

THE ACTION OF BARIUM CHLORIDE ON THE  
VASCULAR SYSTEM. A CONTRIBUTION TO THE  
STUDY OF THE ANTAGONISTIC ACTION OF  
NICOTINE AND CURARE. BY E. P. CATHCART AND  
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IN the course of our experiments<sup>(9)</sup> on the causation of the rise of blood-pressure following the administration of carbon dioxide we naturally considered some of the other substances which are known to produce a rise in blood-pressure. We selected barium chloride for further consideration as it is generally maintained that it acts directly on muscle substance. Dixon<sup>(1)</sup> for example states "so constant is this effect that barium can be employed as a test for the presence of muscle fibre in a tissue." A study of the previous literature is not, however, entirely convincing. It seemed to us that if it could be definitely established that the action of the barium chloride is directly on muscle, this might afford us a definite foundation upon which to base deductions regarding the pressor action of carbon dioxide.

*Previous work.* There is quite a considerable body of literature on the action of barium chloride which has been fully dealt with up to the year 1903 in the monograph of Schedel<sup>(2)</sup>. In the present paper we will only concern ourselves with those investigations which bear directly on its action on muscle and the vascular system. Thomson<sup>(3)</sup> concluded that it acts directly on the musculature of the vessels, and this conclusion was supported by the observation of Kobert<sup>(4)</sup> who carried out perfusion experiments through the portal vein. Bary<sup>(5)</sup> perfused the small intestine and the kidney with a fluid containing barium chloride and found that there was a definite reduction in the rate of flow. He concluded nevertheless that, although the greater part of the action is on the vessel musculature, still the nervous system played some small part in the control of the vessels. Boehm<sup>(6)</sup> was unable

to draw definite conclusions from his experiments as to the mode of its action. He could not determine whether the results he obtained were due to the stimulation of the whole sympathetic system or merely to the specific stimulation of unstriated muscle. Ringer and Sainsbury (7) carried out a series of experiments in which they perfused the pithed tortoise through the abdominal aorta. They found that there was a distinct diminution in the rate of flow following the addition of barium chloride to the perfusing fluid. They concluded that the action was on the muscle alone on account of the fact that the animal employed had its central nervous system destroyed. They unhesitatingly chose the latter of Boehm's alternatives in their conclusions, *i.e.* that the action of barium is specifically on unstriated muscle tissue. Incidentally it may be remarked these authors state that they were unable in their experiments to influence the calibre of the vessels through the nerves apart from direct local action. Schedel (*l.c.*) as the result of his experiments subscribes to the view that the rise in blood-pressure is due to the direct action of the barium chloride on the vessel musculature and is independent of any vaso-motor centre. Dixon (*l.c.*) also believes that the pressor action is of peripheral muscular origin. He states that even the vessels of the lungs and the brain which are generally considered to contain very few vaso-motor nerve endings constrict after the administration of barium chloride.

As regards the action of the barium chloride on the heart all workers are more or less agreed that, in the case of the isolated frog heart, at first it increases the intensity of the cardiac contraction then lowers its frequency and finally stops the heart in systole. In the mammalian heart the final cessation in systole is not such a marked feature. Schedel thinks that this action is due in part to the stimulation of the peripheral vessels and in part to the stimulation of the cardiac musculature itself. Dixon finds that in the case of the frog the ventricular systole is at first prolonged and then the relaxation becomes less and less with final cessation in systole. In the case of mammals the ventricular systole is more complete and the relaxation less; with a very large dose constriction of the coronary vessels takes place and the mammalian heart stops in systole.

As regards the action of barium on voluntary muscle the observation of Brunton and Cash (8) that it produced a veratrine-like effect, an increase in the degree and duration of muscle contraction, has been generally confirmed. Schedel found a preliminary transitory increase in the irritability of muscle which was followed by a distinct fall, the

rate of this fall depending on the degree of the concentration of the barium: the stronger the solution the more rapid the fall. He carried out a series of experiments on isolated muscle, in which he used the barium chloride before and after curare, and concluded that the twitching (initial stimulation), which he got, was not due to the direct action of the barium chloride on muscle substance but on the ends of the motor nerves, whereas the subsequent paralysis which succeeds the twitching was due to the muscle substance being acted upon. Dixon found an increase in irritability. He confirmed the veratrine-like action on voluntary muscle, but found that non-striated muscle passes into a state of tonic contraction. This last effect is well demonstrated in the emptying of the intestine which takes place in almost every experiment in which barium chloride is used.

*Present Investigation. Methods.* The methods which we employed in this investigation are similar to those already described by us<sup>(9)</sup>. The barium chloride and other substances used were injected through a cannula in the jugular vein, the dose given being washed in, in each case, with 3 c.c. of normal saline. The effect of three cubic centimetres of normal saline on the blood-pressure and the heart was found to be negligible. The animals employed were rabbits and the great majority of the experiments were carried out on decapitated animals, as our earlier experiments in 1913 had shown us that the effect of nicotine and curare, in so far as they affected the heart and blood-pressure, was identical in the normal and the decapitated animal.

*Results.* In the present series of experiments we have confined our attention solely to the effects of the barium chloride on the vascular system. We found that this salt invariably produced a rise in blood-pressure, the extent and the duration of the rise depending within the limits of the dosage employed on the amount of barium chloride injected. In our earlier experiments we injected one or two c.c. of a 1% solution and obtained very marked results, whereas in the later ones, as we wished to carry out experiments of longer duration, we reduced the dose to 0.5 c.c. of 0.5% which produced a definite but not too prolonged rise. The effect of the barium on the cardiac musculature was not so constant. There was however a slight tendency to increase in amplitude, and a constant though transient slowing of the rate, as the following protocols I and II clearly show.

## I.

Normal animal moderately deeply anæsthetised. 2 c.c. 1% BaCl<sub>2</sub> were injected into the jugular vein.

		Before	After					
			20 secs.	60 secs.	120 secs.	180 secs.	360 secs.	660 secs.
Rate	Auricle	10.5	8.5	10.5	11.0	10.0	11.0	11.0
	Ventricle							
	} in 3 secs.	10.5	8.5	10.5	11.0	10.0	11.0	11.0
Amplitude	Auricle	8	12	5	13	8	20	20.5
	Ventricle							
	} Average of 3 in mm.	33	17	35	13	17	52	52
Blood-pressure	in mm.	63	135	139	141.5	131	120	111

## II.

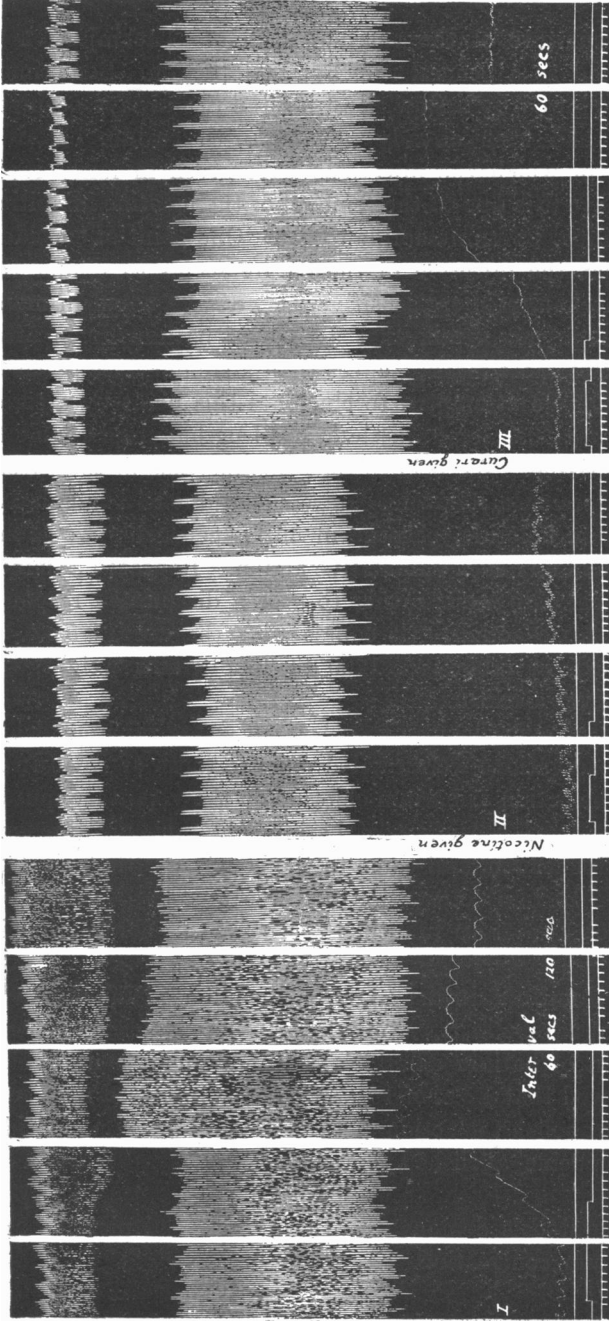
Decapitated animal. 0.5 c.c. of 0.5% barium chloride injected into jugular vein.

		Before	After			
			10 secs.	40 secs.	70 secs.	120 secs.
Rate	Auricle	12	10.5	11.0	12.0	12.0
	Ventricle					
	} in 3 secs.	12	10.5	11.0	12.0	12.0
Amplitude	Auricle	33	imperfect trace: lever caught			
	Ventricle					
	} 3 in mm.	33	22	25	26	28
Blood-pressure	in mm.	39	47	45	42	41

After we had definitely convinced ourselves of the rise of blood-pressure following the injection of the barium chloride we attempted to influence this action and made the discovery that the pressor action, which is inhibited by an injection of nicotine can be restored by a subsequent injection of curare.

In our animals the effect of the injection of 1 c.c. of 1% nicotine tartrate<sup>1</sup> was to produce the characteristic initial rise followed by a fall below the previous level. A subsequent dose of barium chloride failed to produce a rise in the majority of instances. It is true in a few experiments a very slight response was obtained, which, however, was never comparable with that obtained in the same animal with the same dose of barium chloride before the nicotine. Nicotine, therefore, either abolished or partially inhibited the pressor action of the barium salt. If a dose of curare was now given (the dose we employed in the majority of instances was .0054 gm., the preparation being that of Messrs Burroughs and Wellcome) and if this was followed by the injection of barium chloride the vascular response was found to be restored. In other words the antagonistic action of nicotine and curare put forward by Langley for skeletal muscle has been shown to hold

\* <sup>1</sup> We employed this preparation in the majority of our experiments as it was a readily soluble salt which could be obtained pure and the solution of which did not seem to deteriorate so rapidly as the solution of pure nicotine used in our earlier experiments.



**FIG. 1.** Part I. 10.10 a.m. 0.5 c.c. 0.5%  $\text{BaCl}_2$  + 3 c.c. saline into jugular vein. Total time of tracing given, 260 secs. 10.22. 1 c.c. 1% nicotine tartrate + 3 c.c. saline into jugular vein.  
 Part II. 10.27. 0.5 c.c. 0.5%  $\text{BaCl}_2$  + 3 c.c. saline. Total time of trace given, 75 secs. 10.31. 0.064 gm. curare in 1 c.c. water + 3 c.c. saline into jugular vein.  
 Part III. 10.36. 0.5 c.c. 0.5%  $\text{BaCl}_2$  + 3 c.c. saline. Total time of trace given, 141 secs.

good for the musculature of the vascular system. The injection of the curare itself had as a general rule but little action. Sometimes, it is true, it was followed by a slow rise. As the rise always occurred in animals which had been already injected with barium chloride, particularly those in which the injections were given in fairly rapid succession, we believe it is due to the removal of the nicotine inhibition permitting the residual barium chloride to act. One point of considerable interest is that the injection of the curare seems to render the vaso-constrictor mechanism more sensitive, as we have noted in many experiments, although not in all, that a dose of barium given after the curare produces a more marked effect than a similar dose given to the normal animal. We attempted to elucidate this point by a series of experiments upon the skeletal muscle of the frog but were unable to confirm it for this tissue. We believe that this increase in the extent of rise of the blood-pressure, following curare, is not due to a cumulative action of the barium chloride, because in our experiments we found very little evidence of any such cumulative action. Repeated administration of barium chloride tends rather to give a diminished response on account of its toxic action. Of course with the dose, 0.5 c.c. of 0.5%, we employed, in rabbits of 1200 to 1500 grams weight, the toxic action was never a feature.

The only series of experiments, that we are aware of, in which a similar series of observations were carried out are those of Edmunds and Roth(10) on the action of barium chloride on the voluntary muscle of the fowl. They tried the effect of barium chloride, nicotine and curare on the gastrocnemius, and came to the conclusion that nicotine did not inhibit the barium contraction of these muscles, and further that curare did not appear to influence the course of contraction in any way.

In view of the result obtained by Dixon that apocodeine inhibited the pressor action of adrenalin, it was of interest to find if this drug would influence the action of barium chloride. The few experiments which we carried out showed that 1 c.c. of 1% apocodeine inhibited markedly although it did not abolish the action of 1 c.c. of 0.5% barium chloride. This dose of apocodeine abolished completely the pressor action of carbon dioxide.

The following protocols demonstrate the influence of nicotine and curare on the barium contraction.

## III.

Decapitated animal. 0.5 c.c. of 0.5 % barium chloride into jugular vein.

		Before BaCl <sub>2</sub>	After					
			20 secs.	40 secs.	60 secs.	80 secs.	100 secs.	
Rate	Auricle	} in 3 secs.	11	11	10	10	10.5	11
	Ventricle		11	11	10	10	10.5	11
Amplitude	Auricle	} Average of 3 con- tractions in mm.	18	18	20	22	24	23
	Ventricle		66	63	76	80	84	82
Blood-pressure in mm.			36	40	84	72	74	68

1 c.c. 1 % nicotine tartrate, followed by 0.5 c.c. of 0.5 % BaCl<sub>2</sub> five minutes later.

Rate	Auricle	} in 3 secs.	10	9	9.5	9	9	9
	Ventricle		10	9	9.5	9	9	9
Amplitude	Auricle	} Average of 3 con- tractions in mm.	12	16	15	18	16	14
	Ventricle		53	42	50	51	46	43
Blood-pressure in mm.			33	35	38	41	39	35

.0054 grm. curare dissolved in water, followed five minutes later by 0.5 c.c. of 0.5 % BaCl<sub>2</sub>.

						120 secs.	200 secs.	
Rate	Auricle	} in 3 secs.	10	9.5	11	11	11	10
	Ventricle		10	9.5	11	11	11	10
Amplitude	Auricle	} Average of 3 con- tractions in mm.	8.5	9	5	3	10	14
	Ventricle		73	62	60	53	62	68
Blood-pressure in mm.			35	40	61	75	56	44

Langley(11) maintains that the effect of nicotine on skeletal muscle is due to its action on the muscle directly and not on nerve endings, and that nicotine contraction is inhibited by curare. "Curare then must also have an action on the muscle substance." He believes that the only satisfactory explanation of this antagonism of nicotine and curare on muscle is by the supposition that both combine with the same radicle of the muscle. He allows, at the same time, that neither nicotine nor curare, given in the largest doses, prevent the contraction of muscle due to direct stimulation, and naturally deduces from this that, whatever the nature of the substance nicotine and curare combine with, it certainly is not with the directly contractile substance. Thus Langley was led to postulate the presence of a receptive substance in muscle. Fühner(12) objected to Langley's work on the ground that the so-called curare action might be due to the presence of potassium in the curare preparation used, but his objection has been met by the experiments of Boehm(13) who found that curarine also influences the nicotine contraction. Fühner, who carried out his experiments with

guanidine, which he asserts has a curare-like action, comes to the conclusion that substances with curare action influence the motor nerve endings. Edmunds and Roth (*l.c.*), who investigated the action of barium chloride on skeletal muscle, agree "with the generally accepted view of the action of barium as being possibly upon the contractile substance of the muscle cell, while the other drugs mentioned (*i.e.* curare and its antagonists nicotine and physostigmine) would act upon some other constituent of the cell, which might be the 'receptive substance.'" Our experiments lead us to quite another conclusion, and we believe that the examination of the protocols will bear this out. Briefly stated we may say that, if the existence of a receptive substance in Langley's sense be allowed, barium chloride, nicotine and curare all act upon this substance or upon various components of this substance, *i.e.* barium chloride would not seem to have a more peripheral action than either nicotine or curare. It must be admitted that there is an objection to this view, *viz.* that the barium stimulus to the contractile substance of muscle may be inhibited in some way by the nicotine, that is the nicotine may prevent the barium chloride action indirectly. But against any such view is the fact that the subsequent administration of curare not merely antagonises the nicotine action but in all probability actually renders the muscle more sensitive.

Of course it is possible in the case of the vascular musculature that there exists a local mechanism,—ganglia,—which responds to various stimuli.

It is manifest from our experiments and those of many other investigators that as the blood-pressure after the injection of adrenalin will rise, even in a nicotised animal, the point of action of adrenalin is presumably peripheral to or of another order to that produced by barium chloride. Further, as has already been mentioned, apocodeine in the few experiments in which we tried it did not completely inhibit the action of barium chloride.

#### CONCLUSIONS.

(1) The observation of Langley of the antagonistic action of nicotine and curare in skeletal muscle is found to hold good for visceral muscle of the arterioles.

(2) Nicotine completely abolishes or very definitely inhibits the rise of blood-pressure which follows the administration of barium chloride.



(3) The subsequent injection of curare restores and may even intensify this pressor action of barium chloride.

(4) Barium chloride probably does not act directly on the contractile substance of visceral muscle.

(5) Barium chloride and adrenalin do not act upon identical parts of the muscle.

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