PROTECTION FROM CYCLOPROPANE–EPINEPHRINE TACHYCARDIA BY VARIOUS DRUGS *

C. R. Allen, Ph.D., J. W. Stutzman, Ph.D., H. C. Slocum, M.D. and O. S. Orth, Ph.D.†

Madison, Wis.

An injection of epinephrine too low in concentration to produce ventricular tachycardia in the unanesthetized dog will do so with regularity in the same animal after thirty minutes of deep cyclopropane anesthesia (1, 2). Due to this increased irritability of the heart with its subsequent tendency toward ventricular tachycardia and fibrillation when small doses of epinephrine are given, many clinics discourage the use of sympathomimetic drugs during cyclopropane anesthesia.

Our investigations of the mechanisms involved (3) have shown that three conditions are necessary in order to produce cyclopropane-epinephrine tachycardia in the normal dog: cyclopropane must reach the heart; epinephrine must reach the heart; and a brain center above the pons and its sympathetic fibers to the heart must be intact. The tachycardia does not appear after decerebration, the production of lesions in the pons, or bilateral sympathectomy.

From these studies it was believed that four types of chemical agents might be expected to protect the heart from the production of ventricular tachycardia following injections of epinephrine in cyclopropane anesthesia, namely: drugs that depress the myocardium; adrenolytic drugs, i.e. drugs which block the response of the effector organs to epinephrine but not to adrenergic nerve impulses; sympathicolytic drugs, i.e. drugs which block the response of the effector organs to epinephrine as well as adrenergic nerve stimulation; and drugs which produce a functional decerebration. This is an investigation of the protective action of procaine hydrochloride, carbon dioxide, quinidine sulphate, morphine sulphate, ergotamine tartrate, yohimbine hydrochloride, and F 883 (diethyl-amino-methyl-benzo-dioxane).

Methods and Results

Dogs were anesthetized by rebreathing a cyclopropane-oxygen mixture from a 5 liter bag; an endotracheal tube with inflatable cuff was inserted to insure an open airway, and the animals were connected through a soda-lime carbon dioxide absorber to a 100 liter rubber bag

* Aided in part by grants from the Wisconsin Alumni Research Foundation and E. R. Squibb & Sons.

† From the Departments of Physiology and Anesthesia, University of Wisconsin Medical School, Madison, Wisconsin.

containing a 30 to 33 per cent mixture of cyclopropane in oxygen. This anesthetic concentration will maintain unpremedicated dogs in deep surgical anesthesia with at least partial intercostal paralysis. After equilibrating on this constant mixture for thirty minutes, the dogs were injected intravenously with epinephrine in concentrations of 0.01 mg. per Kg. in 5 cc. of normal saline at a constant rate of 1 cc. per ten seconds until ventricular tachycardia was observed in the electrocardiograph, at which instant the injection was terminated. In this way a control dose of epinephrine for each animal was determined which would bring on ventricular tachycardia of significant duration. Electrocardiograms (lead II) were taken at short intervals throughout a five minute period beginning with the injection. The control dose of epinephrine was injected subsequently at half hour and hourly intervals in order to show

TABLE 1

THE PROTECTIVE ACTION OF PROCAINE ON CYCLOPROPANE-EPINEPHRINE TACHYCARDIA

Dog No.	Epinephrine Dose mg./Kg.	Duration of Ventricular Tachycardia			
		Control Epinephrine Response	Procaine 16 mg./Kg. and Epinephrine	Procaine 12 mg./Kg. and Epinephrine	Procaine 8 mg./Kg. and Epinephrine
1	0.006	52″	0″		
2	0.008	42″	0″		
3	0.006	38″			24″
4	0.007	30″	0″		20″
5	0.01	46″	0″	40″	
6	0.006	75″	0″	0″	80″
7	0.01	32″	0″		
8	0.004	24″	0″		
9	0.008	34″	0″	25″	
10	0.006	54″	24″		
11	0.006	47″	11″		
12	0.01	41″	0″		

that the adrenolytic action of cyclopropane (4) was not manifest. This last procedure was necessary in order to determine the duration of the protective action of some of the drugs.

Procaine.—Procaine hydrochloride was selected as one example of a direct myocardial depressant. The reports by Mautz (5), by Beck and Mautz (6), and by Kochman and Daeles (7) have shown that procaine applied directly to the heart reduces the irritability of the myocardium, as evidenced by the increased stimulation necessary to produce extrasystoles or ventricular fibrillation. Van Dongen (8) has shown that novocain will protect the heart from electrically produced flutter, and Shen and Simon (9) have used it to protect dogs from chloroform-epinephrine syncope.

Recently Burstein and Marangoni (10) reported that 5 mg. of procaine per kilogram given either before epinephrine injections or during the stage of ventricular tachycardia reduced the incidence of ventricular

fibrillation in premedicated dogs during cyclopropane anesthesia. Burstein, Marangoni, DeGraff, and Rovenstine (11, 12) found that the intracardiac injection of procaine at the time of fibrillation in dogs effected a return to normal in 66 per cent of the cases.

In our experiments procaine hydrochloride was injected simultaneously with the previously determined control dose of epinephrine. Table 1 presents the results. Nine of 11 dogs were completely protected and the remaining 2 partially protected from the cyclopropane-epinephrine tachycardia when 16 mg. per Kg. of procaine was administered simultaneously. One of 3 animals was completely protected with 12 mg. of procaine per kilogram, but none of 3 with 8 mg. In order to determine the duration of the protective action of procaine 7 dogs were injected with epinephrine under cyclopropane twenty minutes after they had shown complete protection following the simultaneous procaine and

TABLE 2

THE EFFECT OF CARBON DIOXIDE ON CYCLOPROPANE-EPINEPHRINE TACHYCARDIA

Dog No.	Epinephrine Dose mg./Kg.	Duration of Ventricular Tachycardia following Epinephrine Injection			
		CO_2 0%	CO_2 5%	CO_2 12%	CO_2 20-24%
13	0.003	64″	56″		13″
14	0.002	20″	85″	20″	0″
15	0.004	70″	70″		4″
16	0.004	32″	36″		0″
17	0.01	72″	67″		0″
18	0.006	54″	84″		
19	0.006	47″	28″		
20	0.01	41″	30″		
21	0.01	65″		58″	0″

epinephrine injection. Three of the 7 were still completely protected, while 3 showed an average of thirty seconds of ventricular tachycardia. These were considered to be partially protected because their control cyclopropane-epinephrine tachycardia averaged fifty-nine seconds. The other dog died of ventricular fibrillation. Procaine protected none of the dogs sixty minutes after it was injected.

Carbon Dioxide.—Magnus (13) reported that the perfusion of the coronary vessels of the mammalian heart with carbon dioxide causes prompt fibrillation. On the other hand Ketcham, King, and Hooker (14) found that the isolated heart was depressed by all concentrations of carbon dioxide. That low concentrations of this gas stimulate certain centers in the brain and that high concentrations depress the same regions are well known. The experiments on carbon dioxide were instituted to find whether this gas in an anesthetic mixture increased the duration of the cyclopropane-epinephrine tachycardia.

After the control injection of epinephrine had been made the carbon dioxide absorbing canister was removed and sufficient carbon dioxide

added to the anesthetic mixture to give a concentration of this gas that was about 2 per cent lower than was desired for the experiment. The animal was then allowed to build up the carbon dioxide concentration by rebreathing into the reservoir containing the anesthetic mixture. After ten minutes the anesthetic mixture was again analyzed. The carbon dioxide increase by this method was usually 1 per cent per five minutes. Table 2 shows the results of the epinephrine injections under cyclopropane at the various concentrations of carbon dioxide. No decrease in the sensitivity of the heart to epinephrine was noted until the carbon dioxide reached 20 to 24 per cent, when the tachycardias failed to appear.

Morphine.—Robbins, Baxter, and Fitzhugh (15) reported that small doses of morphine favor the development of arrhythmia under cyclopropane. The mechanism involved in this effect may be due to the depression of the S-A node by the increased vagal tonus thereby making discharges possible from ectopic ventricular centers not under vagal control but which are having their automaticity enhanced by the cyclo-

TABLE 3

CYCLOPROPANE-EPINEPHRINE TACHYCARDIAS BEFORE AND AFTER VARIOUS DRUGS

Dog No.	Epinephrine Dose mg./Kg.	Duration of Ventricular Tachycardia		Remarks
		Control Epinephrine Injection	Epinephrine Injected after Administration of the Indicated Drug	
			Morphine	
			8 mg. morphine/Kg. subcu.	
22	0.006	39″	0″	20″ slow ventr. rhythm
23	0.004	17″	0″	90″ slow ventr. rhythm
24	0.006	54″	30″	Partial protection
25	0.005	43″	0″	35″ slow ventr. rhythm
26	0.006	51″	0″	
27	0.004	57″	0″ *	* Morphine alone caused a short period of ventr. rhythm before the epineph. inject.
28	0.006	47″	0″	
29	0.006	54″	42″	
30	0.010	38″	0″ *	
31	0.010	38″	0″	55″ slow ventr. rhythm
			Quinidine	
			Epinephrine injected 10′ after 15 mg. quinidine/Kg. intravenously	
32	0.01	64″	0″	
33	0.01	40″	0″	
34	0.01	56″	0″	A–V nodal rhythm
35	0.01	66″	0″	A–V nodal rhythm
36	0.01	30″	0″	A–V nodal rhythm
37	0.0125	33″	0″	A–V nodal rhythm

TABLE 3—*Continued*

Dog No.	Epinephrine Dose mg./Kg.	Duration of Ventricular Tachycardia: Control Epinephrine Injection	Duration of Ventricular Tachycardia: Epinephrine Injected after Administration of the Indicated Drug	Remarks
			Ergotamine	
			Epinephrine injected 20′ after ergotamine intravenously	
38	0.006	60″	0″	Ergotamine 1/6 mg./Kg.
39	0.008	44″	0″	Ergotamine 1/7 mg./Kg.
40	0.01	36′	0″	Ergotamine 1/8 mg./Kg.
			F 883	
			Epinephrine injected 20′ after 2 mg. F 883/Kg. intravenously	
41	0.01	64″	0″	
42	0.01	76″	0″	
43	0.01	40″	0″ *	*1.0 mg./Kg. F883 before epinephrine gave 22″ V.T. = partial protection
44	0.01	73″	0″ †	†F883 alone caused A-V rhythm before the test epinephrine injection
45	0.01	30″	0″	
46	0.01	54″	0″ †	
			Yohimbine	
			Epinephrine injected 20′ after yohimbine intravenously	Yohimbine dose mg./Kg.
47	0.0125	44″	0″	5.0
48	0.01	40″	0″	1.0
			0″	.5
49	0.005	30″	0″	.25
50	0.01	60″	0″	.25
51	0.01	55″	0″	.20
			40″	.10
52	0.006	39″	0″	.20
53	0.006	52″	0″	.20
54	0.006	60″	32″	.10

propane. Morphine may also favor ventricular autonomy by direct action on the automatic tissue. It has been reported by Porter (16) that morphine increases the incidence of fibrillation after coronary occlusion. Kuré (17) found that this drug potentiated accelerator stimulation in the production of ventricular arrhythmia. Smirnow (18), however, has reported protection with morphine in chloroform-epinephrine syncope. Meek, Hathaway, and Orth (1) have shown that 1 mg. of morphine per kilogram did not modify the usual appearance of cyclopropane-epinephrine tachycardia. It was therefore decided to study the effects of large doses of morphine on this arrhythmia.

Ten dogs were premedicated with 8 mg. of morphine per kilogram injected subcutaneously. After twenty-five minutes the dogs were placed on the anesthetic mixture of cyclopropane and oxygen for thirty minutes and then injected with the control dose of epinephrine. Artificial respiration was done in those cases where the combined action of morphine and cyclopropane caused appreciable respiratory depression. Before the epinephrine injection it was noted that some of the dogs under cyclopropane and morphine showed a bigeminal or trigeminal rhythm due to ventricular extrasystoles. Morphine completely protected 8 of the 10 dogs from cyclopropane-epinephrine tachycardia. However, the epinephrine injection was followed by slow ventricular rhythms of sixty to ninety per minute in 4 of the dogs. In the 2 dogs that did not show complete protection the duration of ventricular tachycardia was reduced. The results are summarized in Table 3.

Quinidine.—Bardier and Stillmunkes (19) have reported that quinidine when given orally decreased the excitability of the heart, and thereby prevented chloroform-epinephrine syncope. Scott (20) found the continued administration completely successful in arresting and preventing ventricular tachycardia in a clinical case.

In our experiments the oral administration of quinidine sulphate in two doses each of 10 mg. per Kg., given one and two hours, respectively, before anesthesia was not effective in protecting against cyclopropane-epinephrine tachycardia. Since smaller intravenous doses of quinidine did not protect, 6 dogs in deep cyclopropane anesthesia were injected with 15 mg. of quinidine per kilogram ten minutes before the control dose of epinephrine was injected. In each case there was complete protection. Results on the 6 dogs are shown in Table 3. Three of the dogs were tested with epinephrine at half hour intervals in order to determine the duration of the protection. This quinidine effect persisted for one, two and one-half and three hours, respectively.

Ergotamine.—Ergotamine tartrate was employed as an example of a sympathicolytic drug. After preliminary trials of higher doses it was found that 1/6 to 1/4 mg. of ergotamine per kilogram injected intravenously was sufficient to give complete protection from cyclopropane-epinephrine tachycardia. Details may be seen in Table 3.

F 883.—Shen (21) has reported that F 883 (diethyl-amino-methyl-benzo-dioxane) protects from chloroform-epinephrine fibrillation. This drug was used in this study because of its sympathicolytic property. Six dogs in deep cyclopropane anesthesia were injected intravenously with 2 mg. of F 883 per kilogram. Twenty minutes later the injection of the test dose of epinephrine was not followed by ventricular tachycardia as is shown in Table 3.

Yohimbine.—Yohimbine hydrochloride was the only adrenolytic drug studied. Shen (21) protected from chloroform-epinephrine fibrillation by the intravenous injection of 1 to 3 mg. of yohimbine per kilogram before injecting the epinephrine.

In our experiments 7 dogs were tested with intravenous yohimbine doses which were decreased from the initial trial dose of 5 mg. per Kg. to 0.2 mg. per Kg. in an effort to find the minimum protective dose. In all cases the protection was complete. In 2 dogs the dosage was reduced to 0.1 mg. per Kg., and the effect was only partial protection. These results are also summarized in Table 3.

PROCAINE

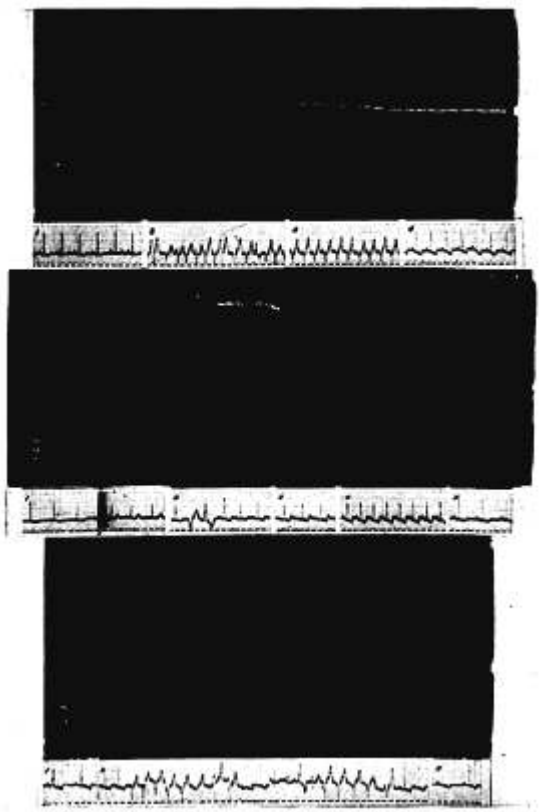

FIG. 1. Blood pressure tracings and electrocardiograms of epinephrine injections under deep cyclopropane anesthesia. *A*. Epinephrine control. *B*. Same dose of epinephrine mixed with 16 mg. procaine per kilogram. *C*. Control dose of epinephrine 30 minutes after the procaine injection.

Blood Pressure

Since several investigators have reported that chloroform-epinephrine syncope (22) and benzol-epinephrine irregularities (23) are due to the inability of the heart to withstand the intracardiac strain imposed by the high blood pressure resulting from epinephrine, direct measurements were made to demonstrate the blood pressure effects of each drug

CARBON DIOXIDE

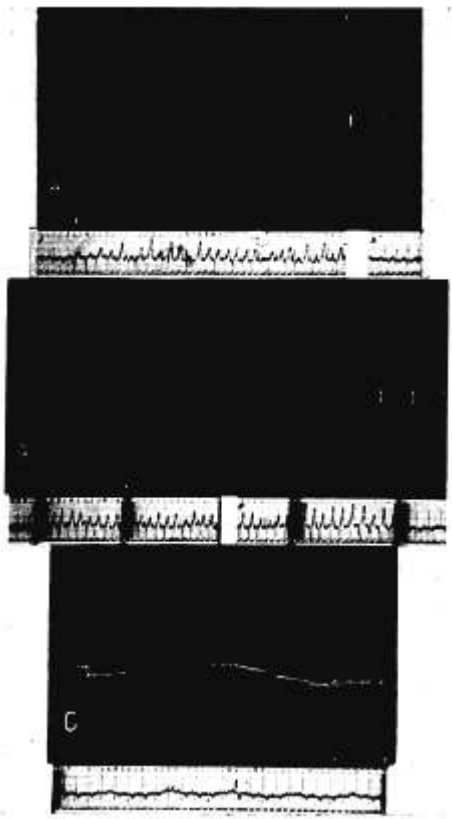

Fig. 2. Blood pressure tracings and electrocardiograms of epinephrine injections under deep cyclopropane anesthesia. *A*. Epinephrine control. *B*. Same dose of epinephrine after the anesthetic mixture contained 12 per cent carbon dioxide. *C*. Control dose of epinephrine after the carbon dioxide concentration amounted to 22 per cent of the anesthetic mixture.

in the concentrations used for protection. Figures 1 to 5 show characteristic records from some of these experiments. In cyclopropane anesthesia yohimbine, ergotamine, and F 883 caused a transient fall in blood pressure followed by a return to the control level within a few minutes. Quinidine and morphine each caused a more or less persistent fall in the blood pressure. Pressor responses to epinephrine either did not occur or were slight with yohimbine, F 883 and carbon dioxide at a time

FIG. 3. Blood pressure tracings and electrocardiograms of epinephrine injections under deep cyclopropane anesthesia. *A*. Epinephrine control. *B*. Response to the subcutaneous injection of 8 mg. morphine per kilogram. *C*. Control dose of epinephrine 30 minutes after the morphine injection.

when there was protection from cyclopropane-epinephrine tachycardia. However, when tachycardia was prevented by ergotamine, quinidine, morphine, or procaine, the rise in blood pressure was comparable or even greater than in the control. Similar results were reported for protection by decerebration or sympathectomy (3).

Ergotamine was effective in preventing cyclopropane-epinephrine tachycardia before any reversal of blood pressure was observed. The threshold for the cardiac effects of this agent is thus lower than for the peripheral vascular effects.

QUINIDINE

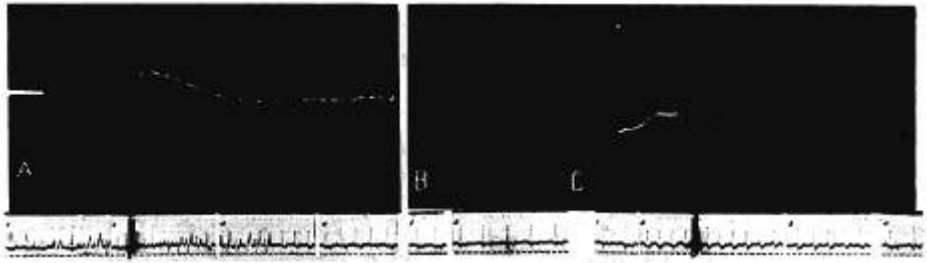

FIG. 4. Blood pressure tracings and electrocardiograms of epinephrine injections under deep cyclopropane anesthesia. *A*. Epinephrine control. *B*. Response to the intravenous injection of 15 mg. of quinidine per kilogram. *C*. Control dose of epinephrine 10 minutes after the quinidine injection.

YOHIMBINE

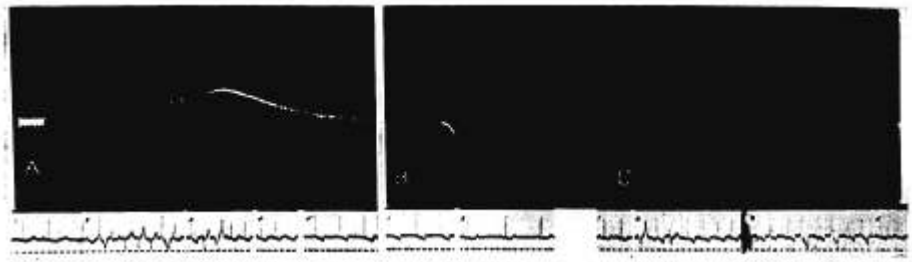

FIG. 5. Blood pressure tracings and electrocardiograms of epinephrine injections under deep cyclopropane anesthesia. *A*. Epinephrine control. *B*. Response to the intravenous injection of 0.2 mg. yohimbine per kilogram. *C*. Control dose of epinephrine 15 minutes after the yohimbine injection.

SUMMARY

Procaine, carbon dioxide, quinidine, morphine, ergotamine, F 883 (diethyl-amino-methyl-benzo-dioxane), and yohimbine have been studied for the prevention of cyclopropane-epinephrine tachycardia. These agents are all protective in proper dosages. The effective amounts per kilogram when administered intravenously are: procaine, 16 mg.; quinidine, 15 mg.; ergotamine, 1/6 mg.; F 883, 2.0 mg.; and yohimbine, 0.2 mg. The morphine dose was 8 mg. per Kg. when given subcutaneously. Twenty to 24 per cent carbon dioxide in the anesthetic mixture also gave protection.

It is believed that procaine, carbon dioxide, and quinidine give protection from cyclopropane-epinephrine tachycardia because of myocardial depression; F 883 and ergotamine, by their sympathicolytic action; yohimbine, through its adrenolytic action; and morphine, by producing either functional decerebration or myocardial depression.

REFERENCES

1. Meek, W. J.; Hathaway, H. R., and Orth, O. S.: The Effects of Ether, Chloroform and Cyclopropane on Cardiac Automaticity, J. Pharmacol. & Exper. Therap. 61: 240–252 (Nov.) 1937.
2. Orth, O. S.; Leigh, M. D.; Mellish, C. H., and Stutzman, J. W.: Action of Sympathomimetic Amines in Cyclopropane, Ether, and Chloroform Anesthesia, J. Pharmacol. & Exper. Therap. 67: 1–16 (Sept.) 1939.
3. Allen, C. R.; Stutzman, J. W., and Meek, W. J.: The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia, Anesthesiology 1: 158–166 (Sept.) 1940.
4. Stutzman, J. W., and Allen, C. R.: The Adrenolytic Action of Cyclopropane, Proc. Soc. Exper. Biol. & Med. In press.
5. Mautz, F. R.: Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery, J. Thoracic Surg. 5: 612–628 (Aug.) 1936.
6. Beck, C. S., and Mautz, F. R.: The Control of the Heart Beat by the Surgeon, Ann. Surg. 106: 525–537 (Oct.) 1937.
7. Kochman, M., and Daeles, F.: Wirkung des Kokains auf das Warmbluterherz unter besonderer Berücksichtigung der Extrasystole, Arch. Internat. Pharmacodyn. 18: 41–63, 1908.
8. van Dongen, K.: Action of Novocaine on Fibrillation of Heart, Arch. Internat. Pharmacodyn. 60: 206–208 (Sept.) 1938.
9. Shen, T. C. R., and Simon, M. A.: Protecting Action of Novocaine upon Chloroform-Adrenalin Ventricular Fibrillation, Arch. Internat. Pharmacodyn. 59: 68–74 (May) 1938.
10. Burstein, C. L., and Marangoni, B. A.: Protecting Action of Procaine against Ventricular Fibrillation Induced by Epinephrine during Cyclopropane Anesthesia, Proc. Soc. Exper. Biol. & Med. 43: 210–212 (Jan.) 1940.
11. Marangoni, B. A.; Burstein, C. L., and Rovenstine, E. A.: Protecting Action of Chemicals Related to Procaine on Ventricular Fibrillation during Cyclopropane Anesthesia, Proc. Soc. Exper. Biol. & Med. 44: 595–596 (June) 1940.
12. Burstein, C. L.; Marangoni, B. A.; DeGraff, A. C., and Rovenstine, E. A.: Laboratory Studies on the Prophylaxis and Treatment of Ventricular Fibrillation Induced by Epinephrine during Cyclopropane Anesthesia, Anesthesiology 1: 167–186 (Sept.) 1940.
13. Magnus, R.: Die Thätigkeit des uberlebenden Säugethierherzens bei Durchströmung mit Gasen, Arch. f. exper. Path. u. Pharmakol. 47: 200–208 (March) 1902.
14. Ketcham, C. S.; King, J. T., and Hooker, D.: Effects of Carbon Dioxide on the Isolated Heart, Am. J. Physiol. 31: 64–74 (Nov.) 1912.

15. Robbins, B. H.; Baxter, J. H., and Fitzhugh, O. G.: The Use of Barbiturates in Preventing Cardiac Irregularities under Cyclopropane or Morphine and Cyclopropane Anesthesia, Ann. Surg. 110: 84–93 (July) 1939.
16. Porter, W. T.: Weiteres über den Verschluss der Coronararterien ulne Mechanische Verletzung, Zentralbl. f. Physiol. 9: 641–647 (Jan.) 1896.
17. Kuré, K.: Ueber die Pathogenese der heterotopen Reizbildung unter dem Einflusse der extracardialen Herznerven, Ztschr. f. exper. Path. u. Therap. 12: 389–459 (Feb.) 1913.
18. Smirnow, A. J.: Ueber den Tonus des Zentrums des n. Vagi, Ztschr. f. d. ges. exper. Med. 57: 554–558 (May) 1927.
19. Bardier, E., and Stillmunkes, A.: Quinine, Quinidine and Epinephrine-Chloroform Syncope, Compt. rend. Soc. de biol. 95: 268–270 (July) 1926.
20. Scott, R. W.: Ventricular Tachycardia with Retrograde Conduction, Heart 9: 297–309 (Dec.) 1922.
21. Shen, T. C. R.: Protective Action of Piperido-methyl-3-benzodioxane (F 933), Diethylamino-methyl-3-benzodioxane (F 883) and Yohimbine upon Chloroform-Adrenalin Ventricular Fibrillation, Arch. Internat. Pharmacodyn. 59: 243–251 (June) 1938.
22. Shen, T. C. R., and Marri, R.: Further Studies on Cardio-Ventricular Fibrillation, Arch. Internat. Pharmacodyn. 64: 57–78 (Feb.) 1940.
23. Allen, W. F.: Contributing Factors to Pulse Changes Resulting from Injection of Epinephrin in Rabbits, J. Pharmacol. & Exper. Therap. 50: 70–78 (Jan.) 1934.

JOINT MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS AND THE NEW YORK STATE SECTION OF THE AMERICAN SOCIETY OF ANESTHETISTS

SQUIBB AUDITORIUM

745 FIFTH AVENUE, NEW YORK CITY

October 9, 1941—7:30 P.M.

1. Business Session of The American Society of Anesthetists.
   (*a*) Election of members.
   (*b*) Change of status from Active to Junior Membership.
2. Business and Economic Session of the New York State Section of The American Society of Anesthetists.
   (*a*) Medical and Hospital Insurance Plans.
   (*b*) Developments in the New York Electrical Code applying to Anesthesia.
   (*c*) Other items.
3. Scientific Session:
   (*a*) "Some Recent Contributions to Resuscitation of the New Born."
   By F. A. D. Alexander, M.D., Professor of Anesthesia, Albany Medical School, Albany, N. Y.
   (*b*) "Role of the Alkaloids of the Belladonna Plan in Clinical Anesthesia."
   By McKinnie Phelps, M.D., Department of Anesthesia, Bellevue Hospital, New York, N. Y.