Antabus. Previously Richert(6) had concluded that Antabus, which blocks the oxidation of alcohol at the acetaldehyde stage, inhibits the oxidation action of xanthine oxidase. Giarman's data led to the inference that xanthine oxidase is one enzyme involved in the metabolism of thiopental. Therefore, one explanation of the prolongation of the thiopental induced sleeping time by alcohol may be that the two compounds compete for the same or a similar enzyme system resulting in a reduced rate of metabolism of thiopental. It is well recognized that such competition for an enzyme system is a common finding for compounds with similar metabolic pathways. An attempt was made during this study to obtain thiopental blood levels in order to clarify the rate of metabolism of thiopental in the presence of alcohol, but the available methods did not give accurate results.

In contrast to the above possible mechanism of action, alcohol in the dose used will result in some central nervous system depression, although this dose in the present experiments did not cause loss of the righting reflex in dogs. In all animals the sleeping time induced by combined alcohol plus thiopental was greater than the sum of the sleeping times induced by either compound administered alone. This indicates a possible synergistic action of alcohol and thiopental administered together.

Summary and conclusions. Thiopental in a subanesthetic dose caused a significant decrease in the reaction time of mice. Alcohol in doses even very near the hypnotic level did not significantly change the reaction time. When the two drugs were given simultaneously, the reaction time was still not significantly changed. The sleeping times of mice, dogs and rabbits given both thiopental and alcohol were significantly longer than the sleeping times when either of the two drugs alone were given.

1. Ahlquist, R. P., and Dille, J. M., *J. Pharm. and Exp. Therap.*, 1940, v70, No. 3.

2. Sandberg, *Finn Acta Physiol. Scand.*, 1951, v22, 30.

3. Giarman, N. J., Flick, F. H., and White, J. M., *Science*, 1951, v114, 35.

4. Chen, James Y. P., and Beckman, Harry, *Science*, 1951, v113, 631.

5. Hemingway, A., Bernat, L. A., and Mashmeyer, J., *J. Lab. Clin. Med.*, 1948, v33, 126.

6. Richert, D. A., Vanderlinde, R. and Westerfeld, W. W., *J. Biol. Chem.*, 1950, v186, 261.

Received October 3, 1951. P.S.E.B.M., 1951, v78.

Elevation of Left Auricular Pressure in Relation to Ammonium Pulmonary Edema in the Cat.* (19234)

STANLEY J. SARNOFF AND HERBERT E. KAUFMAN.

From the Department of Physiology, Harvard School of Public Health, Boston, Mass.

The acute pulmonary edema that follows the administration of large doses of ammonium chloride in the guinea pig, rat, and less frequently, in the cat has been the subject of investigations by Koenig and Koenig(1-3). These authors did not believe that any final understanding of the mechanisms involved was possible on the basis of their data but felt that impulses traveling over pulmonary sympathetic nerve fibers were of paramount importance.

It seemed that additional hemodynamic information would be helpful especially as regards pressure phenomena in the left auricle. Early exploratory experiments in the guinea pig and rat revealed a substantial rise in end-diastolic filling pressure of the left ventricle, but these experiments were in general not technically satisfactory and will not be reported here. Despite the fact that the incidence of ammonium pulmonary edema was lower in the cat than in the other two species, our experiments were performed with that animal largely because of the greater ease

* Aided by a research grant from the National Heart Institute, U. S. Public Health Service.

with which adequate hemodynamic observations could be made.

Method. Cats of both sexes weighing from 1.7 to 4.0 kg were used. Sodium pentobarbital, 35 mg per kg, was given intraperitoneally and a left thoracotomy incision performed while respiration was maintained by means of a modified Starling pump. After the pericardium was incised and a No. 18 thin-walled needle passed into the left auricle, vinylite tubing was passed through the needle, and the latter was withdrawn. The tubing was secured in place, and the chest was closed with evacuation of air from the chest. A second vinylite tubing was passed 3 to 4 inches up the femoral vein in order to record inferior vena caval pressures. A third vinylite tubing was used for the recording of femoral arterial pressures.† All pressures were recorded with electromanometers(4) which fed into a multichannel recorder that registered in rectilinear coordinates. The zero reference base line was the cat's left auricle. In cats No. 3, 5, 6, 8, 10, 12, and 15 (Table I), an attempt was made to reconstitute the animals to their presurgical status by administering intravenously 10 cc of polyvinyl pyrrolidone between 10 and 20 minutes prior to the injection of ammonium chloride. Fourteen cc per kg of 6% ammonium chloride solution was then injected intraperitoneally. Not infrequently, an additional injection of ammonium chloride was required, and these were given as half the original dose. Immediately after the death of the animal the chest was opened, and the heart and lungs quickly removed for examination. Generalized pulmonary edema was diagnosed when foamy fluid was observed to exude readily from the cut section of each lobe when compressed. Microscopic sections were obtained from the lungs of one of the two cats thought to have gross evidence of generalized pulmonary edema.

Results. The cats died in from 8 to 58 minutes after the initial injection of ammonium chloride. Two cats required one additional injection, and one cat required two additional injections before death occurred.

† Supplied through the generosity of Becton-Dickinson Co., Rutherford, N. J.

TABLE I. Changes in Left Auricular and Vena Caval Pressures After the Intraperitoneal Injection of Ammonium Chloride in the Cat.

	Left auricle		Vena cava	
Cat No.	Control	After NH_4CL	Control	After NH_4CL
1	5	15	2	15
2†	3	11	—	—
3	7	18	—	—
5†	2	10	11	15
6*	7	24	7	15
7	3	20	1	8
8	4	13	2	13
10	5	20	9	19
11	3	18	8	18
12	5	13	4	11
15*	9	40	4	17
16	0	16	3	15
Mean	4.4	18.2	5.1	14.6

* Generalized pulmonary edema.
† See text.

All showed the neuromuscular abnormalities (convulsions and twitching) as previously described(2,3). The control levels listed in Table I were obtained from the immediate pre-injection portion of the tracings. The levels listed in Table I as "after NH_4CL" were obtained by estimating the mean pressure for the period after a significant elevation had occurred and was sustained. This was usually the period of 7 to 12 minutes before death. The immediate (2 to 3 minutes) pre-mortem decline was not included in this estimate.

Arterial pressure either rose or fell immediately after the injection. In all but one cat (No. 15), when arterial pressure rose initially, it fell to or below control levels during the period of elevated left auricular pressure.

After the injection of ammonium chloride, left auricular pressure rose an average of 13.8 cm of water and vena cava pressures 9.5 (Table I). Generalized pulmonary edema was observed in 2 of the 12 cats, No. 6 and No. 15. These 2 cats had had sustained left auricular pressures of 24 and 40 cm of water, respectively. The other 10 cats had sustained left auricular pressures of 20 cm of water or below and did not show generalized pulmonary edema. Two of these 10 had localized edema as follows. Cat No. 2, having been on its right side, had the right lower lobe as the most dependent portion of the pulmonary vascular bed. Although its general sustained

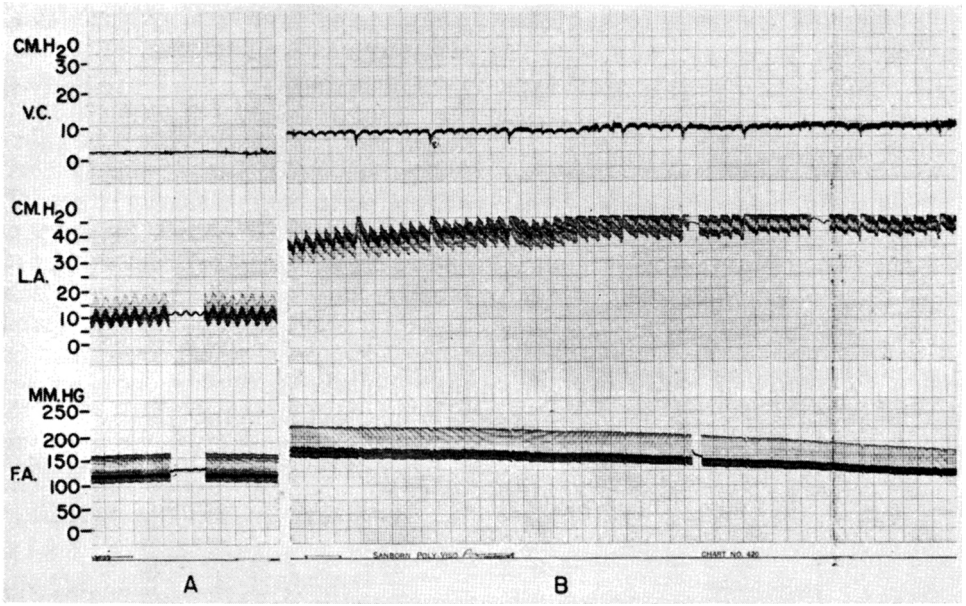

FIG. 1. Cat No. 15. V.C. = vena cava. L.A. = left auricle. F.A. = femoral artery. Chart speed = 1 mm per sec. Solid black lines are electrically integrated (mean) pressures. Others are full pulse pressures. A. One min prior to intraperitoneal injection of ammonium chloride. B. Begins 8 min after injection and ends 3 min prior to death. Generalized pulmonary edema.

left auricular pressure was 11 cm of water, there were several peaks at 27 cm of water during convulsions which lasted between 30 and 60 seconds. At post-mortem a small amount of foam could be expressed from the tip of its right lower lobe. In Cat No. 5 the left middle lobe was traumatized during the operative procedure and was noted to be atelectatic when the chest was closed. Its general elevation of left auricular pressure was 10 cm of water. At post-mortem equivocal edema was present in its left middle lobe. The lungs of all other cats were free of grossly observable edema.

The pre- and post-injection levels of vena cava, left auricle, and femoral arterial pressure from Cat No. 15, which showed generalized pulmonary edema, are shown in Fig. 1.

Discussion. Of the 6 cats examined by Koenig and Koenig(3), 3 developed acute pulmonary edema, while in the above series of 12 cats only 2 developed it. The experimental conditions were different in our group both as regards the administration of a barbiturate adequate for surgical anesthesia and the amount of surgery required. Thus any comparison of the incidence of pulmonary edema is irrelevant. What is thought to be of considerable interest, however, is the fact that in all experiments a significant rise in left auricular pressure did occur after the administration of ammonium chloride and, further, that the 2 cats which developed the highest sustained left auricular pressures (24 and 40 cm of water) were the only ones which developed generalized pulmonary edema.

Two of the several mechanisms considered by Koenig and Koenig, namely, pulmonary venular spasm and a change in pulmonary capillary permeability, are not supported by the above data. Contrariwise, "the mechanical theory of left ventricular failure [was] mentioned only to reject it"(3). It is presumed for the purposes of this discussion that left ventricular failure is a state wherein the left ventricle does not eject blood in such a way as to maintain pulmonary capillary and venous pressures within normal limits. It was felt(3) that left ventricular failure was not important because one rat which developed pulmonary edema did not exhibit arterial hypertension. However, it is a common clinical experience to observe patients in pulmonary edema following a coronary occlusion in

whom the arterial pressure is at or below normal levels.

The fact that dibenamine, a sympatholytic agent, prevented the formation of pulmonary edema(3) is not necessarily an indication that it is blockade of the pulmonary sympathetics which alters the outcome. Cameron and De (5,6) produced rapid, lethal pulmonary edema in the rabbit with the intracisternal injection of thrombin and fibrinogen, and Cruchaud and Vermeil(7) demonstrated that this type of pulmonary edema is also prevented by dibenamine. However, in recent studies on the dog it became clear that the striking elevation of pulmonary capillary pressure that occurs soon after the intracisternal injection of thrombin and fibrinogen is due not to activity of pulmonary sympathetics but rather to impulses traveling over sympathetics to the peripheral vascular bed(8-10). The increased peripheral vascular resistance, as well as the shift of blood from periphery to lung, was shown to be mainly responsible for the elevations of pulmonary capillary pressure that occurred.

Summary. (1) Ammonium chloride was administered intraperitoneally to 12 cats under sodium pentobarbital anesthesia with measurement of left auricular, femoral arterial, and vena caval pressures. (2) Left auricular and vena caval pressures rose significantly in all experiments. Arterial pressures were generally, but not always, lower during the period of the sustained elevation of left auricular pressure than during the control period. (3) Two of the 12 cats developed generalized pulmonary edema. These 2 had sustained left auricle pressures of 24 and 40 cm of water. (4) Although the above experiments do not preclude the possibility that other mechanisms may also be operating, they do suggest that left ventricular failure plays a role in the development of ammonium pulmonary edema in the cat.

1. Koenig, H., and Koenig, R., *Fed. Proc.*, 1948, v7, 67.

2. ———, PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 375.

3. ———, *Am. J. Physiol.*, 1949, v158, 1.

4. Rappaport, M., and Sarnoff, S. J., *Fed. Proc.*, 1949, v8, 130.

5. Cameron, G. R., *Brit. Med. J.*, 1948, v1, 965.

6. Cameron, G. R., and De, S. N., *J. Path. and Bact.*, 1949, v61, 375.

7. Cruchaud, S., and Vermeil, G., *C. r. Soc. Biol.*, 1950, v144, 181.

8. Sarnoff, S. J., *Fed. Proc.*, 1951, v10, 118.

9. ———, *Dis. of Chest*, in press.

10. Sarnoff, S. J., and Sarnoff, L. C., *Circulation*, in press.

Received October 9, 1951. P.S.E.B.M., 1951, v78.

Function and Metabolic Significance of Penicillin and Bacitracin in the Chick.* (19235)

J. F. ELAM, L. L. GEE, AND J. R. COUCH.

From the Departments of Biochemistry and Nutrition, Poultry Husbandry and Biology, Texas A. and M. College System, College Station, Texas.

Elam, Gee, and Couch(1) reported that the fecal microflora of the growing chick was influenced by the feeding of penicillin. These workers reported further that this antibiotic stimulated growth and egg production. Aureomycin has also been shown to increase egg production and hatchability(2). The growth promoting effect of penicillin and terramycin has been explained as an inhibition of *Clostridium perfringens* in the intestinal tract of turkeys by Sieburth *et al.*(3). Halick and

* This work was supported by a grant-in-aid from the Williams-Waterman Fund for the combat of dietary disease, administered by the Research Corporation, New York. Crystalline vit. B_{12} and procaine penicillin (G) were supplied through the courtesy of the Veterinary Division, Merck and Co., Rahway, N. J. The bacitracin was supplied through the courtesy of Dr. H. R. Stiles, Commercial Solvents Corp., Terre Haute, Ind.