THE EFFECT OF THYRO-PARATHYREOIDECTOMY ON THE HEART AND CIRCULATION. Part II. Action of Guanidin on the Heart of the Frog.

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In the first paper of this series(1) quantitative confirmation was given of an observation of Putzeys and Swaen(2) that guanidin sulphate produces a block in the vago-cardiac inhibitory mechanism. It was shown by us that this applied to any salt of guanidin and that the block so produced is more or less removed by the administration of calcium salts. A similar interference occurs after removal of the parathyreoid glands in cats and dogs. Noël Paton and Findlay(3) found that the motor nerve endings in skeletal muscle are first stimulated and later paralysed, and the inhibitory preganglionic synapses on the path to the heart are also paralysed by guanidin(1). The work now submitted was undertaken to determine whether this nicotine-like action of guanidin afforded sufficient explanation for the circulatory disturbances following parathyreoidectomy. The salts of guanidin used were carbonate, hydrochloride, sulphate and lactate. Morrell and Bellars(4) have shown that guanidin is easily dissociated, being 0·8 as strong a base as sodium hydrate. Previous preliminary experiments demonstrated to us that, in the dosage we employed, only the cation was significant. The solutions used were, except where otherwise indicated, neutral to phenolphthalein and isotonic with 0·7 p.c. sodium chloride.

Heart. Heart tracings were taken before and after the administration of guanidin by: (1) injection into the dorsal sac; (2) painting on the heart wholly or partially; (3) bathing the excised heart in guanidin solutions, before and after poisoning with atropine.

Our almost invariable result, no matter how the guanidin was administered, was a marked cardiac retardation.

In all cases in which 1 p.c. guanidin was used the rate of beat decreased and the heart stopped in diastole. When the guanidin was replaced by Ringer's fluid, the rate gradually increased until it was almost

as great as originally. (Cf. exp. 23.) When the heart had been once stopped by guanidin, and had recovered by treatment with Ringer, a longer time in Ringer was required to recover the heart from a subsequent stoppage by guanidin. The effect of more dilute solutions varies in different cases; 0·8 p.c. may have no effect or it may stop the heart; 0·5 p.c. has little or no effect when it is first applied, but may stop the heart after recovery from stoppage by 1 p.c. guanidin; 0·25 p.c. has no effect or only a trifling slowing. When the heart was contracting feebly in Ringer's fluid it was often noticed that after recovery there was a marked increase in the extent of contraction. (Cf. exp. 27.) In others, an increase in the extent of contraction was observed while the heart was immersed in guanidin.

In 10 out of 30 experiments there was an initial acceleration. This is in partial agreement with the work of Putzeys and Swaen(2) who found that guanidin sulphate produced an initial quickening followed by a prolonged slowing of the heart of frogs. This cardiac retardation, in the light of the experiments detailed in Part I of this paper, may be explained by the nicotine-like action of guanidin on the vago-cardiac mechanism. It is well known that nicotine first stimulates and then paralyses the preganglionic fibres. That the slowing might be accounted for by the stimulation of the preganglionic fibres of the vagi by guanidin is shown by the blocking action of atropine. In Table III is shown the effect of bathing the excised heart of the frog in 0·9–1·7 p.c. solutions of guanidin salts after the postganglionic fibres had been poisoned by atropine. After atropine, guanidin, in seven out of eight frogs, accelerated the heart beat. In two frogs cardiac retardation occurs at a later period of guanidin poisoning than would be the case in the non-atropinised frog. It seems reasonable to infer that this slowing of the heart is caused by the atropine having been washed out by the perfusion fluid, and so restoring the postganglionic fibres to the normal state of being conductors of the impulses induced by guanidin. A glance at Table III will serve to confirm this supposition. After bathing the excised atropinised heart in Ringer's solution, guanidin produces a distinct cardio-retardation. There is also no doubt that, after prolonged treatment with guanidin or after large doses, the accelerator fibres are paralysed and thus tend to the slowing of the beat (as suggested by Putzeys and Swaen, *ibid.*).

The initial acceleration reported by Putzeys and Swaen (*ibid.*) and by us in some cases may be due to a stimulation of the endings of the accelerator nerves to the heart. These nerves are untouched by

atropine, and in the atropinised heart quickening is invariably caused by guanidin. Later, or after larger doses, guanidin ceases to stimulate the accelerator nerve endings and thus allows the heart to slow.

EFFECT OF GUANIDIN ON RATE OF BEAT OF THE HEART OF FROGS.

TABLE I. Heart *in situ* (19 expts.).

	Beats per minute			
		After guanidin		
Number of Expt.	Normal	Immediate	2 mins.	4 mins. later
(*a*) Injected.				
1.	36	54	36	30
3.	45	18	9	15
(*b*) Partial Painting.				
4.	45	39	33	30
8.	36	40	24	12
(*c*) Complete Painting.				
14.	54	48	30	24
15.	48	60	48	36

TABLE II. Excised heart bathed in solution (11 expts.).

No. of Expt.	In Ringer's fluid	Strength of Gn., HCl %	Rate in Gn. HCl	Time in Gn. HCl before stoppage secs.	Time in Ringer before recovery secs.	Rate after recovery
23 *a.*	54	1·0	19	—	47	50
b.	50	1·0	—	18	80	48
c.	48	1·0	—	19	120	45
d.	45	1·0	—	23	105	46
e.	46	1·0	—	24	170	40
f.	40	1·0	—	36	190	—
27 *a.*	64	0·25	54	—	—	44
b.	44	0·5	49	—	—	39
c.	39	1·0	—	—	—	28
d.	28	0·25	29	—	—	28
e.	28	0·5	—	33	8	30
f.	30	0·25	32	—	—	—

TABLE III. Excised heart after atropine (8 expts.).

No.	Strength of guanidin HCl %	Normal	After atropine	After guanidin	Ringer	Guanidin	Ringer
32	0·9	30	13	19	22	20 18 15	17
34	1·7	48	13	15...10 (stopped in 7 mins.)	8 mins. in Ringer till started 5–19	14	13

Peripheral vessels. The peripheral blood vessels were perfused with solutions containing salts of guanidin before and after poisoning with atropine. From a comparison of Tables I and II it is obvious that, for

TABLE IV. Perfusion of peripheral vessels (9 expts.).

No.	Ringer	Drops per minute: Guanidin immediate	Guanidin 3 mins.	Guanidin 4 mins.	Guanidin 10 mins.	After atropine	Ringer
			(*a*) Normal.				
42	60	30	50	—	20	4	12
43	70	60	—	30	—	12	—
						3	70 (after 2 hrs.)
			(*b*) Atropinised.				
45	80	80	15	55	—	—	60 (1 min.)
(2nd dose)	60	75	—	—	—	—	80 (2 mins.)
46	60	60	45	2	2	—	—
			(*c*) Nicotine administered.				
47	30	55	20	—	—	—	—

equal doses, guanidin produces a less marked slowing in the excised heart than in the heart *in situ*. The reason for this may be inferred from the perfusion experiments, excerpts from the results of which are to be found in Table IV. (Customary perfusion method (5).) There can be no doubt that neutral guanidin solutions isotonic with Ringer's solution produce a marked constriction of the peripheral vessels of the frog. After having allowed Ringer's solution to pass through the peripheral vessels for some time to wash out the guanidin, an increased output gave indication that a return to the normal vascular output would be only a matter of time. (Frog 43.)

We thought that by the use of frogs that had been poisoned by nicotine or atropine we would be able to localise the action of guanidin. Atropine, in the dosage we employed, had no effect on the peripheral circulation of the frog. Guanidin given to an atropinised frog produces a much more rapid and thorough constriction than when given to an unpoisoned animal. Nicotine, on the other hand, tends to abolish and may even reverse the action of guanidin, producing a vaso-dilation. From these experiments we may conclude that the effect of guanidin on the peripheral circulation of the frog is due to its nicotine-like stimulation of the vaso-constrictor neurons. The fact that nicotine abolishes or reverses the vaso-constriction caused by guanidin, excludes a direct action on structures more peripheral than those neurons.

The reason for the augmented constriction of the peripheral blood vessels on the administration of guanidin to an atropinised frog may be summation. According to Fano(6) atropine either leaves alone or increases the activity of muscular structures whose motor neurons belong to the sympathetic series. Thus it would have either no action,

as we found, or a slight vaso-constrictor one. That is, the increased vaso-constrictor action of guanidin on atropinised frogs may be due to the summation of guanidin- and atropine-excitation of vaso-constrictor neurons.

SUMMARY.

Guanidin salts in low concentrations of 0·25–1·7 p.c. produce:

1. Primary cardiac acceleration probably due to the stimulation of the accelerator nerves to the heart. This is soon followed by

2. prolonged and marked retardation of the heart beat, for which two causes have been adduced, (*a*) stimulation of the vago-cardiac nerves and (*b*) pronounced vaso-constriction with reflex inhibition.

3. By the use of atropine and nicotine, the point of action of guanidin has been localised, viz. a nicotine-like action on the sympathetic neurons.

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