EDEMA OF THE LUNGS AS A CAUSE OF DEATH.*

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Edema of the lung is a frequent terminal event in the course of many diseases, both acute and chronic, and in such cases is commonly interpreted as the immediate cause of death. It constitutes, as is well known, a striking feature in poisoning by most of the noxious gases in modern warfare. It is, therefore, not surprising that in the clinical and pathological reports of these fatal gas cases, death should be regularly attributed to pulmonary edema.

The question as to how edema of the lungs may bring about death has long been discussed. The view generally accepted is that the fluid in the pulmonary alveoli interferes mechanically with gaseous interchange and that when this interference with respiration passes a certain critical point, the patient dies of asphyxia; that is, he drowns in his own fluid. It is not our purpose in this paper to discuss the question as to how edema of the lungs may cause death, but rather the fundamental problem of whether the mere accumulation of fluid in the lung is of itself a serious matter.

During the past 2 years we have had the opportunity of studying the effects of practically all the commonly used war gases under laboratory conditions. About 3,000 dogs and an equal number of other animals have been exposed to gas and then observed clinically and at autopsy. Particular attention has been given to the pulmonary edema, which, as in man, is a fairly constant and, in many cases, a striking phenomenon of the gassed state. These observations, together with the results of some experiments upon what

* This work is an incidental result of more detailed studies in the pathology of war gases which were conducted under the auspices of the Bureau of Mines, the Chemical Warfare Service, and the Office of the Surgeon General, U. S. Army.

may be termed an artificial pulmonary edema produced by filling the lungs of a normal dog with an isotonic salt solution, have led us not only to question the importance of pulmonary edema *per se* as a cause of death, but to conclude that edema of the lungs in general is merely an indicator of some underlying disorder and is rarely, if ever, directly responsible for the death of the patient or animal. These observations are summarized in the following paragraphs.

Animals which die acutely from exposure to any of the gases of the respiratory irritant group, such as chlorine and phosgene, show at autopsy varying degrees of edema of the lungs. Although this is regularly well marked in certain species, dogs for example, there are wide individual variations. In other species, rats and guinea pigs for example, it may be a relatively inconspicuous feature in spite of the fact that these animals are particularly susceptible to the gas.

Likewise dogs which are killed before the action of the gas reaches its maximum effect show striking differences in the amount of fluid in the lungs, and these differences do not harmonize with the variations in the symptoms manifested by the animals. Furthermore, many dogs which pass successfully the critical 48 hour period and are classed as "recovered" often show, when killed, edema of the lungs of greater degree than other dogs of the same experiment which succumbed.

The increased concentration of the blood in the gassed animal, which some investigators regard as a reliable index of the condition of the animal and as a guide to therapy, does not correspond necessarily in any measure with the degree of pulmonary edema present.

The lungs of a normal animal may be filled with isotonic salt solution, thus producing an artificial edema comparable with that found in the gassed state.

Several of the propositions set forth require elaboration and discussion. They are considered in detail below.

Variations in the Degree of Pulmonary Edema in Gassed Animals.

The gross and microscopic picture of the lungs associated with acute gassing has been so thoroughly described in the papers published from this laboratory and elsewhere as to need no repetition

here.[1] As pointed out above, edema of the lungs in dogs is generally well marked, and with the associated congestion constitutes the most striking feature of the autopsy findings. However, among individual dogs dying in the acute stage the degree of edema has been found to vary within relatively wide limits. These differences are obvious to the naked eye, but in order to make satisfactory comparisons, free from the personal equation, we adopted the following method for measuring the degree of edema. This method, which is based on the comparative weights of the lung and empty heart, was suggested and used by Barcroft in the investigations carried on by the British Research Committee.

Method.—The lungs are weighed with the trachea attached, cut to uniform length, and clamped to prevent the escape of edema fluid. The heart is also trimmed uniformly and completely emptied. The normal ratio of the lung weight to the heart weight was obtained by taking an average of sixteen normal animals. This normal ratio was found to be 1:30. Barcroft's higher figure (1:50) is probably the result of a difference in the method of trimming the organs. In gassed dogs we have divided the lung weight by the heart weight, and this quotient by the normal ratio, 1:30. We have termed the resulting figure the "edema index." It represents the percentage increase in lung weight over the normal. This method has been objected to by Eyster[2] who insists that the dried weight method is much more reliable. There are two of these dried weight methods; one, used by some of the French investigators, in which a typical slice of the lung is weighed wet and then after drying, and the second, the method used by Eyster and his assistants,[2] in which the entire lung is dried, the proportion between the wet and the dried specimen indicating the degree of edema. The first method is obviously open to large errors. The second method has the serious drawback of making it impossible to study the lung grossly or microscopically. We have compared the latter method with our more

[1] Winternitz, M. C., and collaborators, Collected studies on the pathology of war gas poisoning, New Haven, 1919; Anatomical changes in the respiratory tract initiated by irritating gases, *Mil. Surg.*, 1919 (in press).

[2] Eyster, J. A. E., Report of the Chemical Warfare Medical Committee, Medical Research Commission (unpublished).

simple lung-heart ratio method in a series of six dogs, and have found that the two methods give results which are approximately the same (compare Columns 9 and 13 in Table I).

TABLE I.

Relation of the Edema of Lung and the Concentration of Blood in Gassed Animals.

Dog No. and breed.	Gas.	Concentration per liter.	Body weight.	Weight of empty heart.	Weight of wet lung.	Weight of dry lung.	Ratio of wet-dry lung.	Ratio of weight of lung-heart.	Red blood corpuscles before gas.	Red blood corpuscles before death.	Percentage increase of red blood corpuscles.	Edema index.
		mg.	*kg.*	*gm.*	*gm.*	*gm.*						
1. Hound.	Phosgene.	82	14.0	155	715			4.60	5,148,000	7,936,000	54	3.53
2. "	"	80	18.5	159	760			5.40	6,068,000	10,870,000	79	3.42
3. Mastiff.	"	75	26.0	170	915			5.40	8,400,000	10,808,000	28	4.15
4. Hound.	"	82	17.8	154	822			5.34	7,172,000	7,640,000	7	4.10
5. Collie.	"	99	17.8	177	570			3.22	6,192,000	11,260,000	82	2.48
6. Mongrel.	"	102	6.4	53	320	27.5	11.7	5.93	8,280,000	10,760,000	30	4.56
7. "	"	112	8.6	92	400	37.0	10.8	4.35	9,385,000	9,824,000	5	3.34
8. "	"	109	11.0	93	375	38.0	9.8	4.04	7,520,000	8,432,000	12	3.11
9. "	"	109	6.8	69	219	24.5	8.9	3.16	9,848,000	9,055,000		2.44
10. Setter.	Chloropicrin.	949	13.6	132	631	61.0	10.3	4.77	8,040,000	12,120,000	51	3.68
11. Mongrel.	Chloropicrin.	840	9.5	103	600	46.0	13.1	5.84	6,276,000	6,458,000	3	4.50
12. Bull.	Chloropicrin.	887	13.6	138	684	66.0	10.3	4.75	7,176,000	9,068,000	23	3.66

The dogs were killed 8 to 13 hours after exposure to phosgene or chloropicrin. Comparison of the figures in the last two columns (edema index and percentage increase in red blood cells) shows that no parallelism exists between the degree of pulmonary edema present and the blood concentration.

In using the lung-heart ratio method of estimating the amount of edema fluid present, we have found that the edema index in a series of dogs gassed under similar conditions varies within relatively wide limits. For example, among 50 dogs dying after exposure to phosgene the edema index ranged from 1.73 to 4.60, and in another series gassed with chloropicrin the extremes were 1.65 and 4.22.

In order to throw further light on the question of the significance of the degree of edema, the following experiment was done. Eight

dogs were gassed with phosgene (concentration 80 to 90 mg. per liter for 30 minutes). Four of the dogs died in from 10 to 15 hours. The remaining four were killed by chloroform. It was found that the average edema index of the four dogs that died was practically the same as that of the four that were killed. It was found also that many of the dogs which passed successfully through the critical 48 hour period and were then placed in the "recovered" group showed, if killed at this stage, a high edema index, often exceeding that of the dogs which had succumbed. It may be stated incidentally that these "recovered" dogs showed no symptoms other than occasional coughing and a slight sluggishness.

Still further evidence of the subsidiary part of edema as the cause of death after inhalation of irritating gases is found in the comparative effects of a gas such as phosgene on animals of different species.

A series of experiments was performed in which a number of different kinds of animals were exposed in the same chamber for 30 minutes to a concentration of 0.27 mg. per liter of phosgene. The time of survival varied as indicated in Table II.

TABLE II.

Species.	Time of survival.
Monkey	3 hrs., 30 min.
Guinea pig	4 " 30 "
Rat	5 "
Rabbit	11 " 30 min.
Mouse	Killed after 12 hrs.
Dog	" " 12 "
Goat	" " 12 ".

The lesions produced in these animals by inhalation of phosgene are essentially alike. In the monkey and goat, for example, which represent the two extremes of susceptibility after exposure to the same concentration, lesions of the lung vary in degree but not in character. The species variation, evidenced by the length of the survival after gassing, in animals which have been killed or have died, may be expressed in part by the rate of development of the pulmonary edema. On the other hand, with some animals (monkey,

guinea pig), the first to succumb to a given concentration show less pulmonary edema than those that survive longer (dog, goat). This is evidence that the edema is in itself not the cause of death but simply one manifestation of a more important underlying change.

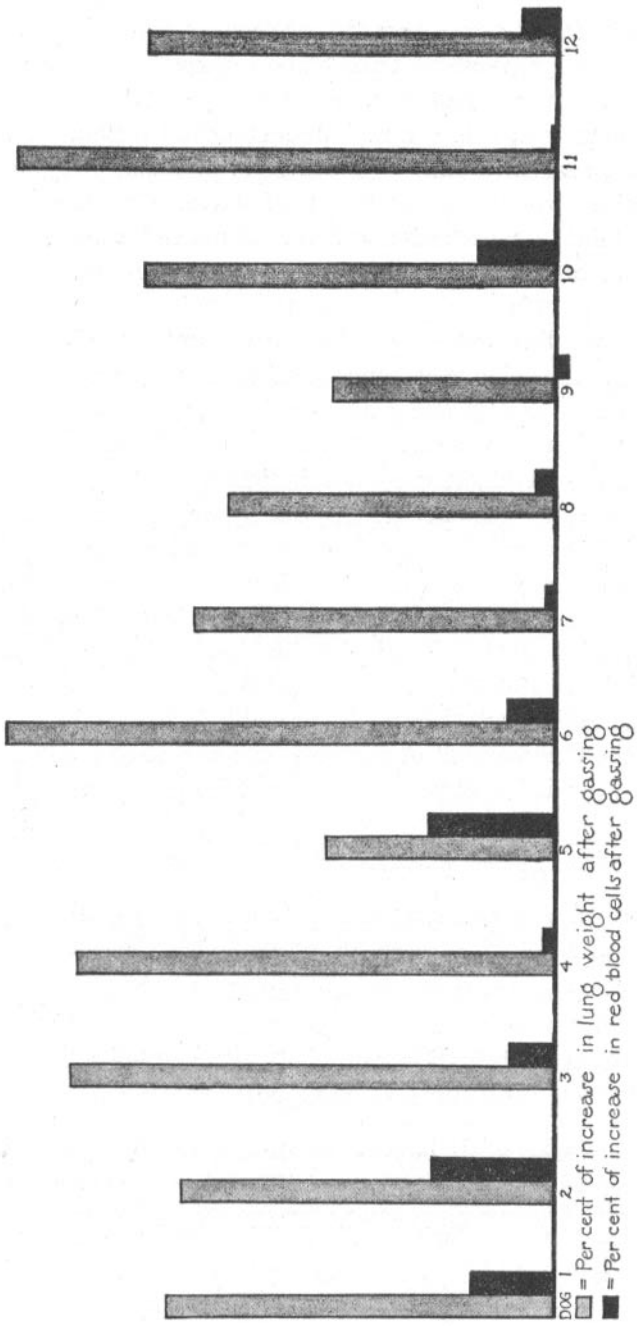
While the pulmonary edema develops more rapidly the more susceptible the species (Table II) the most susceptible show at death less edema than the more resistant ones. This is an indication of the importance of the time interval in the production of the edema.

Relation of the Concentration of Blood and Edema of the Lung after Inhalation of Gas.

Underhill[3] has found that dogs exposed to phosgene, chlorine, or chloropicrin show after a few hours (the time varies with different gases and with individual animals) a well marked increase in the concentration of the blood. Similar changes in the blood of gassed soldiers have been demonstrated repeatedly. The formed elements of the blood as well as the inorganic salts share in the change. Inorganic salts, however, do not follow the same course as the erythrocytes. The result is a marked increase in blood viscosity. Underhill and his assistants have used this blood change as an index of the condition of the gassed animals, and upon it have worked out a method of therapy, the essentials of which are bleeding and subsequent dilution of the residual blood with isotonic salt solution. In applying this method of treatment, which, it may be stated has definitely reduced the mortality among experimentally gassed dogs, it has been assumed that the concentration of the blood is due to the escape of blood serum into the lungs, and that, therefore, the increased viscosity of the blood may be taken as a rough index of the degree of pulmonary edema.

In order to determine whether or not these two phenomena, blood concentration and pulmonary edema, are directly related, the following experiment was carried out. Twelve dogs were gassed, nine with phosgene and three with chloropicrin, the duration of exposure and concentration being such as would be fatal to a majority of dogs exposed. The dogs were killed with chloroform about 10 hours after

[3] Report to be published in the near future.



TEXT-FIG. 1. Comparison of pulmonary edema and blood concentration after gassing.

the exposure to the gas; that is, as soon as the majority began to show serious symptoms. A red blood cell count was made before gassing and again just before the animal was chloroformed, since it has been shown that this is a reliable method for estimating the degree of blood concentration. The degree of pulmonary edema found was determined by the method described above. The figures for the increase in blood concentration and the edema index are recorded in Table I with other data. The results are also graphically shown in Text-fig. 1. It is seen that under the condition of these experiments no parallelism exists between the amount of fluid present in the lung and the degree of concentration of the peripheral blood. It is noteworthy that in one case in which there was a well marked edema of the lung, an actual reduction of blood concentration was found.[4] This experiment does not indicate that the loss of fluid from the blood may not have taken place by way of the lungs and the mouth, but, in our opinion, it does show conclusively that the change in the blood does not serve as an indicator of the amount of fluid present in the lung at any given moment. It suggests further that a therapy guided by the viscosity of the blood cannot be assumed to have any influence on the pulmonary edema, and that the beneficial results obtained by such therapy are probably in no way referable to a change in the fluid content of the lung, which of itself is of secondary importance, as will be emphasized in the following paragraph.

Artificial Edema of the Lungs. Pulmonary Irrigation.

Winternitz and Smith[5] have shown that the lung is much less susceptible to the introduction of fluid than has been generally supposed. Repeated experiments have demonstrated that the lungs can be entirely flooded through the bronchi with isotonic salt solution and that this process of irrigation can continue for at least 2 hours with the introduction of 6 liters of fluid without causing any evident

[4] There is a dilution of the blood, as shown by Underhill, which precedes its concentration with phosgene poisoning. These changes of blood concentration may vary somewhat in duration, etc., and explain the charted findings above.

[5] Winternitz, M. C., and Smith, G. H., Sir William Osler Anniversary Volume, New York, 1919.

harmful changes in bodily well-being or any subsequent serious microscopic lesions in the lung tissue. By means of the use of colored solutions it has been shown that the fluid introduced actually passes throughout the lung, bronchi, bronchioles, and alveoli and does not simply flow back through the trachea without entering the lung.