THE ACTIONS OF PITUITRIN, ADRENALIN AND BARIUM ON THE CIRCULATION OF THE BIRD.

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While the action of the internal secretion of the posterior lobe of the pituitary as represented by extracts of that structure has been extensively studied in mammals and while some work has also been done on its action in the frog[1], so far as we are aware no observations have been recorded upon birds. The differences in the action of certain substances upon the arterioles in different animals[2] suggest the possibility that pituitrin may not act in the bird as it does in mammals. The peculiar results obtained by us with pituitrin have led us also to study the action of adrenalin and the interaction between these substances.

Methods. The blood-pressure was determined from the carotid artery, using either an ordinary mercurial manometer with a float or a mercury manometer with an electric attachment described elsewhere[3]. The ventricular contractions were recorded by a frog heart lever to which a thread, attached by a bent pin to the apex of the heart, was attached. The down stroke indicates systole. The condition of the arterioles was determined by ligaturing off a length of gut and placing it in an ordinary air oncometer, the expansion and contraction of the vessels being indicated by the movement of a bead of water in a glass tube of 100 cm. length and 2 mm. diameter placed upon a millimetre scale[4]. Injections were made into the right jugular vein.

The pituitrin and the adrenalin chloride, 1 in 1000 of Messrs Parke Davis & Co., and the pituitary (infundibular) extract of Messrs Burroughs Wellcome & Co. were used throughout.

[1] Herring. This *Journal*, xxxi. p. 429. 1904.
[2] Dale and Laidlaw. *Ibid.* xliii. p. 183. 1911.
[3] *Quart. Journ. of Exp. Physiol.* v. 1912.
[4] This *Journal*, xliv. p. 410. 1912.

Each c.c. of the pituitary preparations is supposed to be equivalent to 0·2 gram of the posterior lobe of the moist gland preserved with chloretone. Our thanks are due to these two firms, and more especially to the former, for a large supply of these extracts. We have not used extracts of the pituitary of the bird, since the investigations of Herring[1] have shown that the posterior lobe of the bird acts like that of other animals.

Description of Figures. All the tracings are reduced to ½ the original size. Unless otherwise described, the upper trace represents ventricular contraction, the downstroke being systole, and the lower trace the arterial blood-pressure. The abscissa is 4 cms. below the base line except in Figs. 10–13. Time is recorded in seconds.

Arterial blood-pressure and arterioles.

Pituitrin. The intravenous injection of pituitrin, in doses of from 0·5 c.cm. to 1·0 c.cm., with vagi intact or with vagi cut, generally causes an immediate and marked fall of the arterial pressure. (Fig. 1 and Table I.) This occurs whether it be injected quickly in strong solutions

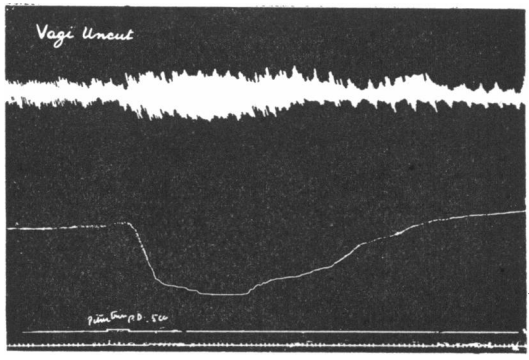

Fig. 1. Injection of 0·5 c.c. pituitrin. Vagi intact.

or more slowly in dilute solution[2] (Fig. 2). The injection of the same dose per unit of body weight, administered in the same manner, was found to give the usual rise of pressure in the mammal (rabbit and cat).

The fall occurs both after and before the injection of atropine in doses sufficient to paralyse the cardiac inhibitory mechanism (Fig. 3). After atropine, the fall is more sustained because the ventricular systole

[1] *Quart. Journ. of Exp. Physiol.* I. p. 262. 1908.

[2] Cf. Miller and Miller. This *Journal*, XLIII. p. 245. 1911.

is not augmented (see p. 422). Sometimes the fall of pressure is preceded by a short and slight rise (Fig. 4).

TABLE I. *Pituitrin.*

	B.-P.		Ventricle			
			Rate		Extent	
	Before	After	Before	After	Before	After
Vagi intact	11·8 cms.	6·4 cms.	3 per sec.	3 per sec.	1·5 cms.	3·9 cms.
	11·6	6·6	6	6	1·8	2·5
	8·6	5·2	8	7	2·1	2·4
	7·6	3·0	6	3+	0·3	0·5
	17·0	11·4	4	5	1·2	4·0
	12·6	10·0	9	7	1·8	2·1
	12·0	10·2	4	4	4·6	6·8
	9·6	7·2	7	7	2·9	4·8
	8·2	7·7	4	4	0·6	0·8
	9·7	6·0	4	5	1·6	2·7
Vagi cut	6·6	4·8	10	9	0·4	0·4
	8·0	5·8	—	5	2·5	3·0
	13·5	8·5	7	7	0·3	0·6
	15·0	10·5	9	8	0·4	0·5
	9·6	7·2	7	7	2·9	4·8
After atropine	10·0	6·5	9	6	1·1	1·2
	6·0	3·8	6	6	0·7	0·7+
	11·8	5·1	7	7	0·2	0·4

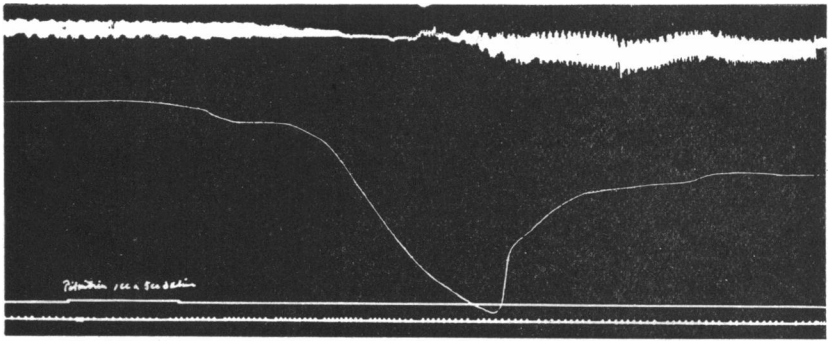

Fig. 2. Injection of 1 c.c. pituitrin diluted 5 times with ·75 % NaCl. Note the initial reduction in the amplitude of ventricular contraction without any rise of arterial pressure, followed by the increase. Vagi cut.

Generally a second dose produces almost as marked an effect as the first, but after repeated doses the fall of pressure is not seen and on several occasions a rise was observed. In one of these, oncometric observations showed that no constriction of the arterioles had occurred.

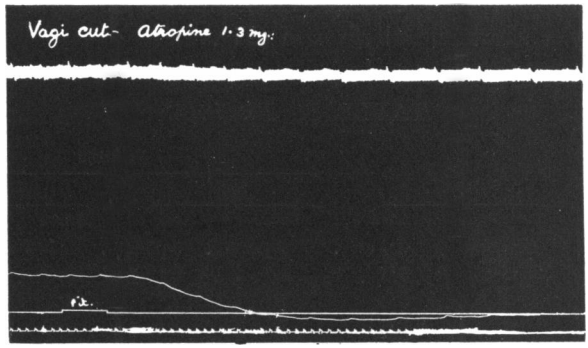

Fig. 3. Injection of pituitrin after paralysis of vagi by 0·13 mg. atropine.

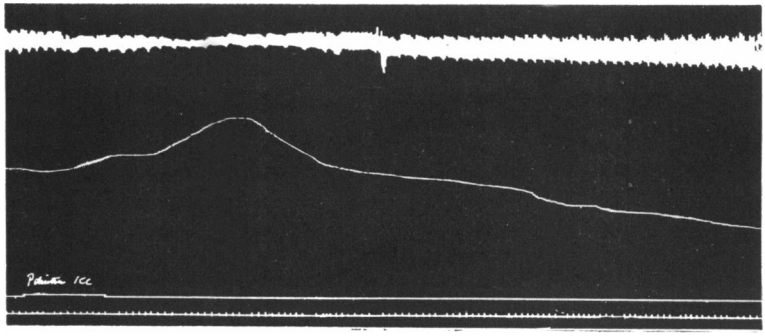

Fig. 4. Injection of 1 c.c. pituitrin. Initial rise of blood-pressure. Here, as in Fig. 2, there is an initial decrease of ventricular contractions.

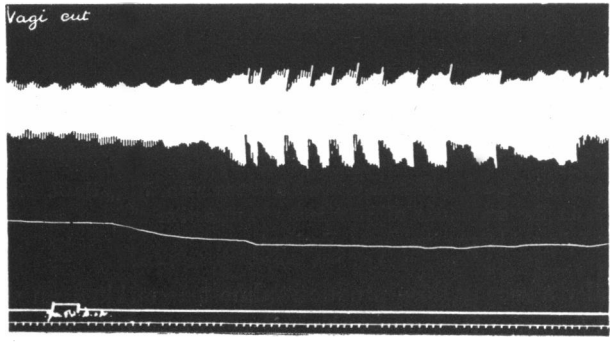

Fig. 5. Injection of ·7 c.c. pituitrin. Increased amplitude of ventricular contraction without a marked fall in arterial pressure.

Sometimes the fall of pressure is not marked (Fig. 5); in these cases the increase in ventricular contraction is marked and is probably sufficient to counteract the effects of arteriole dilatation.

The oncometer readings show that pituitrin causes a marked dilatation of the abdominal blood vessels, thus accounting for the fall in arterial blood-pressure (Fig. 6).

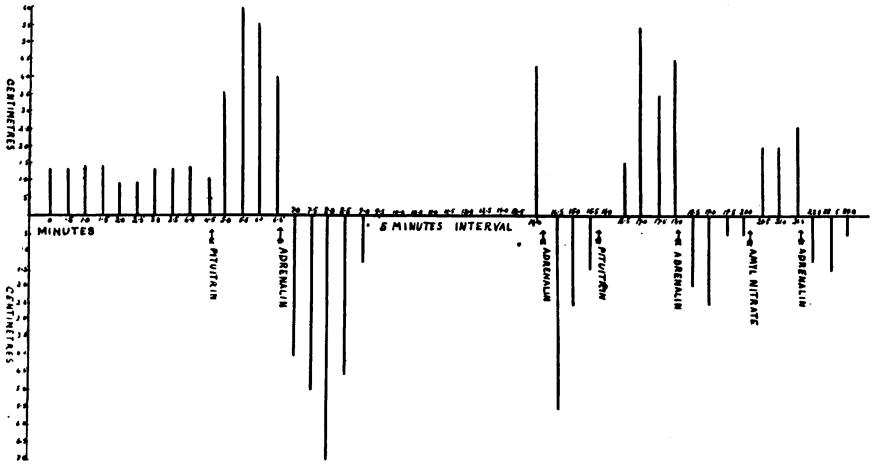

Fig. 6. Oncometer record of loop of gut. Vertical lines above the horizontal line indicate outward movement of bead of water, *i.e.* expansion of vessels. Vertical lines below the horizontal, inward movement, *i.e.* constriction of vessels. Range of movement in cm. Time in ½ minutes. Pituitrin = 1 c.c. Adrenalin, 1st, 2nd and 3rd dose ·5 c.c., 4th c.c. of ·1 p.c. solution. Amyl nitrite, inhalation.

Adrenalin in the bird acts in directly the opposite direction to pituitrin, causing the usual rise of arterial blood-pressure (Fig. 7 and Table II) and the usual constriction of the peripheral visceral vessels, as indicated by the oncometer (Fig. 6).

TABLE II. *Adrenalin.*

	B.-P.		Ventricle			
			Rate		Extent	
	Before	After	Before	After	Before	After
Vagi cut	14 cms.	22 cms.	4 per sec.	6 per sec.	1·5 cms.	0·8 cms.
	6·2	20	6	6	2·9	0·3
	8·2	18·6	4	7	4·3	2·1
After atropine	6·2	12	3	4	0·8	0·3
	4·3	10	6	7	0·5	0·2
	5·1	11·3	6	7	0·4	0·2

The two substances are directly antagonistic, pituitrin causing an immediate fall of pressure during the adrenalin elevation and a dilatation of the peripheral vessels constricted by adrenalin, and adrenalin removing the pituitrin effect (Fig. 8).

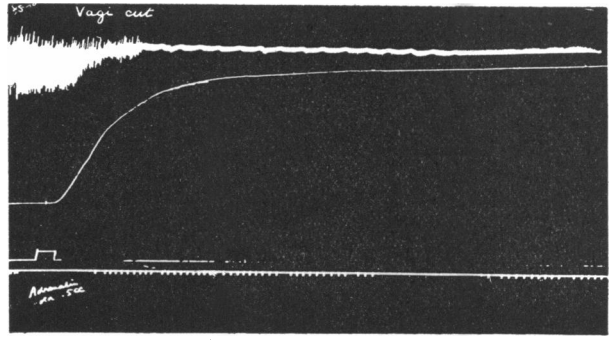

Fig. 7. Effect of 0·5 c.c. of 1 in 1000 of adrenalin chloride (old and weak solution). The amplitude of the ventricular contraction becomes less complete.

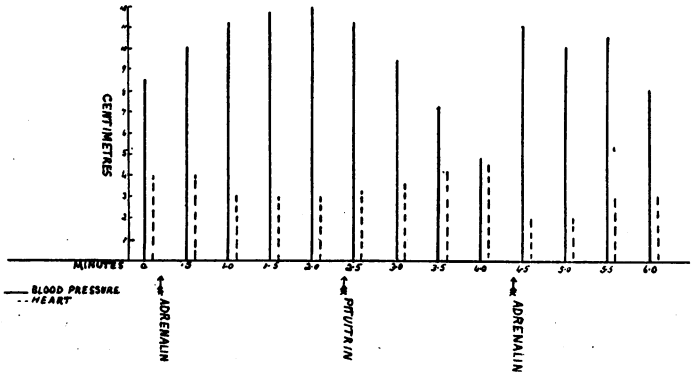

Fig. 8. Antagonistic effect of adrenalin and pituitrin on the arterial blood-pressure ——, and on the ventricular contraction - - - -. The former is the actual pressure in cm.; the latter is magnified ten times. Adrenalin = 1 c.c. of 0·1 p.c. Pituitrin = 0·7 c.c. Intervals of time in ½ minutes.

This antagonistic action of adrenalin to pituitrin is interesting, since, as was pointed out by Dale[1], pituitrin appears to act directly upon the muscle fibres. He found that, when given after ergotoxin in the mammal, it acts like barium in causing a constriction of the vessels and not like adrenalin in causing a dilatation. In the duck it acts as an antagonist to barium. The rise of arterial pressure produced by the

[1] *Biochem. Journ.* IV. p. 427. 1909.

intravenous injection of 1 c.c. of a 1 p.c. barium chloride solution is at once cut down by the subsequent injection of pituitrin (Table III and Fig. 9), and the constriction of the peripheral vessels caused by barium is removed, at least temporarily, by pituitrin (Fig. 9).

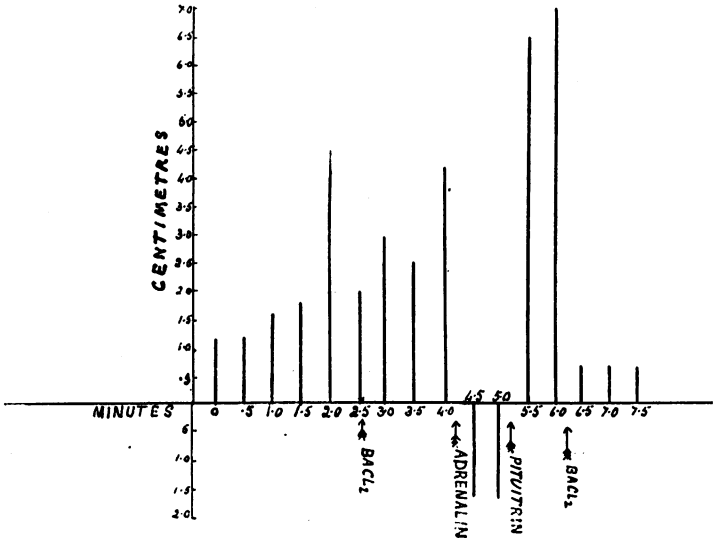

Fig. 9. Oncometer record as in Fig. 6. Reduction of the dilatation of the vessels after pituitrin by the administration of $BaCl_2$.

The antagonism of pituitrin and barium salts would seem to confirm Dale's contention that the action of the former is upon muscle fibres beyond the neuro-muscular junction, but on the other hand the way in which adrenalin antagonises pituitrin, would rather point to the action being upon these terminations. In all probability this is an example of the difficulty of drawing conclusions from the antagonism of drugs, a difficulty which Magnus has already dealt with[1].

Heart.

So far we have found no observations on the action of pituitrin on the avian heart.

Elliot[2] describes the effect of adrenalin in the excised heart of the chelonian as causing increased contraction of the auricles, but not of the isolated ventricles, and he states that the entire heart of the pigeon is

[1] *Ergeb. d. Physiol.* 1908, p. 58.

[2] This *Journal*, xxxii. p. 409. 1904–5.

TABLE III. *Barium Chloride and Pituitrin.*

Blood-pressure.	
Before injection of $BaCl_2$	5·7 cms.
10 secs. after injection of $BaCl_2$... ...	6·9 ,,
20 ,, ,, ,, ...	10·0 ,,
40 ,, ,, ,, ...	10·6 ,,
Pituitrin injected.	
10 secs. after injection of Pituitrin ...	6·7 ,,
20 ,, ,, ,, ...	6·7 ,,
40 ,, ,, ,, ...	6·7 ,,
Heart.	
Beats before injection of $BaCl_2$	5 per second.
,, 10 secs. after injection of $BaCl_2$ ...	6 ,,
,, 30 ,, ,, ,, ...	6 ,,
,, 40 ,, ,, ,, ...	4 ,,
Pituitrin injected.	
Beats 10 secs. after injection of Pituitrin...	3 ,,
,, 30 ,, ,, ,, ,, ...	3 ,,
,, 40 ,, ,, ,, ,, ...	3 ,,
Amplitude before injection of $BaCl_2$ ...	1 cm.
,, 25 secs. after injection of $BaCl_2$	0·8 ,,
,, 40 ,, ,, ,,	0·5 ,,
Pituitrin injected.	
Amplitude 10 secs. after injection of Pituitrin	1·3 ,,
,, 25 ,, ,, ,,	1·3 ,,
,, 40 ,, ,, ,,	0·9 ,,

most vehemently excited when adrenalin is added to the perfused fluid, but that, when the ventricles are then cut away from the auricles, they continue to beat, and the further addition of adrenalin causes excitation of the auricles but no excitation of the ventricles.

Pituitrin. We find that the intravenous injection of pituitrin, in doses of 0·5 to 1·0 c.cm., with vagi intact and with vagi cut, generally has no effect upon the rate of the ventricular contractions, but markedly increases the amplitude of contraction (Figs. 1 and 10 and Table I), whereas in the completely atropinised heart it produces no manifest effect (Fig. 3). The heart must be very completely atropinised for the effect of pituitrin to be completely abolished. Fig. 11 shows that even when only a very slight inhibition can be produced by vagal stimulation, pituitrin still causes an increase in the extent of ventricular contraction. That the increase in the extent of cardiac contraction is not simply a result of the fall in the arterial pressure is shown by the fact that it occurs even in cases where there is no fall in the arterial pressure (Fig. 5). Fig. 4, which is from one of the rare cases in which

an initial rise of pressure occurred, might seem to indicate that a decrease in the amplitude of ventricular contraction is caused by this rise of pressure, but Fig. 2 shows that the initial decrease of ventricular contraction may occur without any rise of arterial pressure. Pituitrin has thus a direct excitor effect upon the heart. Since it acts upon the ventricles it may be concluded that its action is upon the muscle and

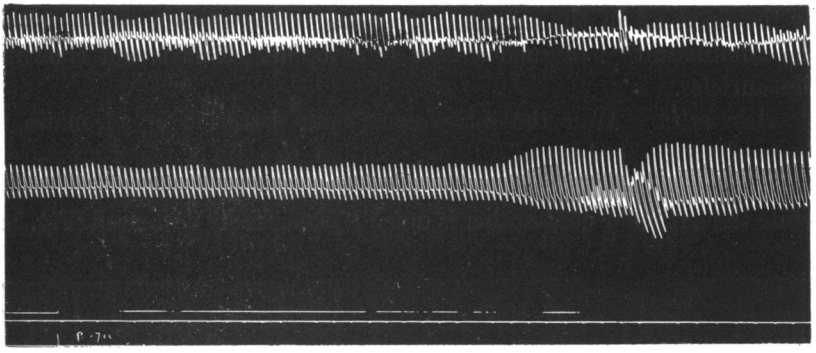

Fig. 10. Effect of 0·7 c.c. pituitrin on the auricle and ventricle. The auricular tracing is not purely auricular, but in part ventricular.

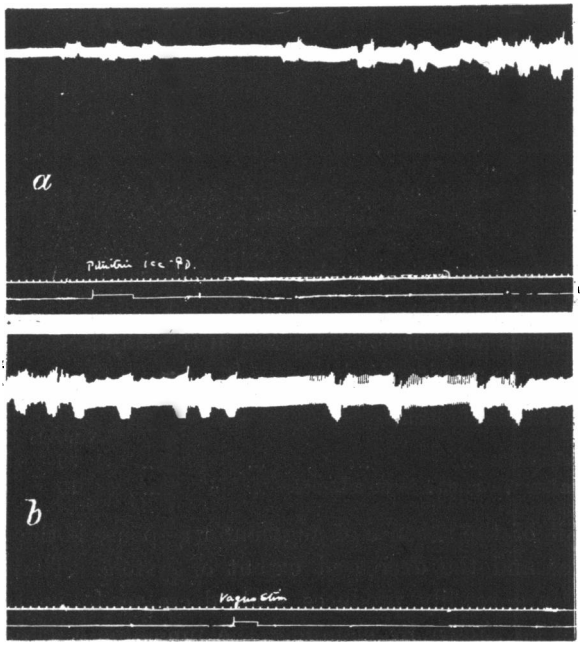

Fig. 11. Increase by pituitrin of the ventricular contraction of the partly atropinised ventricle. Strong stimulation of the vagus causes a slight slowing.

not upon the augmentor mechanism, since, as will be shown in a future paper, the augmentor nerves have no influence on the ventricles. The failure of pituitrin to alter the action of the heart, after the administration of doses of atropine sufficient to poison the inhibitory mechanism, may best be explained on the view that such a dose of atropine is also sufficient to exercise a partial paralysing effect upon the heart muscle[1]. That this is the probable explanation seems to be indicated by the decrease in the extent of ventricular contraction which follows the administration of such a dose of atropine. This is not shown in the auricles.

Adrenalin. After the intravenous administration of adrenalin, in doses of ·05 c.c. to ·1 c.c. of a ·1 p.c. solution, the rise of blood-pressure is always accompanied by a decrease in the extent of ventricular contraction, while the auricular contraction is much less markedly decreased (Fig. 12).

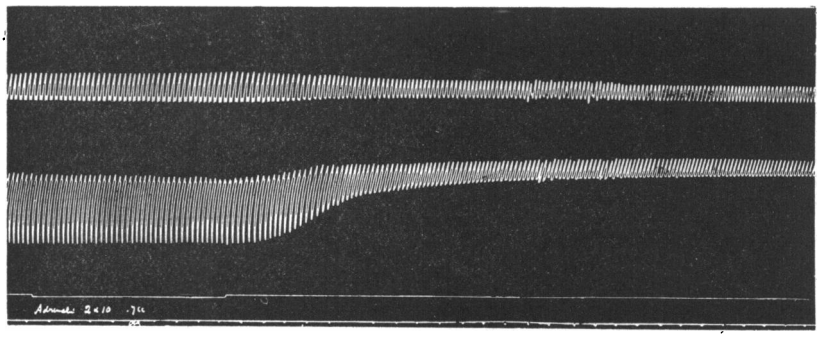

Fig. 12. Effect of adrenalin 0·7 c.c. of a ·1 p.c. solution on the auricle and ventricle. The auricular trace is pure.

The best demonstration of the striking difference in the behaviour of the heart after pituitrin and adrenalin respectively is got by inspection. The former causes an enormous increase in the amplitude of contraction, while the latter as manifestly decreases it.

Extent of contraction in mm.:

	Ventricle	Auricle
Before adrenalin	39	14
30 secs. after ·7 c.c. of 1 in 10 adrenalin	10	9

The result of the absence of augmentor response is the dilatation of the ventricles and the decreased extent of systole. That increase of arterial pressure readily produces such decrease in ventricular contraction may be shown by clamping the innominate arteries.

[1] Magnus. *Ergeb. d. Physiol.* p. 60. 1908.

Extent of contraction in mm.:

	Ventricle	Auricle
Before	32	18
37 secs. after clamp applied to innominate arteries ...	15	9
Immediately after removal of first clamp	25	18
,, ,, ,, second clamp ...	38	19

A similar effect with adrenalin is sometimes got in the mammalian heart towards the end of prolonged experiments. In a kitten, which had had repeated doses of adrenalin, the rise of pressure towards the end of the experiment was accompanied by a marked decrease in the amplitude of ventricular contraction.

The decreased contraction caused by adrenalin in the bird is removed by the administration of pituitrin.

Extent of contraction in mm.:

	Ventricle	Auricle
Before adrenalin	40	14
After ,, ...	10	13
25 secs. after pituitrin 1 c.c.	20	26

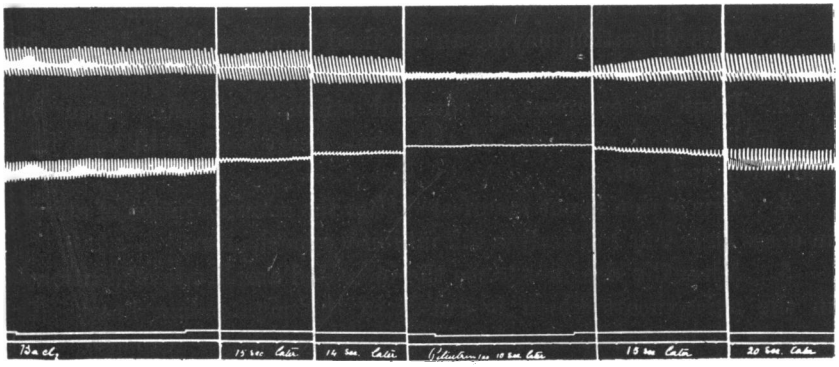

Fig. 13. Effect of $BaCl_2$ (0·5 c.c. of 1 p.c. solution) on the auricle and ventricle, and the antagonistic action of 1 c.c. pituitrin.

This antagonistic action is apparent rather than real. Pituitrin does stimulate the muscle fibres of the heart, but it also relieves the arterial blood-pressure by dilating the peripheral vessels and thus allows of more full systole of the ventricles. That it acts in this way is shown by the fact that in the atropinised heart pituitrin antagonises the adrenalin effect, although it does not directly stimulate the heart muscle.

Barium chloride in doses of 0·1 gm. acts much in the same way as adrenalin. Instead of increasing the extent of ventricular contraction, as in the mammal, it brings about a steady decrease in the systole of auricles and ventricles as the blood-pressure rises, and this effect is

removed by the administration of pituitrin through the dilatation of the peripheral vessels (Fig. 13).

The same effect may be produced after the administration of $BaCl_2$ by bleeding the duck. In one experiment the extent of ventricular contraction after $BaCl_2$ was 9 mm. and, after bleeding from a carotid, it increased to 22 mm.

The different response of the mammalian heart to barium is shown by the result that in an atropinised kitten, after 1 c.c. of 1 in 10 $BaCl_2$, the amplitude of ventricular contractions, as recorded by the lever, was increased from 15 mms. to 20 mms. in 50 sec.

Conclusions.

1. Extracts of the posterior lobe of the pituitary (the pituitrin of Parke Davis & Co.) and the infundibular extract of Burroughs, Wellcome & Co., cause a marked fall of the arterial blood-pressure in the duck, due to a dilatation of the peripheral arterioles. The extent of the fall is modified by the response of the ventricles to the pituitrin.

2. This dilatation may be antagonised by adrenalin and by barium chloride.

3. Pituitrin exercises a powerful stimulating effect upon both the auricles and ventricles of the avian heart both with vagi intact and with vagi cut.

4. This action is not manifested after the administration of atropine in doses sufficient to paralyse the inhibitory mechanism.

5. Adrenalin does not cause the increased amplitude of contraction in the avian heart which it causes in the mammalian heart. This appears to be due to the absence of any augmentor response.

6. Pituitrin and adrenalin have an antagonistic action on the avian heart.

7. The antagonism of pituitrin to adrenalin on the avian heart is in part due to the dilatation of peripheral vessels by which the decrease in the amplitude of cardiac contractions is removed. It is at least in part an indirect, not a direct, antagonism as in the case of the arterioles.

8. The antagonism of pituitrin to barium chloride is of the same kind.

In a future paper the results of observations upon the action of the extrinsic nerves of the heart of the bird will be given. These throw some light upon the peculiar action of the substances considered in the present paper.

The expenses of this and of the preceding investigation were defrayed from a Grant given by the Carnegie Trust of the Universities of Scotland.