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ECBC memo dtd 15 Oct 2015

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SUBJECT: The Experimental Treatment of Phosgene Poisoning.

BY: E. B. Vedder,
H. P. Sawyer.

DATE: March 2, 1925.

PART II.

DECLASSIFIED-DOD Directive No. 5200.9,
27 September 1958

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THE EXPERIMENTAL TREATMENT OF PHOSGENE POISONING.

by

E. B. Vedder
and
H. P. Sawyer

PART II.

March 2, 1925.

THE EXPERIMENTAL TREATMENT OF PHOSGENE POISONING.

PART II.

C. Experimental results - continued.

3. Experimental application of methods of treatment.

The experiments with vagotomized dogs proved that the vagus was not concerned in the production of pulmonary oedema, and that an effectual method of treatment is at least possible. The possibilities of preventing pulmonary oedema after gassing may be logically discussed as follows:

(a). By the neutralization of so much of the gas or its irritant products as possible, thus limiting the damage to the pulmonary tissues.

(b). By the establishment of a vaso-constrictor action which would prevent the dilatation of the pulmonary capillaries thus reducing the fluid outflow.

(c). By so altering the chemical content of the blood as to affect the permeability of the pulmonary capillaries.

(d). By increase of the colloid concentration of the blood, thus raising osmotic pressure in the blood stream and preventing further fluid loss.

Each of these methods as well as combinations of all of them were tried. But before discussing these experimental results, the

general method of the experiments should be described. In our earlier work, several dogs were gassed together at the same concentration. One or two dogs were then treated and one dog kept as a normal control. Later this method was changed. The lethal points for phosgene had already been determined, and since we knew what concentrations would kill, the use of a normal control was unnecessary, and used up an animal that might have been used for treatment. It has always been difficult to obtain sufficient dogs. We therefore simply gassed the dogs to be treated at the desired concentration and treated them. If they lived after gassing at concentrations known to be lethal, it could be assumed that the treatment was of benefit. This conclusion could not be drawn from a single animal, because, owing to individual resistance all dogs do not die even at lethal points. But if four dogs are gassed and all live, or if three out of four live at lethal concentration, it may be concluded with certainty that the treatment received was beneficial. In all cases, exposures of 7½ minutes were used. The lethal point for dogs at 7½ minutes is shown by the following protocol.

7½ MINUTE EXPOSURE.

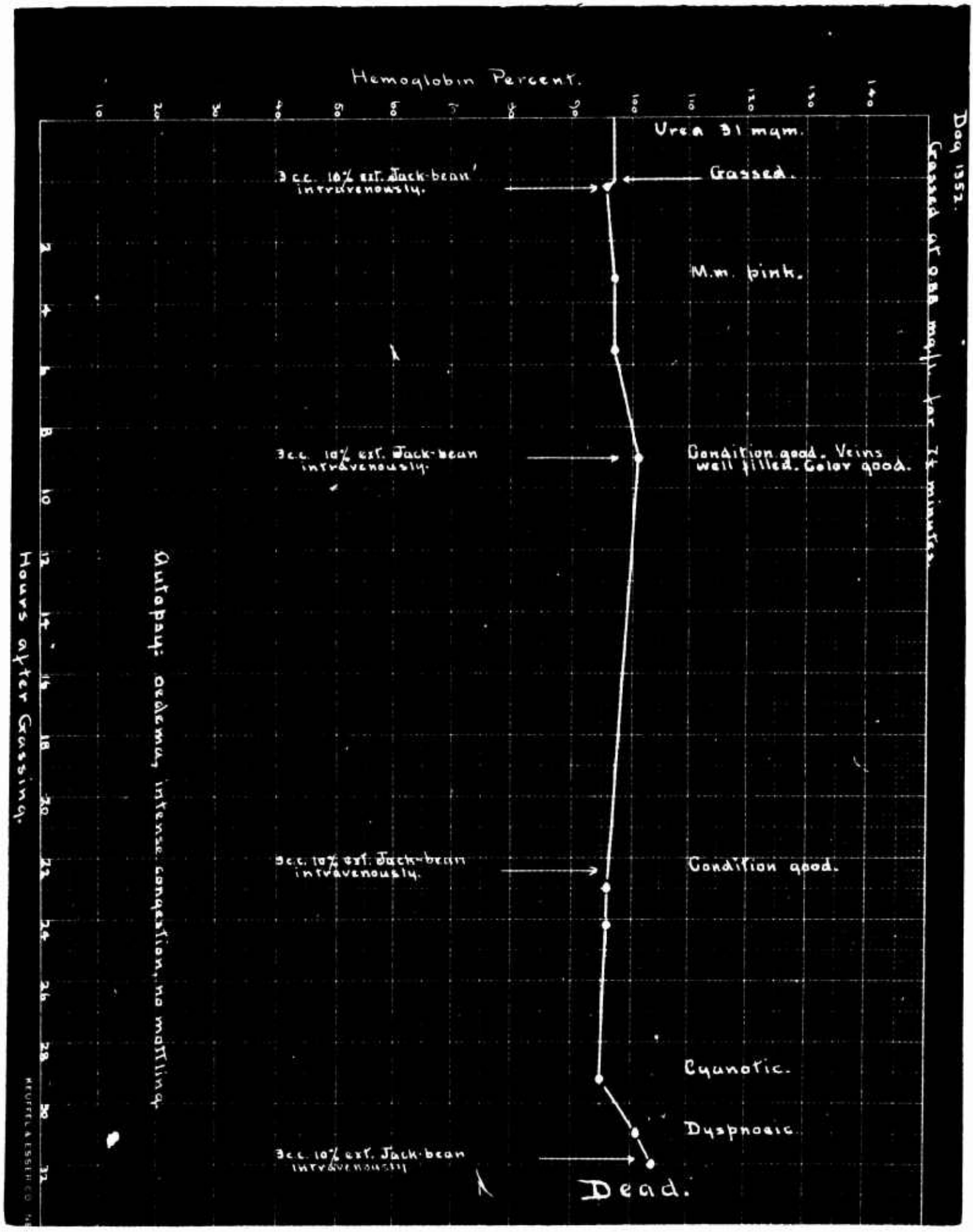
The data from which the minimum lethal concentration for 7½ minutes was derived are tabulated below:

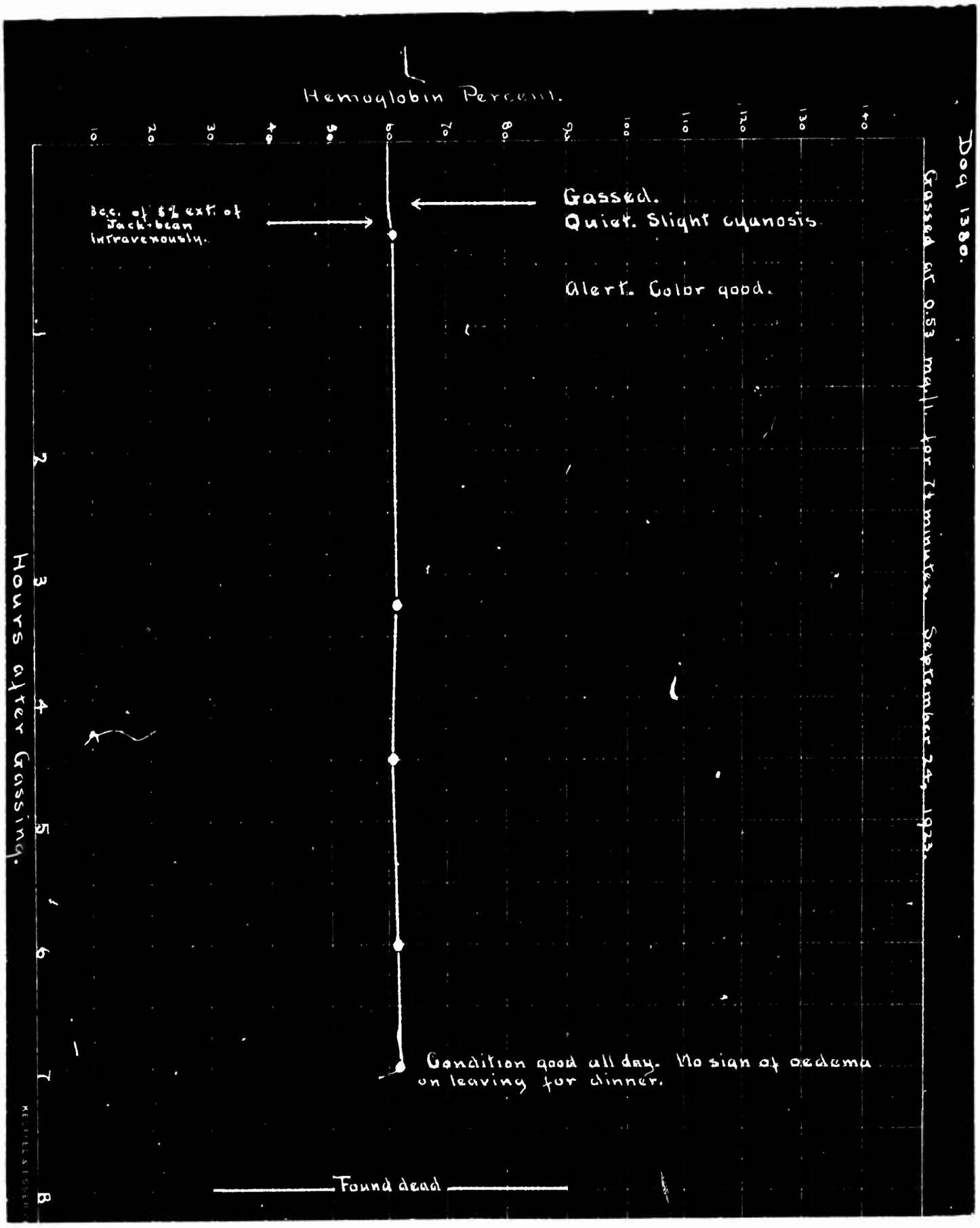
Dog Number	Concentration	Results	
1058	0.52	Recovered	) 1/3
1088	0.55	"	) Av.Conc.
802	0.56	Died after 5 days	) 0.55
1077	0.58	Recovered	)
1061	0.59	Died after 6 days	)
800	0.59	" " 15 hours	)
1089	0.62	Recovered	) 4/7
801	0.62	Died after 15 hours	) Av.Conc.
1044	0.64	Recovered	) 0.62
1049	0.64	"	)
797	0.64	Died after 22 hours	)
1122	0.66	Died after 13 hours	)
1066	0.68	Recovered	)
1107	0.68	Died after 11 hours	)
798	0.69	" " 12 hours	) 5/8
1045	0.69	" " 14 hours	) Av.Conc.
1125	0.70	" " 23 hours	) 0.69
782	0.71	Recovered	)
799	0.71	"	)
798	0.76	Died after 12 hours	)
790	0.77	" " 36 hours	) 3/4
784	0.81	Recovered	) Av.Conc.
788	0.83	Died after 36 hours	) 0.79

The average lethal concentration for 7½ minutes is placed at 0.62 milligrams per liter.

(a) Attempts at neutralization of gas in order to limit damage to tissues. It is supposed that the irritant action of phosgene ($COCl_2$) is caused by the hydrochloric acid produced by the hydrolysis of phosgene in water. When phosgene was first used, it was suggested that this irritant action could be minimized by inhalation of ammonia, and accordingly inhalation of ammonia was prescribed as one of the first aid treatments of phosgene poisoning. But Laqueur and Magnus found experimentally that inhalation of ammonia was not only useless, but was an additional irritant and positively detrimental. Thus of 21 animals that were gassed and treated with ammonia, 9 or 43 per cent died within 72 hours, while of 21 control animals only 7 or 33 per cent died in the same time. The reason for failure is very plain. Ten or fifteen minutes after gassing, the phosgene is all hydrolyzed, the HCl is already in the tissues and ammonia by inhalation does not reach it. However it was suggested by Dr. Kolls, that better results might be secured if ammonia could be carried by the circulation to the tissues concerned, and that this might be accomplished by injections of urease. This enzyme hydrolyzes urea with the production of ammonia.

The commercial tablet form of urease was first used but was found to be variable in strength when tested on a saturated urea solution. An aqueous extract of jack bean meal was found to be more powerful and dependable in its action. This was made by extracting 5 gm. of the meal


Hemoglobin Percent.
10
20
30
40
50
60
70
80
90
100
110
120
130
140
Urea 31 mgm.
Grassed.
3 c.c. 10% ext. Jack-bean intravenously.
M.m. pink.
3 c.c. 10% ext. Jack-bean intravenously.
Condition good. Veins well filled. Color good.
3 c.c. 10% ext. Jack-bean intravenously.
Condition good.
Cyanotic.
Dyspnoeic.
3 c.c. 10% ext. Jack-bean intravenously.
Dead.
Autopsy: oedema, intense congestion, no mottling.
Hours after Grassing.
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
Dog 1952.
Grassed at 9.58 mgm. per 1k minutes.
HEUFFEL & ESSER CO.


Hemoglobin Percent.
10
20
30
40
50
60
70
80
90
100
110
120
130
140
Dog 1380.
Gassed at 0.53 mg/l. for 7½ minutes. September 24, 1923.
Gassed.
Quiet. Slight cyanosis.
Alert. Color good.
Acc. of 6% ext. of Jack-bean intravenously.
Hours after Gassing.
1
2
3
4
5
6
7
8
Condition good all day. No sign of oedema on leaving for dinner.
Found dead

with 50 cc. of water for 30 minutes with frequent shaking and then filtering through cotton to remove the larger particles. Paper filtration seemed definitely to decrease the activity of the extract.

Six dogs were used, the concentration varying from .44 to .88 mgs/l. The time of exposure was uniformly 7½ minutes. The jack bean extract was given intravenously in 1 to 3 cc. doses immediately on removal from the chamber and thereafter as often as the condition of the animal seemed to demand as indicated by the rise in hemoglobin per cent. On the theory that the standard diet given our dogs in the kennels was so low in protein content that but little blood urea was likely to be present, we fed two dogs with a pure meat diet for two days preceding the day of gassing. It must be admitted however that the production of ammonia subsequent to the injection of the urease was not so greatly increased as we had hoped.

One dog gassed at 0.45 mgs/l survived. The others gassed at .44, .53, .86, .86, and .88 died. These results, though far from encouraging, showed one curious fact which gave hope. The usual prompt and steady rise in hemoglobin following the preliminary drop was not seen at all (#1380) or was much delayed (#1352). In those cases where it was not seen, it was probable that an abrupt rise was present but the sudden development of oedema, dyspnoea and death in these animals had prevented the taking of the hemoglobin readings which might have shown it.

The intravenous dose was always followed in from one to three minutes by a marked pallor of the mucous membranes, which changed in five to ten minutes into a pronounced pink flush and lasted for an hour at least, no matter how cyanosed these membranes had been previously. This flushing was always accompanied by an improvement in the appearance and behavior of the dog, an increase in alertness and a decrease in the dyspnoea if the latter had already begun.

Autopsies were done on all animals which died. The findings were:

(1) Increased heart-lung ratio and the presence of oedema.

(2) A general marked vascular congestion much more noticeable than in untreated animals.

(3) Total absence or marked diminution in the typical pleural mottling.

Conclusions:

1. Urease intravenously does not prevent death from oedema.

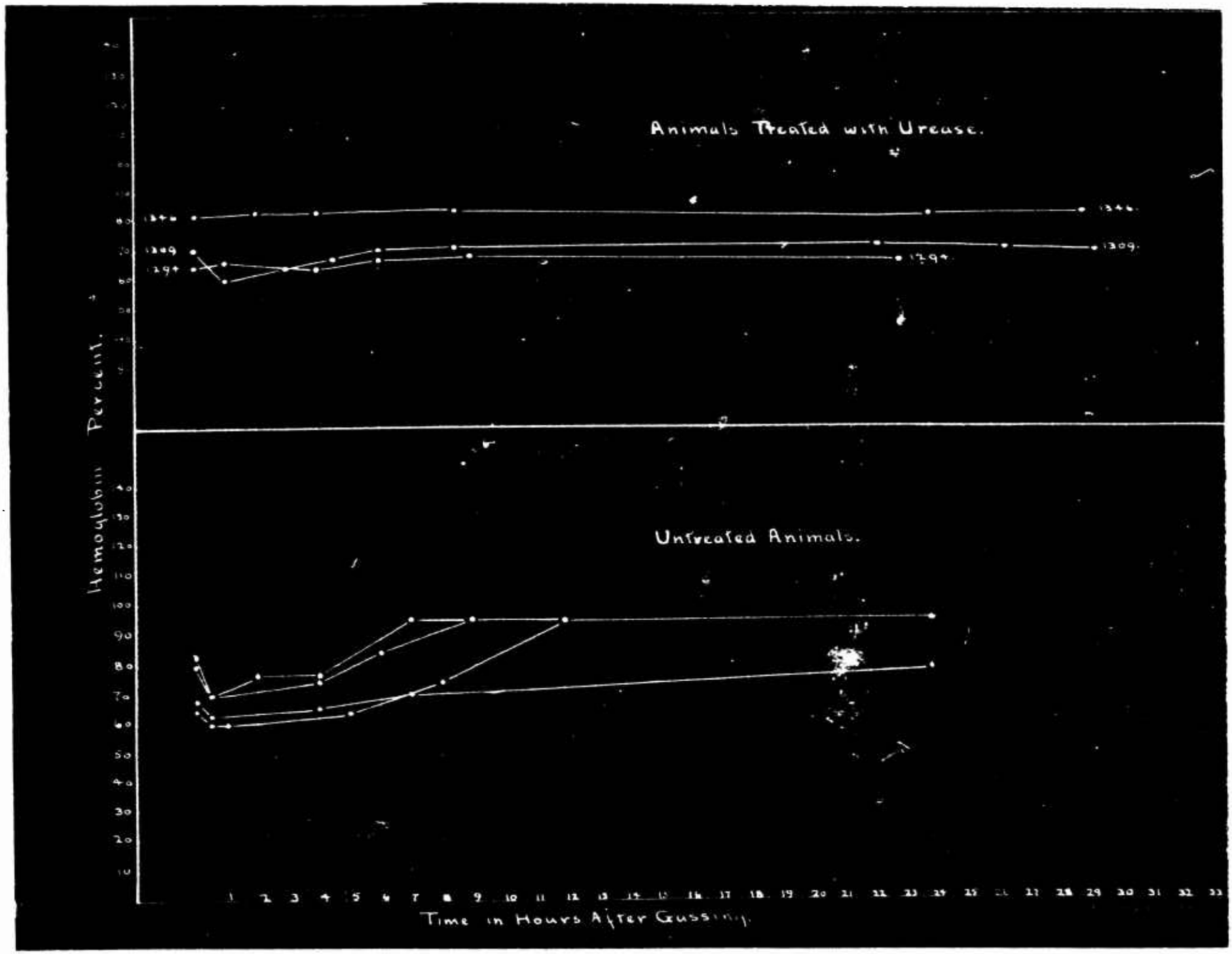
2. Oedema and its lethal symptoms develop finally with great rapidity.

3. The rise in hemoglobin is retarded and the condition of the dog remains good much longer than in untreated controls.

4. Since the damage to the lung tissues has been already accomplished for the most part, the amount of HCl neutralized by the production of NH_3 must be slight. In addition to this action, the ammonia in the circulation must cause some constriction of the pulmonary capillaries, thus delaying the onset of pulmonary oedema.

Dog 1346.

Gassed at 0.45 mg/l. for 7½ minutes. September 5, 1923.


Animals Treated with Urease.
1344.
1309.
1294.
Hemoglobin Percent.
Unfreated Animals.
Time in Hours After Gussing.

Ammonium Carbonate. Realizing the difficulty of obtaining satisfactory extracts of urease in the field, an attempt was made to secure similar results with a simple ammonia salt, and intravenous injection of 5% and 10% aqueous solutions of ammonium carbonate were tried.

The dosage varied from 2 cc. of the 5% solution to 10 cc. of the 10%. Preliminary observations on normal dogs showed that large doses (up to 50 cc. of a 10% solution) could be given. The only symptom observed was the production of a more or less marked convulsion after the large doses lasting from a few seconds to 15 minutes and accompanied by rapid respiration and great pallor of the mucous membranes. The dosage used in the treatment after gassing produced a convulsion in one dog only, following 10 cc. of a 10% solution. The pallor of the mucous membranes and the subsequent flushing were noted here as with the use of urease. The retarding of the rise in hemoglobin was not as marked as that following the urease treatment, nor were any deaths so long delayed.

Four dogs were used and all died. The concentrations were .53, .55, .55, and .61 mgs/l. The exposures were all 7½ minutes.

Autopsies on all these animals showed the production of oedema and increased heart-lung ratio. More marked congestion and less distinct mottling of the pleural surfaces than in untreated animals were noted.

It may be concluded that injections of ammonium carbonate were not as effective as injections of urease.

(b) The use of a vasoconstrictor agency, to prevent the dilatation of the pulmonary capillaries. A number of drugs were considered in this connection and discarded for one reason or another. The only drug that appeared hopeful was emetin. There can be no doubt that emetin exerts a powerful and lasting effect on the capillaries. Thus in amoebic dysentry, bleeding from the bowel ceases in a few hours after the injection of emetin, although it is obvious that the ulcers must be unchanged in so short a time. Emetin has also been highly recommended in haemoptysis. Ipecac was recommended by several authorities for the purpose of lessening pulmonary congestion in gassed cases. Thus emetin might be expected to reduce the pulmonary congestion without affecting arterial tension. Experiments on mice, in which the lungs were examined after injections of emetin, seemed to indicate that the pulmonary capillaries were actually smaller than those in normal controls.

Experimental. Three dogs were gassed at lethal concentrations of 0.65, 0.69 and 0.7 mgs/l. The dose of emetin used was 20 mg. (1/3 gr.). One dog received this dose subcutaneously immediately after gassing and no other treatment. This dog died in 3½ hours. The second dog was given 20 mg. emetin intravenously immediately after gassing and a second injection six hours later. This dog survived 11 hours. The third dog was given a subcutaneous injection of 20 mg. emetin the day before gassing and intravenously immediately after gassing. This dog lived 23 hours.

Even in this small number of cases, much was learned concerning the proper method of using emetin. This drug is absorbed very slowly when injected subcutaneously, but acts promptly when injected intravenously. It is well known that the drug is cumulative in action and therefore must be excreted slowly and must exert its action over at least twenty-four hours. When the dose is given intravenously on removal from the gassing chamber, the vaso-constriction produced is superimposed upon the primary vaso-constriction caused by the phosgene, and is theoretically of no benefit at that time. When given subcutaneously the absorption is slow, and will not in itself save life because the course of gas poisoning is complete before the full effect of the emetin is produced. Nevertheless, such subcutaneous injection exerts some effect throughout the entire course of the poisoning. Since the primary vaso-constriction of the pulmonary capillaries is very brief, especially following lethal or superlethal doses, and since human cases can rarely be treated immediately after gassing, the logical method is to (1) give emetin subcutaneously at the earliest possible moment after gassing. (2) If seen later when pulmonary oedema is commencing, give intravenously.

Following out these principles, a series of ten dogs were gassed at lethal concentrations. They were given a subcutaneous injection of 1/3 grain emetin, soon after removal from the gassing chamber, and an intravenous injection of 1/3 grain emetin, at about the time the primary constriction of the pulmonary capillaries was relaxing as shown by a rising hemoglobin. No other treatment was used. The results are shown in the following table:

Dog #	Conc. in mgs/l	Time of Gassing	Treatment: Hour of Subcutaneous Injection	Treatment: Hour of Intravenous Injection	Change in Hemoglobin	Hours of Life	Results
1779	0.58	9:35	10:00	2:15	Rise 14%	49	Died. No oedema or congestion. Ht. 65, lungs 100. Heart-lung ratio (1:1.5).
1782	0.58	9:35	10:00	2:15	Fall 9%	23	Died. Oedema marked. Ht.110, lungs 440. Heart-lung ratio (1:4).
1783	0.62	9:58	10:10	11:25	Fall 13%	--	Recovered.
1784	0.62	9:58	10:15	11:25	Fall 10%	--	Recovered.
1785	0.605	9:42	10:15	11:30	Fall 18%	--	Recovered.
1786	0.605	9:42	10:20	11:30	Rise 6%	30	Died. Oedema and congestion. Ht.120, lungs 480. Heart-lung ratio (1:4).
1787	0.61	9:54	10:10	11:15	Fall 9%	--	Recovered.
1788	0.61	9:54	10:13	11:15	Fall 2%	38	Died. Marked congestion. Little oedema. Ht. 79, lungs 290. Heart-lung ratio (1:3.6). Subendocardial petechial hemorrhages.
1780	0.67	9:50	10:00	2:10	Rise 15%	8	Died. Oedema. Ht. 145, lungs 470. Heart-lung ratio (1:3.2).
1781	0.67	9:50	10:10	2:10	Rise 10%	7	Died. Oedema and congestion. Ht. 153, lungs 481. Heart-lung ratio (1:3.1).

From this table it may be seen that although dog 1779 finally died, he did not die of pulmonary oedema but of an intercurrent accident. We may therefore say that following this treatment we had five out of eight recoveries, or a percentage of approximately 62 per cent, whereas without treatment at least 60 per cent would have died.

Further, in even the fatal cases the life of the animals was greatly prolonged, dying in 23, 30, 38, and 49 hours, instead of approximately 8 hours. In the case of two additional animals (1780 and 1781) gassed at a superlethal concentration, the emetin failed either to save life, or to noticeably prolong life. We may conclude therefore:

1. That intravenous injection of emetin undoubtedly produces a constriction of the pulmonary capillaries and helps to prevent pulmonary oedema in this manner.

2. The best method of administration is intravenous, at the time the primary constriction is relaxing. A subcutaneous injection should also be given in order that this action may be prolonged over the coming twenty-four hours as the drug is slowly absorbed.

3. This treatment alone, while beneficial, will not save life always even at minimum lethal concentrations. It should be combined with other methods of treatment.

(c) Altering the chemical content of the blood so as to reduce the permeability of the pulmonary capillaries. Wright (Lancet 1896, I, 153) found that a number of conditions, associated with extravasation of blood, such as capillary haemorrhages, and localized oedema, were favorably influenced by the administration of calcium salts. Chiari and Januschke (Schmiedebergs Archiv. 65, 120, 1911) confirmed these results and concluded that calcium salts possessed the property of rendering cells and membranes less permeable and consequently more resistant to inflammatory exudations. Rosenow (Zeitschr. f. d. ges. exp. Med. 1916, 4, 427) injected fluorescein under the skin of rabbits and found that after injection of calcium salts the absorption of this compound was greatly delayed.

Based on these observations, Laqueur and Magnus (Zeit. f. die gesamte Experimentelle Medizin 1921, XIII, 243) used calcium chloride in the treatment of animals gassed by phosgene. They found that a dose of 0.167 gram per kilo, exerted a powerful influence on the course of phosgene poisoning, increasing the percentage of living animals from 20% to 40%. But the intravenous injection of calcium salts is not without danger, causing paralysis of heart muscle and cessation of respiration in excessive dosage. However 0.1 gram per kilo was found to produce no ill effect in animals. There is a small number of cases in which $CaCl_2$ has been used in human cases. Von den Velden (Therap. Monatshefte, 1913, 685) injected a single dose of 5 cc. of 1. per cent $CaCl_2$.

Kawakami (Tokio med. Wochenschr 1913, 2572) injected once or twice daily 5 cc. of 1. per cent $CaCl_2$ without ill results. Bruhl and Buc (Société de Biologie, 1913, 74, 880) injected 20-100 cc. of 3. per cent $CaCl_2$ without injury. However F. von Müller found that when 3 cc. of 20 per cent calcium lactate was slowly injected it was followed by collapse with weak pulse. Toxicity is increased with higher percentages, and increased rapidity of administration. Weak solutions given slowly are comparatively non-toxic even when considerable total dosage of calcium salts is employed. All the evidence therefore indicated that administration of $CaCl_2$ would limit the formation of pulmonary oedema in phosgene poisoning, and that it could be safely administered under certain precautions. It was therefore determined to test it.

Experimental. Dogs were gassed at about the lethal point at which approximately 60 per cent of deaths are to be expected. They were subsequently given an intravenous injection of calcium chloride and no other treatment. When single doses were used they were given within 15 minutes after gassing. When multiple injections were used the initial dose was given from half an hour to an hour and a half after gassing. The results of these experiments are shown in the following table:

Dog #	Conc.	Dose	No. Doses	% Sol.	Results
1761	.60	20 cc.	1	5	Recovered.
1762	.60	20 cc.	1	5	Recovered.
1757	.62	30 cc.	1	5	Died immediately after injection. Autopsy findings negative. Sudden severe convulsion and cessation of resp. prior to heart collapse.
1758	.62	30 cc.	1	5	Died immediately after injection. Autopsy findings negative. Sudden severe convulsions and cessation of resp. prior to heart collapse.
1735	.63	30 cc.	4	5	Recovered.
1736	.63	30 cc.	4	5	Recovered.
1759	.645	20 cc.	1	5	Died. Severe congestion. Less oedema. Mottled. Ht. 93, Lungs 445 (1:4.7). Lived 44 hours.
1760	.645	20 cc.	1	5	Died. Oedema marked, no cough. Little mottling. Ht. 85, Lungs 430 (1:5). Lived 44 hours.
1744	.65	20 cc.	2	5	Died. Severe congestion. Scanty oedema. Slightly mottled. Ht. 80, Lungs 210 (1:2.6). Lived about 16 hours.
1743	.65	20 cc.	3	5	Recovered.

From this table the following deductions may be drawn:

1. The injection as used was not a safe therapeutic procedure. Two of the ten animals died as the direct result of the injection.

2. Of the 8 remaining animals 5 or 62 per cent recovered. The percentage of dogs living was raised from 40 per cent to 60 per cent.

3. Even in the three dogs that died, the onset of oedema was markedly delayed as shown by the entire course of the illness and the delayed death. In two cases the pathological findings and probable cause of death was acute congestion rather than pulmonary oedema.

We conclude that the intravenous injection of calcium chloride solution undoubtedly tends to prevent the formation of pulmonary oedema, but that a 5 per cent solution cannot be employed safely.

Calcium chloride of one per cent and 2½ per cent was injected intravenously in a number of normal dogs without fatality. It is possible that it might be safely used with profit in these concentrations. But in view of the excellent results obtained later with gum glucose and oxygen, the subject was not pursued further. It is obvious that the number of treatments that can be given in the field must be strictly limited, and it was considered undesirable to add to their number one that is at least problematical because of its intrinsic toxicity.

(d) Increase of Colloid Concentration of Blood-gum glucose.

During the war Cannon investigated the phenomena of wound shock. He found that gum-salt solutions used intravenously were valuable in preventing loss of blood plasma due to the affinity of this colloid for fluids.

D. T. Barry, Journal of Physiology, 1923, Vol. 57, p. 368, in an article entitled "Pulmonary Oedema and Congestion in Heart-lung Preparations", adds to the literature of this gum therapy. He discards the salt and uses an aqueous solution of gum acacia and glucose at the strength of 10% for each of these substances. In theory the gum present in the blood stream should prevent escape of fluid from the lung capillaries, while the glucose aids by increasing the osmotic pressure on the side of the blood stream, reversing the outward flow of the plasma and tending to reclaim from the lung tissues some of the lost fluid. The food value of the carbohydrate should also assist in keeping up the strength of the animal during the peak of the phosgene poisoning.

Laqueur and Magnus, "Experimentelle u. theoretische Grundlagen z. Therapie d. Phosgenerkrankung", Zeitsch. f. die gesamte Experimentelle Medizin, 1921, Vol. 13, p. 235, record the treatment of phosgene oedema intravenously by a 25% aqueous solution of glucose. Tney saved 50% of their animals by this means at ordinary lethal concentrations.

It was felt that these findings should be confirmed and further developed if possible.

Gum-salt Therapy.

Two dogs were gassed at a concentration of .68 mg/l and treated intravenously with a 25% solution of gum acacia in normal saline. One was given three doses in amounts of 200, 160, and 235 cc. The second received 200 cc. and later 180 cc. The time of administration and the dose were

governed by the rise in hemoglobin and the general condition of the animals. The first dog died 15 hours after gassing. The second recovered. There was a possibility that too much fluid had been given, thus tending to defeat the end desired. It was decided therefore to discard the saline and add the glucose, decreasing the amount of fluid.

Gum-Glucose Therapy.

25% gum acacia and 18% glucose in an aqueous solution was first used. Subsequently the glucose was raised to 25% strength also. Twelve dogs were used in the series. The dose was uniformly 100 cc. and was given intravenously. The time of dosage was from 1/2 to 5½ hours after gassing, depending upon the rise of hemoglobin in most cases. The concentrations varied from .64 mg/l to .864 mg/l. There were 8 recoveries and 4 deaths.

		Treatment					
Dog #	Conc. mg/l	No. Doses	Amt. Doses	Time after gassing	Result	Hours of survival after gas.	Result
1423	.69	1	100 cc.	5 hr.	Rec.		
1453	.71	1	100 cc.	5½ hr.	Died	12	Oedema marked. Heart-lung ratio 1;32.
1483	.65	1	100 cc.	4¼ hr.	Died	5½	Oedema scanty. Heart-lung ratio 1;2.8.
1484	.67	1	100 cc.	1¼ hr.	Died	26	Oedema scanty. Heart-lung ratio 1;2.3.
1485	.67	1	100 cc.	4¼ hr.	Died	26	Oedema scanty. Heart-lung ratio 1;2.5.
1486	.65	1	100 cc.	5 hrs.	Rec.		
1493	.64	1	100 cc.	½ hr.	Rec.		
1494	.64	1	100 cc.	3/4 hr.	Rec.		
1495	.67	1	100 cc.	1 hr.	Rec.		
1496	.67	1	100 cc.	3/4 hr.	Rec.		
1606	.864	1	100 cc.	2 hrs.	Rec.		
1608	.864	1	100 cc.	1 hr.	Rec.		

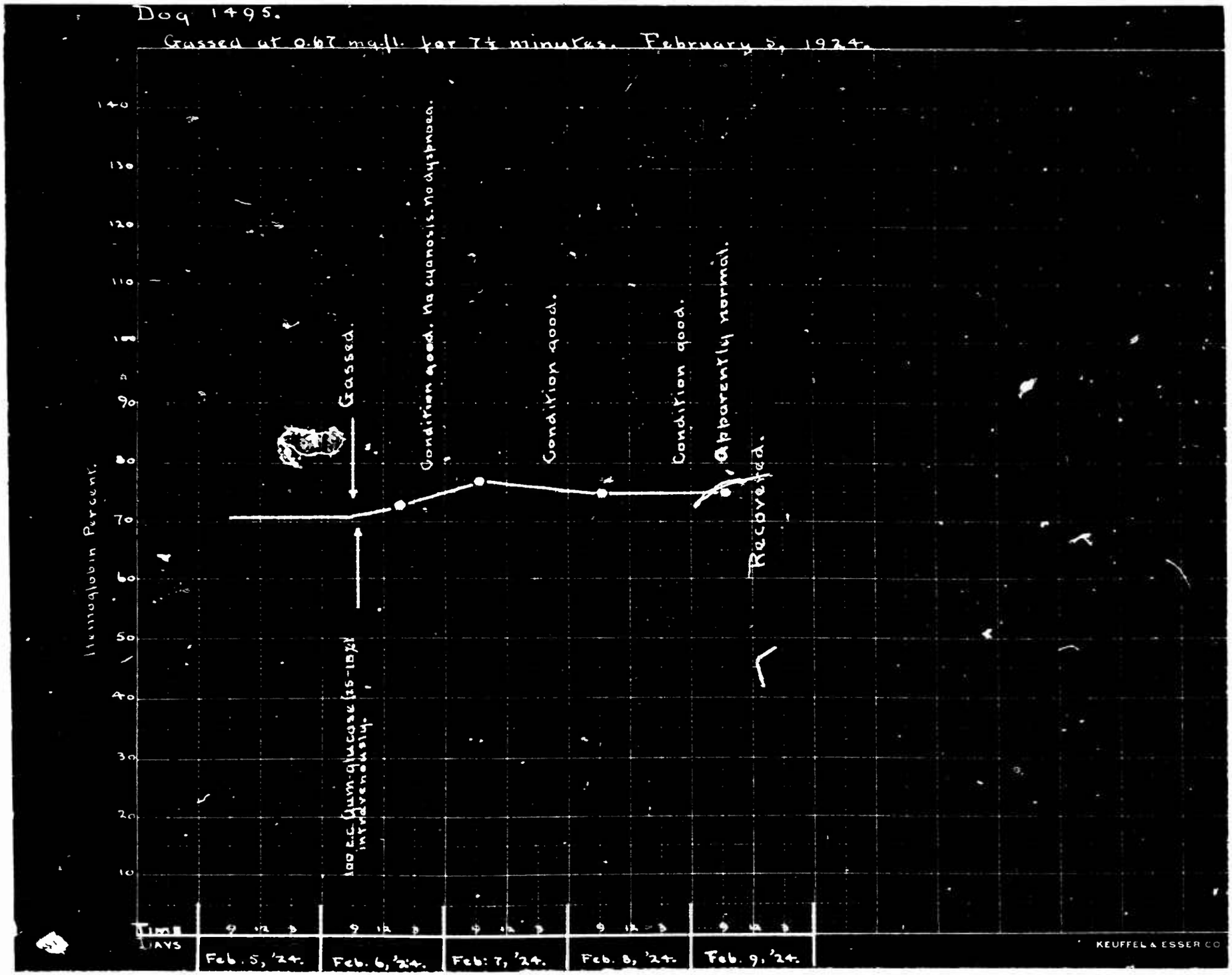
In general it may be said that the dogs recovered who were treated soonest after gassing, though the difference was not great. For the dogs who died the average number of hours between gassing and treatment was 3.8. For the recovered dogs this was 2. The concentration averaged .675 mg/l for the dogs which died and .711 mg/l for those recovering.

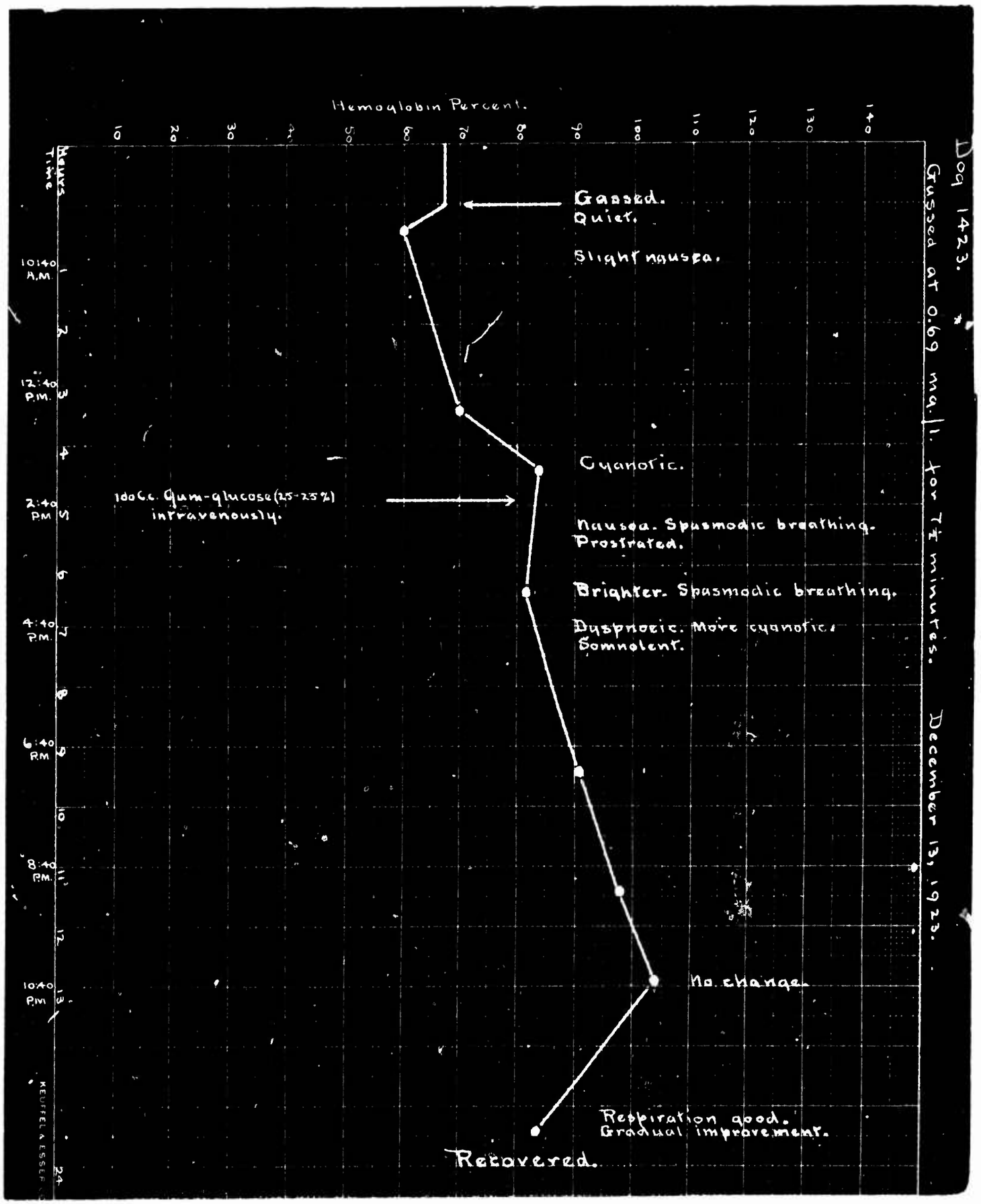
Conclusions:

1. Intravenous injection of gum glucose solution was markedly efficient in preventing the development of pulmonary oedema. By this method alone, 66 per cent of animals gassed at an average concentration of .711 lived, while 60 per cent of untreated animals gassed at .62 will die.

2. The most effective dose is approximately 5 cc. per kilo of body weight as recommended by Barry.

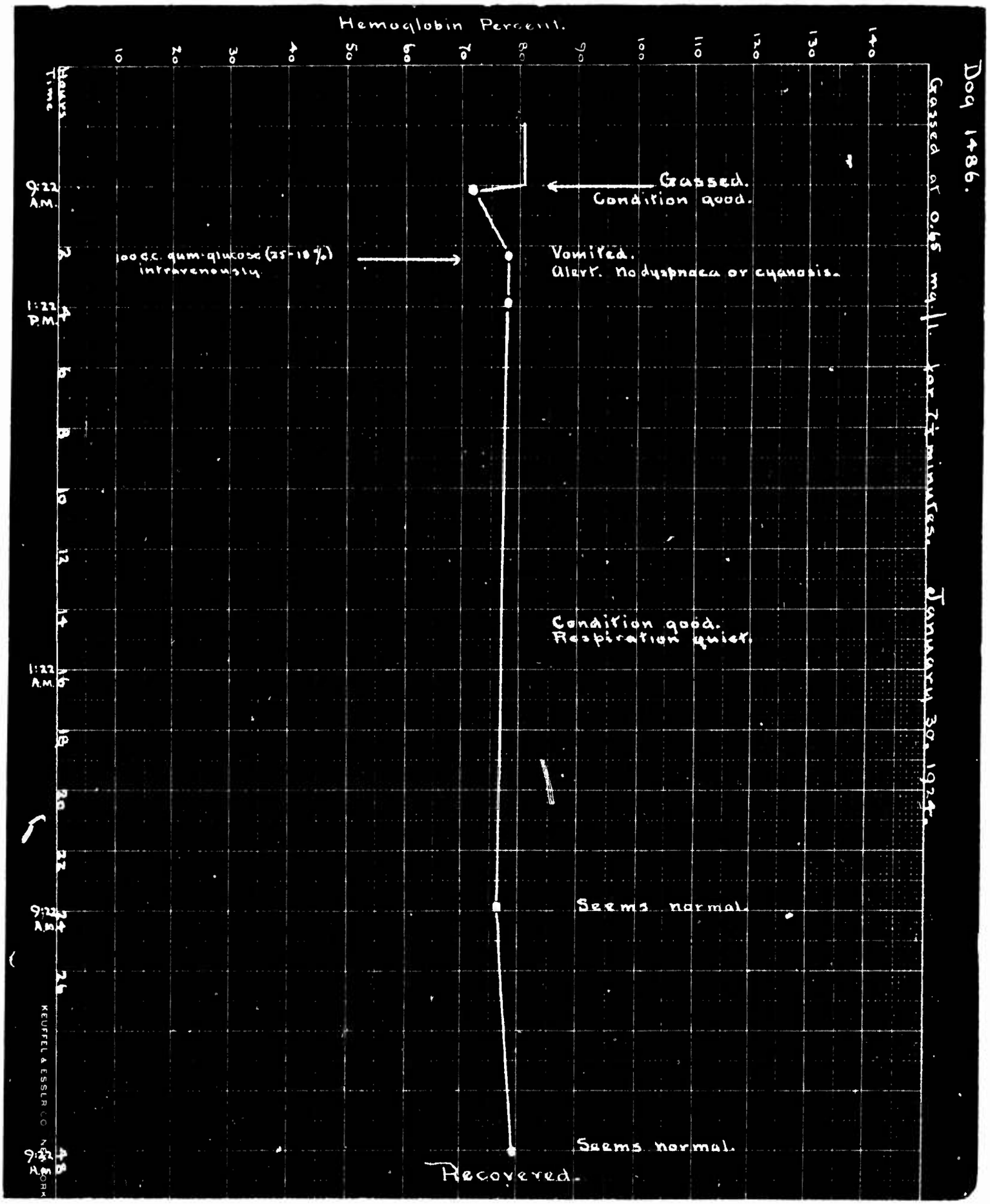
3. To be really effective this treatment should be given early, before much oedema fluid has collected in the lungs. The higher the concentration at which the animal was gassed, the earlier must the treatment be given. This means that after gassing with a lethal concentration (.62) treatment should be given in about two hours. After higher concentrations (.8) treatment should be given about one hour after gassing.


Dog 1495.
Gassed at 0.67 m.g.l. for 7½ minutes. February 5, 1924.
Hemoglobin Percent.
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Gassed.
Condition good. No cyanosis. No dyspnoea.
Condition good.
Condition good.
Apparently normal.
Recovered.
100 c.c. 5% m-glucose intravenously.
Time
Days
Feb. 5, '24.
Feb. 6, '24.
Feb. 7, '24.
Feb. 8, '24.
Feb. 9, '24.
KEUFFEL & ESSER CO



Dog 1423.

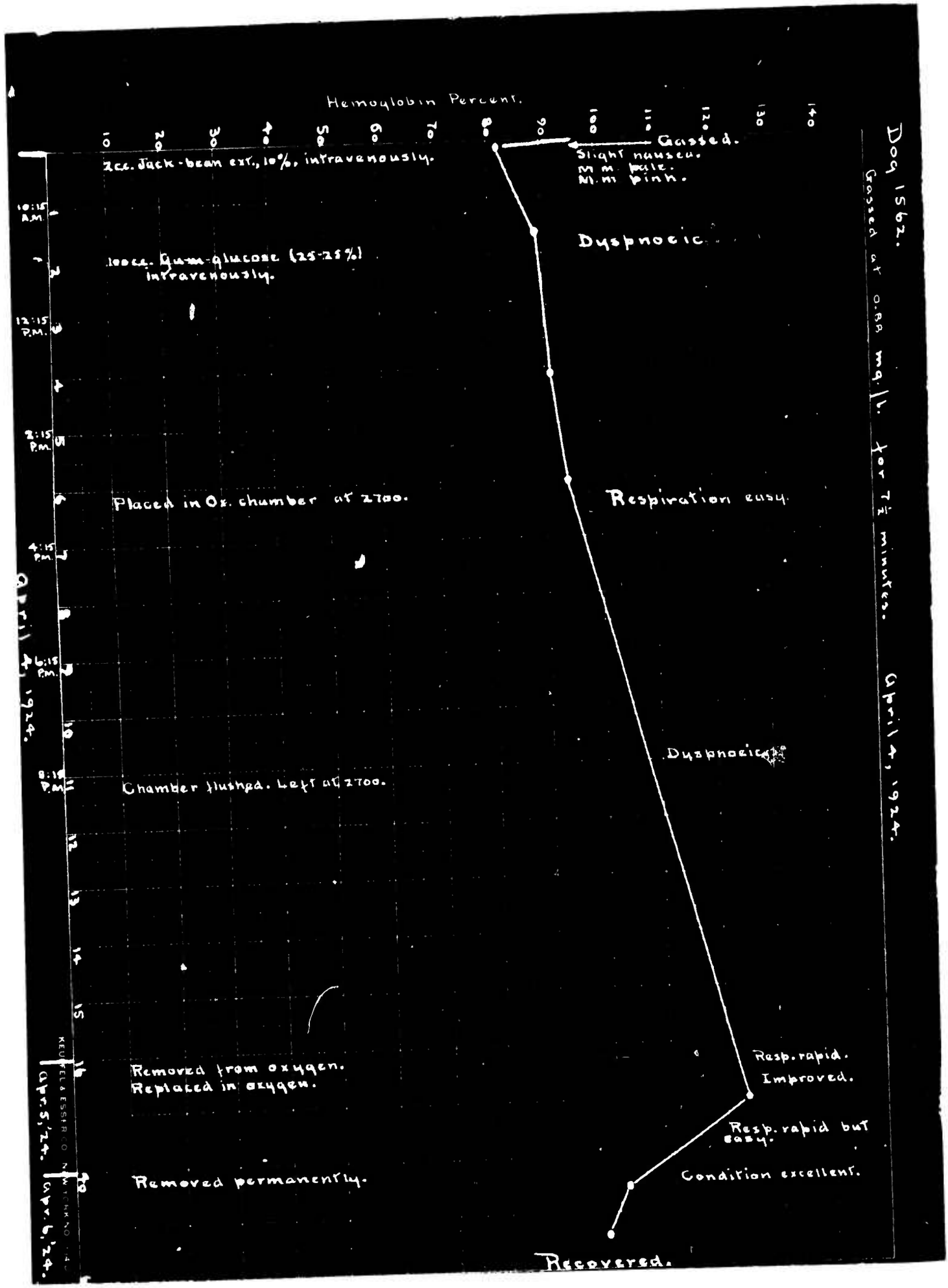
Gassed at 0.69 mg./l. for 1¼ minutes. December 13, 1923.


Hemoglobin Percent.
10
20
30
40
50
60
70
80
90
100
110
120
130
140
Hours
Time
9:22 A.M.
2
1:22 P.M.
4
6
8
10
12
14
1:22 A.M.
16
18
20
22
9:22 A.M.
24
26
9:22 A.M.
48
Dog 1486.
Gassed at 0.65 mg./l. for 7½ minutes. January 30, 1924.
Gassed.
Condition good.
100 c.c. gum-glucose (25-10%) intravenously
Vomited.
Alert. No dyspnoea or cyanosis.
Condition good.
Respiration quiet.
Seems normal.
Seems normal.
Recovered.
KEUFFEL & ESSER CO. NEW YORK

(e) Administration of pure oxygen. In the first part of this report anoxaemia was discussed, and the great benefit to be derived from inhalation of pure oxygen after pulmonary oedema had developed was pointed out. In the course of these experiments we had many occasions for testing this. Thus when a dog had been gassed at superlethal concentrations, and had been treated by one of the methods already outlined, pulmonary oedema developed in spite of the treatment. As the oedema progressed, these dogs became dyspnoeic, the mucous membranes became cyanosed and they showed all the symptoms of severe anoxaemia. In such cases, when it was apparent that the dog would die without further treatment, he was placed in a gassing chamber filled with pure oxygen. The oxygen was maintained in the chamber by a continuous flow of from 2-4 liters of oxygen per minute from oxygen cylinders, and at intervals the chamber was thoroughly blown out with oxygen in order to prevent the accumulation of CO_2. Twelve dogs were treated in this manner as shown by the following table:

Dog #	Conc. mg/l.	Treatment: Other than oxygen	Treatment: Oxygen	Result	No. of hours survived	Autopsy Findings
1518	.775	100 cc. gum-glucose	4 hrs. after gas	Rec.		
1519	.775	same	same	Rec.		
1522	.854	same	4¼ hrs. after gas	Died	20	No oedema. Congestion very severe. Free flood in pleurae and bronchi. Heart-lung ratio 1:3.1. Copious oedema, much of which escapes.
1523	.854	same	same	Died	20	Heart-lung ratio 1:2.6.
1534	.855	same	4½ hrs. after gas	Rec.		
1535	.855	same	same	Rec.		
1540	.82	same	6 hrs. after gas	Died	24	Oedema moderate. Heart-lung ratio 1:2.9.
1541	.82	same	same	Rec.		
1562	.88	100 cc. gum-glucose 2 cc. Jack-bean ext.	same	Rec.		
1563	.88	100 cc. gum-glucose 2 cc. Jack-bean ext.	same	Rec.		
1576	.93	100 cc. gum-glucose gr. 1/3 emetin 2 cc. Jack-bean ext.	34 hrs. after gas	Died	48	Little oedema. Solid congestion. Heart-lung ratio 1:3.7.
1637	.91	100 cc. gum-glucose 5 cc. Jack-bean ext.	24 hrs. after gas	Died	78	Oedema marked. No congestion. Heart-lung ratio 1:3.4.

From this table it will be seen that of these 12 dogs that would surely have died without oxygen, 7 recovered. The results of this treatment were immediately apparent. Dogs that were gasping for breath and to all appearance on the point of expiring,


Hemoglobin Percent.
10 20 30 40 50 60 70 80 90 100 110 120 130 140
Dog 1562.
Gassed at 0.88 mg./l. for 71 minutes. April 4, 1924.
Gassed.
Slight nausea.
m.m. pale.
M.m pinn.
2cc. Jack-bean ext., 10%, intravenously.
10:15 A.M.
Dyspnoeic.
100cc. Gum-glucose (25-25%) intravenously.
12:15 P.M.
2:15 P.M.
Placed in Ox. chamber at 2700.
Respiration easy.
4:15 P.M.
April 4, 1924.
6:15 P.M.
Dyspnoeic.
8:15 P.M.
Chamber flushed. Left at 2700.
Removed from oxygen.
Replaced in oxygen.
Resp. rapid.
Improved.
Resp. rapid but easy.
Removed permanently.
Condition excellent.
Recovered.
April 5, '24.
April 6, '24.
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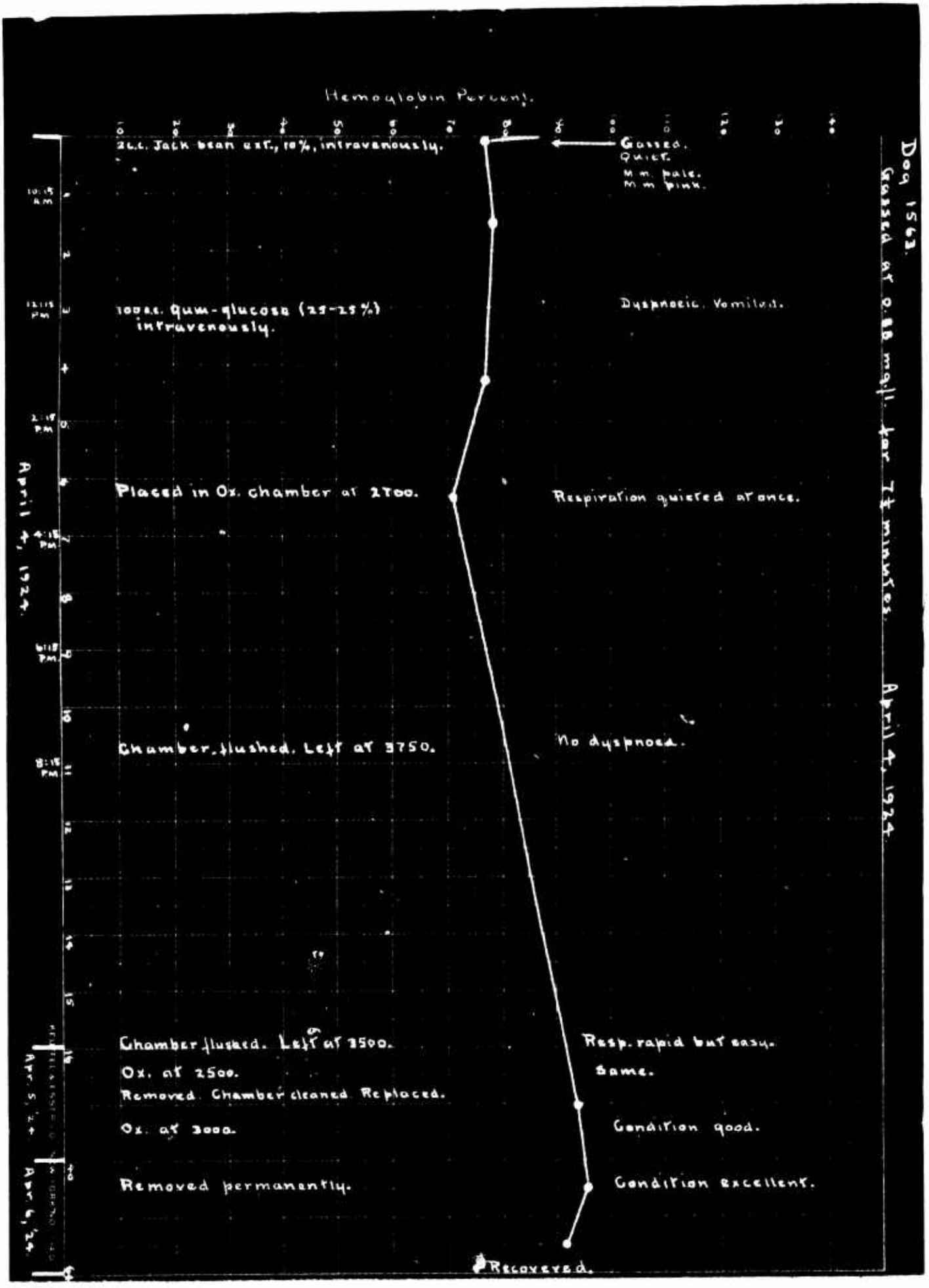
Hemoglobin Percent.
20 c.c. Jack bean ext., 10%, intravenously.
Gassed.
Quiet.
M m pale.
M m pink.
100 c.c. Gum-glucose (25-25%) intravenously.
Dyspnoeic. Vomited.
Placed in Ox. chamber at 2700.
Respiration quieted at once.
Chamber flushed. Left at 3750.
No dyspnoea.
Chamber flushed. Left at 3500.
Ox. at 2500.
Removed. Chamber cleaned. Replaced.
Ox. at 3000.
Resp. rapid but easy.
Same.
Condition good.
Removed permanently.
Condition excellent.
Recovered.
Dog 1563.
Gassed at 0.88 mg/l. for 14 minutes. April 4, 1924.
April 4, 1924.

would become quiet within a few minutes after being placed in the chamber. Their respirations became normal and they would go to sleep quite peacefully. This was practically invariable. After from 12 to 24 hours in the chamber, the dogs were removed. In some cases dyspnoea commenced again shortly after removal from oxygen. In fact each of the five deaths occurred after the dogs were removed from the oxygen, when they were removed before the pulmonary oedema had been sufficiently absorbed. None of these dogs died while in the oxygen chamber.

Conclusion: Inhalation of pure oxygen will save many cases, even after pulmonary oedema is fully developed and patients are practically moribund.

How long can pure oxygen be administered with Safety? It was discovered by Lorraine Smith in 1898 (Journal of Physiology, 1897-8, Vol. XXII, 315 and Vol. XXIV, 1899, p. 19) that oxygen at moderately high partial pressure is irritating to the epithelial tissue of the lungs. If the high percentage of oxygen be kept up for a sufficient period, the animal dies. On post mortem the blood vessels are extremely congested and there is ex[illegible]monary oedema. The higher the pressure, the shorter is the time [illegible] the lungs are able to withstand the effects of the oxygen.

Since the administration of oxygen is absolutely essential in overcoming the anoxaemia that results from phosgene poisoning it becomes necessary to determine how long pure oxygen at atmospheric pressure can be inhaled without producing the fatal effect observed by Lorraine Smith. Bornstein and Stroink

(Deutsch. Med. Wooh. 1912, XIV, 95) found that dogs and monkeys could breathe 60% oxygen at atmospheric pressure continuously for several months without injury. But Schmidt and David found that breathing 90-94 per cent oxygen killed mice quickly and that 40-60 per cent killed guinea pigs in three days. Loewy and Meyer (Veroffentlichungen a.d. Geb. des Militärsanitätswesens Heft 74, Berlin 1919) experimented on rats, guinea pigs, rabbits and dogs. Briefly they found that pure oxygen is harmless for 8-10 hours. After breathing pure oxygen for 36 hours, one rat out of sixteen died. After 46-47 hours all the animals suffered, and some died. After breathing pure oxygen for three days, fifty per cent of the animals died and the others were sick. There was a very great individual variation in susceptibility among the experimental animals.

We have performed a few experiments ourselves to check these results. Mice have very delicate lungs and are quite susceptible to the effects of oxygen.
(1) 5 mice were exposed for seven hours to an oxygen percentage varying between 96 and 98 per cent. They were unharmed, and living 10 days later.
(2) 5 mice were then exposed for 30 hours to an oxygen percentage of 98.2-98.4. At no time was any distress noted, but one mouse died after 10 hours. It was half eaten by the other mice and post mortem examination was impossible. At the end of 30 hours the four other mice were living and apparently well. Two mice were killed for examination of the lungs. The other two mice were living and well 10 days after the experiment. The lungs of the two mice killed showed considerable congestion and oedema.
(3) A dog was exposed for six hours to an oxygen percentage of 98. He was removed in good condition, and suffered no ill effects.

(4) A dog was exposed for 30 hours to oxygen varying in percentage from 97-98.2. The dog was removed in good condition apparently suffering from no distress whatever, and was alive and normal ten days later.

(5) This experiment was performed to determine how long a dog could breathe pure oxygen by leaving him in the cage until he died. The dog was placed in the chamber at 9.45 A.M. 2-18-24. He was fed and watered each day during the experiment at 3 P.M., otherwise the cage was not opened. The per cent of oxygen was maintained by a constant flow of oxygen from a cylinder over a flowmeter which was set at 1500 cc. per minute. Unfortunately the flow varied during the night. The temperature of the cage varied between 17°C. - 20°C.

The following readings were made of the gas percentage:

2-18-24	3 P.M.	Oxygen	91.7 per cent
		CO_2	1.3 " "
		Humidity	97. " "
2-19-24	8.15 A.M.	Oxygen	71. per cent
		CO_2	7. " "
		Humidity	94. " "
	1.15 P.M.	Oxygen	91. per cent
		CO_2	3.8 " "
		Humidity	97. " "
	3.00 P.M.	Oxygen	94.8 per cent
		CO_2	2.2 " "
		Humidity	97. " "
2-20-24	8.10 A.M.	Oxygen	93.8 per cent
		CO_2	3.3 " "
		Humidity	94. " "
	1.15 P.M.	Oxygen	96.3 per cent
		CO_2	1.7 " "
		Humidity	98. " "

	3.00 P.M.	Oxygen	98. per cent
		CO_2	2.7 " "
		Humidity	95. " "
2-21-24	6 A.M.	Dog died.	

This dog was exposed under very unfavorable conditions as regards humidity and carbon dioxide, to an oxygen percentage that varied for the most part between 91 and 96 per cent. He died after approximately 68 hours of this exposure. At the post mortem examination, the lungs were found to be greatly congested and oedematous, and the trachea and bronchi were filled with foamy fluid. He died from acute pulmonary oedema. However the dog appeared perfectly well for 48 hours. He refused to eat and suffered from some respiratory distress after about 54 hours, and became progressively worse until he died.

From this data it appears probable that men could breathe pure oxygen (95-98%) for 36 hours without serious injury, but that after this period the use of pure oxygen would become increasingly dangerous. Men are known to have breathed pure oxygen for 8 hours using the oxygen mine rescue apparatus, without injury. This information is sufficient for our purposes in the treatment of phosgene poisoning. It has been shown that air enriched with oxygen to 40-60 per cent can be breathed indefinitely, and it will never be necessary to administer pure oxygen except in very serious cases during the peak of the oedema and resulting anoxaemia. Probably no case will need to breathe pure oxygen longer than 24 hours. No more oxygen than is required should be given, not only to avoid the danger of excessive oxygen, but

chiefly in order to conserve the oxygen supply. Gassed cases may be treated best in a ward in which the air is enriched to 40-60 per cent oxygen, reserving several small cylinders with the face mask and rubber bag for the administration of pure oxygen to the most serious cases, who show symptoms of anoxaemia even in this percentage of oxygen. Such conditions will rarely be found in the field hospitals where most cases gassed by pulmonary irritants must be treated. However such hospitals, ambulances, and when possible aid stations should be supplied with oxygen cylinders with proper facepieces (Haldane apparatus) whenever there is any prospect that our troops may be exposed to gas warfare.

SUMMARY OF CONCLUSIONS:

1. Injection of urease did not save life, but did appear to improve the condition of gassed animals. Ammonium carbonate failed to give as good results.

2. Intravenous injection of emetin causes constriction of the pulmonary capillaries and greatly delays the onset of pulmonary oedema.

3. Intravenous injections of calcium chloride undoubtedly decreases the permeability of the pulmonary capillaries and delays the onset of pulmonary oedema, and thus saves the life of gassed animals. However it is itself toxic, and there is grave danger in its use.

4. Intravenous injection of gum-glucose solution (25 per cent gum and 25 per cent glucose) may entirely prevent the development of pulmonary oedema, especially if it is administered soon after gassing.

5. Administration of pure oxygen will often save life after all other means have failed.

RECOMMENDATIONS FOR FIELD TREATMENT OF CASES GASSED BY PULMONARY IRRITANTS.

Although the investigation of this subject is by no means complete and has been discontinued at this point from lack of time and opportunity to pursue it further, certain procedures for future treatment are strongly suggested.

At the close of the war, venesection followed by oxygen were the methods of treatment that had justified themselves by their results. It now appears that injections of emetin may be given with advantage, subcutaneously at once, and intravenously later, possibly at collecting stations. Further intravenous injections of gum glucose solution, which could be given at collecting stations, appear to give even better results than venesection.

Finally the great value of administration of pure oxygen is emphasized since it is capable of saving even cases that appear moribund. The supply department should certainly make provision for furnishing all of these remedies. The use of urease and calcium chloride is not recommended, the first because of the difficulty of administration and the second because of its danger.

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THE EXPERIMENTAL TREATMENT
OF PHOSGENE POISONING.

Work begun: December 1922.
Work completed: January 1925.

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DEPARTMENT OF THE ARMY
US ARMY RESEARCH, DEVELOPMENT AND ENGINEERING COMMAND
EDGEWOOD CHEMICAL BIOLOGICAL CENTER
5183 BLACKHAWK ROAD
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REPLY TO
ATTENTION OF

RDCB-DPC-RS

15 October 2015

MEMORANDUM THRU Director, Edgewood Chemical Biological Center, (RDCB-D/Dr. Joseph Corriveau), 5183 Blackhawk Road, Aberdeen Proving Ground, Maryland 21010-5424

FOR Defense Technical Information Center, 8725 John J. Kingman Road, Ft Belvoir, VA 22060

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Encl

RONALD L. STAFFORD
Security Manager

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