It may

arise because there is a diminished blood supply in the lung nutrient vessels via the aorta, due to the damming back of the blood, or because the right heart continues its pumping action against the emboli obstructions, increasing thereby the permeability of the turgid pulmonary capillaries. Then, again, in the diminished nutritional supply of the heart, there may result a disproportionate activity of the cardiac chambers with the left weaker than the right.

A group of methods can be gathered under the caption "Injury to Pulmonary Capillaries," either from within the vessels or from without. The blood flowing within the vessels may be altered, for example, diluted, as in Cohnheim's and Lichtheim's hydremic plethora animals, or in perfusion of isolated heart-lung preparations (Jacobj, Evans, Lovatt, etc.), a collapse in the normal permeability of the lung capillaries results, with the escape of fluid into the extracapillary space, rupturing of the alveoli, and finally filling of the air spaces. The blood may be concentrated, resulting in an anoxemia. The capillary endothelium may be injured directly with acetic ether (Löwit, Miller and Mathews) administered intravenously, or by ammonia (Magnus et al, Modrakowski). A number of French workers have attempted to produce pulmonary edema by electrical stimulation of the exposed lung and have thought that the results obtained suggested a nervous element. They insist on a reflex dilatation of the lung vessels (Jores, Teissier and Guinard). There seems to be little experimental evidence for this point of view. Another possible cause for the pulmonary injury is the production of acid products in the lung interstitial tissue due to altered blood in the nutrient vessels of the lung (Fischer).

Injury outside of the pulmonary capillaries may result from a destruction of the respiratory epithelium, as, for example, by toxic gases (Lehmann, Pettenkofer, Kockel, Roos, Modrakowski, Schäfer, Hill). Fluid would escape into the air spaces due to increased permeability of the alveolar wall resulting from the injury. Another form of injury to the respiratory epithelium might follow bronchiolitic spasm, as in chlorin gas poisoning (Barbour and Williams).

The inflammatory type of pulmonary edema, which Sahli insisted on as the chief type in man (confirmed by Welch), might be considered as a combination of intravascular and extravascular injury. Hamburger brought proof to show the lymphagogue power of certain bacteria and their products in the blood stream. Pathologic evidence also indicates that bacteria can invade the interstitial pulmonary tissue and induce an edema by altering the physicochemical conditions. It is also evident that injury of the lungs in gassed individuals results in diminished resistance to bacterial invasion.

A great mass of work has been done, initiated by Welch, in showing the onset of pulmonary edema in all conditions in which the

mechanical efficiency of the left ventricle is reduced to a greater extent than that of the right ventricle. The pressures in systemic and pulmonary vessels were recorded to prove this assumption. Welch was the first to show that injury or compression to the left ventricle was followed by a pulmonary edema. Others feel that thrombi in the left coronary artery might do this. Then, again, the toxic action on the left ventricle of rapid intravenous injections of epinephrin seems to corroborate Welch's assumption (Beidl, Auer and Gates, Meltzer, Bouchard and Claude). Probably, the cardiac disproportion is the cause of the edema of asphyxia, whether agonal or not, or, at least, it is a contributing cause. Some observers feel that the heart is the primary cause of edema in certain types of gas poisoning, indicated by its dilatation and change in venous pressure.

It is conceivable that a pulmonary edema may be the resultant of a group of causes. For example, a toxic substance might injure both lung and heart simultaneously, and as the edematous fluid finds an easy outlet, the heart may be developing an asymmetrical pumping activity and thereby massing the blood on the venous side of the lungs. Or a vicious circle might be produced. A substance might induce edema in the first place by injury to the lung parenchyma. This might result in a concentration of blood, which would in turn reduce its oxygen carrying capacity and result in a decreased efficiency of the heart due to poor nutrition. Finally, this might lead to an increase in blood in the right heart, with a greater seeping of fluid through the dilated pulmonary capillaries into the air spaces.

It would seem that the work which has been done on experimental pulmonary edema indicates that the mechanism of causation of pulmonary edema must be sought for beyond the immediately obvious cause, as, for example, intravenous emboli; intravenous injection of drugs like epinephrin and muscarin and toxic chemicals, such as acetic ether, silver nitrate, collargol, etc.; injury to the chambers of the left heart, particularly the ventricle; infusions of large amounts of fluid, with or without vagal section; electrical stimulation of lung tissue directly; inhalation of irrespirable gases and vapors (chlorin, hydrogen sulphid, hydrochloric acid, etc.); ligations and compressions of aortic and pulmonary branches; occlusion of bronchi and bronchioles; alterations in the content or amount of blood; obturation of chambers of the left heart; increasing the venous inflow; overriding the maximum cardiac output; and decreasing the oxygen supply to the lung parenchyma.