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The Pharmacology of Pyraconitine and Methylbenzaconine Considered in Relation to Their Chemical Constitution

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III. *The Pharmacology of Pyraconitine and Methylbenzaconine considered in Relation to their Chemical Constitution.*

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In a previous paper ('Phil. Trans.,' B, 1898, vol. 190, p. 239) we have shown that an entire change in the physiological action ensues on the withdrawal of the acetyl group from aconitine, as is seen in the action of benzaconine, the first hydrolytic product of aconitine, from which it differs in containing an atom of hydrogen in the place of one acetyl group. This alkaloid is devoid of the characteristic physiological action and extraordinary toxicity of aconitine, whilst in respect of its action on the heart it is in the main antagonistic to that of the parent alkaloid. In order to study further the remarkable dependence of the physiological action of this alkaloid on the presence of the acetyl group, we have examined the action of two derivatives of aconitine which we have obtained in this research, viz., pyraconitine and methylbenzaconine.

Pyraconitine was first prepared by one of us (Dunstan and Carr, 'Trans. Chem. Soc.,' 1894, vol. 65, p. 176) by heating aconitine at its melting point, when the acetyl group is expelled as one molecule of acetic acid and the alkaloid pyraconitine remains. This compound, therefore, differs in composition from aconitine by the loss of one molecule of acetic acid and from benzaconine by one molecule of water.

Methylbenzaconine was obtained from aconitine by heating it with methyl alcohol in a closed tube ('Proc. Chem. Soc.,' 1896, p. 159). A remarkable reaction takes place, in which the acetyl group is ejected as acetic acid, a methyl group taking its place. This alkaloid therefore differs from aconitine in containing a methyl group in the place of an acetyl group, and from benzaconine in containing a methyl group in the place of one atom of hydrogen. The examination of its physiological action would therefore be the means of studying the result of replacing in aconitine the negative radical acetyl by the positive methyl group, and also of studying the effect of the introduction of methyl in modifying the physiological action of benzaconine.

The acetyl group of aconitine evidently occupies an exceptional position in the molecule of aconitine. So far as we are aware it is the only acetyl compound at

present known which exchanges this group for methyl when it is heated with methyl alcohol. We have examined the behaviour of numbers of different types of acetyl derivatives from this point of view, and can find none analogous to aconitine.

For the study of their physiological action these alkaloids have been specially purified and employed as hydrobromides in aqueous solution.

Contrasting the physiological action of pyraconitine with that of aconitine, as described in the present paper, we find, as might be anticipated from our previous results, that through the removal of the acetyl group the great toxicity of aconitine is nearly entirely abolished, and the characteristic features of aconitine poisoning are no longer produced by pyraconitine.

Contrasting the physiological actions of benzaconine and pyraconitine, which differ from each other empirically by one molecule of water, pyraconitine, the anhydride, is the more active compound. Both these alkaloids, divested of the acetyl group of aconitine, are relatively weak and feebly toxic when compared with the parent alkaloid.

Although benzaconine and pyraconitine exhibit a strong similarity in the physiological effects they produce, there are differences between them which are probably more considerable than they would be if pyraconitine were merely the anhydride of benzaconine.

The substitution in aconitine of methyl for acetyl, which occurs in the formation of methylbenzaconine, has led to a very considerable reduction in toxicity, but has introduced a curare-like effect similar to that first observed by Crum-Brown and Fraser ('Edinb. Roy. Soc. Trans.,' vol. 25, p. 151) from the introduction of methyl into the molecule of an alkaloid. Methylbenzaconine is, however, more toxic and generally more powerful than benzaconine, chiefly owing to the presence of the methyl group.

Section IV.—Pyraconitine.

Beyond a faint and transitory bitter taste pyraconitine (·5 to 1 milligramme) placed on the tongue produces no noticeable effect. There is no local tingling, numbness, or anæsthesia, neither is salivation materially increased.

On Heart and Blood Pressure of Etherised Animals. (*Cats.*)

Pyraconitine is an active reducer of the blood pressure, the fall occurring without preliminary rise, and progressing until only 25 to 50 millims. of mercury is registered. At this point the decline becomes very gradual in character, even under lethal doses. Slowing of the heart is the chief cause of this fall, and is due mainly to a direct effect upon the organ, as double vagus section produces only a partial and transitory acceleration. Peripheral vagus stimulation remains effective throughout poisoning.

Impaired action of the vaso-motor centre also favours the occurrence of a low blood pressure.

Lethal Dose.—Experiments upon etherised cats, in which artificial respiration was maintained, showed a dose of ·00649 gramme per kilogramme to be lethal in two hours, and ·0056 about 20 minutes later.

Cat of 2850 grammes, etherised throughout, in warm box. Preparation as usual for simple blood-pressure experiment. Both vagi divided. Registration of respiration from chest-wall.

Time.	Blood pressure.	Pulse.	Resp.	Vagus and sciatic stimulation.	Notes.
mins.	mm.				
0	95	175	23	V. coil 10 20 millims. ↙ Sci. 8 21 „ ↗	Inject ·005 gramme pyraconitine hypodermically.
17	86	171	23		
45	82	125	19		
72	65	122	15		
81	—	—	—	V. coil 10 25 „ ↙ Sci. 8 8 „ ↗	
93	—	—	—	—	Inject ·005 gramme pyraconitine.
132	68	101	12		
164	56	92	12	V. coil 10 25 „ ↙ Sci. 8 6 „ ↗	Pulse dicrotic. Inject ·0025.
182	64	90	9		
215	52	76	5	V. coil 8 15 „ ↙ Sci. 6 5 „ ↗	
230	—	—	—	—	Gentle artificial respiration commenced. Inject ·0015 gramme atrop. sulph. by femoral vein.
240	70	87	—	—	Experiment terminated.

In this experiment ·0125 gramme in all of pyraconitine was given, or about ·004 gramme per kilogramme.

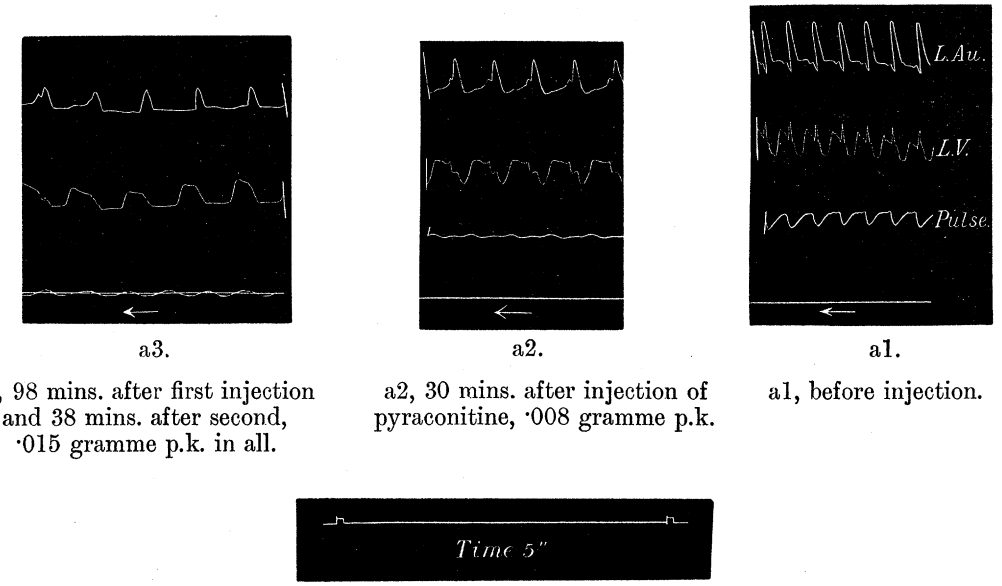
Experiments in which the chest wall was opened and the movements of the auricle and ventricle recorded, showed that as the effect of pyraconitine progressed, there was seldom ventricular irregularity or asequence upon auricular action. The irregularity in rhythm (when it did appear) took the form of a temporary non-sequence of the ventricle to every second auricular beat. On vagus section the heart was slightly accelerated and the pressure rose temporarily, whilst, if the nerve was stimulated, some slowing was always produced. This slowing became less in degree; it was succeeded by acceleration of rhythm. The auricular and ventricular systole became less vigorous, the diastole retarded, until towards the end a deliberate forceless systole of the ventricle with long diastolic pause was recorded.

Before injection of pyraconitine (the levers write upwards in systole), pulse 158 per 1 minute (pyraconitine, a1).

30 minutes after injection of ·008 gramme, 109 per 1 minute (a2).

98 minutes after first injection, and 38 after second (·015 gramme in all), 76 per 1 minute (a3).

Pyraconitine on Mammalian Heart (Auric. and Ventcl.) and Pulse.



a3. a3, 98 mins. after first injection and 38 mins. after second, ·015 gramme p.k. in all.

a2. a2, 30 mins. after injection of pyraconitine, ·008 gramme p.k.

a1. a1, before injection.

The Vagus and Vaso-motor Apparatus.

Pyraconitine is at first stimulant to the vagus mechanism both centrally and within the heart, whilst ultimately the controlling action of the stimulated nerves is reduced but not abolished. Vagus section causes temporarily a quickening of the slowed heart, and thereafter atropine may accelerate the pulse by 12–15 per minute, the pressure rising in consequence, though not to the original level.

Pyraconitine appears from the first to depress the function of the vaso-motor (vaso-constrictor) centres, so that central sciatic stimulation (the vagi being divided), stoppage of insufflation, &c., cause only a brief and inconsiderable rise of pressure. The peripheral splanchnics retain a considerable proportion of their activity throughout. No marked diminution in function of motor-nerves (phrenic and sciatic) has been observed.

The respiratory centre is early and directly depressed (as well as secondarily by the low blood pressure), and threatens to fail in action, thereby necessitating artificial respiration. Nevertheless, at a late phase of poisoning, the stoppage of insufflation may stimulate sufficiently to cause a few feeble movements. Death in

animals receiving lethal doses of pyraconitine is primarily due to central respiratory failure.

Action of Pyraconitine on Rabbits—Effect on Respiration and Temperature.

The lethal dose lies between ·0038 and ·004 gramme per kilogramme. An excessive lethal dose (·005 per kilogramme) produces little effect at first beyond an inconsiderable acceleration, followed by slowing of respiration, until in 18 minutes to 20 minutes a sudden dyspnœic struggle occurs, the animal falling unconscious on the side, the limbs extended, the pupils dilated, and death supervening. On rapidly exposing the heart, the right side of the organ with large venous trunks are found to be much engorged. The auricles, however, continue beating (in one instance for 30 minutes), and the ventricles contracting feebly. The rapidity of the toxic action of this body given in lethal dose might be supposed to point to cardiac failure as a primary cause, were it not found that artificial respiration, when employed early, postpones or even obviates the lethal issue. No œdema or extravasation is found in the lung substance.

The depressed condition of the circulation contributes powerfully to the respiratory collapse.

Sublethal doses produce a reduction of respiratory rhythm to below the normal; occasionally this is preceded by a transitory acceleration. Dyspnœa may attend the former as well as the latter condition. The temperature is reduced from 1–1°·5 C., but this is recovered from in 2–2½ hours, and become thereafter slightly hypernormal. Salivation is only rarely produced.

The rapid action of pyraconitine is suggestive of prompt absorption, but whether the early recovery is due to the high speed of elimination, cannot yet be stated with certainty, though this is highly probable.

Experiment.—(Sublethal dose.) A full-grown rabbit (respiration, 70; rectal temperature, 40°).

0 minute.	Received pyraconitine, ·00033 gramme per kilogramme hypodermically.					
10 minutes.	No excitement, occasional grinding of teeth. Respiration, 81. Temperature, 39°·7.					
30	,,	Respiration, 54.	Temperature, 39°·4.	Tends to rest on side, but rises promptly. Pupils dilated. Ears warm.		
45	,,	Respiration, 42.	Temperature, 39°·4.	Quiet. Ears warm.		
60	,,	,, 48.	,,	39°.	No marked dyspnœa.	
75	,,	,, 52.	,,	39°·3.		
90	,,	,, 58.	,,	39°·8.	Power in limbs returned.	
240	,,	,, 68.	,,	30°·3.	Feeding, not abnormal.	

Experiment.—(Lethal dose.) A full-grown rabbit received ·004 gramme per kilogramme, to which it succumbed in 30 minutes. Temperature rose ·1° C., and then declined by ·4° C. Respiration slowed from the first. There was paresis, especially of hind limbs, but slight convulsions preceded death.

In a further experiment, with a distinctly hyperlethal dose (·00425 per kilogramme), death resulted in 6 minutes 30 seconds.

Action of Pyraconitine on Guinea-pigs.

The lethal proportion is about ·0038 per kilogramme, and the symptoms are in the main similar to those witnessed in the rabbit, though clonic spasm is more frequently witnessed in guinea-pigs.

Action of Pyraconitine on Frogs.

The lethal dose is ·048 per kilogramme for *R. esculenta* and ·05 per kilogramme for *R. temporaria.*

These results were obtained from summer frogs.

No symptoms of excitement follow immediately on injection, the animal being quiescent; the position assumed low, and the movements elicited short, slapping, and tremulous. The general reflexes are sharp at first, and suggestive of a hyperæsthetic state, but subsequently impaired, whilst the conjunctival reflex is relatively long maintained. Spasm (*opisthotonos*) is developed late (2–3 hours) after moderate poisoning, and this symptom may recur during the ensuing 24 hours. The spasm, which is generally provoked in the first instance by spontaneous movement, is of short duration, and is not produced by subsequent movement or contact so readily as is the strychnine spasm, there is consequently much less exhaustion of the cord induced. When the action of the drug is passing off, the animal for a time shows abnormal excitement of movement, the spring being wild and forcible. A large dose is rapidly lethal through circulatory failure, thus a proportion of ·053 gramme per kilogramme arrested the heart (*R. esc.*) in 90 minutes, limb reflexes outlasting this event by 50 minutes. When, however, a dose only slightly sublethal greatly interferes with the circulation, the cord reflex may be impaired for a time, hyperæsthesia and a mildly tetanic state appearing at a later stage.

On Cord Reflex.—All experiments conducted on brainless frogs with vascular ligature applied to one leg, go to show that reflex is, excepting in the class of case just referred to above, but little affected on the side open to circulation of pyraconitine, and that there is no evidence that reflex centres in the cord or sensory or motor nerves at the periphery are primarily depressed in their function. The reflex becomes slightly retarded on both sides after large but sublethal doses. In no reflex experiment has tetanic spasm been observed, and this fact points to the medullary or possibly cerebral origination of those movements which are seen in the uninjured

animal. Ensuing excitement of movement is not demonstrable in the brainless frog.

On the Heart.—The heart of an etherised frog exposed *in situ*, the vagi being also prepared, showed the following phenomena after pyraconitine :—

II. Heart beating 16–17, completely arrested by vagus stimulation.

0	minute.	Inject into dorsal sac, ·002 gramme pyraconitine per kilogramme.
10	minutes.	Heart, 16.
25	,,	Heart regular. Vagus arrests.
55	,,	Injected ·001 per kilogramme.
75	,,	14. Ventricle sometimes misses a beat. Vagus arrests.
85	,,	Beating 12A to 6V.
100	,,	,, 12A to 6V. Vagus checks.
320	,,	,, 8A to 4V. ,, actively controls.
380	,,	Vagus stand-still maintained for 1 minute. (Coil 5.)
420	,,	,, 8A to 2V.

The most obvious results are a slowing of the auricles and ventricle. Later, a single ventricular beat in sequence to two, or ultimately to many, auricular beats. The auricle if much slowed is frequently found to be in sequence with every second sinus beat. Acceleration of the ventricle and tendency to restoration of the normal sequence after contact with atropine, are also recognised.

To illustrate the last point : in one case of advanced pyraconitine effect the auricle was beating 20, the ventricle 2, per 1 minute. Two applications of a drop of 1 per cent. atropine sulphate solution brought the ventricle in 30 minutes up to 8, and in 2 hours it was beating steadily 16 per 1 minute, the auricle also 16.

Perfusion of the ventricle by pyraconitine ·1 milligramme causes some retardation in the diastolic phase, whilst larger amounts are followed by weakening of the systolic force. If beating spontaneously, the rate is at first slightly accelerated and then much slowed.

On Sensory and Motor Nerve and Muscle.

Reference to the result of reflex experiment make it clear that there is no marked effect, sensory or motor, produced by pyraconitine (in doses of lethal proportion) at the periphery. Further, repeated contrasts of the reaction of nerve-muscle preparations derived from companion limbs, to one of which a vascular ligature has been applied, have shown that after a moderate degree of poisoning there is but little effect produced upon minimal excitability, whilst the poisoned muscle responds almost as well as the unpoisoned, to both indirect and direct stimulation. Even with the

greatest extent of poisoning compatible with continued absorption and distribution of the alkaloid by the heart, the work capacity of the muscle, indirectly stimulated, is not at first seriously impaired; but on repeatedly stimulating, a fatigue effect is more easily produced, and the rigid contraction produced by faradisation tends to break down.

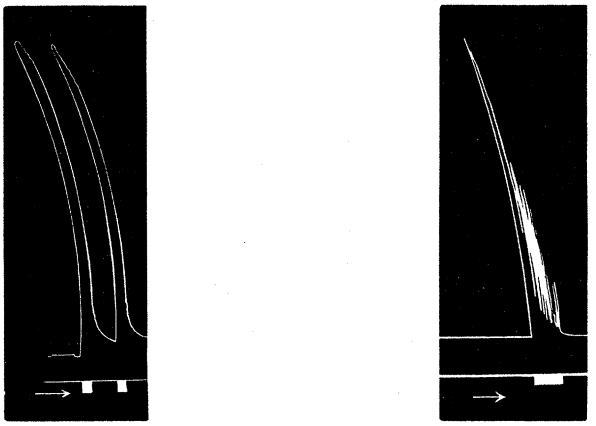
Experiment.—Rana esculenta of 25 grammes; brain destroyed; vascular ligature applied to left leg. Injected pyraconitine ·06 per kilogramme into dorsal sac. Just before circulation ceased, two muscle-nerve preparations were made and tested. Fig. b1–b2.

Minimal excitability (poisoned side) indirect, 19 centims.
direct, 10 ,,
,, ,, (ligatured side) indirect, 25 ,,
direct, 11 ,,

On repeated stimulation, a good and well maintained series of contractions to opening induction shocks was registered, but response to the interrupted current soon failed. Lever × 7. Wt. 10 grammes.

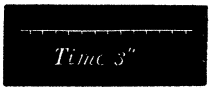
Muscle-Nerve Stimulation, Frog poisoned by Pyraconitine, ·06 p.k.

Ligatured side. Poisoned side.



b1. b2.

Tet. nerve coil 13. Tet. nerve coil 8.



	Contraction to single induction shocks.		Faradisation for 10 seconds.		
	Indirect.	Direct.	Indirect.	Direct.	
Ligatured side	33 millims.	33 millims.	57 millims.	52 millims.	Contraction to indirect faradisation is better sustained, to direct is practically equal on the two sides (b1).
Poisoned side .	32–30 ,,	31–32 ,,	49 ,,	51 ,,	The contraction to indirect faradisation tends to break down (b2).

The main effects of pyraconitine may be thus summarised. Its local application is devoid of the effects characteristic of the aconitines. Its chief action upon the heart is to cause slowing partly from vagus irritation, partly from depression in function of intrinsic rhythmical and motor mechanisms.

There is less tendency to want of sequence in the cardiac chamber walls than is observed after the aconitines and benzaconine.

The vagus apparatus remains active in degree after doses somewhat in excess of the lethal, the slowed heart of pyraconitine being accelerated both by vagotomy and by atropine.

Activity of respiration is reduced (by central depression) to a degree incompatible with life, as is the case after aconitine and benzaconine. The peripheral motor nerves and muscular tissues are not at this time markedly affected. Artificial respiration prolongs life, but the slowed heart and the greatly reduced blood pressure tend to a final issue.

The spinal cord is impaired in its reflex function, apparently secondarily to reduced circulation in its structure.

A tendency to tonic spasm in frogs is late in appearing and of moderate degree. It has not been seen after destruction of brain and medulla. It is further succeeded by a curious condition of exaggerated motility.

Neither muscular nor intramuscular nervous tissue are strongly influenced by pyraconitine in lethal or somewhat hyperlethal doses.

The lethal dose per kilogramme frog's weight is practically about twelve times that which is lethal per kilogramme rabbit's weight.

Section V.—Methylbenzaconine.

Taste.—The taste of methylbenzaconine is transitorily and by no means intensely bitter. It does not occasion the local effects of aconitine.

Methylbenzaconine on Heart and Blood Pressure of Etherised Animals. (*Cats.*)

Though by no means an active cardiac poison, the effect of methylbenzaconine is well defined. Pulse slowing is developed from the first, the ventricle filling well, and continuing to beat with considerable force. The slowing is not materially affected by vagus section nor by atropine administration. Associated with the slowing and contributing to the fall of blood pressure which accompanies it, is reduced activity of the vaso-motor centre, and, to a lesser extent, of the vascular constricting action of the splanchnic, but in neither respect does this progress to complete suspension of function.

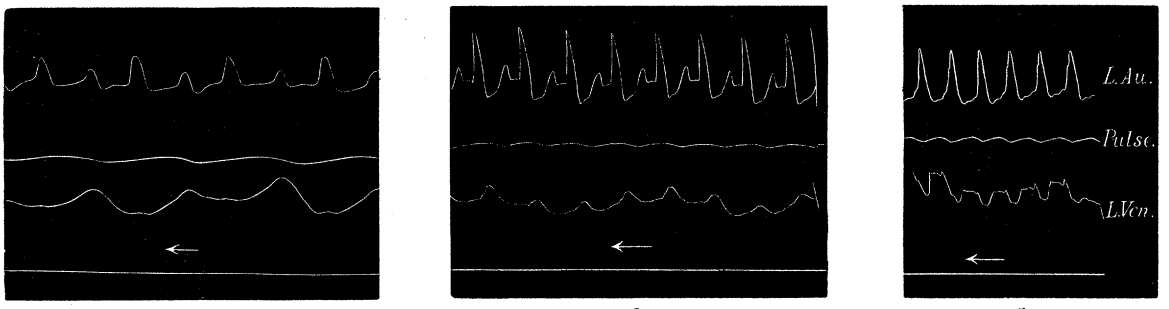
Out of four experiments in which the cardiac vagus reaction was specially examined, total loss of function was seen twice, whilst in the other two a fall of blood pressure, equal to only a few millimetres of mercury, followed. Slowing of the heart progresses until a very deliberate but steady pulse, which may have only one-half to one-third of the original speed, is recorded.

The changes in rhythm of the various parts of the heart are interesting. At first the auricles and ventricles, though slowed, hold their due sequence, but after a considerable interval they begin to show an alternating character of beat, of which the second is feebler in character; and whilst the auricular contractions remain distinct, the ventricular coalesce, so that the second becomes a mere wave on the major systole. Diastole of both auricles and ventricles is imperfect, the walls relaxing imperfectly, whilst their systole, as poisoning progresses, becomes less complete. (Small doses slow the heart without weakening the systole, though the diastole is somewhat retarded.) It is usually observable that, as the entire failure of the ventricle to follow every second auricular beat is established, some acceleration of the rhythm of the latter occurs, so that it approximates to, or may actually reach, the original rate. In one experiment the auricles and ventricles, originally beating 144 (c1), were slowed in one hour and a-half by a dose of ·004 gramme per kilogramme weight to 126, the pressure having fallen from 120 to 62. At this time paired ventricular beats appeared, and 30 minutes later the ventricle was beating steadily at 96, the auricles at 192 per 1 minute (c2), every second auricular being partial in character, whilst 24 minutes subsequently the ventricles and pulse were 45 per minute and the auricles 90 (c3). A trace of inhibitory effect was still recognisable on strong vagus stimulation, but the rhythm was unaffected by injection of atropine, and persisted until immediately before death. This relationship of ventricular and auricular rhythm, though the most usual, is not the only one observed, the ventricle occasionally failing to follow every third or every fourth (d1) auricular beat, or a complex ventricular movement having a bigeminal character, but resulting in a single pulse, may follow two or three (e1) auricular systoles. (Close inspection reveals fluctuation in the strength of the auricular contractions.) A normal sequence may be established shortly before death.

Methylbenzaconine produces much impaired action of the medullary centres, which are affected directly, and no doubt secondarily also, by the low blood pressure.

The observation that vagus section does not accelerate the heart has been referred to.

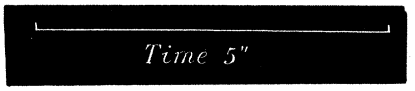
Methylbenzaconine on Mammalian Heart and Pulse.
(The levers write upwards in systole.)



c3. c3, taken 24 mins. later.

c2. c2, after injection of methbenzacn., ·004 gramme p.k.

c1. c1, before injection.



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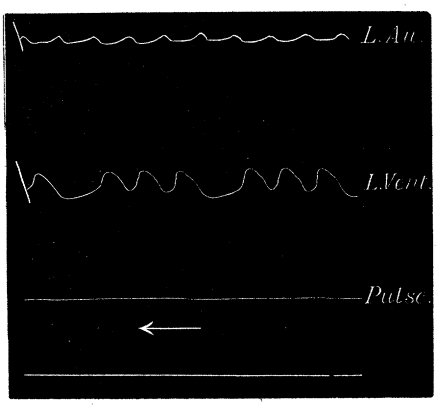
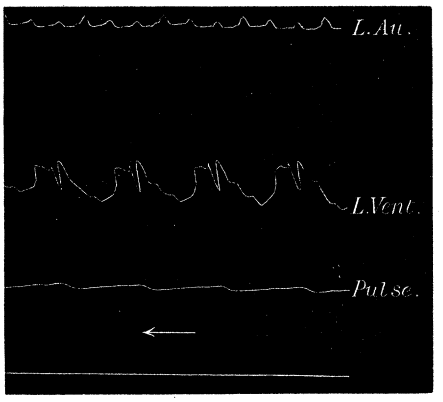
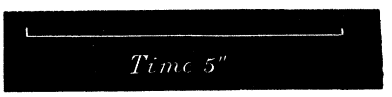


d1, 120 mins. after methylbenzacon., ·0125 gramme p.k. Four auric. to three ventcl. contractions.



e1, three auric. to one effective ventcl.



The vaso-constrictor centre is early depressed by methylbenzaconine, its response to sensory stimulation becoming feeble as poisoning proceeds, and to this as well as to the slowed pulse the steady and extensive fall of pressure is due. The innervation of the vessels is slightly interfered with, as splanchnic (peripheral) stimulation is reduced in effect, though operative in degree, throughout.

The respiratory centres are early and progressively reduced in activity. Whilst intramuscular motor nerves are depressed in function, in no instance has the reaction of the sciatic been suspended even by lethal doses of methylbenzaconine.

Experiment.—Cat of 3020 grammes, etherised, placed in warm box, cannulas in trachea and right carotid artery. Left splanchnic, left vagus, and left sciatic divided, on electrodes. Pericardium opened. Left auricle and left ventricle attached to recipient tambours in pneumatic connection with recording tambours (the movement upwards of the levers indicating systole). Insufflation through ether bottle by means of warm air.

Time.	Blood pressure in millimetres of mercury.	Left auricle, ventricle, and pulse.	Notes.
mins. 0	120–123	160–163	Blood pressure steady. Vagus stimulation (12) pressure, 22 millims. Splanchnic (10), 22 millims. Injected methylbenzaconine (·0025 gramme per kilogramme) hypodermically.
8	116	162	
17	103	159	Pressure falling very steadily.
33	93	165	
50	84	162	Splanchnic stimulation as before. Vagus stimulation, 12 millims.
68	—	—	Sciatic stimulation, 13 millims. Inject methylbenzaconine (·0016 gramme per kilogramme).
78	65	—	Splanchnic stimulation as before. Vagus stimulation, 11 millims. Sciatic stimulation, 9 millims.
88	61	155	Cut remaining (R.) vagus. No acceleration. Stopping respiration caused fall of blood pressure.
110	48	148	Vagus stimulation inoperative. Splanchnic stimulation, 10 millims. Sciatic stimulation, 6 millims.
136	54	120	Bigeminal beat of ventricle.
158	56	120	Auricle regular. Only first systole of ventricle effective. The second inoperative beat disappeared under vagus stimulation.
171	62	160 Au. 80 V.	Rhythm steady. Two auricular to one ventricular.
172	—	—	Inject methylbenzaconine (·0029 gramme per kilogramme).
190	65	166 Au. 83 V.	Rhythm steady. Splanchnic stimulation, 20 millims. rise. Sciatic stimulation. Short rise with sudden fall.
245	47	148 Au. 74 V.	No rise on stopping artificial respiration.
264	—	—	Inject atropine sulph., ·0016 gramme, into peritoneal cavity.
312	52	158 Au. 79 V.	
325	48	150 Au. 75 V.	Stopping artificial respiration. Steady fall of pressure. Five faint gasping respirations occurred as pressure fell.

In this experiment, in the course of about three hours methylbenzaconine was injected in quantities which altogether represent a proportion of ·007 gramme per kilogramme. The doses are repeated at long intervals, but this proportion, even if given at a single dose, is still distinctly sublethal. It will be noted that slight pulse acceleration was caused by atropine.

The action of methylbenzaconine towards mammals is transitory, elimination apparently taking place very rapidly. This observation does not apply to frogs.

Action on Respiration and Temperature of Rabbits.

A medium dose of methylbenzaconine causes some retching, grinding of the teeth, and salivation, a lethargic state with failure of strength primarily in the muscles supporting the head and in the fore limbs. The hind legs are affected later. Respiration becomes slow and jerking or abrupt in character. The heart continues to beat vigorously ; slight anæsthesia is present. Temperature (internal) is gradually reduced, the maximal fall being recorded about 80 minutes after administration. Respiration begins to accelerate before, or at the same time as, the rise of temperature commences.

Rabbit of 1900 grammes. Temperature 39°·9–39°·4. Respiration 80°–84°.

Mins.		Temp.	Resp.
0	Injected hypodermically methylbenzaconitine ·0085 gramme per kilogramme	—	—
10	Slight licking and chewing movement	38°·8	60
20	As above	38·5	48
25	Head droops. Lies. Tends to fall on side	—	—
30	Hind limbs much weaker	38·2	48
40	Chewing occasionally, very slight salivation. Attempts to rise, sinking of head attended by jerking movement. No noticeable anæsthesia. Paresis as before	38·0	44
50	Ataxic. No anæsthesia	38·2	56
70	Urinated. Tremor in buccal and jaw muscles	38·4	52
80	. . . . .	38·6	60
90	. . . . .	38·8	80
105	Ataxic symptoms disappearing. Beginning to sit up	—	—
120	Moving more spontaneously	39·2	80
130	. . . . .	39·4	76
150			
180	Lively. Runs and eats	40·4	68

Experiment with Lethal Effect.—Full-grown rabbit (respiration 72, rectal temperature, 38°·5) received ·0095 methylbenzaconine per kilogramme hypodermically.

12 minutes. Quiet. Sinks on belly. Chewing at intervals. Respiration, 46.
14 ,, Rolled on side, but runs if roused. Respiration, 48; no true dyspnœa. Struggles but weakly if lifted up.
18 ,, Cannot run. Very slight salivation.
21 ,, Ear pale. Pupil contracted. No chewing. Head low. Hind legs weak. Looks sleepy. On attempting movement drifts from side to side.
25 ,, On side, cannot rise. Makes feeble running movements. Pupil contracted, sensitive. Temperature, 37°·6. Respiration, 24.
29 ,, Respiration fainter, and death without spasm. Pupil dilated.

On opening the pericardium all the cavities of the heart are found to be dilated. Vermicular movements of ventricles. On bleeding, auricles begin to beat steadily, 36 per minute, ventricles replying to mechanical stimulation or induction shock. Sciatic stimulation causes twitch at 31 and good series of contractions at 30 centims.

The action of smaller doses may be thus summarised:—

·0043 methylbenzaconine per kilogramme body weight caused a fall of ·3° C., and transitory slowing of respiration by 10 per minute.

·006 per kilogramme caused fall of 1° C., and slowing of respiration by 18 per minute; slight paresis, mainly in fore limbs.

On Guinea-pigs.

·0095 gramme per kilogramme proved very rapidly lethal to guinea-pigs, whilst ·0075 was occasionally so. The lethal proportion lies between these figures.

The symptoms are grinding of teeth, salivation, retching, drooping of head, developing paralysis of the limbs with inco-ordinated movement, especially of the hind legs. Clonic movement of the head develops, and persists for some time. Dyspnœa, which shows exacerbations, accompanied by retching and scrambling movements, is a marked symptom. Nasal and lachrymal secretions are increased, and there are frequent evacuations of soft dejecta.

Unless the animal is kept in a warm atmosphere, a large fall of temperature with prolongation of symptoms of poisoning results. Thus an animal which received ·008 gramme per kilogramme, and was kept at a temperature of 15° C., showed a fall of no less than 5°·6 C. (39·7 to 34·1). Cold rigors were prominent in this experiment.

In another experiment ·007 gramme per kilogramme caused a fall of 5° C., whilst

the respiration, though dyspnœal, never fell below 48 per 1 minute. Voluntary movement was greatly impaired, but began to return before the temperature rose.

Methylbenzaconine on Frogs (Rana. esc. *and* Rana. temp.).

There is no evidence of sensory excitement after large sublethal doses, though movement may be rather restless at first. Lethargy, with restriction or absence of voluntary movement, supervenes. Fibrillation occurs in many muscles, and if movement is induced this condition is exaggerated. Respiratory movement outlasts conjunctival reflex. The general reflexes fall some minutes after respiration has ceased. Fibrillation outlasts reflex failure. Before reflex disappears a feeble and unsustained spasmodic contraction of the limbs has been occasionally seen.

When the animal has become quite motionless examination of the web shows persistent action of the heart, and this condition may last for 36 to 48 hours, when reflex (general) begins to return, succeeded by eye reflex and respiration.

If the iliac vessels of one side are ligatured (under ether) before injection is made, it is found that reflex persists in this leg for a considerable time after it has disappeared from the open side, and further that stimulation of the latter causes cross reflex in the former whilst itself failing to respond by movement. Stimulation of the fore arm or trunk is followed by the same effect, longitudinal conduction being maintained. Intramuscular motor-nerves are therefore reduced or suspended in their function before the sensory are much involved. The action upon the cord by methylbenzaconine, except after very large doses, is relatively slight and transitory in character, for, even at the height of poisoning, when reflex has almost or completely disappeared from the protected leg, the injection of strychnine will develop short but distinct spasm of its muscles.

The following table shows the order in which some of these effects occur; the results are taken from experiments upon *R. esculenta* made in June and July :—

Dose of methyl-benzaconine per kilogramme.	Respiration abolished.	Reflex gone.		Fibrillation ceases.	Excitability of sciatic nerve gone to induction shock.
		Eye.	General sensory.		
	mins.	mins.	mins.	mins.	mins.
·02	122	75	not quite	217	not quite
·05	80	60	84	130	139
·08	62	48	75	89	—
·1	16	12	25	32	—

Lethal Dose.—In June recoveries usually occur (*R. temp.*) after doses of ·088 and once after 0·1, but not beyond this point. A proportion of ·11 may be regarded as

lethal for summer specimens of *R. esc.* In winter the resistance is less, the heart failing gradually under doses of ·075 per kilogramme. For *R. temp.*, examined in January, recoveries were usual but not universal up to ·078 per kilogramme, above this proportion the heart failed.

Whilst smaller doses are not active towards muscular tissue, except by somewhat increasing its excitability, larger ones certainly are so, the contraction being feeble from the first, or becoming so on their repetition, when contrasted with those yielded by the muscle sheltered from the local effect of the poison.

Experiment. (June.)

R. esculenta. Under ether, vessels of right leg ligatured. After complete recovery from the anæsthetic inject methylbenzaconine

0	minute.	·083 gramme per kilogramme into dorsal sac.
10	,,	No sign of local irritation, the animal has, however, been moving about.
30	,,	Quiescent, apathetic, position low. All reflexes impaired. Gets off back.
35	,,	Left foot chiefly moved when right stimulated. Eye reflex very feeble. Respiration slow and intermittent. Web of left foot spread occasionally in spasmodic manner. Fibrillation in trunk and right leg muscles.
45	,,	Eye reflex gone, but both legs occasionally moved spontaneously, the right very feebly, the left with much force. Does not get off back.
60	,,	No respiration. No right reflex but cross to left. Sensation, however, reduced on open side.
120	,,	Reflex of left leg to its own stimulation and from stimulation of arm or right leg. Fibrillation gone.
240	,,	Left reflex active. Pupil contracted (of course no reflex). Circulation excellent in the right leg.

Decapitated. On destroying cord, only the left leg moved.

Muscle-nerve preparations examined.

No reaction obtained by stimulating the nerve of preparation from right (poisoned) leg. The muscle, though yielding a fair contraction at first, soon shows evidence of fatigue.

The protected (left) nerve-muscle preparation gives excellent and well sustained contractions both to indirect and direct stimulation.

The fibrillation, which is so uniformly present after injection of this derivative, is not suspended in a limb by nerve section nor yet by destruction of the spinal cord, it is therefore peripheral in causation.

On Reflex.

The brain having been destroyed in specimens of *R. temp.* or *R. esc.*, on the succeeding day vascular ligature was applied to one leg and the reflexes were thereafter tested. Subsequently to injection of methylbenzaconine, withdrawal of the foot on the open side soon fails whilst persisting on the side of ligature, a cross reflex is elicited from the former to the latter for a varying but often considerable period (when the dose is moderate), showing that sensory nerves retain some function (though it is impaired) after intramuscular motor nerves have been put out of action by access of the poison. If the dose is carefully adjusted direct reflex may be preserved on the ligatured side for 24 to 36 hours, whilst the other leg is immobilised, but larger amounts suspend the reflex activity of the cord to acid stimulation. As the open leg is immobilised before the fore legs, stimulation of the latter causes movement of the protected side at a time when the poisoned leg is unmoved, showing that longitudinal conduction is possible.

Injection of Strychnine.

If a frog, poisoned as just described, receives a dose of strychnine, as reflex fails on the open side, a feeble clonus breaking down into fibrillation will be produced there, whilst the protected side passes into rigid spasm. This clonus speedily fails, whilst spasm in the protected leg is long maintained, and may even persist until it reappears in the poisoned limb. Strychnine arouses spasm, though it may be unsustained and weak in character on the protected side when no peripheral stimulation is followed by reflex response, so that this function of the cord is apparently more resistant towards methylbenzaconine than is that of the cutaneous sensory nerves. Strychnine spasm reappears in the poisoned limb shortly before reflex movement is resumed in it.

On the Frog's Heart.

Methylbenzaconine in small and medium doses does not materially affect the rhythm, and the force of the ventricular systole is well maintained. From perfusion experiments an actual increase in systolic force, with some delay in relaxation during diastole, is recognisable. The gradual perfusion of the apex with doses ranging from ·0005 gramme to ·000005 has such a result. Large sublethal and lethal doses affect the rhythm, especially by hindering sequence of auricles and ventricle upon every second or third beat of the sinus, or similarly by interrupting sequence of ventricle upon the auricles. The systolic force is much reduced.

There is a tendency to group beating when the ventricle is ligatured on the cannula at the groove.

The stimulated vagus which has been proved operative in slowing or altogether arresting the heart before injection, soon evidences a declining inhibitory action after large doses of methylbenzaconine, so that in 30 minutes there is only a slight slowing, and in 50 minutes to 60 minutes an absence of all effect, the heart showing absolute indifference to all vagus stimulation. At a later period the inhibitory action of the stimulated sinus is also interfered with, but it is not in all cases that this is entirely suspended. Out of six experiments directed to this point, in all of which the vagi were put completely out of action, the sinus retained some restraining action in four, in two only was it rendered indifferent to stimulation.

The heart arrested by toxic doses of methylbenzaconine may sometimes be aroused to temporary action by vagus stimulation, the auricle usually beating for some time before the ventricle follows.

Action on Sensory Nerves.

There is some slight impairment in the activity of the sensory nerve fibres at a time when intramuscular motor-nerves are put out of action by methylbenzaconine, and further depression in their function is observable subsequently.

Action of Methylbenzaconine on Motor Nerves and Muscle.

It has been already noted that large doses of the alkaloid may altogether abolish excitability of intramuscular motor-nerves of frogs, and that the muscle substance becomes involved also, so that the work capacity, especially as elicited by repeated faradisation, is slightly reduced, fatigue being readily developed. Smaller doses are followed by impaired response to indirect, but full response to direct, stimulation. Such an effect is shown in the record of an experiment.

Experiment.—In a decerebrated *R. temp.* of 32 grammes, the left leg vessels were ligatured, and methylbenzaconine, ·05 gramme per kilogramme, injected. The usual symptoms ensued. At the time of making the preparation (3 hours later) there was moderate reflex from the left foot to itself (the extension being accompanied with slight stiffness of the limb muscles and tension of the swim web); the right leg was not moved from its own stimulation, but there was a slight cross reflex from it to the left. The heart beating well, 22 (systole prolonged), two auricular beats to one ventricular.

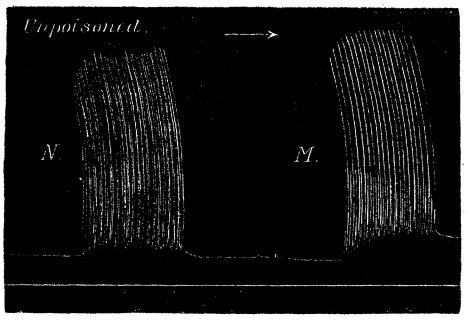
Destruction of the cord provoked movements in both hind limbs.

Minimal excitability (ligatured side), N 20 centims. M 13·5.
,, ,, (poisoned ,,), N 12 centims. M 14·5.

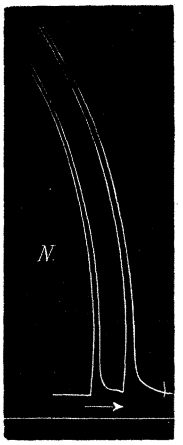
Stimulation of the latter, f 2, by series of induction opening shocks, gave reactions

of 25 millims, falling to 18 after 36 contractions. The stimulation (direct) of the muscle gave a good series of contractions of 32 millims., f 4.

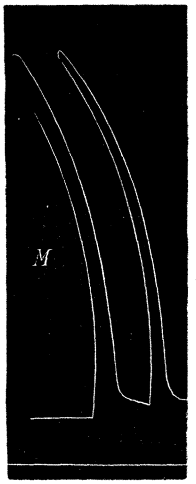
Musc.-Nerve preparations from *R. temp.*, partly Poisoned by Methylbenzaconine, ·05 gramme.
Tet. taken after stim. by single induction shocks.



0 ind. shock every 1 sec.
f 1, stim. of nerve. f 3, stim. of muscle (direct).

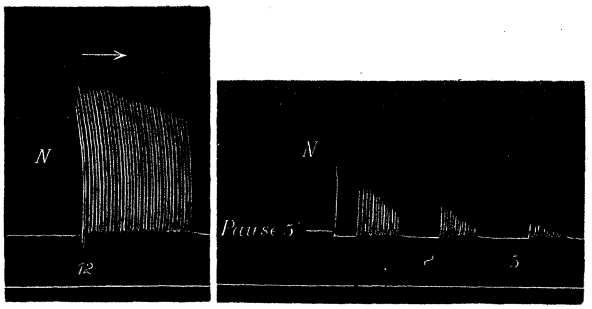


Coil 12.
f 5, tet. indirect



Coil 8.
f 6, tet. direct.

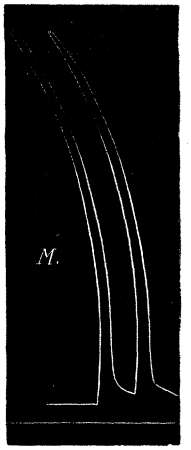
Poisoned.



0 ind. shocks.
f 2, stim. of nerve.

Tet. (indirect), no reaction.

f 4, stim. of muscle.



f 7, tet. direct.

The nerve now failed utterly on restimulation, and no tetanic contraction could be obtained from the strongest stimulations.

Tetanus of muscle, 61 millims., f 7.

Ligatured side: indirect stimulation by opening shocks 26 to 31 millims., f 1; well maintained. Direct, 33 millims., f 3.

Faradisation: indirect, 61 millims., f 5; direct, 61 millims., f 6.

The intramuscular nerve endings rapidly fail in function under stimulation, and intervals of rest do not in any way reinstate excitability. The recovery of reaction on resting after such a failure (which is so characteristic of the benzaconine muscle indirectly stimulated) has not been witnessed after methylbenzaconine.

Muscle Curve.—The curve of the muscle derived from a frog exposed to large doses of methylbenzaconine becomes more rapidly elongated on repeated stimulation than does that derived from the protected muscle. Further, the second summit of the curve tends to increase at the expense of the first, which undergoes rapid diminution.

The action of methylbenzaconine may be summed up as follows :—

It is very feeble in its toxicity when contrasted with aconitine, but is stronger than benzaconine.

Small and medium doses, whilst slowing the heart, do not cause any failure in sequence, but larger doses have this effect. They act upon the rhythm of the organ, involving the movement of both auricle and ventricle, whilst ultimately the sequence of the latter upon the former is impaired, so that it follows only a certain proportion of the auricular "leads." This block is not removed by atropine. Whilst the passage of the ventricle into diastole is at first retarded, the contractile power of the myocardium is ultimately reduced by methylbenzaconine.

The cardiac vagus is depressed in action, and its inhibitory function is ultimately suspended by large doses, neither section of the vagus nor atropine administration relieving the slow and faulty action of the organ.

There is evidence of slight primary stimulation of reflex cord centres when ligature of vessels prevents the masking of this condition by the peripheral action of the poison. The subsequent impairment in cord reflexes is later in occurring, and of much shorter duration than the action of methylbenzaconine upon intra-muscular motor nerves.

In mammals the paralytic symptoms are predominant; the fall of temperature is in part attributable to this cause, as well as to the changes in the circulation. The clonic movement and salivation (observed in a certain stage of the action of methylbenzaconine, especially upon guinea-pigs) are suggestive of the action of a near ally of aconitine. In frogs, however, there is no semblance to an aconitine effect, unless its very feeble action towards sensory nerves, or its much more powerful action upon motor nerves, be thus viewed.

Motor nerves are greatly affected by doses which are distinctly below the lethal for cold-blooded animals, the action being curare-like in character. Muscular tissue is, after the action of large doses, more susceptible of fatiguing influences. Fibrillation in muscles to which the poison has access is more common than after aconitine or any other derivative examined.

These observations support in the main the contention of Crum-Brown and Fraser, that the introduction of methyl into the molecule of certain spasm-producing

alkaloids masks the effect of these by occasioning a curare-like action at the periphery.

Contrasted Effects of Pyraconitine and Benzaconine.

Of these two alkaloids pyraconitine is approximately six to seven times more toxic towards mammals (rabbits and guinea-pigs) than benzaconine, and five to six times more so towards frogs. They are alike in their action upon mammals, in so far as they are non-irritant, that they slow the respiration without preliminary acceleration, that they slow the heart and reduce the blood pressure to a very low level, that they cause paresis, and in guinea-pigs clonic movements, and that respiratory failure is the immediate cause of death. They differ, in so far that pyraconitine acts more rapidly but for a shorter period, whilst fatal termination of poisoning is preceded by convulsions which are very rare after benzaconine. Benzaconine alters the sequence of the ventricles upon the auricles much more usually, and to a greater extent than pyraconitine, though, if asequence is developed, it has the same general character (the auricular second beat being blocked from the ventricle). Whilst pyraconitine stimulates the cardiac vagus both centrally and within the heart (section and atropine causing acceleration), and finally occasions only a limited reduction in its activity, benzaconine produces but little stimulation, and ultimately suspends the vagus inhibitory action. Under these conditions atropine is, of course, inoperative. Both accelerate the heart in small, but slow it in large, dose. Frogs poisoned by benzaconine lose the power of voluntary movement, then reflex disappears, and finally the circulation is arrested, but after pyraconitine, reflex outlasts the heart's action. Late spasm occurs after the latter but not after the former. Whilst in lethal doses pyraconitine has no effect beyond somewhat favouring fatigue and reducing excitability of motor-nerves, benzaconine greatly impairs their function, and in thorough poisoning, may suspend it entirely.

Contrasted Effects of Methylbenzaconine and Benzaconine.

Methylbenzaconine is from three to four times more toxic towards rabbits and guinea-pigs than benzaconine, and from twice to thrice as toxic towards frogs (*R. temp.* and *R. esc.*). In mammals slight salivation, retching movements, and muscular tremor are characteristic effects of the former, but dyspnœa, ataxia, and paresis are also seen after benzaconine. Of the two, methylbenzaconine is distinctly less depressent towards the heart. Slowing of the pulse and want of sequence of ventricular and auricular action occurs after both, but is a much earlier symptom after benzaconine, which causes much more disorder in the motor mechanism. On the other hand, the intra-cardiac vagus is put out of function more rapidly by methylbenzaconine. Death after either poison is rarely preceded by spasm. Neither of

the two compounds causes any local sensory irritation in frogs, but methylbenzaconine produces active fibrillation in the muscles to which it gains access, and develops a complete curare-like action much more prominently than does benzaconine, the heart continuing to beat strongly. Benzaconine, in dose sufficient to cause such an effect at the periphery, acts disastrously upon the circulation. In partial poisoning by methylbenzaconine the characteristic rapid failure on stimulation of the intra-muscular motor nerves is well marked, but the subsequent recovery on resting, so characteristic of benzaconine, has not been observed.

Contrasted Effects of Methylbenzaconine and Aconitine.

The toxicity of aconitine is roughly eighty to one hundred times that of methylbenzaconine towards rabbits and guinea-pigs, and much the same proportion holds for summer and winter frogs respectively. Whilst slight tendency to salivation and retching movements are produced by methylbenzaconine, and are in so far suggestive of a slight aconitine action, the absence of initial acceleration of respiration, of local irritation and dyspnœal convulsions, and the predominance of paralytic symptoms, are points of difference. The action upon the heart is entirely distinct, for the pulse is slowed by methylbenzaconine, the auricles eventually beating more rapidly than the ventricles, the action of the poison proceeds uniformly and without the intermissions which characterise aconitine, whilst the early phenomena of vagus stimulation have little in common. The general symptoms of poisoning in frogs have scarcely a point of similarity; quiescence, rapid failure of reflex and voluntary movement, without impairment of the cardiac action, are distinctive of methylbenzaconine, whilst excitement with great motility and greater persistence of voluntary movement follow aconitine. Fibrillation is much more pronounced after the former, though it is only a transitory phenomenon. The action of the two substances upon the heart differs widely in frogs as it does in mammals, whilst the curare-like action of the derivative on motor nerves is not produced by aconitine in doses which just suffice to arrest the heart.

It is true that large but sublethal doses of aconitine are followed by a condition of almost complete paralysis which lasts for several days, but during this time there is slight voluntary and reflex movement, the nerve endings are not inactive, and the circulation is usually of the feeblest character; all conditions which are not found in the period of quiescence following methylbenzaconine.