pyridinium acetate inhibited the metamorphosis of tadpoles induced by thyroxine. The degree of inhibition of metamorphosis appeared proportional to the relative concentration of the drug. (2) *N*-(2,5-dihydroxyphenyl) pyridinium acetate, 200 mg/kg body weight, did not lower the rate of oxygen consumption of normal rats nor prevent the acceleration of oxygen consumption induced by *dl*-thyroxine, 2 mg/kg body weight.

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The Potentiating Effect of Alcohol on Thiopental Induced Sleep.* (19233)

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Studies of the action of thiopental on rats (1) show that alcohol tolerant animals are much more resistant to thiopental than are normal rats. The induction time of alcohol anesthesia in mice is significantly reduced when the animals are premedicated with a barbiturate(2). Observations of a different nature show that the sleeping time of thiopental treated animals is greatly prolonged by premedication with Antabus(3). However no evidence is available concerning the effect of alcohol on thiopental sleeping time. The present report is concerned with the effect of alcohol in subanesthetic doses on the duration of sleep produced by thiopental. Attempts were made to determine an analgesic effect of alcohol and the influence of thiopental on alcohol analgesia.

Methods and materials. Initially an attempt was made to determine the effect of thiopental, alcohol and combined thiopental-alcohol administrations on the response of mice to a painful stimulus. The apparatus described by Chen and Beckman(4) was used for determining analgesic effect. This consisted of a metal chamber which was open to the atmosphere only through a reflux condensor. The chamber was partly filled with an azeotropic mixture of ethyl formate and acetone which has a boiling point of 55°. The chamber was heated with a hot plate so that the azeotropic mixture boiled continuously. The mice were dropped on the top of this container 2 minutes after intravenous injection of the drugs. The time required for the animal to respond by licking its hind foot was determined with a stop watch and was recorded as the reaction time.

Observations of the duration of sleep produced by the intravenous administration of thiopental, alcohol, and combined thiopental-alcohol were made. The thiopental dosage

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TABLE I. Effect of Alcohol, Thiopental and Alcohol Plus Thiopental on the Reaction Time in Mice.

Animal group	No. of animals	Drug	Dose	Reaction time, sec	Stand. dev.	Probability of diff.*
A Control	59	0		9.92	± 3.17	
B "	10	.09% saline sol.	1 ml	6.91	± 2.71	Comparing A and B, P = .10
C Test	9	Thiopental	5 mg/kg	4.01	± .80	B C, <.001
D "	10	Alcohol	1000 "	7.6	± 2.19	B D, >.50
E "	10	Alcohol+ thiopental	1000 " 5 "	5.94	± 1.95	B E, >.20

* Probability according to Student "T" test.

TABLE II. Effect of Alcohol, Thiopental and Alcohol Plus Thiopental on Sleeping Time of Mice, Rabbits and Dogs.

Animal Group*	Drug	Dose (mg/kg)	Mean sleeping time (min)	Stand. dev.	Probability of diff.†
Mouse	Thiopental	30	6.7	± 2.78	P = <.001
	Alcohol	1000	.5	± .2	
	Thiopental + Alcohol	30 + 1000	32.7	± 8.6	
Rabbit	Thiopental	25	21.4	± 2.7	P = <.001
	Alcohol	1000	12.5	± 4.5	
	Thiopental + Alcohol	25 + 1000	117	±28.6	
Dog	Thiopental	20	38.8	±15.6	P = .001
	Alcohol	1000	0		
	Thiopental + Alcohol	20 + 1000	71.5	±18.5	

* 10 animals in each group.
† Probability according to the Student "T" test.

was: Mice—30 mg/kg; Rabbits—25 mg/kg; Dogs—20 mg/kg. All animals received 1000 mg/kg alcohol as a 10% solution in isotonic saline. The combined thiopental-alcohol dosage contained these same amounts of the drugs. Sleeping time was designated as the time during which the righting reflex was absent. The righting reflex was recorded as being present when the animal would voluntarily roll to its side when placed on its back. Blood levels of alcohol were determined in the rabbits and dogs using the technic of Hemingway, Bernat and Mashmeyer (5).

Results. Table I indicates that intravenous thiopental in a subanesthetic dose in mice caused them to react to the painful stimulus more quickly than did the control animals in which nothing was injected, or in which only saline was injected. When alcohol was injected in a subanesthetic dose there was no significant change in the reaction time to pain. Larger doses were not used because they caused loss of consciousness, therefore making it impossible for the animal to give the characteristic sign that it was experiencing pain. When both alcohol and thiopental were given simultaneously, the mice did not show a significant change in their reaction time to the painful stimulus (Table I).

Table II presents that data obtained in experiments to determine the sleeping time induced by alcohol and thiopental injected separately and together in mice, rabbits and dogs. In all animals a significant increased duration of sleep is induced by administration of both alcohol and thiopental when compared with either compound administered alone. In these experiments whole blood showed maximum concentrations of alcohol in the range of 150 to 200 mg % in all animals used in the study.

Discussion. The foregoing data indicate that the sleeping time induced by thiopental is significantly prolonged by the simultaneous administration of alcohol. Giarman *et al.* (3) noted that the thiopental sleeping time could be prolonged by pretreatment with

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.

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

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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

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