at the left costal margin in the experimental animals. In the controls the cardia was found 1 cm below the diaphragm; 4-5 cm cephalad to the left costal margin.

5. In the pneumoperitoneum group the spleen was found at the costal margin. As a result of the ptosis of the viscera the root of the mesentery was stretched. In the control animals the spleen was found in contact with the inferior surface of the diaphragm.

6. Since the visceroptosis had produced a long intraabdominal esophageal segment making the entire stomach readily accessible, a total gastrectomy and a conventional loop 2 layer silk esophagojejunostomy was more readily accomplished in the group of animals prepared with pneumoperitoneum. Because the intra-abdominal segment of esophagus in the pneumoperitoneum group was invested with a serosa and subserosa, the esophagojejunostomy was stronger than could be achieved in the control group since in this latter group the esophageal muscularis was not covered with serosa.

Summary and conclusion. 1. Pneumoperitoneum produces (a) an intra-abdominal herniation of the lower end of the eosphagus (b) a ptosis of the stomach, liver, spleen and the root of the mesentery, displacing the first 3 structures from beneath the costal margin and therefore making them more accessible for surgical procedures. 2. Pneumoperitoneum employed in the dog, prior to total gastric resection, proved valuable. As a result of the intra abdominal herniation of the lower segment of the esophagus, the displacement of the cardia of the stomach to the level of the costal margin, and the mobility of the root of the mesentery, the stomach was readily resected and an esophagojejunostomy established.

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Cardiac Effects of a Hypotensive Veratrum Derivative in Dogs Premedicated with Digitalis or Quinidine.* (18532)

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This investigation of the effects of Veriloid† on the electrocardiogram (EKG) of dogs premedicated with toxic dosages of digitalis or quinidine was undertaken because of a clinical impression that cardiac side actions of veratrum preparations and of digitalis or quinidine may be additive(1,2).

Method. Four series of experiments were done on adult mongrel dogs weighing 5 to 15 kg. Series I: Veriloid,‡ 1 mcg/kg/min for 10 minutes,§ was infused by vein into unanesthetized dogs. Thirty minutes from the beginning of that infusion, atropine sulfate, 0.05 to 0.25 mg/kg, was administered intravenously.

Series II: Dogs were premedicated with toxic dosage of a digitalis preparation. Drugs used were digitoxin,‡ 0.2 or 0.3 mg/kg, and ouabain,‡ 0.05 to 0.07 mg/kg. Evidence for toxic digitalization was obtained by EKG one hour after ouabain, 24 hours after digitoxin.

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† Veriloid (registered trade mark of Riker Laboratories, Los Angeles) is a biologically standardized (dogs) extract of Veratrum viride of constant hypotensive potency.

1. Fries, E. D., personal communication.

2. Meilman, E., and Krayer, O., *Circulation,* 1950, v1, 204.

‡ Grateful acknowledgement is made to Abbott Laboratories for digitoxin, to E. Fougera and Co. for Ouabain Arnaud and to Riker Laboratories for Veriloid used.

§ This dose produces average fall of 30% ± 12 in mean arterial pressure with recovery in 30-90 min. in dogs anesthetized with pentobarbital; no tachyphylaxis to a second injection exists after recovery.

TABLE I. Incidence of Cardiac Rhythms in Unanesthetized Dogs After Intravenous Medication (all control rhythms sinoauricular) (SA).

Changes in rhythm	Due to: Veriloid infusion	Digitalis compounds	Digitalization followed by Veriloid infusion	Quinidine HCL	Quinidine HCL followed by Veriloid infusion
SA, no change	22	10	6	13	15
SA to partial block	3	4	1		1
SA to complete block		2	2		
SA to ventricular		2	2	2	
Partial block, no change			2		
Complete block, no change			1		
Complete block to VT*			2		
VT, no change			2		
Partial block to SA			1		
SA to SA with Vext S†		2	1		

* VT = Ventricular tachycardia.
† Vext S = Few ventricular extrasystoles.

Veratrum and atropine sulfate were then administered as in Series I. Series III: Quinidine HCl 15 mg/kg or 25 mg/kg was infused at a rate of 5 mg/kg/min into dogs. Series IV: Animals, premedicated with quinidine HCl as in Series III, were five minutes later infused with the veratrum preparation as in Series I. Changes in cardiac-rate, rhythm and QT/RR ratio were observed in Lead II of the EKG. The stylus remained under constant observation and records were obtained at 5 minute intervals during the course of each experiment.

Results and discussion. Part I. *Effect of a veratrum derivative upon the EKG of dogs:* All dogs utilized for this study had control SA rhythm without obvious abnormality. The only changes in cardiac rhythm (Table I) in the 25 animals tested were 3 cases of AV block. The bradycardia (Table II) produced was found to be a function of the control rate (Fig. 1). The administration of atropine sulfate corrected the bradycardia and abolished the partial AV blocks. Thus the effects of Veriloid on the electrocardiogram are explicable on a basis of an increase in vagal tone.

Part II. *Effect of a veratrum derivative on the EKG of dogs premedicated with toxic dosage of digitalis:* Emesis was observed in all dogs receiving digitalis compounds (Series II) in these toxic dosages. Cardiac arrhythmias were seen in 10 of the 20 animals, (Table I) the remainder showed bradycardia (Table II). This rate reduction was found to be independent of the original rate (Fig. 1). On a basis of direct comparison of the rhythm of individual animals, it was clear that in 13 of the 20 dogs veratrum produced additive cardiac effects after digitalis (Table I). The pacemaker was displaced downward in 6; prolongation of the P-R interval was seen in 4; partial AV block in 2 and acceleration of a ventricular rhythm of 60 to 200 in one animal. In the other 7 digitalized animals no change in the rhythm occurred in 6 and 1 improved.

Further slowing of the heart occurred on administration of veratrum to the eleven digitalized animals which maintained SA rhythm (Table II). The effect of atropine sulfate in dosage of 0.05 to 1.0 mg/kg was to abolish the bradycardia produced by digitalis and the veratrum compound in those animals with an SA pacemaker, and to shift the pacemaker upward in all others.

These results are consistent with an additive action of the veratrum preparation upon the digitalized heart. Digitalis is said to exert its bradycardic action through reflex vagal stimulation and a direct action upon the myocardium(3). Veriloid, apparently by increasing the vagal tone above the level produced by digitalis, elicits a further decrease in heart rate. Vagal depression of supraventricular irritability probably accounted for the downward shifting of the pacemaker since atropine resulted in increased rates and a shift of the pacemaker upward. There were 4 dogs in which an SA rhythm was not observed following atropine sulfate after digi-

3. Gold, H., Kwit, N. T., Otto, H., and Fox, T., *J. Pharm. and Exp. Therap.*, 1939, v67, 224.

TABLE II. Heart Rate in Beats/Min. in Unanesthetized Dogs Which Maintained SA Rhythm After Various Medications.

Series	No. dogs	Control	After digitalis	After quinidine, 15 mg/kg	After quinidine, 25 mg/kg	After Veriloid*
I	25	100 ± 24				62 ± 18
II	11	102 ± 23	82 ± 23			53 ± 15
III	8	117 ± 19		165 ± 23		
	6	87 ± 19			103 ± 14	
IV	10	113 ± 19		146 ± 38		96 ± 17
	6	104 ± 12			104 ± 13	104 ± 13

talis and veratum. These may have been demonstrating a direct myocardial effect of digitalis.

Part III. *Effect of a veratrum derivative upon the EKG of dogs premedicated with quinidine hydrochloride:* The most notable change in the EKG of animals receiving only quinidine HCl in dosages of 15 or 25 mg/kg was a rise of the Q-T/R-R ratio greater than that expected for the heart rate change produced. In all records negative T waves became less negative, and upright T waves became higher. An increased heart rate was observed following the administration of quinidine, 15 mg/kg, averaging 35 beats/minute. Generalized twitching of skeletal muscle was produced. The veratrum preparation produced slowing of the heart rate in dogs premedicated with 15 mg/kg but not in those with 25 mg/kg quinidine HCl (Table II). The combination of agents produced no effects on rhythm except that one dog, demonstrating a shifting pacemaker after quinidine, converted to SA rhythm with veratrum. The T wave changes associated with the administration of quinidine tended to revert toward the control pattern after Veriloid.

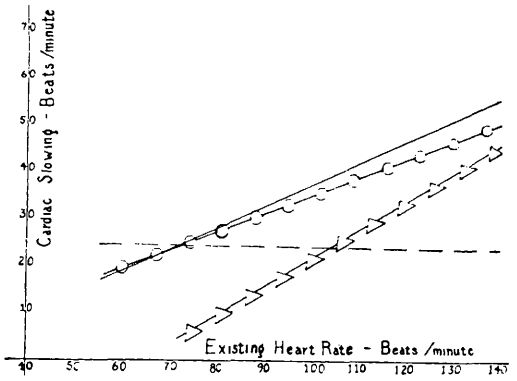

FIG. 1.

Regression lines expressing the relationship between control heart rates and heart rate decrement after intravenous medications. (For method see Snedecor, G. W., *Statistical Methods* (4th Ed.), Ames, Iowa State College Press, 1946, p. 117). ———— Veriloid, 1 mcg/kg/min. for 10 min. (SD = ±14.53, r = 0.59, t = 3.42, equation: y = —10 + 0.48x). - - - - Digitalis compound in toxic dosage (SD = ±11.3, r = 0.01, equation: y = 25 —0.008x). ○-○-○ Veriloid 1 mcg/kg/min. for 10 min. in dogs premedicated with toxic digitalis dosage. (SD = ±12.0, r = 0.61, t = 2.30, equation: y = —5 + 0.41x). Δ-Δ-Δ Veriloid 1 mcg/kg/min. for 10 min. in dogs premedicated with quinidine hydrochloride 15 mg/kg (SD = ±13.0, r = 0.89, t = 5.48, equation: y = —40 + 0.62x).

The heart is reported to be progressively blocked to vagal stimulation by quinidine(4). Since the cardiac slowing of veratrum derivatives is presumed to be a vagal effect, the absence of bradycardia from Veriloid following higher dosage of quinidine might be expected.

In this series of 66 observations with a heart rate average of 104 the normal QT/RR ratio averaged 34%. The ratio was found to vary as a straight line function of the existing rate. The same was true after the drugs with two exceptions: Dogs which received quinidine HCl alone at 25 mg/kg, and those which received veratrum and quinidine at 15 or 25 mg/kg showed an increase in the ratio greater than might have been expected from the change in heart rate.

These data do not support the current clinical concept that veratrum derivatives are contraindicated in patients receiving quinidine.

Summary. Veriloid, a reproducible hypotensive derivative of *Veratrum viride*, was

4. Hiatt, E. P., Brown, D., Quinn, G., and MacAuffie, K., *J. Pharm. and Exp. Therap.*, 1945, v85, 55.

administered in dosage of 1 mcg/kg/minute for 10 minutes to unanesthetized dogs. Similarly the veratrum derivative was administered to unanesthetized dogs premedicated with toxic dosages of digitalis preparations and to others premedicated with toxic dosages of quinidine hydrochloride. The degree of cardiac slowing from the veratrum derivative was found to be a function of pre-existing cardiac rate. No such relation was found for the bradycardia produced by digitalis. Dogs which received digitalis and veratrum showed profound bradycardia. This action appeared to be mediated by increased vagal tone since the slowing was abolished by atropine. Rhythm disturbances due to digitalis were exaggerated by veratrum. A rise in Q-T/R-R ratio above that to be expected by changing cardiac rate was associated with the administration of quinidine hydrochloride. In normal animals and in those which received digitalis, Veriloid or both, the ratio was found to vary as a straight line function of the existing heart rate. Neither quinidine alone at 15 or 25 mg/kg nor quinidine and veratrum produced appreciable incidence of arrhythmias. Cardiac slowing was observed in dogs receiving veratrum after the 15 mg/kg dose of quinidine but not after the 25 mg/kg dose.

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Action of Tri-Ethylene Melamine in Mice.* (18533)

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Cytotoxic action has been demonstrated with tri-ethylene melamine, a compound which is structurally related to the hydrolysis products of the nitrogen mustards. In a series of *in vitro* studies on lymph nodes from patients with reticulum cell sarcoma, chronic lymphatic leukemia, and lymphosarcoma, inhibition of fibroblast growth was noted(1), as well as granular disintegration of lymphocytes(2). Successful *in vivo* inhibition of certain sarcomas and leukemias in lower animals(3-7) has been obtained, as well as clinical remission in patients with malignant lymphomas(8,9) and a case of mycosis fungoides(9). Signs of toxicity were evidenced by a dramatic fall in white blood cell count(9,10), with a decrease (9,10) or an increase(9) in polymorphonuclear cells. The effect on erythrocytes was negligible, though the rat erythropoietic system was more sensitive(10). Repeated administration of effective doses at prescribed intervals was necessary in clinical application (9) and therefore the duration of toxic effect was important.

The pharmacological studies on tri-ethylene melamine were undertaken to observe the general toxic effect, as well as the latent period and duration of toxicity. The latter was of great importance since repeated administra-

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