Failure of Antihistaminic Drug "Phenergan" to Protect Against Acute Pulmonary Edema. (17351)

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Halpern and his co-workers have developed the thesis that antihistaminic drugs owe much of their therapeutic effectiveness to a primary influence upon cellular permeability, aside from their property of competitive inhibition of histamine. This concept is based in part on the observation that N-(β-dimethylamino-α-methylethyl)-phenothiazine (3277 R.P. or Phenergan) protects guinea pigs and rabbits from pulmonary edema produced by an overdose of epinephrine[1,2] or by certain poison gases, such as chloropicrin.[3]

On the other hand, Stone and Loew[4] failed to obtain protection by pyranisamine (Neo-Antergan) in rabbits with epinephrine-induced pulmonary edema. The same authors[5] also could not confirm the observation that Phenergan protected rabbits. In one series (8 animals) they obtained a reduced mortality but no reduction in pulmonary edema, as judged by lung weight. It seemed of interest to determine whether Halpern's results could be confirmed in our laboratory, and also whether Phenergan would affect pulmonary edema produced by administration of ammonium salts, as described by Koenig and Koenig.[6] If it could be shown that pulmonary edema produced by two such widely different means could be alleviated by an antihistaminic drug, support would be added to Halpern's view that such drugs may primarily affect cellular permeability.

Methods. The rats used in this study weighed about 200 g. Both Carworth and Holtzmann rats were employed, and as no difference was noted in results obtained with the two strains, they have been combined in the summary. The guinea pigs varied from 300 to 500 g in weight. Pulmonary edema was produced as follows: epinephrine chloride was injected in the forelimb vein of guinea pigs, 0.6 mg per kg (the dose used by Reuse[3]); ammonium chloride was administered intraperitoneally, the dose being 400 mg per kg for rats, and 600 mg per kg for guinea pigs, as described by Koenig and Koenig.[6]

Phenergan was chosen as the antihistaminic drug, because Halpern has stated that its effect on cellular permeability was greater than any others he used. We administered Phenergan subcutaneously, except to a few of the rats, where the intraperitoneal route was employed. The dose was the same as that used by Halpern and by Reuse; namely, 20 mg per kg, except in 2 groups of rats where the dose was doubled. Thirty to 60 minutes (usually the latter) were allowed to elapse between injection of Phenergan and of epinephrine or ammonium chloride. The lot of Phenergan used was manufactured in France, and obtained from Societé des Usines Chimiques Rhone-Poulenc, Paris.

Results. The syndrome of acute experimental pulmonary edema in rats and guinea pigs has been adequately described by Koenig and Koenig.[6] The signs and gross findings at autopsy described by them were seen in the majority of our animals.

The results are summarized in Table I. It is evident that Phenergan, even in the relatively large doses used, did not protect the animals from pulmonary edema as judged by lung weight, nor did the antihistaminic drug reduce the mortality, nor prolong the survival

[1] Halpern, B. N., Hamburger, J., and Cruchaud, S., *Acta allerg.*, 1948, **1**, 97; Halpern, B. N., and Cruchaud, S., *Compt. rend. soc. biol.*, 1947, **141**, 1038; Vermeil, G., Halpern, B. N., and Cruchaud, S., *Compt. rend. soc. biol.*, 1949, **143**, 77.

[2] Reuse, J., *Compt. rend. soc. biol.*, 1948, **142**, 638.

[3] Halpern, B. N., and Cruchaud, S., *Compt. rend. Acad. d. sc.*, 1947, **225**, 1194.

[4] Stone, C. A., and Loew, E. R., *Fed. Proc.*, 1949, **8**, 335.

[5] Stone, C. A., and Loew, E. R., PROC. SOC. EXP. BIOL. AND MED., 1949, **71**, 122.

[6] Koenig, H., and Koenig, R., PROC. SOC. EXP. BIOL. AND MED., 1949, **70**, 375.

TABLE I.
Lack of Protective Effect of Phenergan Against Acute Pulmonary Edema Produced by Epinephrine or Ammonium Chloride.

Exp. No.	Treatment	Avg body wt, g	Dose of phenergan, mg/kg	Mortality ratio*	Median survival time,† min.	Avg lung wt,‡ g/kg body wt
		Rats				
I	NH_4Cl	199	—	8/15	35	11.6
II	" + phenergan	220	20	4/10	20	18.2
III	" + "	206	40	8/10	24	14.6
IV	Phenergan	196	40	0/10	—	6.2
V	No drug	212	—	0/4	—	7.7
		Guinea pigs				
VI	NH_4Cl	461	—	8/10	8	10.4
VII	" + phenergan	408	20	12/12	8	8.6
VIII	Epinephrine	436	—	6/7	7	19.7
IX	Epinephrine + phenergan	423	20	8/8	7	20.3
X	No drug	450	—	0/5	—	6.8

* Mortality ratio = number dead/number used.
† Excluding those surviving indefinitely.
‡ Avg lung wt in experimental groups include only those animals which succumbed after injection. Control animals were sacrificed under pentobarbital anesthesia.

time of the animals which died. The difference in lung weight between Groups VI and VII is not significant ($P > 0.05$), but Group VII differs significantly from control Group X ($P = 0.02$), as does Group VI ($P < 0.01$). In all the other cases, the differences between experimental and control groups are obvious from inspection of the table.

Discussion. The lung weights of the guinea pigs succumbing to epinephrine were greater than in those receiving a lethal dose of ammonium chloride. It may therefore be assumed that pulmonary edema was not maximal in the latter group, and may not have been the sole cause of death. Stone and Loew[5] have also expressed the view that pulmonary edema may not have been the sole cause of death in their epinephrine treated rabbits. The overall mortality rate in all our animals receiving edema-producing drug without Phenergan was 22/32 or 69%, while in those receiving Phenergan in addition to the toxic agent it was 32/40 or 80%. Our results are in agreement with the statement of Stone and Loew,[5] that Phenergan did not protect the animals against pulmonary edema, although we did not observe the lower mortality rate which they reported in their animals.

Koenig and Koenig[6] believe that the pulmonary edema produced by ammonium chloride is a specific action of the ammonium moiety, and is not related to the acidosis produced by NH_4Cl. Other ammonium salts also induced pulmonary edema, while acidosis produced by other means did not. However, they did not publish data indicating the degree of acidosis produced by the various agents they used, and it is therefore impossible to judge the validity of their conclusions.

The divergence between our results and those of Reuse[3] is not easy to explain. He used guinea pigs about twice as large as those herein reported. He also used epinephrine ascorbate, while the epinephrine we used was Adrenalin chloride (Parke, Davis), a glandular extract containing an unknown amount of nor-epinephrine. Halpern[1] stated that Phenergan did not prevent the blood pressure and cardiac effects of epinephrine, but Reuse[7] found that Phenergan in large doses inhibited both the pressor effect and the apnea produced by small doses of epinephrine. This effect, however, lasted only a few minutes, and probably does not explain the partial protection which he observed. Even in Reuse's experiments, Phenergan did not offer complete protection against epinephrine-induced pulmonary edema, as the

[7] Reuse, J., *Ann. soc. roy. d. sciences med. et nat. d. Bruxelles*, t. II, 1949.

mortality ratio was 5/14 in the Phenergan-treated animals, compared to 11/14 in those receiving 0.55 - 0.6 mg per kg of epinephrine without Phenergan. In the group to which 1.2 - 1.5 mg per kg of epinephrine was administered, 8 of 11 Phenergan-treated animals died.

Our results, as well as those of Stone and Loew, do not lend support to Halpern's hypothesis that Phenergan opposes the formation of pulmonary edema by virtue of the property of inhibiting cellular permeability.

Summary. The antihistaminic drug, Phenergan (3277 R.P.), in doses of 20 or 40 mg per kg, failed to protect rats or guinea pigs against the pulmonary edema induced by injection of ammonium chloride, and also offered no protection against epinephrine-induced pulmonary edema in guinea pigs.

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Maintenance of Spontaneous Activity within the Cerebellum.*† (17352)

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The hitherto unsuspected widespread projection of the cerebellum[1] to the cerebral cortex and the ease with which facilitation[2] and suppression[3] of cortically and reflexly induced movements can be produced by cerebellar excitation emphasizes the need to answer the interesting but intricate question, what is the cerebellar influence on the rest of the nervous system? One approach to an answer is the study of mechanisms underlying the maintenance of the fast electrical activity of the cerebellum. The best study yet made on the nature of this electrical activity was that by Dow[4] who not only described it in great detail, but also studied the influence of various drugs on it and related the activity to muscular tone.

In the present study we have confirmed many of Dow's observations and extended the problem into an analysis of intrinsic cerebellar mechanisms which maintain what is probably the fastest electrical activity within the nervous system.

Methods. In mature cats, decerebrated, or placed under ether, nembutal, dial, chloralosane, or various combinations of the above mentioned anesthetics, the calvarium was removed to expose all parts of the cerebellum except the anterior one-half of anterior lobe and paraflocculus and flocculo-nodular lobe. Bipolar and monopolar silver wire as well as saline-cotton wick pick-up electrodes were used to introduce the cerebellar activity into Grass Model 111 amplifiers. The amplified electrical activity was observed and photographed on a five-inch cathode ray tube.

Results. The first question was: Does this fast electrical activity result from the driving of the cerebellum by extrinsic centers or is it something intrinsic to the cerebellum? As shown in Fig. 1a, the activity results from intrinsic mechanisms within the cerebellum. The electrical activity in this preparation was normal despite the fact that 5 days previous all afferent and efferent fibers (verified histologically) had been cut. Previously, Dow[4] reported fast electrical activity following "acute incomplete section of the cerebellar peduncles in four experiments" and Spiegel[5] also observed it

Further support for this observation is given

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1 Henneman, E., Cooke, P., and Snider, R. S., *Am. J. Physiol.*, 1948, **155**, 443.

2 Snider, R. S., and Magoun, H. W., *Med. Proc.*, 1948, **7**, 117.

3 Snider, R. S., Magoun, H. W., and McCulloch, W. S., *Med. Proc.*, 1947, **6**, 207.

4 Dow, R. S., *J. Physiol.*, 1938, **94**, 67.

5 Spiegel, E. H., *Am. J. Physiol.*, 1937, **118**, 569.