THE RELATIONSHIP OF VARIOUS ANESTHETIC AGENTS TO THE ACTION OF PITUITRIN, PITRESSIN AND PITOCIN * †

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INTRODUCTION

SEVERE side-effects subsequent to the administration of posterior pituitary preparations have recently been reported by several authors. Apparently the first case report of side-effects resulting from the use of pituitrin alone was that of Vidal in 1928. In the abstract summarizing this report, DeLee (1) mentioned that he had seen several cases of "pituitrin shock" but we have been unable to find specific accounts of them. Subsequent reports of untoward effects caused by posterior pituitary extracts (2, 3, 4) also were termed "pituitrin shock" and either occurred in the absence of anesthesia or the possible role of the anesthetic agent in their production was not considered.

In 1941 Adelman and Lennon (5) listed seven instances of "pituitrin shock" occurring during anesthesia and since then other reports have appeared (6, 7). Four additional unpublished cases have come to our attention in which death was attributed to the combination of cyclopropane and pituitrin. The associated complications reported were either (a) of a respiratory nature such as laryngospasm, bronchorrhea, bronchoconstriction and massive pulmonary collapse or (b) of a circulatory type with signs of pulmonary edema and peripheral collapse.

There has been a tendency to attribute undesirable effects of pituitrin to either of two mechanisms: (1) a manifestation of anaphylaxis owing to sensitivity to a posterior pituitary preparation, or (2) a result of coronary constriction with its sequelae of myocardial hypoxia, cardiac dilatation and decreased cardiac output (8, 9).

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The supply of pituitrin, pitocin and pitressin used in this study was purchased on the open market.

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In some of the reported cases, in which an incompatibility with the anesthetic agent was implied, other factors existed including respiratory obstruction or depression of respiration by sedative drugs.

Notwithstanding meager clinical information the problem becomes important to the anesthesiologist as recent reports indicate (10, 11, 12, 13). The incidence of so-called pituitrin shock probably is greater than generally realized, and it may be associated with anesthesia. Accidents which have occurred following administrations of pituitary preparations to anesthetized patients make it particularly desirable to re-evaluate the pharmacologic actions and therapeutic uses of these preparations and to study possible incompatibilities which they might have with various anesthetic agents.

In an attempt to determine whether or not any evident incompatibility exists, three posterior pituitary preparations, pituitrin, pitressin and pitocin, have been administered to dogs during cyclopropane anesthesia. Other anesthetic agents and unanesthetized animals have been similarly employed for tests in which only pituitrin was used.

METHODS

A total of 26 dogs was used in 84 experiments in this study. The anesthetic agents employed were cyclopropane, ether, chloroform, nembutal, chloretone and procaine. Unanesthetized dogs also were tested. The data of table 1 indicate the separate experiments with the various agents in which the animals were tested with pituitrin, or during cyclopropane anesthesia with each of the pituitary fractions. The anesthetic agent was diluted with oxygen to assure its presence in an adequate amount at all times in the respired atmosphere. No drugs were administered for preanesthetic medication.

Anesthesia with each of the three inhalational agents was accomplished by use of a closed system and maintained by endotracheal to-and-fro absorption. Surgical anesthesia of second to third plane was maintained for a sufficient time to achieve approximate equilibration with the agent being used. Animals anesthetized with chloretone and nembutal were intubated and given oxygen. In those experiments in which procaine was employed as a spinal analgesic, oxygen was supplied if any respiratory embarrassment was anticipated. Throughout the study notation was made of any changes in character and rate of respiration.

Each of the drugs to be tested was administered intravenously. Pituitrin was employed in a dose of 1 unit per kilogram of body weight, diluted to 5 cc. and injected at a uniform rate during an interval of fifty seconds. Pitressin was used similarly in a dosage of 2 units per kilogram and pitocin in a dosage of 1 unit per kilogram. These amounts definitely are large but correspond to those used by others (14) and were chosen in an attempt to reveal possible deleterious cardiac effects.

With a direct-recording electrocardiograph, control records from the three standard leads were taken at the beginning of each experiment. The pattern of deflection of the stylus was observed continuously thereafter and records were taken at intervals of ten seconds during the first minute while the drug was being injected, at intervals of fifteen seconds in the second minute and at thirty to sixty second intervals for as long as twelve to fifteen minutes.

TABLE 1

SEPARATE EXPERIMENTS WITH THE VARIOUS ANESTHETICS. EACH ANIMAL WAS TESTED WITH PITUITRIN OR DURING CYCLOPROPANE ANESTHESIA WITH EACH OF THE PITUITARY FRACTIONS. THE OCCURRENCE (+) OR ABSENCE (−) OF CARDIAC IRREGULARITIES IS INDICATED

Dog Number	Pituitrin with:						Cyclopropane with:		
	Unanesthetized	Spinal Analgesia	Chloretone	Chloroform	Ether	Nembutal	Pituitrin	Pitocin	Pitressin
A							+		
B							+		
C	+				−	−	− 0 0		
D						—	−		
E					−				
F					−				
G				−			− 0		−
H	+						−		−
I	+						−	+	− 0
J	0 +			+			0	−	+
K	+		K − −				0	− 0	− −
L				−			0	− −	−
M	+					−	K − 0 0	−	
N			K − −				−		
O			K − −						
P	+	K + +							
Q		K + +							
R	+	K + +					K − − −	−	+
S		+					−		
T	+	+					−	−	+
U	+	+							−
V	+	+							
W	+	+					+	−	−
X	+	+					−	−	+
Y							+ +	+	
Z							− −		

K = 0.04 cc. total dosage of pituitrin; all other amounts of this fraction were 1 unit per kilogram.

O = unable to determine cardiac effects in experiments so marked.

Direct blood pressure recordings were made in the majority of the experiments by cannulation of a femoral or carotid artery. By the use of aseptic technics the animals were saved for subsequent experiments so that comparisons of the effects of different anesthetic agents or different pituitary fractions could be made on the same dog (15). This avoided the possibility of tachyphylaxis or the necessity of test-

ing for residual effect owing to previous administration if made on the same day. On those occasions when tests of more than one of the fractions was desired in the same experiment, an interval of twelve to twenty minutes was allowed between administrations. The phenomena of tachyphylaxis when observed during this procedure will be noted later.

A combination of epinephrine and pituitrin was used in some experiments. The same 1 unit per kilogram dose of pituitrin was used plus the amount of epinephrine (usually 5 to 10 gamma per kilogram) which caused ventricular tachycardia for the individual dog with the particular anesthetic agent used. In other instances epinephrine was given approximately two minutes after pituitrin and at various intervals thereafter for as long as an hour.

Control injections of dilute acetic acid adjusted to a hydrogen ion concentration of the same value as that of the pituitrin solutions were made in order to rule out the possibility that this factor might influence blood pressure or cardiac rhythm.

EFFECTS ON BLOOD PRESSURE

The earliest investigations with pituitary extracts revealed discrepancies in the results obtained which were attributed to the different methods used in the preparation of the extracts. A growing concept, however, that the variability of action was the result of experimental conditions, particularly to anesthesia, can be traced to the original work of Howell who in 1898 (16) stated: "the results were . . . somewhat variable in detail and apparently slightly different according to the anesthetic employed." Subsequent investigations (17, 18, 19) revealed the importance of anesthesia in greater detail, as is noted by Geiling (20) in 1926 in a review of the action of pituitary extracts.

Kamm and others (21), in 1928, were successful in obtaining an almost complete separation of the pressor and oxytocic fractions of posterior pituitary extract using dogs anesthetized with chloretone as the test animal for the pressor assay. Chloretone was recognized as the anesthetic of choice for this assay (22), and it was shown that ether, chloroform or incomplete chloretone anesthesia did not lower the blood pressure sufficiently to give adequate results. Evidence soon was given by Raginsky, Ross and Stehle (23) to show that with chloretone, a drug which lowers the blood pressure and dilates the coronaries, the pressor effect is always present in dogs; with ether it is sometimes absent, and with phenobarbital there is a depressor effect rather than the anticipated elevation of blood pressure. In 1932 Grollman and Geiling (24) stated that anesthetized animals often do not show compensatory changes in the circulation and that this fact may explain variations in the results obtained with pituitary fractions.

TABLE 2

THE EFFECTS ON CARDIAC RHYTHM AND BLOOD PRESSURE PRODUCED BY PITUITRIN, PITRESSIN, OR PITOCIN DURING THE INDICATED ANESTHETIZATIONS

Anesthetic Agent during Tests with Pituitrin, 1 unit/kg.	No. of Animals	No. of Experiments	No. of Animals with Arrhythmia	No. of Animals with Blood Pressure Rise	No. of Animals with Blood Pressure Fall
Chloretone	3	3	0	3	0
Spinal	9	9	9	3	4*
Ether	3	3	0	2	1
Chloroform	3	3	1	1	2
Nembutal	3	3	0	0	3
Cyclopropane†					
with Pituitrin, 1 unit/kg.	18	24	4	4	11
with Pitressin, 2 unit/kg.	12	14	4	0	10
with Pitocin, 1 unit/kg.	10	10	2	7	0
Unanesthetized					
Pituitrin, 1 unit/kg.	13	14	13	—	—

* Two others showed no significant change.
† Blood pressure determinations were not made in all experiments.

An analysis of the blood pressure curves which we obtained after the intravenous injection of pituitrin into anesthetized dogs confirms and extends the observations of previous workers. The data are summarized in table 2. Three dogs anesthetized with chloretone had a rise of pressure as the table indicates. Since Gruber (25) suggested that the rise of pressure seen as a response to administration of pituitrin during chloretone anesthesia is in part due to the presence of an initial very low blood pressure caused by chloretone itself, an effort was made to cause similar conditions of hypotension by producing spinal analgesia with procaine. The changes in blood pressure levels in 9 dogs following spinal analgesia were not remarkable, however, and even in two instances in which the animals had complete analgesia of the anterior limbs, the control blood pressure was not altered significantly. The deviations from normal in response to injections

FIG. 1A. The effect of the intravenous injection of 1 unit per kilogram of pituitrin upon the blood pressure of a dog given nembutal. All illustrations are of injections of this dosage in a 5 cc. volume, made at a steady rate in a fifty second interval.

of pituitrin were not great. In three experiments during spinal analgesia there was a slight rise, in four a slight fall, and in two instances there was essentially no change. Results likewise were variable when ether or chloroform was the anesthetic agent, while with nembutal 3 dogs exhibited marked falls of blood pressure, as the tracing of figure 1A indicates.

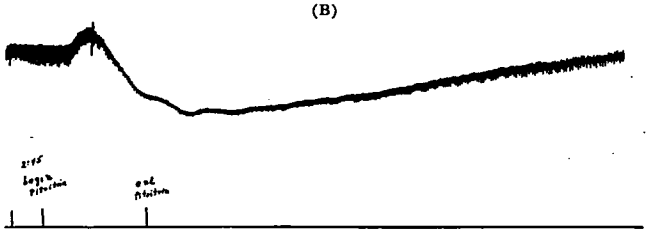


FIG. 1B. The effect of the 1 unit per kilogram dosage of pituitrin on the blood pressure when cyclopropane was used as the anesthetic.

With cyclopropane as the anesthetic agent the responses of blood pressure after the injection of pituitrin usually resulted in a characteristic pattern of alteration, as is illustrated by figure 1B. This type of response was observed in 13 experiments with 11 dogs in which blood pressure recordings were made. It consisted of an initial slight rise of twenty seconds or less duration followed by a pronounced and prolonged fall lasting up to several minutes, with a subsequent gradual recovery to the normal level. In a very few instances a secondary rise succeeded the abrupt fall. In no instance did the elevations in pressure equal the magnitude or duration of the characteristic fall. A striking example of what could be termed "pituitrin shock" occurred in one experiment during anesthesia with cyclopropane and is illustrated in figure 2. Blood pressure in this experiment remained at approximately zero for three minutes before the beginning of recovery. Throughout this period spontaneous respirations continued.

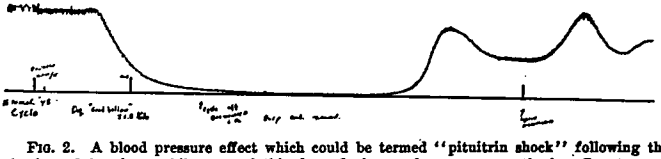


FIG. 2. A blood pressure effect which could be termed "pituitrin shock" following the injection of 1 unit per kilogram of this drug during cyclopropane anesthesia. Spontaneous respirations continued throughout the period of almost three minutes during which the pressure remained near zero.

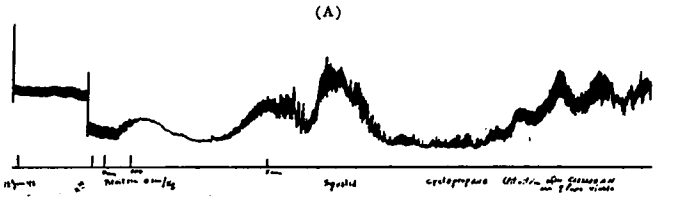


FIG. 3A. A record of the blood pressure from a dog before and following cesarean section. The low pressure caused by the surgical procedure and the periods of elevation of pressure produced by a single administration of 1 unit per kilogram of pituitrin are to be noted.

In three experiments with 2 other dogs, rises of not very great magnitude were observed and there was no fall below the original level. Two additional elevations occurred in pregnant dogs in which pituitrin was given immediately after delivery by cesarean section when the blood pressure was at a low level. The record of one of these experiments is shown in figure 3A. These were the only instances in which hypotension was present similar to that usually produced by chloretone anesthesia. When each of these animals had returned to an essentially normal state a month later, pituitrin was again injected during cyclopropane anesthesia. The response of the blood pressure, then under more nearly normal conditions, resulted in a pattern of alteration comparable to that of the 9 other animals similarly tested and previously described, as figure 3B indicates. Since Gruber (25) and Melville (26) have observed falls in blood pressure in unanesthetized animals similar to those observed in our experiments during cyclopropane anesthesia, blood pressure determinations were not made in the 14 experiments of this study in which anesthetic agents were not used.

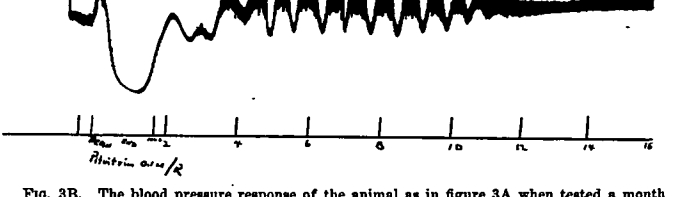


FIG. 3B. The blood pressure response of the animal as in figure 3A when tested a month later. At this time, when the dog had attained an essentially normal state, the pattern of alteration of blood pressure was comparable to that of 9 other normal animals similarly tested, as described in the text.

Variations in Doses of Pituitrin.—During anesthesia with chloretone, spinal or cyclopropane the effects of a small dosage of pituitrin (0.04 cc. total), as employed by Kamm (21) for pressor assay, were investigated in addition to the effects of a dose of 0.1 cc. per kilogram used throughout the rest of the study. With chloretone either dosage consistently produced an elevation of pressure. With cyclopropane, however, small doses caused a rise and large doses a fall in pressure. In the dogs with spinal analgesia small doses had a definite pressor action and with larger doses the results included both rises and falls as previously noted.

Garnier and Thaon, in 1906 (27), obtained pressor effects with small doses and depressor effects with large doses. Raginsky, Ross and Stehle reported similar results (23).

The Effects of Pituitrin and Epinephrine.—The extent of the relationship between the action of pituitrin and epinephrine on blood pressure was tested by simultaneous administration of these compounds: by administration of epinephrine at intervals of ten to fifteen minutes

TABLE 3

THE SEQUENCE OF INJECTIONS OF EPINEPHRINE AND PITUITRIN IN EXPERIMENTS DURING CYCLOPROPANE ANESTHESIA. AN INTERVAL OF FIVE MINUTES OR MORE ELAPSED BETWEEN EPINEPHRINE INJECTIONS AND FROM TWELVE TO TWENTY MINUTES BETWEEN PITUITRIN ADMINISTRATIONS

Expt. No.	Epinephrine*			Pituitrin, unit/kg.			Epinephrine* and Pituitrin†	Epinephrine*			Pituitrin
1	2.5	3.75	5.0		1.0			2.5			
2	2.5	5.0	7.5		1.0						
3				0.5	1.0						
4					1.0	2.0		2.5	5.0		
11	5.0	7.5	10.0		1.0		2.6				
13	5.0	10.0			1.0		10.0				1.0
14							5.0				1.0#
15	7.5						7.5	7.5			
24	5.0				1.0			5.0	5.0		
29	5.0				1.0			5.0	5.0		
30					1.0			5.0	5.0	5.0	
42	5.0	10.0	10.0								
44				K	K	1.0					
45				K	1.0			10.0			
46	5.0	10.0			1.0			10.0	10.0	10.0	
56					1.0						
69					1.0						
70					1.0						
71					1.0						
76					1.0						
77					1.0						
78					1.0			5.0	10.0		
79					1.0			10.0	15.0		
80					1.0						

* All dosages of epinephrine are expressed as γ per kilogram.
† All dosages of pituitrin in these combined injections were 1 unit per kilogram.
K = The Kamm dose for pressor assay—0.04 cc. total.
# = Followed by a test with epinephrine 5 γ per kilogram.

TABLE 4

THE SEQUENCE OF INJECTIONS OF EPINEPHRINE AND THE VARIOUS PITUITARY PREPARATIONS IN EXPERIMENTS DURING CYCLOPROPANE ANESTHESIA

Expt. No.	Epinephrine*	Pitocin, units/kg.	Pitressin, units/kg.	Epinephrine*	Pitocin, units/kg.	Pituitrin, units/kg.	Epinephrine*
17			2.0 2.0	7.5			
18			2.0 2.0				
19			2.0	10.0			
20	5.0		2.0	5.0			
21			2.0				
28			2.0		1.0		10.0 10.0
32			2.0		1.0		10.0 10.0
43	5.0 (3)						
47	5.0						
48	5.0 (6)						
74			2.0				
75			2.0				
81			2.0				
82			2.0				
83			2.0				
22	5.0	1.0	2.0			1.0	
23	5.0	1.0	2.0			1.0	
25		1.0					
26		1.0		10.0		1.0	10.0
27		1.0		5.0 10.0		1.0	10.0
58		1.0					
72		1.0		10.0			
73		1.0		10.0			
84		1.0					
9		1.0					

* All dosages of epinephrine are expressed as γ per kilogram.

( ) The indicated numbers of successive injections of epinephrine were made to test for a possible adrenolytic effect of cyclopropane.

before pituitrin, or by the injection of epinephrine begun two minutes after pituitrin had been given, and at other intervals for as long as an hour afterward. The simultaneous injection of the two drugs produced only an elevation of pressure. Epinephrine before pituitrin did not modify the effect on blood pressure from that produced by pituitrin alone. Epinephrine injected during the period of low blood pressure caused by pituitrin initiated an immediate rise in pressure which in several instances exceeded the elevation produced by the same dose of epinephrine when administered as a control. Epinephrine at longer intervals after pituitrin produced an unqualified rise each time. The sequence of such injections is indicated in table 3.

The Effects of Pitressin and Pitocin.—The effects of pitressin or pitocin on blood pressure during cyclopropane anesthesia were compared with those of pituitrin when tested on the same animals on different days. Eight dogs received all three preparations in different experiments and 4 additional animals had comparisons made between two of the fractions, as indicated in table 4. In 10 dogs pitressin produced a characteristic alteration of blood pressure similar to that seen

with pituitrin (figure 4B). Pitocin caused definite though small rises of pressure (figure 4A) in 7 of these animals. This was probably owing to the small amount of the pressor fraction it contains.

Tachyphylaxis.—Since the work of Howell in 1898, it has been known that pituitary extracts cause tachyphylaxis. The interactions of the pituitary preparations on the blood pressure during cyclopro-

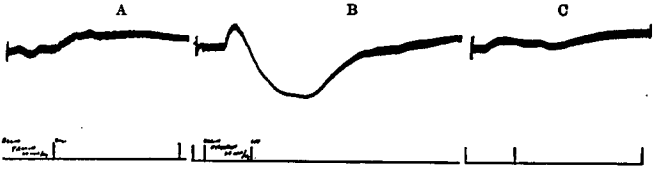


FIG. 4. The effects on the blood pressure of successive administrations of pitocin, pitressin and pituitrin. Intervals of twelve minutes and twenty minutes, respectively, occurred between the injections. Characteristic responses to (A) pitocin and (B) pitressin occurred, but tachyphylaxis then existed to (C) pituitrin, from the previous administration of pitressin.

pane anesthesia were investigated in this respect. It was found, as might be expected, that pitressin as well as pituitrin produces definite tachyphylaxis to itself and each to the other (figure 4C). There was no evidence of tachyphylaxis between pitocin and either pitressin or pituitrin, nor of repeated doses of pitocin so far as could be observed by the methods in use.

ARRHYTHMIAS

Arrhythmias of various types caused by pituitary extracts have been reported since 1898 when Cyon (28) observed pulsus bigeminus in experimental animals. Garnier and Thaon, in 1906, noted effects on cardiac rhythm (27) and in 1913, Claude, Porak and Routier (29), using MacKenzie's polygraph, described sinus arrhythmia and extrasystoles in man. Electrocardiographic changes in animals were reported by others in 1913 (30, 31). The papers of Melville (32), Gruber and Kountz (33), and Resnik and Geiling (19) should be consulted for the more recent work.

Weakening of the heart beat, cardiac dilatation and decrease in output after pituitrin injection have been observed and described by several authors (18, 34). Attempts to explain these deleterious cardiac effects have emphasized three possible mechanisms: (1) a direct action on the myocardium, probably by inhibition of oxidative processes; (2) vagal stimulation through the cardio-inhibitory center, and (3) coronary constriction with subsequent hypoxia of the myocardium.

Coronary constriction due to pituitrin has been known to occur since Pal (35) demonstrated it in isolated rings of artery in 1909, and it has been confirmed quite well by other investigators. The excellent work

of Green, Wegria and Bayer (36) and of Dearing, Barnes and Essex (37) can be cited in this regard. Melville, in 1938 (32), concluded that coronary constriction was responsible for the diminished cardiac action and that vagal reflexes played a small part in the total response. The work of Bacq and Dworkin (38) and of Mack. Sawyer and Ettinger (39), however, seems to attribute a greater role to the cardiac nerves, both vagus and sympathetic. Youmans and others (40) emphasized that anesthesia depresses vagal reflexes. This may account for the variations observed between unanesthetized and anesthetized subjects.

Electrocardiographic observations were made by us in 81 experiments in which the pituitary fractions were tested and in 36 of them there was alteration of cardiac rhythm. Many of the animals were used for studies with several of the anesthetic agents tested but did not necessarily have arrhythmias with each agent, as is evident from the summary of experiments given in table 1.

There was definite evidence of an initial slowing in heart rate in many of the experiments and in a large majority of the remainder, brief initial acceleration was followed by a prolonged and pronounced decrease below the rate at the time the drug was injected. In the use

TABLE 5

CARDIAC IRREGULARITIES WHICH OCCURRED IN DOGS UPON THE ADMINISTRATION OF 1 UNIT PER KILOGRAM OF PITUITRIN DURING THE INDICATED ANESTHETIC PROCEDURES AND OF PITRESSIN AND PITOCIN DURING CYCLOPROPANE ANESTHESIA

	Cyclopropane with:			Pituitrin with:					
	Pituitrin	Pitressin	Pitocin	Chloroform	Spinal	Conscious	Ether	Nembutal	Chlorotone
No. of animals	18	12	10	3	9	13	3	3	3
No. of experiments	22	14	10	3	9	14	3	3	3
Experiments with:									
No irregularities	17	10	8	2	0	0	3	3	3
S-A Tachycardia	1				1				
S-A Block	1		2		5	2			
S-A Extra Systole	1	1			2	7			
Coupling	1	1			5	8			
Auricular flutter and fibrillation	1								
Auricular flutter and sinoauricular rhythm					2	11			
A-V Block	2	1			5	8			
A-V Extra systole	1	1			2	1			
A-V Rhythm	2	1	1		2	4			
Ventricular extra systole and premature contraction	3	3		1		1			
Slow ventricular rhythm	1					1			

The injection of pituitrin in 2 different animals during cyclopropane anesthesia resulted in the occurrence, respectively, of bundle branch block and ventricular tachycardia in five second bursts. One other animal with cyclopropane and one when conscious had marked cardiac slowing with repeated periods of four to five seconds of asystole.

of pituitrin only, in 49 experiments in which this point could be analyzed, there was an initial slowing in 22 and secondary slowing in 11 other experiments. Three other animals had transient slowing and then prolonged acceleration in rate and only 4 had primary and continued accelerations. Ten of 12 animals in which pitressin was used and 7 of 10 in which pitocin was employed had ultimate slowing. The declines in rate were from 15 to as much as 100 beats per minute. Several of the animals had declines to rates of only 17 to 30 per minute.

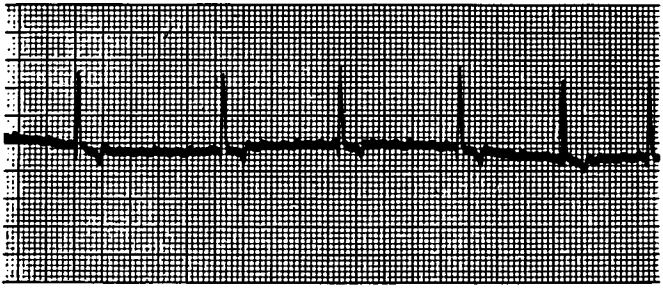


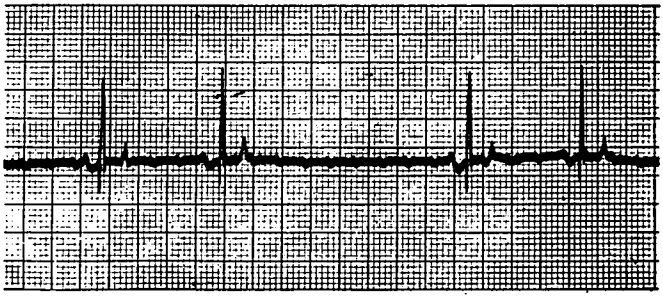
FIG. 5. Electrocardiogram following administration of pituitrin during cyclopropane anesthesia which shows the simultaneous occurrence of auricular flutter and auricular fibrillation.

Arrhythmias of nearly every type were produced in the course of the investigation and predominated when pituitrin was injected into the group of conscious animals, or into those having spinal analgesia, as the data of table 5 indicate. Each of the 13 conscious animals and each of the 9 with spinal analgesia had some type of arrhythmia, as did 4 of the 18 anesthetized with cyclopropane. In one of these during cyclopropane anesthesia auricular flutter and auricular fibrillation occurred simultaneously, as is illustrated in figure 5. One of 3 tested during chloroform anesthesia exhibited ventricular premature contractions. No irregularities were produced when pituitrin was used during 3 experiments each with ether, chloretone or nembutal as the anesthetic agent. Irregularities were produced in 4 of 12 animals when pitressin was tested during cyclopropane anesthesia. Arrhythmias were observed in 2 of 10 animals tested with pitocin during cyclopropane anesthesia. These irregularities consisted of brief periods of sino-auricular block accompanied in one instance by auriculoventricular nodal rhythm.

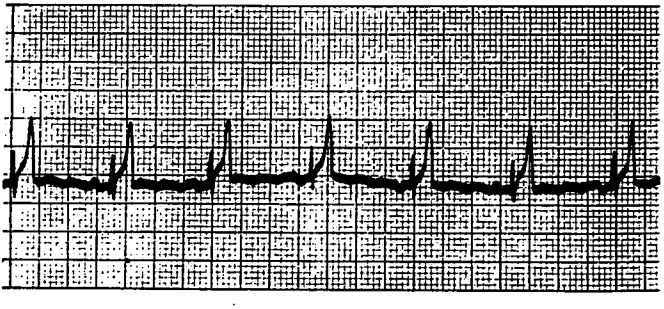
Some of the types of arrhythmias require special comment. In the conscious animal sino-auricular extra systoles, coupling of sino-auricular beats and auriculoventricular block each occurred in 50 per

cent or more of the 14 experiments. Even more striking was the appearance simultaneously of auricular flutter and sino-auricular rhythm in 11 experiments. Electrocardiograms illustrating these dual rhythms are presented in figure 6. The mechanism for this can be explained if one considers that the circuit for the flutter is timed so that refractory tissue is not encountered in passage of some of the normal sinus impulses. Evidence of the occurrence of this unusual combination of rhythms appeared in an illustration of a previous investigation (32), but no comment or statement of its recognition was included. The phenomenon was also noted by others who were inclined to believe it an artefact (33). Careful analysis of the time relationship of the P and "f" waves in the 11 experiments offers conclusive evidence that two entirely independent pacemakers were functioning simultaneously, frequently for periods of as much as five

(A)



(B)



(C)

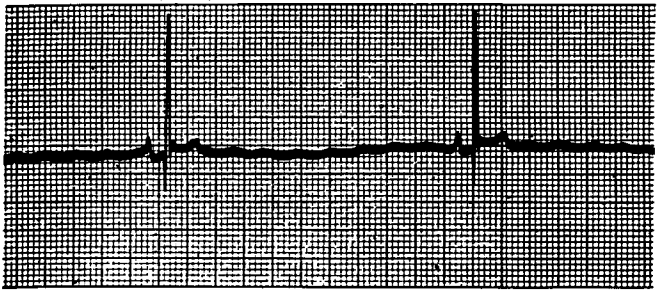


FIG. 6. Electrocardiographic records from 3 of the 11 conscious animals, in which there was the simultaneous occurrence of auricular flutter and sino-auricular rhythm initiated by pituitrin, 1 unit per kilogram intravenously.

minutes.* The onset of such dual rhythm was from thirty seconds to three or four minutes after injection of the pituitrin and in one instance the two rhythms continued for thirteen minutes.

Sino-auricular and auriculoventricular nodal blocking were common in animals with spinal analgesia. The animals anesthetized with cyclopropane and tested with either pituitrin or pitressin had ventricular premature contractions as the most frequent arrhythmia.

A condition closely approaching cardiac arrest occurred in 2 experiments in which there were asystoles for repeated periods of four and five seconds. One of these was in an animal anesthetized with cyclopropane, but the other was a conscious animal. These asystoles are illustrated in figures 7A and 7B. This type of irregularity might closely parallel the condition which prevails in clinical accidents as published in reports.

Effects of Epinephrine-Pituitrin Combinations on Cardiac Rhythm. —Since marked sensitivity to epinephrine is known to occur during cyclopropane anesthesia it seemed desirable to determine whether or not the injection of pituitrin might increase or otherwise modify this sensitivity. It was further desirable to determine whether or not epinephrine modifies the effects of pituitrin, a point which has been investigated with other anesthetic agents by Kepinow (41), Niculescu (42), Rossler (43) and Melville et al. (44).

All animals were, therefore, standardized to the dose of epinephrine which would just cause ventricular tachycardia during cyclo-

* An alternative interpretation of these tracings could be that they represented a rapid sino-auricular rhythm with auriculoventricular blocking. The close proximity of the "f" to the P wave in the first complex of figure 6A, of the third complex of figure 6B, and of the first complex of figure 6C seems to refute such an interpretation.

pane anesthesia, and the following procedures were then tried with such a dose of epinephrine: (a) epinephrine was injected and followed by pituitrin; (b) epinephrine and pituitrin were injected together; (c) pituitrin was followed after two minutes by epinephrine, and (d) epinephrine was injected at longer intervals after pituitrin. Epinephrine before pituitrin did not modify in any way the alteration in rhythm seen after giving pituitrin alone. Following administration of pituitrin there appeared to be definite protection for periods of up to sixty minutes against the ventricular tachycardia produced by epinephrine. Complete protection was observed in all 7 experiments in which this effect was tested. There was eventual return of ventricular tachycardia when the same dose of epinephrine was injected. This proved that the pituitrin gave a real protective action instead of there being merely an adrenolytic effect from cyclopropane.

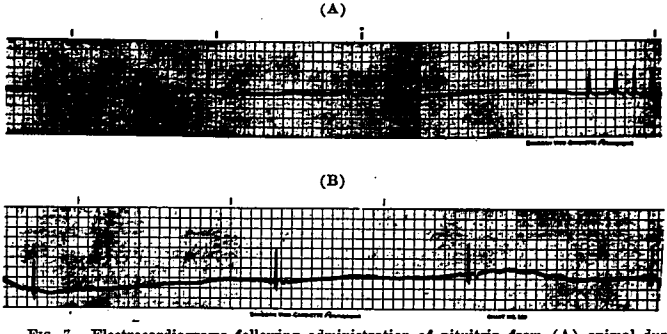


FIG. 7. Electrocardiograms following administration of pituitrin from (A) animal during cyclopropane anesthesia and (B) a conscious animal. In each instance a condition occurred which closely approached cardiac arrest since there are evident periods of asystole of four or five seconds duration.

The Effect of Light Cyclopropane Anesthesia.—Since it became evident that there were marked and consistent arrhythmias following injection of pituitrin in those animals which were not subjected to general anesthesia (conscious), and that in those during deep inhalation anesthesia the arrhythmias observed were of a less severe nature, we deliberately studied effects of pituitrin and pitressin during light cyclopropane anesthesia. It was thought, too, that these experiments would more closely approximate the situation as described in the clinical cases reported. Eight experiments were performed with light cyclopropane anesthesia and 6 of the animals exhibited cardiac irregularities upon injection of the drug. Included in this lightly anesthetized group were the 2 pregnant animals in which cesarean section was performed. One of these exhibited no irregularity

but the condition of the other deteriorated so rapidly that had not vigorous artificial ventilation with oxygen been instituted, the animal most certainly would have died (figure 3A). One month later when the latter animal had apparently completely recovered from the operation, pituitrin was again injected during cyclopropane anesthesia. Marked irregularities were again produced.

Other Effects.—Several other effects occurred quite frequently. Some of these have been noted previously in the monograph by Van Dyke (45) and the review (20) by Geiling.

Cyanosis of mucous membranes and peripheral blanching were constantly observed corollaries of administration of pituitrin or pitressin regardless of the presence of anesthesia. The excessive salivation which often accompanies cyclopropane anesthesia in dogs ceased abruptly for considerable periods following injection of pituitrin.

As evaluated by the changes in character of respiration, administration of pituitrin seemed to increase the depth of anesthesia and some of the dogs showed a visible expiratory effort. Marked acceleration to rates as high as 300 per minute also was recorded. Tidal volume was reduced and in several instances there was apnea which required artificial ventilation with oxygen.

Although the respiratory effects of pituitary extracts were not studied as intensively as the cardiovascular actions, they are an important factor in connection with problems of anesthesia. Slowing of respiration in rabbits was noted by Mairet and Bosc in 1896 (46). Since then other authors have repeatedly described shallow respiration and apneic periods in experimental animals (20). The explanations offered have been on the basis of either bronchial constriction or anemia of the respiratory center because of constriction of medullary vessels.

Regurgitation, retching and vomiting which mechanically may cause some degree of respiratory obstruction and hypoxia were initiated frequently after administration of the pituitary fractions. If an adequate airway is not maintained the lack of oxygen could be the *modus operandi* for cardiac irregularities. Defecation and urination also were produced with regularity.

Ataxia of the hind limbs, causing the unanesthetized animal to fall or walk with difficulty when placed in an upright position fifteen to twenty minutes after administration of pituitrin, was observed and attributed to deficient circulation.

COMMENT

Since there is such known variability of action of pituitrin as modified by anesthesia, the possibility of a pituitrin-cyclopropane incompatibility should be considered. Greene, in 1942 (7), and Belinkoff, in 1944 (47), believed there is an incompatibility. It was thought by

these authors that the additive effects of the two parasympathomimetic drugs are potentially dangerous and that their combined use in patients with vagotonic tendencies would be contraindicated. The views of these authors are based on clinical observations. Laboratory evidence shows that cardiac output is increased during moderate surgical anesthesia with cyclopropane (48). Thus it seems probable that anesthesia with this agent might decrease the deleterious cardiac effects following the injection of pituitrin rather than adding to them. This is consistent with the findings of this study.

In most of the recent clinical reports of fatal accidents attributed to the combination of cyclopropane and pituitrin the question of incompatibility is proposed and accepted without further analysis. Actual evidence of a definite incompatibility is exceedingly slight. Indeed, the experiments of this study tend to prove the absence of any such potentiation or incompatibility.

The pertinent and significant findings here reported can be cogently summarized as follows:

1. Marked falls of blood pressure usually were produced by pituitrin or pitressin administrations during anesthesia with the agents used in this investigation.
2. Epinephrine caused return of blood pressure to normal levels.
3. There was evidence of peripheral and coronary circulatory insufficiency which in a damaged heart might lead to accident—particularly if the added factor of hypoxia from some other cause already exists or occurs concomitantly.
4. Cardiac irregularities were produced by pituitrin and pitressin in all of the conscious animals and in a large percentage of lightly anesthetized animals.
5. Irregularities were infrequent during deeper anesthesia although a slowing of the pulse almost always was caused.
6. After pituitrin injection epinephrine is not likely to cause ventricular tachycardia. Ordinarily, epinephrine would cause tachycardia practically routinely during cyclopropane anesthesia in the dog.
7. Pitocin does not produce any marked deleterious effects with respect to blood pressure or cardiac rhythm.

Various authors have noted that species variations are exhibited by the posterior pituitary preparations (49, 46). Therefore, conclusions and extrapolations from observations of animal experimentation are to be viewed with caution and the implications therefrom cannot with impunity be transferred to man. With some reservations, however, a working concept can be formulated from laboratory work which will serve until such time as it is affirmed or denied by additional observations on man. Clinical studies designed to accomplish this are in progress.

A consideration of our results and of the work previously reported leads us to the following concept:

Pituitrin causes coronary constriction and potentially a resultant myocardial hypoxia.

Generalized hypoxia may result after administration of pituitrin or pitressin from either: (a)a modification of respiratory activity in such a way as to reduce effective exchange, or, (b) the stimulation of gastrointestinal contractions with frequent retching, vomiting or regurgitation which may mechanically interfere seriously with respiratory exchange.

Cardiac dysfunction in the presence of anesthesia is more likely in the state of preexisting myocardial hypoxia.

Since effects are more marked in unanesthetized or lightly anesthetized animals, then changes are most likely to be seen during recovery from an anesthetic, when (a) pituitrin has been administered just shortly before; (b) obstruction (retching) is most likely, and (c) some toxic agent (anesthetic) is still present in the myocardium.

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EXAMINATION DATE ANNOUNCED

AMERICAN COLLEGE OF ANESTHESIOLOGISTS

The next written examination for Fellow of the American College of Anesthesiologists will be held on April 15, 1950. Examination centers will be announced later.