glutamic acid and vitamin B_{12} to cases of pernicious anemia in relapse results in an excellent hematologic and clinical response(13).

Vit. B_{12} and at least one other growth factor are present in the mucosa of the stomach of the pig(11,14). No attempt was made to determine the vit. B_{12} activity of the extract used in the present study. However, since there was no response to the ingestion of this material after one week, followed by hematologic and clinical improvement when it was combined with 10 μg of vit. B_{12}, it would appear that there was not enough present for therapeutic efficacy when administered alone.

Conclusion. The oral administration of an extract of swine duodenal mucosa and subminimal doses of vitamin B_{12} to patients with pernicious anemia in relapse is followed by a suboptimal reticulocyte response and satisfactory hematologic and clinical improvement.

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Experimental Pulmonary Edema. III. Hypoglycemia, a Cause of Pulmonary Edema.* (17747)

EATON M. MACKAY AND ELDEN F. PECKA, JR.

From the Scripps Metabolic Clinic, La Jolla, Calif.

During a study of long continued hypoglycemia in the rat(1) it was found that death from respiratory failure always ensued and there was marked edema of the lungs. Some time before death the pulmonary pathology was evidenced by the oozing of blood-tinged serous fluid from the nostrils of the comatose animals. This recalled the edema of rats after an overdose of epinephrine(2,3) and the possibility occurred to us that the effect of insulin was, at least in part, an overproduction of epinephrine resulting from the hypoglycemia. At the time we were able to demonstrate measurable concentrations of epinephrine by bioassay in the blood of rats with insulin shock. Removal of the adrenal medullas with sufficient time allowed for regeneration of the cortical tissue prior to insulin treatment failed to prevent the development of the pulmonary pathology in most rats. We have now studied the hypoglycemia lung edema further with special reference to the effect on it of an adrenergic blocking agent.

Experimental. The rat (Slonaker strain(4)) groups were made up of equal numbers of both sexes within a weight range of 40 g. To produce a hypoglycemia the rats were fasted for 24 hours and given 2 units of regular and 2 units of protamine insulin (u-40)† per 100 g body weight by subcutaneous injection. One group had been adrenalectomized the preceding day and another group had their adrenals demedullated the week before. After they succumbed to the hypoglycemia the lungs were removed and weighed. Our data are summarized in Table I.

Discussion. Prior adrenalectomy (Grp. 2) reduced the degree of pulmonary edema as measured both by inspection and lung weight but this may have been due to the naturally poor condition of the animals when tested. However demedullation of the adrenals (Grp. 3) from which the animals had completely recovered reduced the degree of edema of the lung just as much. It seems probable then that hypersecretion of the adrenal medulla due to hypoglycemia definitely contributes to the occurrence and extent of pulmonary

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† Kindly supplied by Dr. F. B. Peck of Eli Lilly and Co.

TABLE I.

Group No.	No. rats	Avg body wt, g	No. rats with lung edema	Avg degree of edema	Lung wt per 100 g body wt, g	% control
			Controls—no treatment			
1	24	116	0	0	.60 ± .05	100
			Insulin treated			
2	28	114	27	2.1	1.29 ± .14	215
			Insulin 2 hr after 2 mg SKF 501/kg			
3	24	119	1	0	.57 ± .03	95
			Insulin after adrenals demedullated			
4	8	155	6	1.0	.84 ± .09	140
			Insulin after adrenalectomy			
5	16	152	14	1.6	.94 ± .11	158

edema. The adrenergic blocking agent, N-(9-fluorenyl) - N-ethyl-β-chlorethylamine-HCl,‡ for practical purposes prevented the hypoglycemia pulmonary edema entirely. It was administered as described before(5).

What then is the mechanism of the hypoglycemia lung edema described here? The chief theories as to the mechanism of pulmonary edema have recently been briefly reviewed by Paine and Smith(6) and in more detail by others(7,8). In short the leading theories are that it is due to left ventricular failure in relation to right heart action on one hand or neurogenic due to intense stimulation of the vasomotor nerves to the lungs either directly or as a result of reflexes arising in the various viscera, the heart, etc. Visscher's group(9) does not separate these as two mechanisms. Their hypothesis, in the case of the pulmonary edema associated with increased intracranial pressure, is that brain compression is associated with increased vagal tone, and the latter results in bradycardia, lowered cardiac output, high pulmonary vascular pressures and lung edema.

It is unlikely that hypoglycemia produces left ventricular failure directly. The greatly lowered blood sugar could easily impair the nutrition of the cardiac musculature but if this were the cause of the edema an adrenergic blocking agent could hardly prevent it. Much more likely is that a volley of impulses come down the sympathetic innervation of the lungs (and heart?) as a result of the stimulation of the autonomic system and medullary brain centers known to be afforded by an insufficient supply of glucose(10). The adrenergic blocking agent used presumably prevents these stimuli from reaching the lungs (and heart?).

Summary. Albino rats of the Slonaker Strain when kept in a state of hypoglycemia by insulin injections for a period of some hours invariably develop a fatal pulmonary edema. Adrenalectomy and adrenal demedullation reduce the degree of edema but fail to prevent it. Adequate doses of the adrenergic blocking agent, N-(9-fluorenyl)-N-ethyl-β-chlorethylamine-HCl, prevent this hypoglycemia lung edema entirely. It is suggested that this type of pulmonary edema is neurogenic in origin due to the influence of glucose lack on the nerve centers where the vasomotor fibers to the lungs and heart originate.

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