THE EFFECT OF THYRO-PARATHYROIDECTOMY ON THE HEART AND CIRCULATION. By DAVID BURNS and ALEXANDER McL. WATSON.

Part I. Action on Nervous Control of the Heart.

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Although, practically all who have made observations on dogs after removal of the parathyroid glands, have noted the characteristic tachycardia, no extended research has been carried out on its cause. Falta and Kahn(1) recorded the reaction of the blood-pressure to adrenaline after thyro-parathyroidectomy in one dog. The intravenous injection of 0·75 mg. of adrenaline on the second day after the operation caused a more rapid rise of blood-pressure than in the normal animal. They state that a condition of hyper-excitability of the sympathetic nervous system results from parathyroidectomy. Carlson(2) considers that, in the dog and cat, cardiac activity was not greatly altered by ablation of the parathyroids. He attributes any increase, in rate and strength of the beat during severe tetania parathyreopriva, to the increased muscular activity. Hoskins and Wheelon(3) studied the reaction to adrenaline, nicotine and pituitrine, of dogs, before, and two days after parathyroidectomy. Taking the height of blood-pressure as an index, they found that the action of these drugs was augmented after extirpation of the parathyroids. They conclude that parathyroid destruction, in dogs, results in a marked increase in vasomotor irritability—involving all components of the vasomotor mechanism, sympathetic cells, myoneural junctions and musculature.

It is somewhat dangerous to draw too definite conclusions from experiments in which animals suffering from parathyroid tetany are compared with other apparently normal animals. Caution must also be exercised in deciding how far a change in the working of the cardiac mechanism two days after the operation is primarily dependent upon the removal of the parathyroid glands, and how far it is secondary to the

increased muscular activity, alterations in respiration, loss of appetite, etc., which accompany the parathyroid tetany. It appeared to us that the evidence afforded by the work already done in this laboratory (4, 5 and 6) that the symptoms of tetania parathyreopriva are due to the presence of excessive amounts of guanidin and the methyl guanidins in the blood would justify us in investigating whether the action of these substances can in any way explain the tachycardia of tetany.

It may be noted incidentally that (7) McCarrison's theory of the origin of tetany is in no way antagonistic to our results. He maintains that *a* primary cause of tetany is intestinal toxæmia. Thus, one may infer from his work, that the infection of the alimentary canal with certain anaërobic organisms, originating generally from a water supply contaminated with fæcal drainage, results in disease of the thyro-parathyroid structure, and the appearance of the symptoms of tetany. In no wise does he controvert our argument that the *cause of the symptoms* following parathyroidectomy, or occurring in idiopathic tetany, is poisoning with guanidin or its methyl derivatives.

Some investigations have been made on the action of guanidin and similar bases on the heart. Putzey and Swaen (8) gave the sulphate of guanidin to frogs, and obtained, first, an increase in rate, followed by a marked slowing of the heart. Jacobj and Hagenberg (9) showed that tetra-methyl ammonium compounds had a muscarin-like action on the frog's heart. Marshall (10) studied the action of quaternary ammonium compounds on the heart of the cat and of the rabbit, both under the influence of anæsthetics, and also on unanæsthetised decerebrate animals. He found, that in the anæsthetised animal tetra-methyl ammonium chloride caused a fall of blood-pressure and a diminution of the frequency of the heart beat. He attributes the fall of pressure to two causes (*a*) vascular dilatation, (*b*) decreased cardiac action. Decerebrated animals differ in reaction from anæsthetised animals in one point only —the fall of blood-pressure is preceded by a rise due, he says, to uncontrolled stimulation of the vasomotor centres. He notes a peripheral muscarin effect and a central stimulation of the vasomotor centre. Führer (11) pointed out that guanidin and muscarin may be compared in their action to that of the univalent alkaline metals and that the salts of divalent metals like calcium were capable of negativing the action of guanidin and univalent metals alike. He considers that the quaternary ammonium compounds act in the same way as the univalent organic cations. Burn and Dale (12) confirmed Marshall's work. They lay emphasis on the two different types of action shown by methyl-ammonium

compounds, *i.e.* a powerful nicotine action sufficient to account for its action on the circulation without having recourse to a hypothetical action on the vasomotor centre etc.—and a muscarin action.

Since the completion of our work, Bovshik(13) has published an abstract of a paper by himself and Sinalnicoff, on the influence of guanidin and its methyl derivatives upon the circulation. They do not state what animals they used, presumably mammals were employed. They obtained with di-methyl guanidin: (*a*) a temporary fall of blood-pressure followed by a long continued rise, accompanied by cardiac retardation; (*b*) on section of the vagi during the period of rising blood-pressure a further increase of the pressure and an acceleration of the heart. This was obtained even after exclusion of all vessels below the diaphragm. They conclude that di-methyl guanidin acts principally on the peripheral nervous and muscular elements of the vessels, and that the existence of vessels of only the upper part of the body is sufficient to increase the pressure. We fail to follow the reasoning by which the latter part of their conclusion is reached. If the lower vessels are excluded by ligature of the abdominal aorta and of the vena cava inf., the administration of the same dose of methyl guanidin per kilo would result in an infinitely greater concentration of the drug in the vessels of the upper part of the body, than would be the case where the whole circulation is open to the drug. They found that mono-methyl guanidin was less active than the di-methyl salt: while guanidin carbonate had no action at all. The concentration of salt used by them was low, viz. 5 mgrms. per kilo. This want of action of guanidin carbonate in small doses is in agreement with the results of Noël Paton and Findlay (*ibid.*) who could detect no alteration in the electrical excitability of rabbits after the intra-muscular administration of this base in amounts under 100 mgrms. per kilo. In order to produce the symptoms of guanidin poisoning these latter workers gave, to cats, from 30 to 120 mgrms. of guanidin hydrochloride per kilo (intra-muscular injections).

The following experiments were planned to determine the action, if any, of the salts of guanidin on the vago-cardiac inhibitory mechanism. The increase of the pulse rate after parathyroidectomy could be explained in one of three ways. Either a block occurred in the path of the inhibitory impulse, or excitation of the accelerator nerves took place, or quickening was due to alterations in vascular tone. Tracings were taken by the method usually employed in this laboratory(14) of the auricular and ventricular beats and of the variations of blood-pressure. All the animals

employed were fully anæsthetised except Cat 4 which had been decerebrated by Sherrington's method. In all both carotids were ligatured and a cannula inserted in the left ext. jugular v. for the administration of the drug. The vagi were cut. By means of a Bischhausen (Berne) graduated inductorium and an Edison standard storage battery, the minimal current required to be applied to the R. or L. vagus to produce decided cardiac inhibition was determined before and after the administration of the drug. The salts employed were either the carbonate, hydrochloride or lactate of guanidin and the results were similar in each.

TABLE I. Minimal effective stimuli in normal animals before and after guanidin and the effect of calcium lactate.

Animal	Salt	Dose mgrms. per kilo.	Before guanidin L.	Before guanidin R.	After guanidin L.	After guanidin R.	After Ca lactate L.	After Ca lactate R.
Rabbit 1	Carbonate	300	14	—	ineffective	—	—	—
„ 2	„	300	17	—	„	—	—	—
„ 3	„	300	14	14	under 4	at 14	19	20
„ 4	„	300	14	14	„ 14	under 14	—	—
Cat 1	„	300	14	14	„ 10	„ 10	—	—
„ 2	Hydrochloride	50	no effect at 0	17	—	„ 16	—	16
„ 3	„	100	„	16	—	„ 16	—	16 stoppage
„ 4	Carbonate	300	16	24	under 8	„ 8	16	24
„ 5 (Decer.)	Lactate	200	18	20	„ 11	„ 12	19	20
Dog 1	„	1200	20	—	at 8	—	22	—
„ 2	„	1200	—	—	under 12	under 12	14	—

It is obvious that in every case the administration of guanidin salts, in doses of from 50 mgrms. to 1200 mgrms. per kilo, interferes with vagal inhibition of the heart of rabbits, cats and dogs. If the mean of the determinations be taken, we see that the minimal points of stimulation, before the administration of guanidin, were obtained for both vagi with the secondary coil 17 cms. from the primary. After the injection of a salt of guanidin, the coil might be pushed in to 10 cms. without producing a slowing of the heart or a fall of blood-pressure. In six out of the eleven animals, viz., two rabbits, three cats (including the decerebrated cat), and one dog, a short increase of pulse rate resulted from vagal stimulation. Guanidin was given to two parathyroidectomised cats and then the minimal effective stimulus applied to the left vagus. This produced a momentary increase in the amplitude of the ventricle with a slight decrease in the height of the auricular beat. In all cases the administration

of a solution of calcium lactate restored the inhibitory mechanism to normal.

To determine whether calcium lactate produces the same effect on parathyroidectomised animals as it does after guanidin observations were made upon parathyroidectomised cats.

TABLE II. Minimal effective stimulus in parathyroidectomised animals and the effect of calcium lactate.

Animal	Days after p'ectomy	Symptoms	After p'ectomy L.	After p'ectomy R.	After Ca lactate L.	After Ca lactate R.
Cat 6	3	Depression	12	12	14	12
„ 7	3	Respir. spasms	12	14	20	—
„ 8	—	Severe depression	16	22	—	—
„ 9	5	Slight tetany	12	14	20	16
„ 10	7	No symptoms	20	16	24	24
„ 11	—	Marked tetany	14	14	—	—
„ 12	9	Slight „	12	12	—	—

Omitting Cat 10 which showed none of the characteristic signs of parathyroid tetany the results may be summarised as follows: after parathyroidectomy the minimal effective stimuli were obtained with the secondary coil at 13 cm. (L. vagus) and 14 cm. (R. vagus). These figures may be compared with the mean (Table I) found for normal cats—viz.—16 and 19 cm. It is worthy of note that the normal animals gave a typical stoppage on vagal stimulation with these strengths, the parathyroidectomised animals merely showed slowing. After the injection of calcium lactate solution, typical inhibition was produced as in normal animals with the secondary coil at 19 and 18 cm. for left and right vagal stimulation respectively. With the exception of Cat 1, section of the vagi caused a slight increase in the pulse rate in parathyroidectomised cats.

Guanidin intoxication and parathyroid tetany produce an interference with vago-cardiac inhibition which is removed by salts of calcium. These two states, guanidin poisoning and parathyroidectomy, differ from one another only in degree.

In order to determine whether guanidin acts on the nerve, on the synapses, on the terminal ganglia or on heart muscle itself, a series of experiments was carried out on twelve frogs. The results are given in Table III.

A. After painting the neighbourhood of the sino-auricular junction of the frog's heart with salts of guanidin, stimulation of the medulla with the previous minimal effective stimulus, produced, as in vagal

stimulation of the mammal, no inhibition of the heart's action. Stimulation of the crescent with the minimal stimulus effective for the normal heart resulted generally in an increase in the rate of beats. The application of a stronger stimulus produced, first, an increase in rate, then a typical slowing.

TABLE III.

	Frog	Salt and pt of application of guanidin in solutions isotonic with 0·75% NaCl.	Minimal effective stimuli Before guanidin Med.	Before guanidin Cresc.	After guanidin Med.	After guanidin Cresc.
A.	1	Cresc. Carbonate	8	14	under 8	at 14
	2	„ „	10	18	„ 10	under 18
	3	„ „	15	17	„ 15	at 15
	4	„ „	13	17	„ 13	„ 17
	5	„ Lactate	14	14	„ 10	„ 14
	9	„ „	12	16	„ 10	„ 14
	10	„ „	12	14	„ 10	„ 14
B.	6	Whole heart „	12	16	at 12	Total inhibition.
	8	„ „ „	13	18	under 10	under 10 later at 14
	I	„ „ Carbonate	12	12	„ 8	at 8
	II	„ „ „	10	12	„ 6	under 6
	III	„ „ „	12	12	„ 8	at 8
	9 (*a*)	„ „ — Lactate	12	16	„ 10	„ 12

The results are here summarised.

Before guanidin		After guanidin (applied about crescent)			
Med.	Cresc.	Med.		Cresc.	
11	15	under	10	at 14	slight

Salts of guanidin therefore have a poisoning action on the vago-cardiac synapses, and when painted about the region of the crescent (necessarily in small amount), a slight poisoning effect on the terminal ganglia.

B. After painting the whole heart with a guanidin solution, stimulation of the medulla was non-effective whatever the strength of the current, while stimulation of the crescent, in five out of six frogs, produced an acceleration of the heart rate. In two cases the inhibitory path was completely blocked, no stimulus being effective. Three frogs gave a typical cardiac slowing on the application of a stronger stimulus to the crescent.

Before guanidin		After guanidin (applied to whole heart)			
Med.	Cresc.		Med.		Cresc.
12	14	under	7	at	10

These results indicate that guanidin has first a nicotine action, poisoning the synapses, and, after more extensive application (larger dose) an atropine action causing paralysis of the terminal ganglia in the heart of the frog.

These results also show that guanidin does not paralyse the sympathetic (accelerator) mechanism in the heart. This is deduced from the quickening of the heart on stimulation of the crescent.

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