EFFECTS OF N, N-DIBENZYL BETA-CHLOROETHYL AMINE (DIBENAMINE) ON THE CARDIOVASCULAR ACTIONS OF ADRENALINE, ACETYLCHOLINE, PITRESSIN AND ANGIOTONIN

by

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A THESIS

Presented to the Department of Physiology
and the Graduate Division of the University of Oregon Medical School
in partial fulfillment
of the requirements for the degree of
Master of Science

June, 1947

APPROVED:

[redacted]

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[redacted]

(Chairman, Graduate Council)

May 23, 1947

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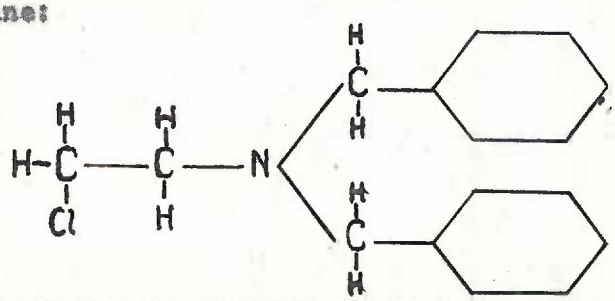
INTRODUCTION

Adrenergic and cholinergic visceral efferent nerves alter the activity of visceral effector cells by liberation of adrenaline and acetylcholine, respectively, at the neuro-effector junctions. Various compounds interfere with transmission of impulses at visceral neuro-effector junctions. There are satisfactory blocking agents for cholinergic nerves. For example, the action of acetylcholine on most visceral effectors may be blocked by relatively small doses of atropine. There is no satisfactory agent for blocking the action of adrenergic nerves. Several compounds have been shown to interfere with the action of adrenaline upon certain types of visceral effector cells. Among these compounds are various derivatives of ergot, several dioxane compounds, yohimbine, and priscol[1]. However, each of these compounds fails to block some of the actions of adrenaline or is impotent except in toxic doses.

Recently, Nickerson and Goodman[2][3][4][5] described a new agent which has adrenolytic actions. This compound is N, N-dibenzyl beta-chloroethyl amine:



This chemical is dispensed as the hydrochloride under the trade name, Dibenamine. It is a white, crystalline, solid which is stable in acid

solution and unstable in neutral or alkaline solution. In alkaline solution an ethylene-imine ring is formed, and this will combine with thiosulfate. Nickerson[3] found that administration of thiosulfate to animals would prevent the adrenolytic effects of Dibenamine. Dibenamine is only slightly soluble in water, but is soluble in 95% ethanol or in propylene glycol.

When Dibenamine is injected rapidly it produces an abrupt fall in arterial blood pressure, and the pressure usually returns to normal levels within about 30 minutes. When the drug is injected slowly, the arterial blood pressure may show no significant change. Within 30 minutes after the injection of Dibenamine, the pressor action of adrenaline is blocked in some species and is reversed in others. In cats the pressor action of adrenaline is reversed after Dibenamine and the depressor response is proportional to the dosage of adrenaline until a maximal fall in pressure is produced. Nickerson and Goodman[5] also demonstrated that the vasoconstriction produced by splanchnic (adrenergic) nerve stimulation was blocked by Dibenamine, but this required larger doses than those required to prevent the pressor action of circulating adrenaline.

Nickerson and Goodman[5] found that responses to adrenaline, or to adrenergic nerve stimulation, in various other visceral effectors were blocked. The nictitating membrane of the cat was relaxed and ptosis was produced after administration of Dibenamine. Mydriasis, widening of the palpebral fissure, and retraction of the nictitating membrane due to adrenaline, or to electrical stimulation of the cervical sympathetic nerve, were abolished or greatly reduced by Dibenamine. Pilomotor responses to adrenergic nerve stimulation were prevented.

Certain actions of adrenaline were not blocked by Dibenamine[5]. There was no interference with the inhibitory action of adrenaline upon the isolated small intestine of the rabbit and rat. The inhibitory action of adrenaline on the non-pregnant cat uterus in situ was unaffected by Dibenamine. The adrenaline-induced inhibition of the motility of an intestinal segment, in the form of a Thiry fistula in the unanesthetized dog, was not blocked by Dibenamine during the time when there was maximal interference with the pressor actions of adrenaline[6]. At present, adrenolytic effects of Dibenamine have been observed only in effectors showing an excitatory response to adrenaline, and they have not been observed in the effectors showing an inhibitory response to adrenaline.

Acceleration of the rate of the innervated heart was observed by Nickerson and Goodman[5] following adrenaline injection in anesthetized animals under the influence of Dibenamine. Raab and Humphreys[7] have reported that injection of Dibenamine causes a mild diminution of the cardio-accelerator effect of stimulating the stellate ganglion. Dibenamine also protects against the production of ventricular fibrillation by adrenaline in animals under cyclopropane anesthesia[4][8].

The present study is concerned with the cardiovascular actions of Dibenamine and with the effects of Dibenamine upon the cardiovascular responses to adrenaline, acetylcholine, pitressin, and angiotonin.

GENERAL METHODS

Dogs weighing between 8 and 12 kilograms were used. The experiments were run in two series. In one series, the animals received either Nembutal or morphine-ether anesthesia; in the other series, they were unanesthetized. In the anesthetized animals blood pressure and heart rate were recorded from the femoral artery by the use of a mercury manometer. Intestinal volume was recorded by means of a plethysmograph, according to the method of Hoskins and Gunning[9][10]. In the unanesthetized animals, heart rate was recorded by the use of an electrocardiograph. All the unanesthetized animals were trained to lie quietly on the table while drugs were being injected.

Dibenamine was prepared for injection by dissolving 200 mgm. in approximately 15 cc. of propylene glycol, and this was diluted with an equal amount of water. Injection of the solution was begun within 2 to 5 minutes after preparation. A period of five minutes or longer was required to complete the injection.

RESULTS

A. Anesthetized dogs.

Six dogs were used in obtaining direct blood pressure records of effects of test doses of the compounds before and after Dibenamine. Three dogs received Nembutal (1 gr. per 5 pounds) and three received ether after premedication with morphine (¼ gr.) The compounds were injected into the exposed femoral vein. Precautions were taken to prevent mixing of blood with acetylcholine prior to its injection.

The data from the six animals are listed in table I. In five of the experiments the reversal of the pressor action of adrenaline by Dibenamine was demonstrated. This is illustrated in figure 1. The reversal action began to appear within 20 minutes after the injection of Dibenamine; it became maximal within 30 minutes, and persisted for over four hours. The degree of fall in blood pressure caused by adrenaline after Dibenamine was proportional to the dose of adrenaline. These results confirm those of Nickerson and Goodman(5).

Adrenaline typically produces an initial active constriction of vessels in the intestinal wall in animals under morphine-ether anesthesia. This is indicated by the fact that the intestinal volume shows an initial decrease in spite of a rising blood pressure(11). In the one animal studied, the active vasoconstriction was prevented by Dibenamine. A record illustrating this result is shown in figure 2.

In the atropinized animal acetylcholine produced its typical pressor effect. After Dibenamine the atropinized animal exhibited a pure fall in blood pressure in response to acetylcholine injection. In figure 3 the alteration by Dibenamine of the effect of acetylcholine

(Continued on p. 11)

TABLE I

Data on Anesthetized Animals

Dog number and weight in kilos	Anesthetic	Drug given before Dibenamine	Blood pressure change before Dibenamine	Drug given after Dibenamine	Time after Dibenamine	Blood pressure change after Dibenamine
1. 10	Nembutal	Adrenalin (2 cc. of 1:100,000)	+70 mm.	Adrenalin (2 cc. of 1:100,000)	20 min.	-70 mm.
				Adrenalin (2 cc. of 1:100,000)	60 min.	-90 mm.
2. 10	Morphine ether (left vagus cut)	Adrenalin (2 cc. of 1:100,000)	+24 mm. to -30 mm.	Adrenalin (2 cc. of 1:100,000)	20 min.	none
				Adrenalin (4 cc. of 1:100,000	24 min.	none
				Atropine (1/50 gr.)	30 min.	
				Adrenalin (4 cc. of 1:100,000)	50 min.	-22 mm.
				Adrenalin (4 cc. of 1:100,000)	60 min.	-48 mm.
				Adrenalin (1 cc. of 1:100,000)	81 min.	-90 mm.

TABLE I (cont.)

Dog number and weight in kilos	Anesthetic	Drug given before Dibenamine	Blood pressure change before Dibenamine	Drug given after Dibenamine	Time after Dibenamine	Blood pressure change after Dibenamine
3. 14	Morphine ether (both vagi cut, both carotid sinuses excised			Adrenalin (2 cc. of 1:100,000	30 min.	none
				Pitressin (10 units)	40 min.	+450 mm. to -425 mm.
				Adrenalin (2 cc. of 1:100,000)	80 min.	-30 mm.
4. 11	Nembutal (rt. vagotomy, rt. cervical sympathectomy, rt. carotid sinusectomy; lt. vagus ligated	Adrenalin (1 cc. of 1:100,000)	+55 mm.	Adrenalin (1 cc. of 1:500,000)	30 min.	-30 mm.
				Adrenalin (1 cc. of 1:100,000)	32 min.	-60 mm.
		Angiotonin (5 units)	+34 mm.	Angiotonin (5 units)	33 min.	+56 mm.
		Angiotonin (5 units 10 min. after dose)	+34 mm.	Pitressin (2 units)	36 min.	+100 mm.
5. 10	Nembutal	Atropine (1/50 gr.)				
		Acetylcholine (10 mgm.)	+120 mm.	Acetylcholine (10 mgm.)	30 min.	-50 mm.
6. 10	Morphine ether	Adrenalin (4 cc. of 1:100,000)	+42 to -21 mm.	Adrenalin (4 cc. of 1:100,000)	60 min.	+4 to+6 to -16 mm.
				Pitressin (10 units)	70 min.	+76 mm.

Figure 1

The effect of adrenaline on the blood pressure of an anesthetized dog before (left) and after (right) Dibenamine.

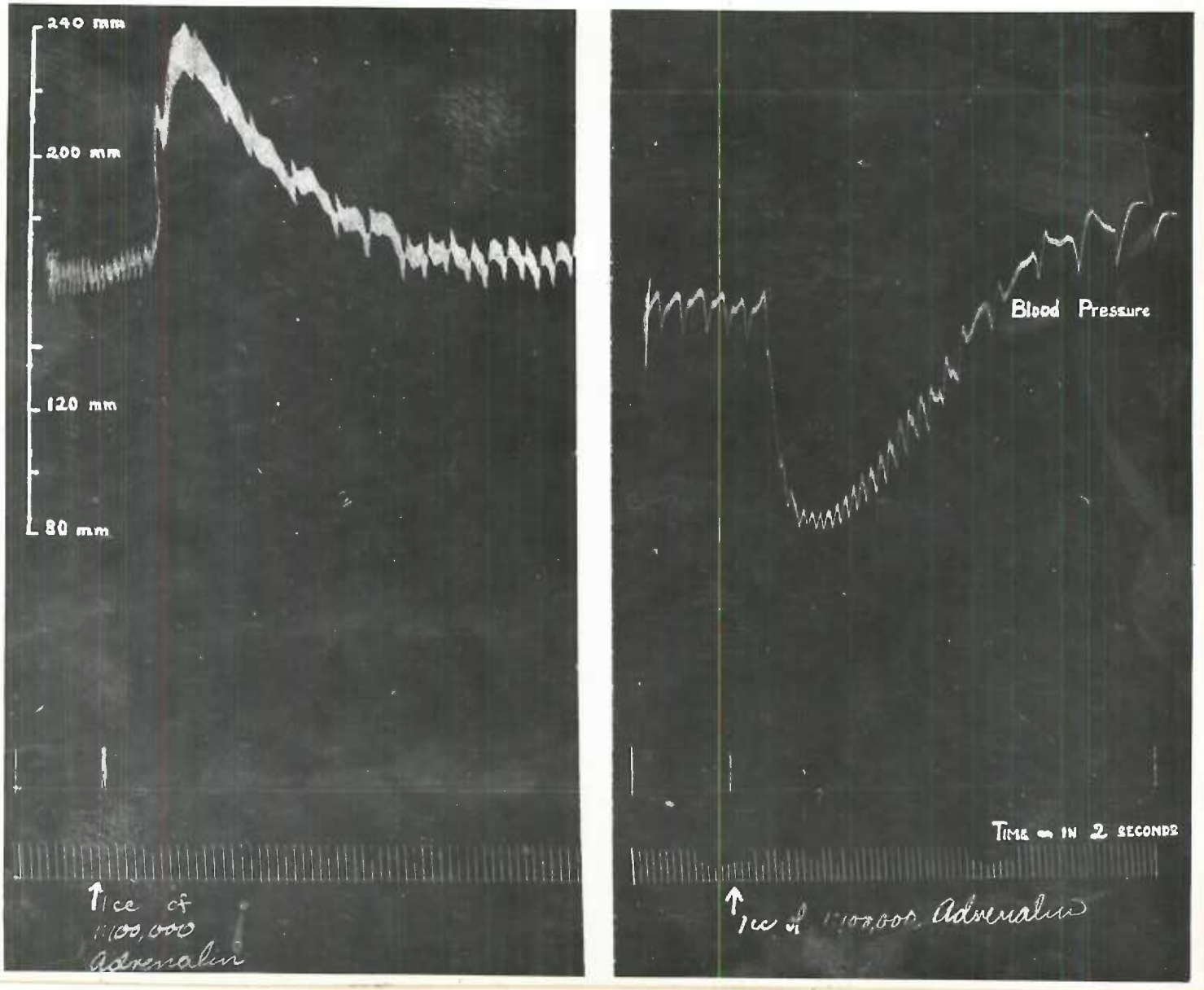

240 mm
200 mm
120 mm
80 mm
1 cc of 1:100,000 Adrenalin
Blood Pressure
Time in 2 seconds
1 cc of 1:100,000 Adrenalin

Figure 2

The effect of adrenaline on intestinal volume and blood pressure of an anesthetized dog before (upper record) and after (lower record) Dibenamine. The upper curve on both records represents intestinal volume, the lower curve represents blood pressure.

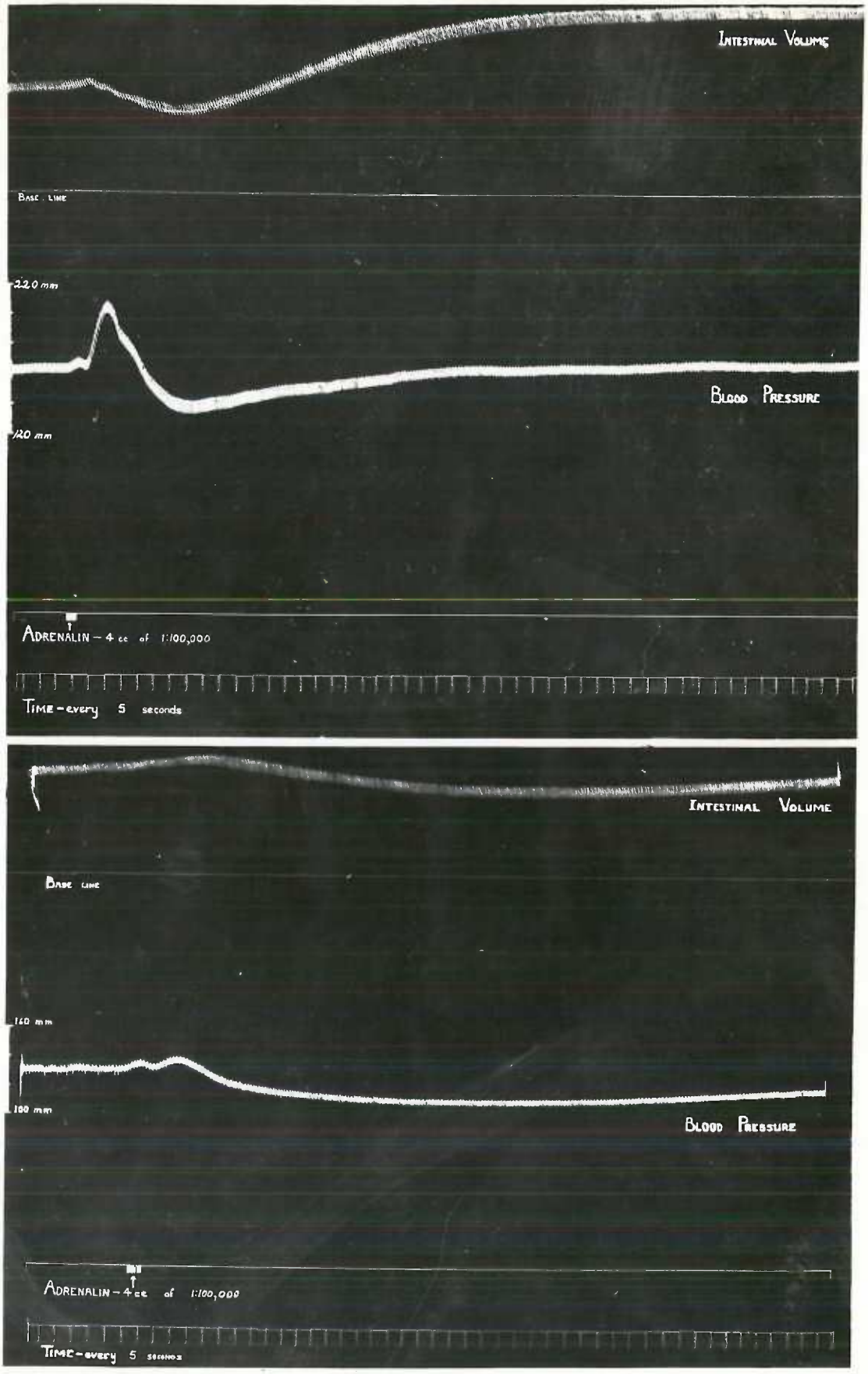
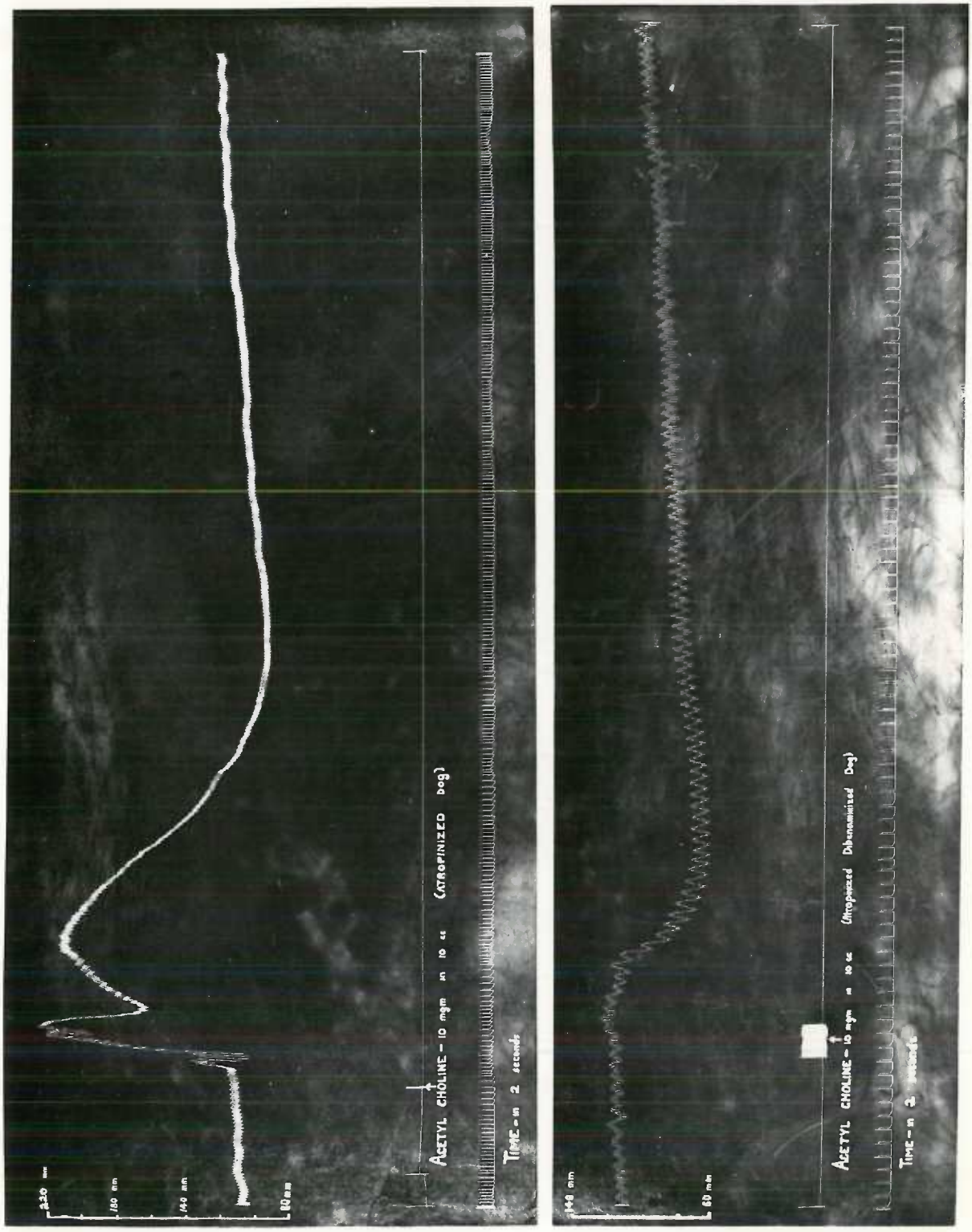

Intestinal Volume
Base Line
220 mm
Blood Pressure
120 mm
Adrenalin – 4 cc of 1:100,000
Time – every 5 seconds
Intestinal Volume
Base Line
160 mm
100 mm
Blood Pressure
Adrenalin – 4 cc of 1:100,000
Time – every 5 seconds

Figure 3

The effect of acetylcholine on blood pressure of an anesthetized, atropinized dog before (upper record) and after (lower record) Dibenamine.


220 mm
180 mm
140 mm
80 mm
ACETYL CHOLINE – 10 mgm in 10 cc (ATROPINIZED Dog)
TIME – in 2 seconds
140 mm
80 mm
ACETYL CHOLINE – 10 mgm in 10 cc (Atropinized Dibenamined Dog)
TIME – in 2 seconds

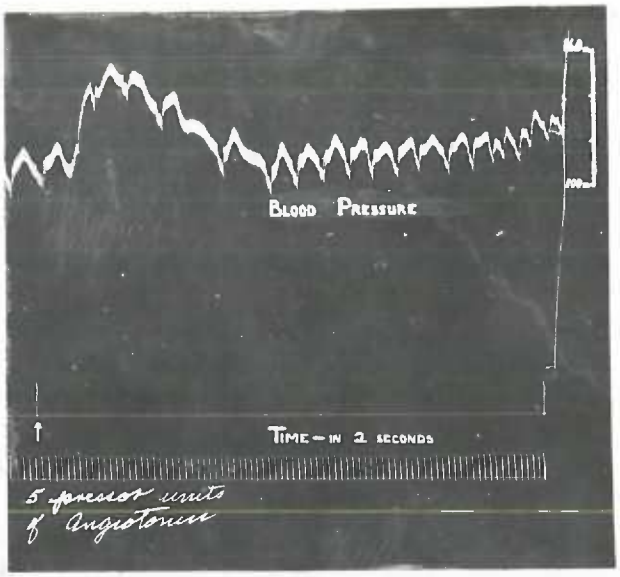
upon blood pressure is illustrated. Nickerson and Goodman[5] performed the same type of experiment and obtained similar results. These results are in accord with the generally accepted interpretation that the rise in blood pressure produced by acetylcholine in atropinized animals is dependent on liberation of adrenine.

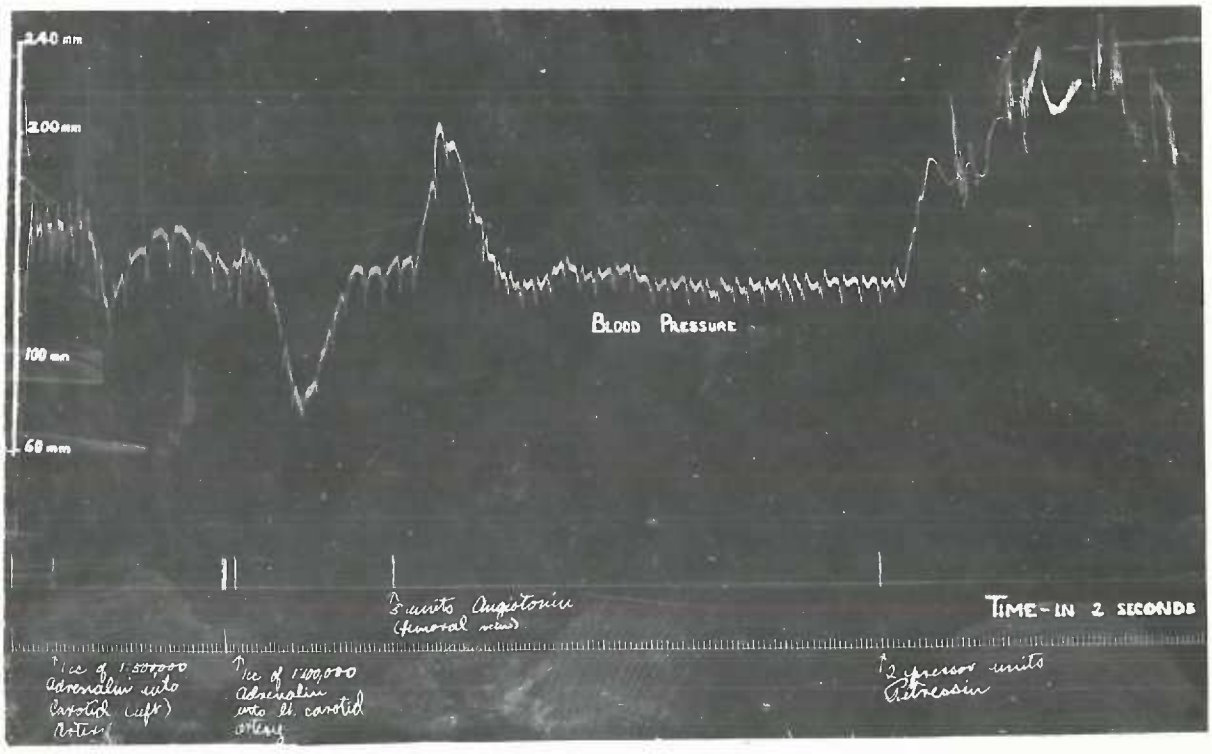
The pressor actions of pitressin and angiotonin were tested before and after Dibenamine. The data tabulated for three dogs show that at the time when the pressor action of adrenaline was reversed there was no interference with the pressor actions of either pitressin or angiotonin. These results are illustrated in figure 4.

In one animal, in which neurogenic hypertension had been produced by sino-aortic denervation, Dibenamine alone caused a profound fall in blood pressure. Such a fall is not caused by Dibenamine in an anesthetized animal with sino-aortic nerves intact. It is known that sino-aortic denervation causes a high vasoconstrictor tonus[12]. Therefore, it is to be expected that a depressor effect of Dibenamine itself would be demonstrated in these animals if the actions of vasoconstrictor nerves are blocked by it.

Figure 4

The effect of angiotonin on the blood pressure of an anesthetized dog before (upper record) and after (lower record) Dibenamine. The lower record also illustrates the effects of adrenaline and pitressin on the blood pressure of this animal after Dibenamine.


BLOOD PRESSURE
TIME – IN 2 SECONDS
5 pressor units of Angiotonin


240 mm
200 mm
100 mm
68 mm
BLOOD PRESSURE
3 units Angiotonin (femoral vein)
TIME – IN 2 SECONDS
1 cc of 1:500,000 Adrenalin into Carotid (left) retrograde
1 cc of 1:100,000 Adrenalin into lt. carotid artery
2 pressor units Pitressin

B. Unanesthetized dogs.

Heart rate was studied in eight unanesthetized dogs. Six of these were intact; one had the heart denervated, and the other had the spinal cord transected at the level of T_{12}. The effects of adrenaline, acetylcholine, pitressin, and angiotonin upon heart rate were recorded before and at stated intervals after administration of Dibenamine. During each series of drug injections a needle was placed in the vein and kept open with isotonic saline. At the desired time the syringe containing the exact amount of drug to be injected was substituted for the syringe containing saline, and the drug was injected rapidly. Ample time was allowed for restoration of the resting heart rate between injections of the test compounds.

1. Effects of Dibenamine on heart rate. Dibenamine alone caused an increase in heart rate in each of the six intact animals. The maximal increase above the basal rate ranged from 46% to 95%, and it occurred in 10 to 25 minutes from the beginning of the injection. Usually the rates returned to the resting level within one to three hours.

2. Effects of adrenaline on heart rate before and after Dibenamine. Continuous electrocardiographic records were obtained during the test dose of adrenaline (2 cc. of a 1-100,000 dilution) in four dogs before and after administration of Dibenamine. The results of the individual experiments are given in table II. The averages of the rates for the four animals are graphed in figure 5.

The test dose of adrenaline produced a maximal decrease in rate of 45% to 57% in the four intact animals before Dibenamine. Since the only direct action of adrenaline upon the sino-auricular node

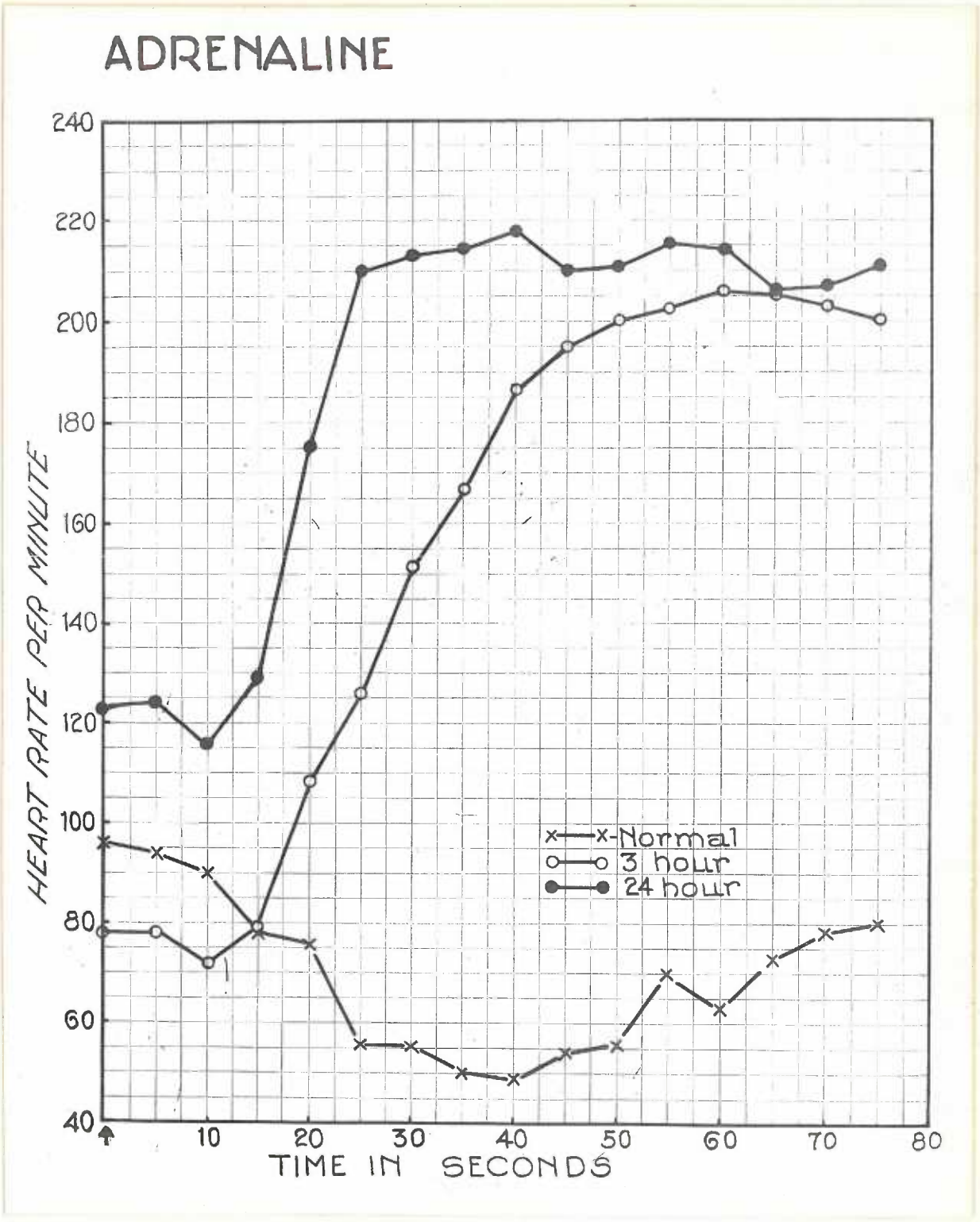
TABLE II

Effects of 2 cc. of a 1:100,000 solution of adrenaline on heart rate of intact unanaesthetized dogs before and after Dibenamine

Animal no.	Weight in kilos	% change in heart rate	"Basal" heart rate	Heart rate / minute after injection; calculated in successive 5 seconds intervals														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
NORMAL DOGS BEFORE DIBENAMINE																		
3b	11	-57%	112	98	99	72	97	59	51	53	49	42	59	59	60	56	56	60
4	13	-49%	100	100	109	103	61	59	60	51	62	75	76	96	90	102	124	120
6	9	-45%	66	69	70	52	53	49	45	48	36	36	36	44	44	45	47	44
7	10	-53%	105	110	80	84	75	58	66	49	49	62	51	81	69	88	84	99
DOGS 3 HOURS AFTER DIBENAMINE																		
3b	11	+163%	67	96	81	109	181	195	207	204	214	226	229	228	228	227	223	221
4	13	+ 97%	94	95	82	84	118	143	168	172	178	181	182	185	194	182	182	181
6	9	+233%	62	60	62	68	53	68	126	166	193	203	200	206	202	199	199	193
7	10	+206%	69	71	75	66	62	96	100	126	162	169	189	194	210	213	208	204
DOGS 24 HOURS AFTER DIBENAMINE																		
3b	11	+102%	118	133	114	124	172	207	203	215	238	228	234	239	232	229	230	227
4	13	-150%	139	126	126	168	168	196	197	198	207	207	206	200	197	191	200	197
6	9	-158%	76	72	65	84	108	178	189	196	188	147	144	157	165	152	146	167
7	10	+ 64%	161	167	167	192	233	261	262	247	250	259	260	264	260	252	253	252

Figure 5

The effect of adrenaline (2 cc. of a 1:100,000 dilution) on the heart rate of 4 unanesthetized dogs. Crosses indicate the effect of adrenaline before Dibenamine, circles indicate the effect 3 hours after Dibenamine, and dots indicate the effect 24 hours after Dibenamine administration.


ADRENALINE
HEART RATE PER MINUTE
240
220
200
180
160
140
120
100
80
60
40
10
20
30
40
50
60
70
80
TIME IN SECONDS
x—x-Normal
o—o 3 hour
●—● 24 hour

is excitatory, this bradycardia is best explained on the basis of reflex activation of cardio-inhibitory nerves during a rise in blood pressure.

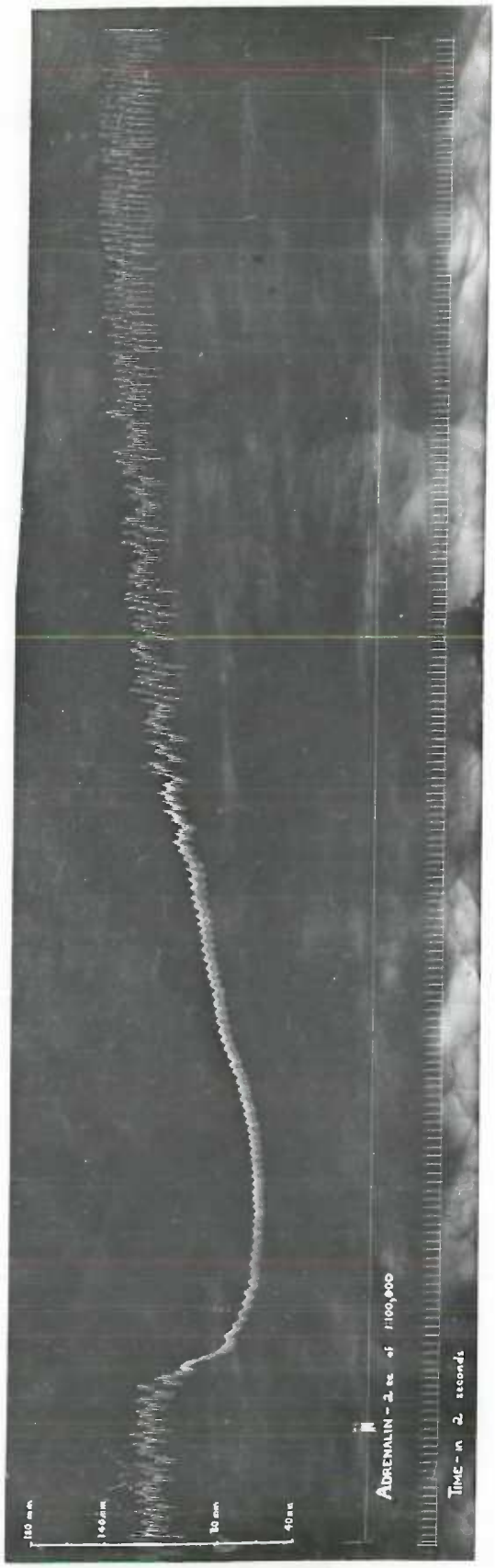
Three hours after Dibenamine had been administered the average heart rate was 19 beats per minute slower than the average of the control rates. At this time the test dose of adrenaline produced an acceleration of 97% to 208% above the rate preceding the injection. Acceleration was clearly evident within 20 seconds after the injection of adrenaline and progressed smoothly to a plateau at about 50 seconds. It was still maintained at 75 seconds. The effects of adrenaline on the heart rate 24 hours after Dibenamine are similar to the effects seen 3 hours after Dibenamine.

The reversal of the effect of the test dose of adrenaline on the heart rate of unanesthetized animals by Dibenamine may be readily explained if it is considered that adrenaline causes a fall in blood pressure in the unanesthetized animals after they have received Dibenamine. If such is the case, a smooth cardiac acceleration would be expected because of the combination of the direct accelerator influence of adrenaline and the reflex accelerator influence of the fall in blood pressure. This interpretation is supported by the observation that in an unanesthetized animal, with spinal cord transected at T_{12} so that blood pressure could be recorded from the femoral artery, Dibenamine caused a pronounced depressor response after the injection of the test dose of adrenaline. This is illustrated in figure 6.

The striking cardiac acceleration in response to adrenaline after Dibenamine would seem to indicate that the cardiac effects of adrenaline or of cardio-accelerator nerves are not blocked. However, a large

Figure 6

The effect of adrenaline one hour after Dibenamine administration on the blood pressure of an unanesthetized dog with spinal cord transected at T_{12}.


160 mm
140mm
80 mm
40mm
ADRENALIN - 2 cc of 1:100,000
TIME - in 2 seconds

part of this acceleration could be on the basis of decreased tonus of cholinergic cardio-inhibitory nerves. The effect of Dibenamine on the responses of the sino-auricular node to adrenaline can be determined only by the use of a denervated heart. In one animal the heart was chronically denervated by a series of three operations which resulted in bilateral removal of the sympathetic chains from the stellate through the 4th thoracic ganglia inclusive and bilateral section of the vagi in the midcervical region. In this preparation a partial blocking of the effects of adrenaline on the sino-auricular node was clearly demonstrated. The results are illustrated in figure 7. These results suggest the possibility that the acceleration of the innervated heart by Dibenamine is due in part to direct action on the sino-auricular node.

3. Effects of Dibenamine on the cardio-accelerator response to acetylcholine. The brief hypotension produced by intravenous injection of acetylcholine elicits a typical cardio-accelerator response. The acceleration is due largely to reflex activation of adrenergic nerves and to liberation of adrenine (13). Five animals were given a test dose of 1 mgm. of acetylcholine at 3 hours and again at 24 hours after the administration of Dibenamine. In figure 8 a curve is shown which illustrates the average of the cardio-accelerator responses to the test dose of acetylcholine in 23 animals. The other two curves in figure 8 illustrate the averages of the cardio-accelerator response to acetylcholine in four animals at 3 hours and at 24 hours after Dibenamine. The results from the individual experiments are listed in table III. The degree of acceleration was at least as great after Dibenamine as before. In both the normal animals and in those under

Figure 7

The effect of 2 cc. of a 1:500,000 dilution of adrenaline on the heart rate of an unanesthetized dog with denervated heart. Crosses indicate effect before Dibenamine, circles indicate effect after Dibenamine, and dots indicate effect 24 hours after Dibenamine administration.

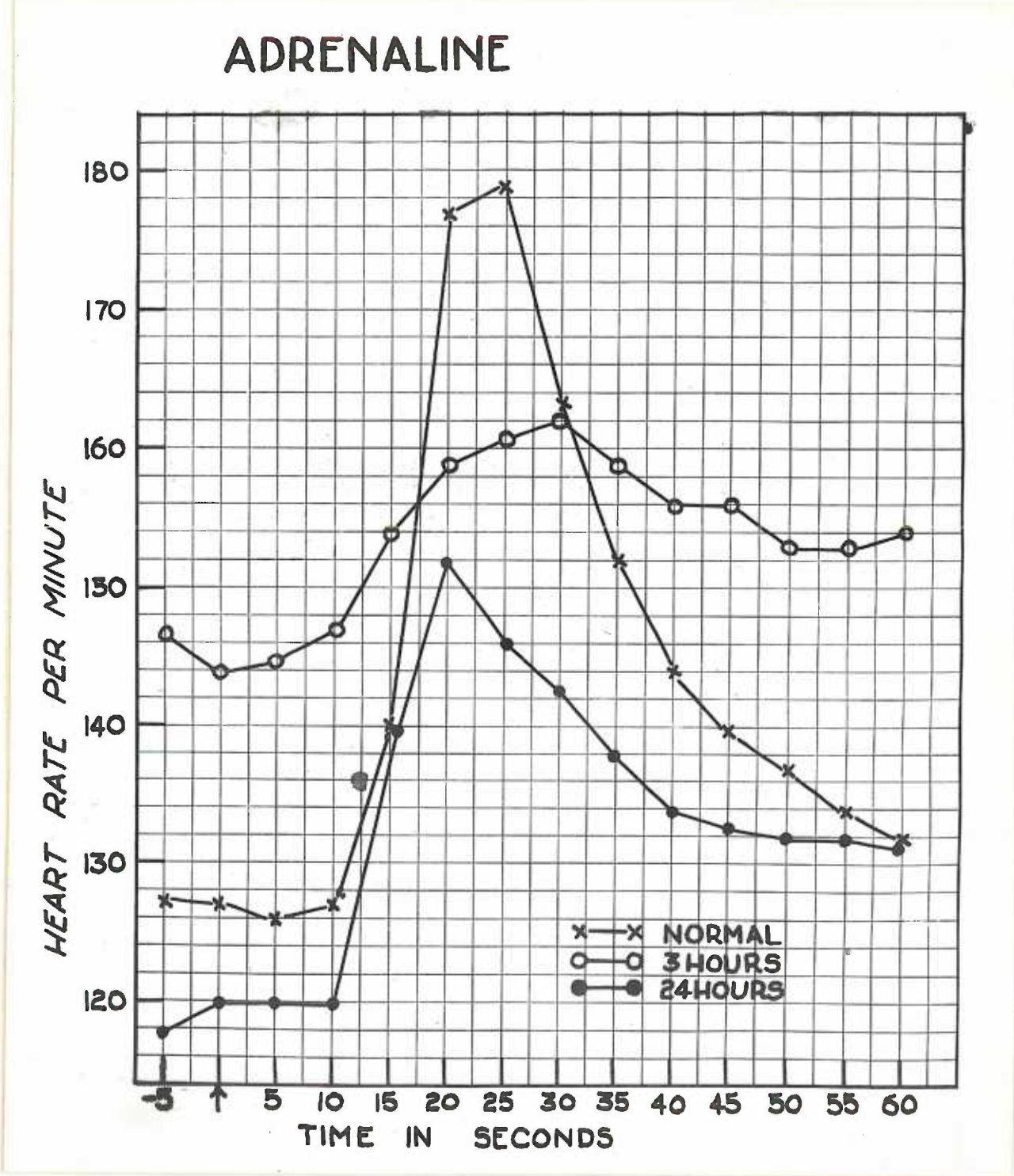

ADRENALINE
HEART RATE PER MINUTE
180
170
160
150
140
130
120
-5
5
10
15
20
25
30
35
40
45
50
55
60
TIME IN SECONDS
NORMAL
3 HOURS
24 HOURS

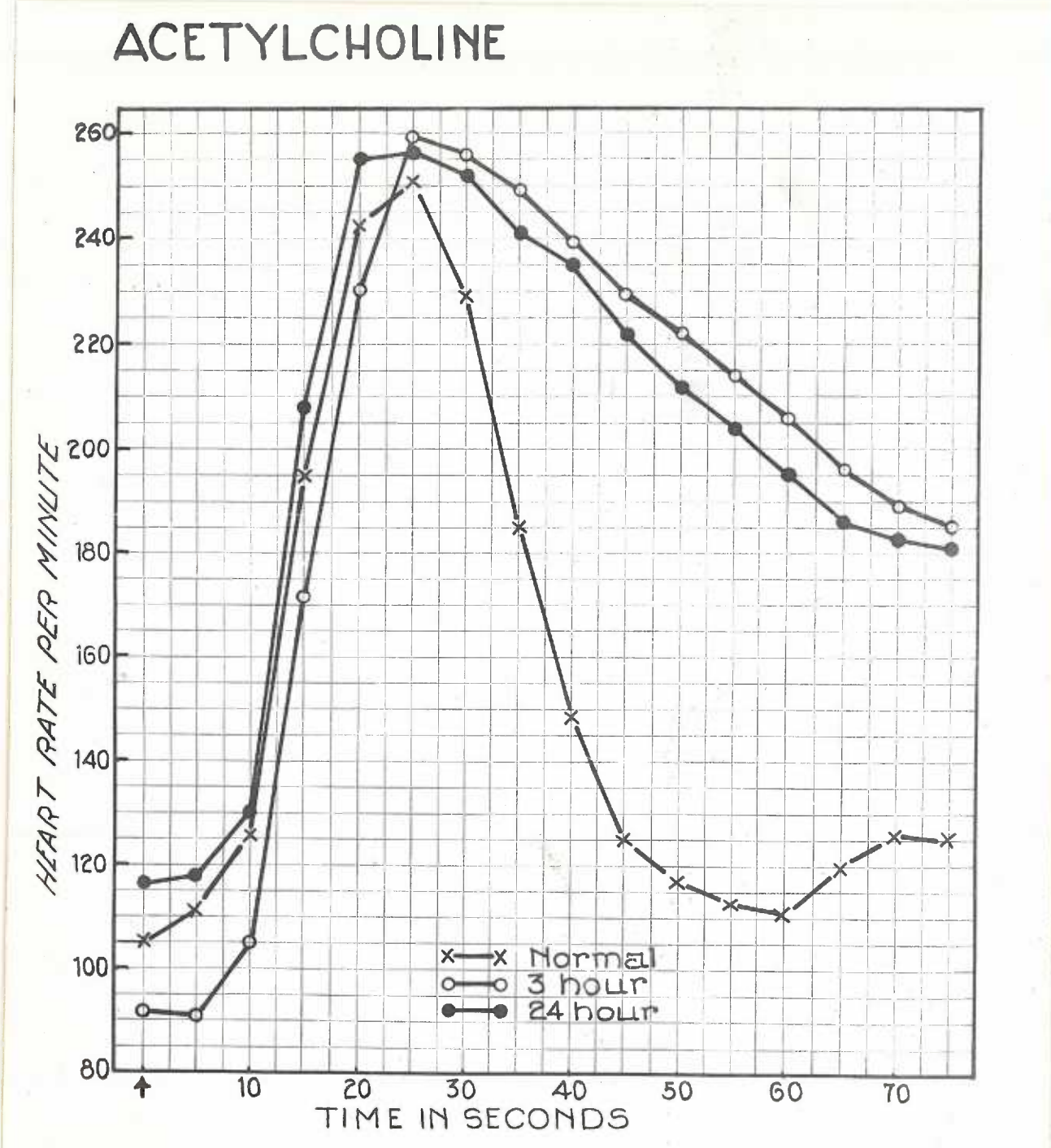
TABLE III

Effects of 1 mgm. of acetylcholine on heart rate of intact, unanesthetized dogs before and after Dibenamine

Animal no.	Weight in kilos	% change in heart rate	"Basal" heart rate	Heart rate / minute after injection: calculated in successive 5 second intervals														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AVERAGE OF 23 NORMAL DOGS BEFORE DIBENAMINE																		
		+145%	105	111	126	195	243	281	329	185	148	125	117	113	111	120	126	125
DOGS 3 HOURS AFTER DIBENAMINE																		
3a	11	+189%	101	96	132	222	258	287	290	282	270	252	240	225	217	201	195	192
3b	11	+212%	89	95	84	138	253	283	289	288	286	276	273	264	258	242	230	224
6	9	+264%	73	78	106	199	240	264	265	259	239	229	218	202	180	174	162	154
7	10	+ 93%	104	95	99	129	169	201	181	168	161	160	159	166	169	169	168	169
DOGS 24 HOURS AFTER DIBENAMINE																		
3a	11	+133%	127	134	175	285	298	298	294	289	276	261	256	232	213	201	198	189
3b	11	+152%	118	120	123	204	280	287	289	284	284	277	265	260	253	241	236	228
4	13	+104%	122	126	169	234	245	249	244	240	229	200	181	170	166	163	160	159
6	9	+133%	99	84	89	180	223	231	229	204	204	189	179	181	170	167	167	163
7	10	+ 91%	130	124	103	147	329	317	304	190	184	182	178	179	174	169	167	166

Figure 8

The effect of 1 mgm. of acetylcholine on the heart rate of unanesthetized dogs before and after Dibenamine. Crosses indicate the effect on 23 normal dogs, circles indicate the effect on 4 dogs receiving acetylcholine 3 hours after Dibenamine, and dots indicate the effect on 4 dogs receiving acetylcholine 24 hours after Dibenamine administration.


ACETYLCHOLINE
HEART RATE PER MINUTE
260
240
220
200
180
160
140
120
100
80
10
20
30
40
50
60
70
TIME IN SECONDS
Normal
3 hour
24 hour

the influence of Dibenamine, the maximum increase in heart rate in response to acetylcholine occurred at 25 seconds. In the normal animals the rate fell off rapidly, to reach a resting level within 50 to 60 seconds, but in the animals under Dibenamine the return to the resting level was quite delayed. The persistence of the fast rate would indicate that Dibenamine interferes with the restoration of the blood pressure to the normal level after a test dose of acetylcholine.

4. Effects of Dibenamine upon the cardio-inhibitory response to pitressin and angiotonin. The experiments with the anesthetized animals have shown that the pressor actions of pitressin and angiotonin are not impaired by Dibenamine. These compounds produce profound reflex bradycardia in unanesthetized dogs during the rise in blood pressure resulting from their vasoconstrictor action[14]. If the vasoconstrictor action of these compounds is not blocked by Dibenamine, they would be expected to produce the typical cardio-inhibitory response. The effects of a test dose of 1½ pressor units of pitressin before and after Dibenamine were studied in four dogs, and the effects of a test dose of 20 pressor units of angiotonin were studied in three dogs. The data from the individual experiments are given in tables IV and V. The averages of the cardio-inhibitory responses to pitressin in four dogs at 3 hours and at 24 hours after Dibenamine are shown in figure 9, and these are compared with a curve showing the averages of 14 normals. The effect of pitressin on the blood pressure of the dog with spinal cord transected at T_{12} is illustrated in figure 10.

From these results it is evident that Dibenamine does not alter the cardio-inhibitory responses produced by the injection of pitressin and angiotonin. This would indicate that there is no impairment of the

TABLE IV

Effect of 1½ pressor units of pitressin on heart rate of intact, unanesthetized dogs before and after Dibenamine

Animal no.	Weight in kilos	% change in heart rate	"Basal" heart rate	Heart rate / minute after injection calculated in successive 5 second intervals														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AVERAGE OF 14 NORMAL DOGS BEFORE DIBENAMINE																		
		-75%	108	105	100	87	41	34	29	29	27	30	32	35	45	40	43	44
DOGS 3 HOURS AFTER DIBENAMINE																		
3b	11	-74%	98	95	94	81	47	30	34	31	37	40	63	72	62	85	24	24
4	13	-28%	65	83	83	82	73	48	52	48	48	51	48	48	48	48	54	55
6	9	-56%	108	118	102	64	52	48	55	60	64	65	66	62	74	70	72	52
7	10	-81%	77	84	75	57	37	26	14	16	17	17	30	50	43	50	48	52
DOGS 24 HOURS AFTER DIBENAMINE																		
3b	11	-83%	112	118	97	89	36	33	19	19	26	24	31	45	47	110	31	25
4	13	-85%	95	100	88	67	27	23	17	14	14	15	21	24	25	31	37	47
6	9	-78%	84	81	87	70	30	25	21	24	25	26	39	40	43	47	49	43
7	10	-80%	172	175	135	57	73	50	48	56	51	39	37	50	46	47	32	46

TABLE V

Effect of 20 pressor units of angiotonin on heart rate of intact, unanesthetized dogs before and after Dibenamine

Animal no.	Weight in kilos	% change in heart rate	"Basal" heart rate	Heart rate / minute after injection calculated in successive 5 second intervals														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
NORMAL DOGS BEFORE DIBENAMINE																		
8	8	-39%	201	196	139	153	162	150	147	132	126	122	135	131	132	136	139	140
9	9	-40%	94	93	91	76	67	64	64	60	94	120	90	60	56	63	69	60
DOGS 3 HOURS AFTER DIBENAMINE																		
8	8	-49%	300	299	265	192	179	171	161	156	153	165	187	165	169	165	162	183
9	9	-62%	110	111	110	96	70	55	65	45	57	48	103	42	46	60	57	63
7	10	-43%	88	99	81	74	82	56	53	50	50	50	65	58	75	58	63	63

Figure 9

The effect of 1½ units of pitressin on the heart rate of unanesthetized dogs. Crosses indicate averages from 14 animals before Dibenamine, circles indicate averages from 4 dogs 3 hours after Dibenamine, and dots indicate averages from 4 dogs 24 hours after Dibenamine.

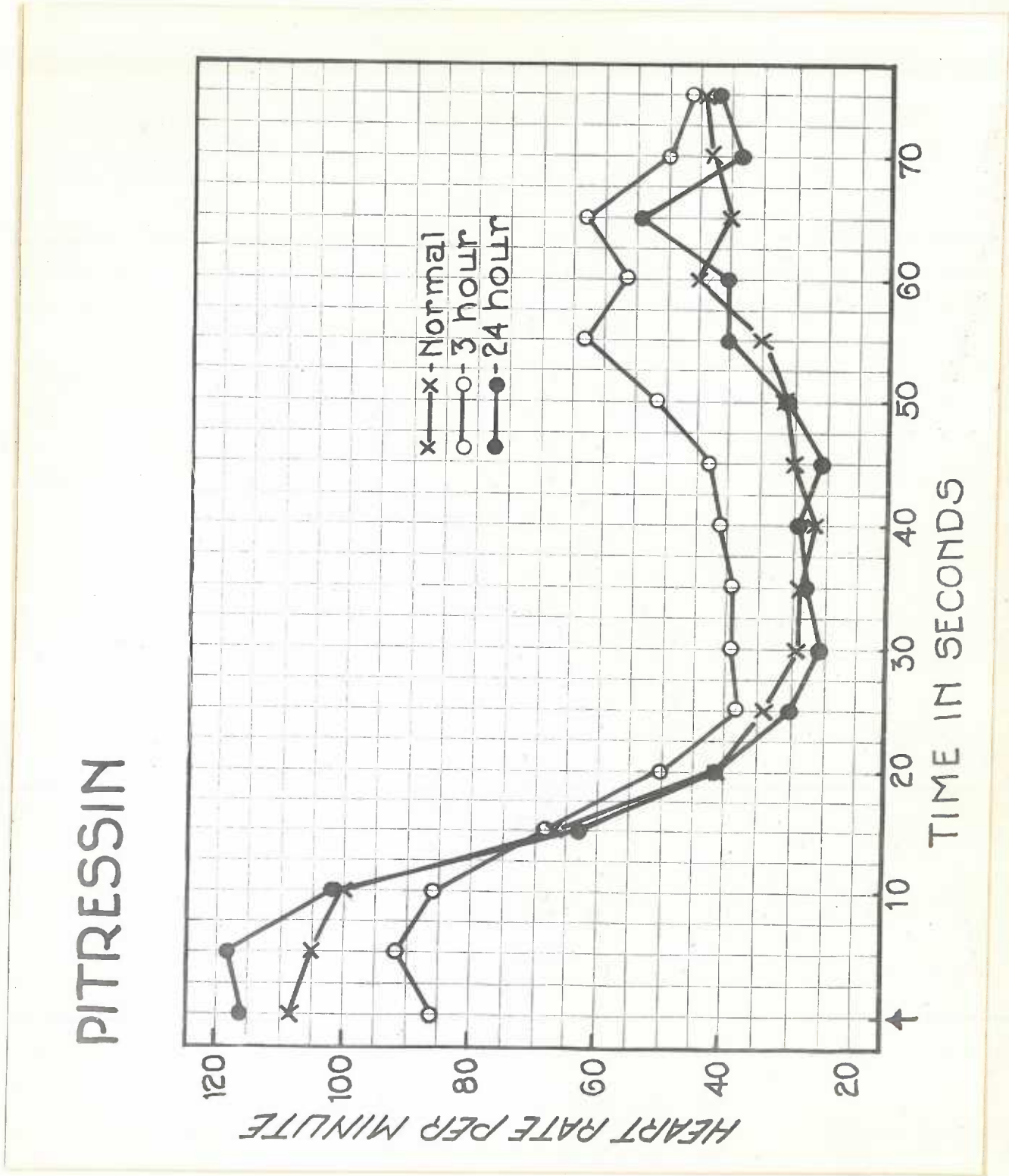
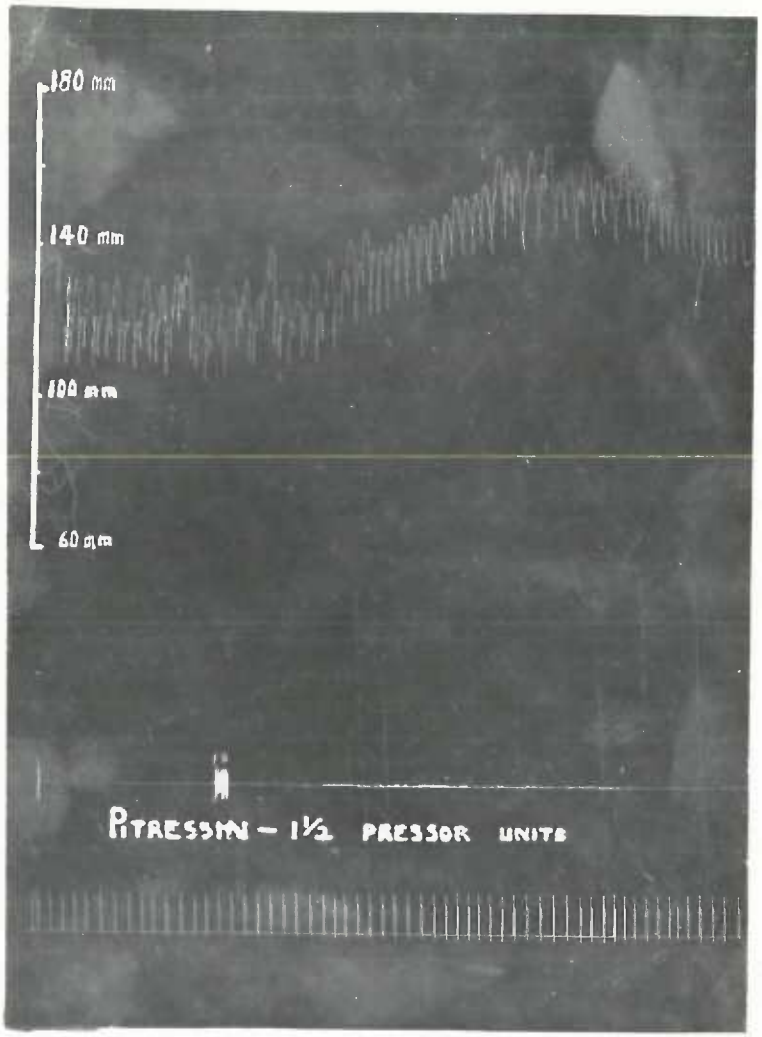

PITRESSIN
HEART RATE PER MINUTE
120
100
80
60
40
20
10
20
30
40
50
60
70
TIME IN SECONDS
x-x Normal
o-o 3 hour
•-• 24 hour

Figure 10

The effect of pitressin after Dibenamine administration on the blood pressure of an unanesthetised dog with spinal cord transected at T_{12}.


180 mm
140 mm
100 mm
60 mm
PITRESSIN – 1½ PRESSOR UNITS

vasoconstrictor action of these compounds by Dibenamine.

The fact that the vasoconstrictor action of adrenaline is blocked while the vasoconstrictor actions of pitressin and of angiotonin are not blocked indicates that Dibenamine interferes with the receptive mechanism of the smooth muscle cell while it leaves the contractile mechanism intact.

DISCUSSION

In previous experiments concerning the pharmacological actions of Dibenamine anesthetized animals have been used[2][3][4][5][7][8]. It is well known that anesthetic agents frequently alter the effects of a compound being studied. In the present study experiments upon anesthetized animals were performed to confirm the results of previous experiments, and further investigations were carried out in unanesthetized animals. Adrenaline was used as a test compound in unanesthetized dogs to determine if the changes in heart rate observed would be such as to indicate a reversal of its pressor action without an impairment of its cardio-accelerator action. The purpose of using acetylcholine as a test compound is clear when it is remembered that the brief hypotension produced by the direct effect of acetylcholine causes a secondary, reflex activation of cardio-accelerator nerves and liberation of adrenaline. Therefore, if a compound actually blocks all of the effects of adrenaline and of adrenergic nerves, it should block the secondary effects of acetylcholine upon the cardiovascular system.

The results indicate that Dibenamine blocks the vasopressor action of adrenaline in unanesthetized dogs. Moreover, it is evident from experiments with the denervated heart that the cardiac acceleration due to the direct effects of circulating adrenaline on the sino-auricular node is partially blocked by Dibenamine. The persistence of the fast heart rate caused by acetylcholine in animals under the influence of Dibenamine indicates an impairment of the compensatory vasoconstrictor mechanisms.

The results show that an amount of Dibenamine which is sufficient to reverse the pressor action of adrenaline in the intact animal is insufficient to impair cardio-accelerator responses to hypotension. The cardio-accelerator response is due mainly to activation of adrenergic nerves to the sino-auricular node. Although the stimulatory effect of these nerves on the sino-auricular node is not blocked, the stimulatory effect of circulating adrenaline is decreased. It appears to be a general rule that Dibenamine blocks the effects of injected adrenaline more readily than it blocks the effects of activation of adrenergic nerves. If so, an analogy may be drawn between the actions of Dibenamine on adrenergic systems and of atropine on cholinergic systems, since it is well known that atropine blocks the effects of injected acetylcholine more readily than it blocks the effects of activation of cholinergic nerves.

The blocking action of Dibenamine has been observed only in excitatory adrenergic systems. All of the various excitatory adrenergic mechanisms which have been studied have been demonstrated to be blocked, in some degree, by Dibenamine(5)(15)(16), but no inhibitory adrenergic system has been shown to be blocked(5)(6). Effects on adrenergic vasodilator mechanisms have not been studied adequately, but it seems evident that vasodilator responses are not prevented. Until further evidence is presented, it can be said that Dibenamine blocks only excitatory adrenergic mechanisms.

Both angiotonin and pitressin are known to act directly on the contractile mechanism of smooth muscle. The fact that Dibenamine does not alter the vasopressor effects of either of these compounds, at the same time that the adrenaline reversal is evident, indicates

that Dibenamine acts on the receptive mechanism of the effector cell while leaving the contractile mechanism intact. Nickerson and Goodman(5) have suggested that the blocking action of Dibenamine may be on the basis of a partial destruction of the receptive mechanism in the effector cells which have an excitatory adrenergic innervation.

SUMMARY AND CONCLUSIONS

The actions of Dibenamine on the cardiovascular system and on the cardiovascular adjustments caused by adrenaline, acetylcholine, pitressin, and angiotonin have been studied in anesthetized and unanesthetized dogs.

Dibenamine caused a slight decrease in blood pressure in anesthetized animals with buffer nerves intact. In an animal with sino-aortic areas denervated, Dibenamine produced a profound fall in blood pressure. In unanesthetized dogs Dibenamine produced an increase in heart rate which persisted for 1 to 3 hours.

Dibenamine reversed the pressor actions of adrenaline in both the anesthetized and the unanesthetized dog. The active vasoconstriction caused by adrenaline in the intestine was prevented. The vasopressor response to acetylcholine in the atropinized animal, which is considered to be caused by liberation of adrenaline, was reversed by Dibenamine.

A test dose of adrenaline which caused reflex cardiac slowing in normal unanesthetized dogs produced severe cardiac acceleration after administration of Dibenamine. The compensatory cardiac acceleration produced by injection of a test dose of acetylcholine was undiminished and prolonged in animals under the influence of Dibenamine.

In an unanesthetized dog with denervated heart the stimulatory effect of adrenaline on the sino-auricular node was partially blocked by Dibenamine.

Dibenamine did not alter the pressor action of pitressin or

angiotonin in anesthetized dogs. The reflex cardiac inhibition produced by pitressin and angiotonin in unanesthetized dogs was not altered by Dibenamine.

The results of all of the experiments are in accord with the following interpretations concerning the actions of Dibenamine:

1) Dibenamine interferes with the excitatory actions of adrenaline but does not prevent inhibitory responses to adrenaline.

2) The excitatory responses to injected adrenaline are impaired more readily than the responses evoked by activation of excitatory adrenergic nerves.

3) The effects of activation of some excitatory adrenergic nerves are blocked more readily than others.

4) Dibenamine interferes with the actions of adrenaline by altering the receptive mechanism of the smooth muscle cell, and it leaves the contractile mechanism intact.

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