17293. Studies of Experimental Pulmonary Edema. I. Pulmonary Edema from *l*-Epinephrine and *l-nor*-Epinephrine (Arterenol).*

EATON M. MACKAY AND ELDEN F. PECKA, JR.
From the Scripps Metabolic Clinic, La Jolla, Calif.

Large doses of epinephrine result in death, accompanied by an acute pulmonary edema in various species.[1-3] Studies of pulmonary edema caused by a number of compounds suggested that the mechanism may be by way of the release of pressor amines from the adrenal medulla. The recent discovery that this organ contains[4-9] and releases *l-nor*-epinephrine[10] as well as *l*-epinephrine made it desirable to compare the production of pulmonary edema by these compounds.

Experimental. Unfasted guinea pigs were used with equal sex distribution in the various groups. The *l*-epinephrine† and the *l-nor*-epinephrine (*l*-arterenol) were administered as the hydrochlorides in 0.9% NaCl in concentrations near 0.1%. In those experiments in which it was used, the adrenergic blocking agent, N-(9-fluorenyl)-N-ethyl-β-chlorethylamine-HCl ("SKF-501")‡ was dissolved in saline as a 0.1% solution for doses of 2 mg/kg 10-15 minutes before the pressor amine. The solutions were given intravenously via the penile vein in males and intracardially in female animals. There were 6 guinea pigs in each group. The degree of pulmonary edema was determined by the weight of the lungs.[3]

Results. Our data are summarized in Table I. The *l*-epinephrine, except in the dose of .001 mM/kg (from which they recovered and were sacrificed with ether an hour later), was rapidly fatal. Groups 3 and 4 survived an average of 11 and 4 minutes respectively. On the basis of previous experience, *l-nor*-epinephrine was used in larger doses than the epinephrine but although the higher doses (Groups 8 and 9) prostrated the animals, they recovered and were etherized an hour after the drug was given. Higher doses of *nor*-epinephrine were required to cause pulmonary edema and with the highest dosage used, .004 mM/kg, it failed to exceed that which resulted from one-fourth as much epinephrine.

These results are in accord with those of Tainter, Tullar and Luduena[11] who found that the LD_{50} of intravenously administered *l-nor*-epinephrine in mice is eight times less than that for *l*-epinephrine. Undoubtedly these results were in part due to pulmonary edema.

Stone and Loew,[3] and others have shown that certain adrenergic blocking agents are capable of reducing epinephrine-induced pulmonary edema in animals and this effect has been used as one measure of the effectiveness of adrenergic blocking agents. We administered N-(9-fluorenyl)-N-ethyl-β-chlorethylamine ("SKF-501"), a β-haloalkylamine, 10-15 minutes before the pressor amines. It prevented the occurrence of any symptoms whatever or of grossly measurable pulmonary edema otherwise induced by toxic doses of either *l*-epinephrine or *l-nor*-epinephrine.

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† The *l*-epinephrine (Adrenalin) used was a specially purified sample of the natural product for which we are indebted to Dr. Leon A. Sweet of Parke, Davis & Company. It contained only a trace of *l-nor*-epinephrine (arterenol).

‡ We are indebted to Dr. Glen E. Ullyot of the Smith, Kline & French Laboratories for generous supplies of "SKF-501."

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TABLE I.
Pulmonary Edema Caused by *l*-epinephrine and *l-nor*-epinephrine in Guinea Pigs.

Group No.	Dose of drug, mM/kg body wt*	Avg body wt, g	Avg lung wt g/100 g body wt	% change
Controls				
1	0	540	0.55 ± .09	—
l-epinephrine				
2	.0010	585	1.27 ± .14	+131
3	.0015	520	1.72 ± .13	+210
4	.0020	615	1.62 ± .06	+191
l-epinephrine preceded by N-(9-fluorenyl)-N-ethyl-β-chlorethylamine HCl†				
5	.0020	605	0.55 ± .08	0
6	.0050	630	0.56 ± .08	+ 2
l-nor-epinephrine (*l*-arterenol)				
7	.0020	515	0.97 ± .16	+ 76
8	.0030	480	1.13 ± .18	+105
9	.0040	505	1.25 ± .26	+127
l-nor-epinephrine preceded by N-(9-fluorenyl)-N-ethyl-β-chlorethylamine HCl†				
10	.0040	550	0.51 ± .12	— 7
11	.0050	510	0.58 ± .11	+ 5

* 1 mM epinephrine = 183 mg and 1 mM *nor*-epinephrine = 169 mg. † Adrenergic blocking agent known as "SKF-501" (see text).

Summary. 1. As measured by lung weight a lesser degree of pulmonary edema is produced by toxic doses of *l-nor*-epinephrine than smaller but toxic doses of *l*-epinephrine.

2. N-(9-fluorenyl)-N-ethyl-β-chlorethylamine, a β-haloalkylamine adrenergic blocking agent, prevents all symptoms and the development of pulmonary edema due to toxic doses of either *l*-epinephrine or *l-nor*-epinephrine.

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17294. The Mechanism by Which Dibenamine Blocks Pituitary Activation in the Rabbit and Rat.

CHARLES H. SAWYER, J. E. MARKEE, AND JOHN W. EVERETT.
(Introduced by Duncan C. Hetherington.)
From the Department of Anatomy, Duke University School of Medicine, Durham, N. C.

Markee, Sawyer, and Hollinshead[1,2] presented strongly indicative evidence that hypothalamic control of the release of luteinizing hormone from the rabbit hypophysis is exerted via a neurohumoral mechanism of which an adrenergic mediator is the final component. Ovulation, significant of LH release, was induced by injecting tiny amounts of adrenalin directly into the adenohypophysis.[2] Sawyer *et al.*[3,4] reported confirmation of the adrenergic nature of the secretion stimulus by blocking copulation-induced ovulation with the adrenergic-blocking agent dibenamine (N,N-dibenzyl-β-chloroethylamine).[5] Everett, Sawyer, and Markee[6,7] extended the investigation

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