mal. Other groups of 20 rats each were gastrically premedicated with single doses of isopropyl alcohol, 1250 mg/kg, diphenylhydantoin, 100 mg/kg, or phenobarbital, 50 mg/kg; and 1 hour later these rats were given the convulsants in the same doses as in the controls. The doses of isopropyl alcohol and phenobarbital were those found previously to be the maximal which would not produce undesirable motor depression.

In doses which did not cause motor ataxia, isopropyl alcohol compared favorably with phenobarbital in preventing and ameliorating the convulsions of metrazol. This alcohol was superior to phenobarbital in antagonizing thujone seizures; but the alcohol was less effective than phenobarbital against picrotoxin. Diphenylhydantoin afforded protection against picrotoxin convulsions only.

Summary. Analyses of blood isopropyl alcohol and blood acetone in relation to elevation of cortical threshold to electric stimulation suggest that the alcohol itself is responsible for the anticonvulsant effect. The ketonemia, nonetheless, may contribute a share. Other secondary and tertiary alcohols (2-butanol, 3-pentanol, and 2-methyl-2-butanol) effectively raised the cortical threshold, with or without acetonemia. Isopropyl alcohol was capable of antagonizing metrazol and thujone convulsions but was not effective against picrotoxin seizures.

Received April 19, 1950. P.S.E.B.M., 1950, v74.

Therapy of Paroxysmal Pulmonary Edema by Anti-Foaming Agents (17858)

ALDO A. LUISADA*

From the Laboratory of Cardiology, The Chicago Medical School, Chicago, Ill.

In spite of accepted therapeutic measures, paroxysmal pulmonary edema still has a high mortality. For this reason, any new drug or aid may be of importance. It has long been known(1) that large amounts of fluid may be tolerated in the respiratory passages as long as no foam is formed. When the latter occurs, increased volume of the fluid and modified physical properties cause severe effects by blocking the small bronchi and adding the effects of anoxia to those already causing pulmonary edema. For this reason, a systematic study of several anti-foaming agents introduced into the respiratory passages was undertaken.

Material and method. The study was made in a series of 100 white, male rabbits weighing between 1.6 and 2 kg. Paroxysmal pulmonary edema was induced by the standard method previously used by the author(2) and slightly modified by Glass(3). Adrenalin Parke and Davis was injected slowly into the marginal vein of the ear, 2 cc of the one to one thousand solution being injected in one minute. The following anti-foaming substances were tested: (a) ether; (b) octyl alcohol;† (c) capryl alcohol;‡ (d) 95% ethyl alcohol; (e) sorbitan triolate (Span 85).§ The rabbits were placed into a box with a glass cover and each of the above drugs was sprayed into it at frequent intervals by means of an atomizer. The action of the drug was prolonged for 10 minutes prior to the injection of adrenalin and then until

* The author is indebted to the U. S. Public Health Service for aid in this investigation by a Cardiovascular Teaching Grant from the National Heart Institute.

1. Laqueur, E., and DeVries Reilingh, D., *Deut. Arch. klin. Med.*, 1919, v130, 310.

2. Luisada, A. A., *Arch. Exp. Path. u. Pharm.*, 1928, v132, 313.

3. Glass, A., *Arch. Exp. Path. u Pharm.*, 1928, v136, 72.

† n-octyl alcohol, supplied by Eastman Kodak Co.

‡ methyl-n-hexacarbinol, supplied by Eastman Kodak Co.

§ This substance was obtained through the courtesy of the Atlas Powder Co.

TABLE I.
Influence of Various Anti-foaming Agents on Adrenalin Pulmonary Edema.

Drug	% of survival at LD_{50} (6 min.)	Avg survival (min.) and standard error*	Avg lungs/body ratio and standard error*	No. of animals	Beneficial effect
(Normal animals)	—	—	0.455 ± 0.021	4	—
Adrenalin (controls)	50	15.5	1.55 ± 0.035	12	—
Span 85	25	6	1.48 ± 0.094	4	0
Heavy alcohols (inhal.)	70	20.6	1.30 ± 0.098	10	x
Ether (inhal.)	100	29	1.15 ± 0.266	5	x
Morphine (subcut.)	90	35	1.01 ± 0.109	10	xx
Ethyl alcohol (inhal.) (subanesth. dose)	90	35	0.95 ± 0.092	20	xx
Ethyl alcohol (intrav.) (subanesth. dose)	60	18.6	1.29 ± 0.263	5	x
Ethyl alcohol (G-I) (anesth. dose)	100	33.5	0.76 ± 0.130	7	xxx
Morphine (subcut.) + ethyl alcohol (inhal.)	100	42.4	0.68 ± 0.048	10	xxxx
Morphine (subcut.) + oxygen under pressure	100	43.6	0.60 ± 0.051	5	xxxx

* Standard error $= \sqrt{\frac{\Sigma\Delta^2}{(n)\ (n-1)}}$

death of the animal. However, if the rabbit survived, at the end of 60 minutes it was sacrificed for control of the lungs. For this reason, the longest survival time was actually 60 minutes. In order to control the action of ethyl alcohol, this was also given intravenously in a subanesthetic dose (5 cc per kg of a 25% solution); by stomach or rectum in anesthetic dose (8-10 cc per kg of a 50% solution); or associated with morphine sulfate. The latter was given in dose of 10 mg per kg by subcutaneous injection; adrenalin was administered 30 to 40 minutes later. Ether was given in subanesthetic dose. Further controls were made with morphine and oxygen. Pure oxygen was given under a pressure of 3 to 4 cm H_2O through a tracheal cannula in morphinized rabbits. Adrenalin was injected soon after starting the oxygen jet.

Evaluation of the outcome was done in the following way: observation of the animal; possible outpour of foam from the mouth, nostrils or cut trachea; macroscopic appearance of the lungs; lungs body ratio. The latter was obtained by dividing the weight of the lungs in grams by that of the animal in grams and multiplying the result by 100. Controls on normal rabbits showed that, by this method, an average ratio of 0.45 is obtained.

Results. *Span 85* did not change the severity of the edema and seemed to abbreviate the survival time. *Heavy alcohols* slightly increased the survival time and decreased the severity of the edema while subanesthetic doses of ether also helped somewhat. *Ethyl alcohol* by inhalation had a marked action, revealed by the fact that the average survival time was doubled and the average lungs/body ratio was decreased, from 3 times, to twice the normal. This effect of ethyl alcohol was as favorable as that of *morphine* (see table). Equivalent subanesthetic doses of ethyl alcohol by intravenous injection had a less favorable effect. On the contrary, larger doses of alcohol causing anesthesia, given by gavage or enema, had a marked favorable action, slightly superior to that of inhalation alcohol.

Combined therapy by means of morphine plus inhalation of ethyl alcohol or by morphine plus oxygen under pressure gave excellent results, revealed by the lack of edema and by a long survival time.

Discussion. The stability of a foam is based upon the character of the air-fluid interface, namely on the surface tension of the fluid. Any substance capable of modify-

ing the surface tension in such a way as to decrease the foam, is called *an anti-foaming agent*. The favorable action of anti-foaming agents was revealed by the above mentioned experiments. However, this action was either enhanced or reduced by other properties of the drugs. Both Span 85 and heavy alcohols seemed to exert some unfavorable effect which neutralized their anti-foaming action. It is possible that coating of the mucosa or plugging of bronchioles by droplets of these fluids accounts for the result. Ether's anti-foaming effect was probably partly counteracted by its irritant action which increased bronchial and alveolar congestion. Ethyl alcohol proved to be the best. Controls with equivalent subanesthetic doses injected by vein and with larger, anesthetic doses given via g-i tract revealed that a twofold effect is obtained through the use of inhaled alcohol: one favorable action is local, and consists of the reduction of foam; the other is general and is based on its depressant effect on the nerve centers. This is revealed by the fact that, in order to obtain comparable effects, parenteral alcohol has to be given in much larger doses than when inhaled. The useful action of alcohol is revealed by the fact that it is equivalent to that of morphine: 9 out of 20 animals had slight or no edema of the lungs; 10 out of 20 survived more than 50 minutes; 19 out of 20 had no bloody foam from the nostrils.

Association of parenteral morphine with alcohol by inhalation gave excellent results. Statistical analysis was made of the data obtained in two series of experiments comparing alcohol by inhalation with alcohol by inhalation plus parenteral morphine. It was proven that statistically $t_{28} = 4.0$, which corresponds to a probability of less than 0.1%; therefore, the means of the two lungs/body ratios are different, and the combination of the two drugs is superior to each of them alone.

As shown by previous studies, air and oxygen under pressure are effective in the treatment of acute pulmonary edema caused by adrenalin(4,5). In our experiments, morphine plus oxygen under pressure saved a great number of animals. Comparison between this series and that treated by morphine plus alcohol by inhalation showed that the results obtained by using either of the two methods are equivalent. The combination of all 3 remedies, morphine, oxygen under pressure and alcohol vapors seems, therefore, to be indicated in clinical cases. The only reason why it was not tried in our experimental series is that, in adrenalin pulmonary edema, the results were already so good with 2 of the remedies that further improvement could not be expected through the addition of a third.

Summary. Experiments were performed with anti-foaming agents by inhalation in rabbits in order to decrease the severity of pulmonary edema caused by a standard dose of intravenous adrenalin. Poorly volatile drugs (heavy alcohols, Span 85) failed to exert any favorable effect. Ether gave only a slight improvement. Ethyl alcohol exerted an important favorable action. This action is partly due to the anti-foaming property of alcohol and partly to its action on the central nervous system. Combination of parenteral morphine with alcohol by inhalation gave the best results.

The author wishes to acknowledge the technical assistance of Miss Edith B. Shafer and is indebted to Dr. A. R. Goldfarb for statistical analysis.

4. Emerson, H., *Arch. Int. Med.*, 1909, v3, 368.
5. Barach, A. L., Martin, J., and Eckmann, M., *Ann. Int. Med.*, 1938, v12, 754.

Received March 24, 1950. P.S.E.B.M., 1950, v74.