17090. Effect of *l*-Epinephrine and *l*-Arterenol on Egg White Edema in the Rat.*

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A number of reports[1,2,11] have described an extensive edema resulting from the intraperitoneal or intravenous administration of egg white in the rat. The cause of the edema is unknown. There is no evidence that it results from a foreign protein reaction as part of a protein hypersensitivity peculiar to the species. The edema may be of a type similar to *p*-phenylenediamine edema which has a peculiar cephalic distribution in cats, rabbits[3-9] and man[10] and which does not depend on previous exposure to the causative agent.

Selye[1] and Leger and Masson[11] observed that "alarming stimuli" inhibit the reaction and the latter workers also described a protective effect of antihistamines in large doses as did Brown and Werner[12] a fact which we have confirmed.† We have noticed that the edema is prevented by much smaller amounts of phenylethylamine pressor drugs and the object of the present communication is to record this observation.

Experimental. Freshly filtered or lyophilized and redissolved raw eggwhite in doses of 0.5 ml was injected intraperitoneally into albino rats of the Slonaker strain, of either sex, and of body weight ranges of 100 to 400 g. The incidence and degree of the edema of the face and extremities were estimated three hours afterward. The incidence was expressed as percentage and the degree by the 0 to 4 + method, averaging the reactions of the face, forefeet and hind feet.

The drugs were injected subcutaneously at the same time as the eggwhite. The drugs reported here included *l*-epinephrine-HCl (Parke, Davis) and *l*-arterenol-HCl (Sterling-Winthrop).

In supplementary experiments to determine the effect of injection route and solvents, *l*-epinephrine-HCl in saline was injected intramuscularly 30 minutes after the eggwhite, and in another experiment subcutaneously in oil.[13] In both cases a comparison was made with the effect of epinephrine injected subcutaneously at the same time as the eggwhite.

Results. The results are summarized in Table I which includes 403 rats.

The results show that under the experimental conditions used, the minimal preventative dose of *l*-epinephrine-HCl is about 100 micrograms/kg when injected subcutaneously at the same time as the eggwhite. When injected intramuscularly, 30 minutes after eggwhite, a slightly greater protection occurred; and when injected subcutaneously in oil, the protective dose was about half this. The minimal preventive dose of *l*-arterenol-HCl was about 2500 μg/kg, thus, this substance is about 1/25 as active as *l*-epinephrine-HCl. Isuprel-HCl [*l*-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol-HCl], a "sympathin-I-mimetic" depressor amine, was inactive up to doses of 25 mg/kg which were toxic.

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3 Hanzlik, P. J., *J. Ind. Hyg.*, 1923, **4**, 386.

4 Gibbs, O. S., *J. Pharm. Exp. Therap.*, 1923, **20**, 221.

5 Tainter, M. L., and Hanzlik, P. J., *ibid.*, 1924, **24**, 179.

6 Tainter, M. L., *ibid.*, 1926, **27**, 201.

7 Tainter, M. L., *ibid.*, 1928, **33**, 129.

8 Gibbs, O. S., *ibid.*, 1931, **42**, 65.

9 Cohen, M. B., *ibid.*, 1933, **48**, 235.

10 Malosetti, H., Fernandez, G. J., and Migliaro, E., *Arch. Uruguayos Med. Cir. y Espec.*, 1947, **31**, 25.

11 Leger, J., and Masson, G., *Ann. Allergy*, 1948, **6**, 131.

12 Brown, B. B., and Werner, H. W., *J. Lab. Clin. Med.*, 1948, **33**, 325.

† Pyribenzamine and phenergan [(dimethyl-amino-2-methyl-1-ethyl)-N-dibenzo-*p*-thiazine] were tested. The latter was over twice as effective as the former. 10 mg/kg administered subcutaneously at the same time as the eggwhite injection nearly completely inhibiting the edema, while for pyribenzamine, 25 mg/kg were required.

13 Keeney, E. L., *Bull. Johns Hopkins Hosp.*, 1938, **62**, 227.

TABLE I.
Effect of *l*-Epinephrine and *l*-Arterenol on Eggwhite Edema in Rats.

Drug used	Dose, μg/kg	No. indiv. exp.	No. rats used	Avg % incidence of edema	Avg degree of edema in affected rats
None	0	16	94	90%	2.5+
Epinephrine subcutaneous	5	2	12	85	4
" "	25-30	5	49	95	3
" "	35-40	5	32	90	3
" "	50-55	8	64	95	3.5
" "	60-75	3	21	65	3.5
" "	100	2	11	10	trace
" "	140-150	2	10	40	"
" "	200	1	5	20	"
" "	275	1	5	0	0
" "	550	1	5	0	0
Epinephrine intramuscular	25	1	8	100	3.0
" "	50	2	14	50	1.5
" "	75	1	6	35	2.5
" "	100	2	14	10	trace
" "	200	1	8	0	0
Epinephrine in oil, subcut.	40	1	5	0	0
Arterenol subcutaneous	100	2	10	90	2.5
" "	200	1	5	60	2.5
" "	400	1	5	80	2.5
" "	500	1	5	80	2.5
" "	1000	1	5	80	1.0
" "	2500	1	5	20	trace
" "	3000	1	5	0	0

Discussion. Gibbs, Hanzlik and Tainter[4-7] found that sympathetic nerve stimulation, drugs which cause release of epinephrine from the adrenal medulla, and vasoconstrictor drugs all inhibit *p*-phenylenediamine edema. Eggwhite edema is similar in this respect. Selye's[1] and Leger and Masson's[11] observations of a protective effect of "alarming stimuli" might be interpreted as a result of release of epinephrine from the adrenal medulla. Experiments designed to elucidate this point are in progress.

In the course of this work, it was observed that intravenous Evans' blue dye was extravasated into the edematous areas of the eggwhite response, notably the feet, ears, nose, lips and tongue. This is similar to *p*-phenylenediamine injury.[5] In both types of edema, *l*-epinephrine is more inhibitory than other pressor substances studied thus far. The present study would indicate therefore that *l*-epinephrine is a much more powerful arteriolar vasoconstrictor (depressor of capillary blood pressure) than *l*-arterenol. In spite of this, the latter has been reported to be 1 to 5 times more active than *l*-epinephrine in raising the arterial blood pressure[14-16] and has been thought to be the augmentor hormone of the sympathetic nervous system.

The antihistamines tested, pyribenzamine and phenergan, were 1/100 and 1/250 as active, respectively, as *l*-epinephrine, in preventing the edema.

Summary. l-epinephrine in a subcutaneous dose, 100 μg per kg, inhibits eggwhite edema in the rat. *l*-arterenol is about 1/25 as effective. Isuprel is inactive.

Since submitting the present manuscript, several papers have appeared which have demonstrated the presence of considerable quantities of *l*-arterenol in naturally derived epinephrine preparations, such as the one used in the present study. The use of synthetic *l*-epinephrine, therefore, would have enhanced the difference in activity of *l*-epinephrine and *l*-arterenol reported here.

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15 Euler, U. S. von, *Acta Physiol. Scand.*, 1948, **16**, 63.

16 Luduena, F. P., Ananenko, E., Siegmund, O. H., and Miller, L. C., *J. Pharm. Exp. Therap.*, in press.

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