IV. *The Pharmacology of Aconitine, Diacetyl-Aconitine, Benzaconine, and Aconine,
considered in relation to their Chemical Constitution.*

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CONTENTS.

INTRODUCTORY

Since the time of Störk, few problems in Pharmacology have received more attention than the action of aconite (*Aconitum napellus*), or its alkaloid, but whether extracts of the whole plant have been employed, as by the earlier observers, or alkaloidal substances, as by the later, the drug and its components do not, as yet, occupy a well-defined position from either the pharmacological or therapeutical aspect.

Recorded observations have frequently been so discrepant and contradictory with regard to one another, that even the fundamental points of action of aconite and aconitine still remain in a condition of unsettlement and dispute. It may safely be stated that with regard to no other object of such extensive research has there been obtained so scanty a harvest of facts. As illustrative of these divergences, the following may be quoted :—

The cause of death by aconite is alleged by Sharpey to be syncope; by Sir Benjamin Brodie,* to be asphyxia; by Fleming,† to be due to overwhelming depression of the nervous system, or asphyxia, or both.

Aconitine acts fatally, according to Böhm with Wartmann,‡ by poisoning the

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* 'Physiological Researches,' 1851.
† 'Aconite, Prize Theses,' London, 1845.
‡ 'Verh. d. Physikal. Med. Gesellsch. in Würzburg,' 1872.

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heart ; whilst by MURRAY (*a*), by MACKENZIE (*b*), by LEWIN (*c*), and by LABORDE (*d*), its lethal action is referred to the respiratory system.   Wide variations occur in the estimations of the lethal dose.

The spinal cord is alleged by ASCHSCHARUMOW (*e*) to be unaffected, whilst BÖHM and WARTMANN (*f*) speak of abolition of reflex phenomena before volition.

LIEGOIS, with HOTTOT (*g*), saw the cord powerfully depressed by aconitine.

Peripheral nervous structures, whether motor or sensory, are stated to be acted upon in different ways, so that whilst MACKENZIE (*h*) speaks of a stimulation of sensory nerves, followed by depression, ASCHSCHARUMOW (*i*) denies that his aconitine produced any anodyne action.   These authors are not agreed as to the effect upon motor nerve terminations, and whilst MACKENZIE is supported by WEILAND (*j*), LIEGOIS with HOTTOT (*k*), GUILLAND, and LANGAARD (*l*), in attributing a paralysing action to the alkaloid, ASCHSCHARUMOW endorses the view of BÖHM with WARTMANN, that no paralysis is produced.

WEILAND (*m*) describes the muscle curve of an aconitine muscle as very similar to that so characteristic of veratrine, whilst the majority of observers see no marked departure from the normal.   Slighter divergences of opinion with regard to the action upon the heart are evident ; by RINGER with MURRELL (*n*), the myocardium as well as intracardiac nervous structures are believed to be the seat of action, whilst the latter are chiefly affected according to BÖHM with WARTMANN.

LEWIN (*o*) regards the nervous " excito-motor " elements as mainly involved.

As indicated already, certain observers believe the cardiac phenomena in warm-blooded animals to be entirely secondary to a profound effect upon respiration.

These allegations may suffice to indicate the confused and inexact state of existing information regarding the action of aconite and its chief alkaloid.

Such a contradiction in results obtained by highly-skilled observers seems strongly suggestive of the conclusion that identical substances have not invariably been

(*a*)   ' Philadelphia Med. Times,' 1878.

(*b*)   ' Practitioner,' 1879.

(*c*)   ' Exp. Unt. über die Wirkung des Aconitines,' Berlin, 1875.

(*d*)   ' Tribune Medicale,' 1892–3.

(*e*)   ' Arch. f. Anat.,' vol. 2, 1866.

(*f*)   ' Verh. d. Physikal. Med. Gesellsch. in Würzburg,' 1872.

(*g*)   ' Journ. de Phys.,' 1861.

(*h*)   *Op. cit.*

(*i*)   *Op. cit.*

(*j*)   ECKHARD's ' Beiträge,' vol. 3.

(*k*)   ' Arch. de Phys.,' 1875.

(*l*)   ' Archiv f. pathol. Anat.,' vol. 79.

(*m*)   *Op. cit.*

(*n*)   ' Journ. of Physiology,' vol. 1.

(*o*)   ' Ueber die Wirkung des Aconitines, &c.,' Cent.B., 1875.

employed by them, and that what have been taken to be single substances have been, in reality, mixtures of several aconite alkaloids.

We therefore decided to examine the pharmacological action of the pure alkaloids of several varieties of aconite and their derivatives, specially prepared free from contamination with other substances. It was believed that, by examining the pure specimens of aconite alkaloids which had been in part examined previously, fresh facts might be ascertained which would remove the present obscurity, whilst many new compounds were available for extending the enquiry not only into their individual effect, but into the relationship which this might present to their chemical constitution.

The portion of the research which is described in the present paper has been carried out with pure specimens of the alkaloids aconitine, benzaconine and aconine, the chemistry of which has been fully studied since 1891 by one of us in conjunction with his assistants and pupils, and forms the subject of numerous papers which have been communicated to the Chemical Society, and printed in the 'Journal of the Chemical Society.' As these papers contain a full account of the chemical composition and properties of the various aconite alkaloids, it will not be necessary to do more now than summarize, for reference, the chief properties of the substances employed in this enquiry.

Aconitine is the poisonous alkaloid contained in *Aconitum napellus*.* It is a crystalline base, melting at 188°–189°, very sparingly soluble in water, but readily dissolved by alcohol. Its alcoholic solution is dextro-rotatory, whilst solutions of its salts are lævo-rotatory.† Even a very dilute solution produces a characteristic tingling and numbness of the tongue and lips. The alkaloid suffers decomposition when heated to its melting point; a molecular proportion of acetic acid is lost, and an alkaloid, pyraconitine, remains.‡ The hydrolysis of the alkaloid occurs in two stages. In the first, which is best effected by heating a salt of aconitine in a closed tube with water,§ a molecular proportion of acetic acid is formed and an alkaloid produced which is named *benzaconine*, the chief constituent of the picraconitine and napelline of previous observers.‖ Further hydrolysis, by alkalis or acids, resolves benzaconine into aconine and a molecular proportion of benzoic acid, and these are the final products of hydrolysis.

A characteristic qualitative reaction of aconitine is the formation of a crystalline purple precipitate of aconitine permanganate when a faintly acidified solution of an

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* 'Journ. Chem. Soc.,' 1891–1897 *et seq.* DUNSTAN and INCE, 'Journ. Chem. Soc.,' 1891; DUNSTAN and UMNEY, *ibid.*, 1892.

† DUNSTAN and INCE, *loc. cit.*

‡ DUNSTAN and CARR, *ibid.*, 1894.

§ DUNSTAN and CARR, *ibid.*, 1894.

‖ DUNSTAN and HARRISON, *ibid.*, 1893; DUNSTAN and CARR, *ibid.*, 1893; DUNSTAN and HARRISON, *ibid.*, 1894.

aconitine salt is mixed with a solution of potassium permanganate.* Most aconitine salts crystallise well from a solution in water, and in experiments on the physiological action of this alkaloid an aqueous solution of the hydrobromide has been employed.

Neither the composition nor constitution of aconitine can be regarded as settled. In determining the exact formula by which the composition is best expressed, there is the difficulty of deciding between several formulæ which represent the composition of the alkaloid within the limits of experimental error. ALDER WRIGHT[†] adopted the formula $C_{33}H_{43}NO_{12}$ as best expressing the composition. Later observers, JÜRGENS, LÜBBE, and ourselves have accepted a formula either identical with or differing slightly from that of WRIGHT, as indicating the composition of aconitine and its derivatives, whilst EHRENBERG and PURFÜRST have suggested the formula $C_{32}H_{43}NO_{11}$. Recently FREUND and BECK[‡] have proposed for aconitine the formula $C_{34}H_{47}NO_{11}$ instead of that employed by us, $C_{33}H_{45}NO_{12}$, since they have obtained by the ultimate analysis of pure alkaloid nearly two per cent. more carbon than has been found by ALDER WRIGHT and his colleagues, by JÜRGENS, by LÜBBE, or by ourselves. The question of composition is, therefore, still unsettled, and can probably only be finally decided by the analysis of simpler derivatives of aconitine than have been hitherto dealt with. The constitution of aconitine cannot be disposed of until more is known of the simpler derivatives and decomposition products. For the purposes of the present discussion it may be regarded as *acetyl-benzaconine*, but nothing is at present known of the constitution of aconine. Commercial specimens of aconitine vary considerably, many of them being mixtures.§ Until quite recently the pure alkaloid was not an article of commerce.

Diacetyl-aconitine is an alkaloid obtained from aconitine by acting upon it with acetyl chloride,‖ and differing from it in containing two acetyl groups in the place of two atoms of hydrogen. It is a crystalline base melting at 158°, very sparingly soluble in water, but readily in alcohol. A solution of its hydrobromide in water was used for the determination of its physiological action. This solution, like that of an aconitine salt, produces a persistent tingling and numbness of the tongue and lips.

Benzaconine, the product of the partial hydrolysis of aconitine, occurs with aconitine in *Aconitum napellus*,¶ and is the principal constituent of the substances named napelline and picraconitine by previous observers. It was first named by us *isaconitine*, as its percentage composition was found to agree within the limits of

* DUNSTAN and CARR, 'Pharm. Journ.,' 1896.

† ALDER WRIGHT, 'Journ. Chem. Soc.,' 1877.

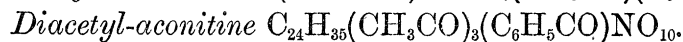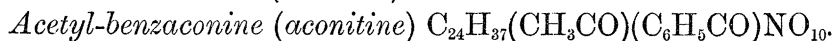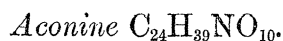‡ FREUND and BECK, *Ber.*, 1894.

§ DUNSTAN and CARR, *ibid.*, 1893.

‖ DUNSTAN and CARR, *ibid.*, 1895.

¶ DUNSTAN and UMNEY, *loc. cit.*

experimental error with that of aconitine.* The base is amorphous and separates from a solution in alcohol and ether as a varnish ; it dissolves sparingly in water. Solutions of the alkaloid and of its salts are very bitter, but do not produce the tingling of the tongue and lips which is so characteristic of aconitine. Like aconitine, solutions of benzaconine are dextro-rotatory, whilst those of its salts are lævo-rotatory. When hydrolysed, benzaconine furnished aconine and benzoic acid. Although the base has not been crystallised, the salts of benzaconine crystallise easily. For the experiments on the physiological action an aqueous solution of the hydrobromide has been employed. Since benzaconine differs from aconitine only in the absence of an acetyl group, attempts have been made to re-form aconitine from benzaconine by replacing this group. These attempts have, however, failed. Benzaconine does not furnish under the several conditions tried a monacetyl derivative, and the compounds which have been prepared containing more than one of these groups do not exhibit any of the characteristic properties of aconitine, and would seem to be isomeric, not identical ; thus the triacetyl-benzaconine is isomeric with triacetyl-aconitine, and tetracetyl-benzaconine isomeric, not identical, with triacetyl-aconitine.†

Aconine is the final basic product of the hydrolysis of aconitine, with which it occurs in *Aconitum napellus*.‡ It is an amorphous alkaloid readily soluble in water and in alcohol though not in ether. Its solutions are sweet in taste, alkaline in reaction, and dextro-rotatory, like aconitine and benzaconine ; the salts of aconine being also lævo-rotatory. The salts are crystalline ; a solution of the hydrobromide has been used for the experiments described in this paper.

Adopting for the present WRIGHT's modified formula for aconitine, the following formulæ and names represent the alkaloids dealt with in the present paper :—§

> *Aconine* $C_{24}H_{39}NO_{10}$.
> *Benzaconine* $C_{24}H_{38}(C_6H_5CO)NO_{10}$.
> *Acetyl-benzaconine (aconitine)* $C_{24}H_{37}(CH_3CO)(C_6H_5CO)NO_{10}$.
> *Diacetyl-aconitine* $C_{24}H_{35}(CH_3CO)_3(C_6H_5CO)NO_{10}$.

As aconitine has been so largely used by other experimenters, its action will be treated of in greater detail than will be necessary when considering its derivatives or its allies obtained from other varieties of aconite.

The modes of action of aconitine, diacetyl-aconitine, benzaconine and aconine respectively have been tested with regard to the following points :—

* DUNSTAN and HARRISON, *ibid.*, 1893 ; and DUNSTAN and CARR, *ibid.*, 1894.

† DUNSTAN and CARR, *ibid.*, 1895.

‡ DUNSTAN and UMNEY, *ibid.*, 1892.

§ See further, DUNSTAN, " The Nature of Aconitine," ' Pharm. Journ.,' March, 1894, and " Collected Papers from the Research Laboratory of the Pharmaceutical Society," vol. 2, 1896.

1. Their effect upon the blood-pressure, pulse, and respiration of anæsthetised cats.

2. Their general effect, and especially their action upon temperature and respiration of rabbits, and (occasionally) of guinea-pigs.

3. Their general toxic action upon frogs, and upon the following organs and functions of other animals, separately examined :—Circulation, respiration, cord, reflex, motor and sensory nerves, and muscles.

4. Their lethal dose towards some or all of the various animals employed.

Whilst the scope of this paper will be limited to these alkaloids, there are many other alkaloids and derivatives closely allied to aconitine which have been under examination, and it is intended to present a further communication concerning these with as little delay as possible. Among them may be named pseudaconitine, the alkaloid of *A. ferox*, japaconitine, the alkaloid of *A. japonicum* or *Fischeri*, as well as several new derivatives of aconitine.

The chemical part of this enquiry, for which one of us (D.) is responsible has been conducted at first in the Research Laboratories of the Pharmaceutical Society, and afterwards in the Laboratories of the Scientific Department of the Imperial Institute. The pharmacological experiments have been made (by C.) in the Department of Materia Medica in the University of Aberdeen.

SECTION I.—ACONITINE.

Freshly-prepared aqueous solutions of aconitine hydrobromide were employed, representing ·00025 and ·000025 gram of actual alkaloid per cub. centim. of water. The solution was run into a finely-calibrated pipette by KÄHLE, graduated to the ·01 cub. centim., and from this it was removed by a very fine capillary pipette, bulbous in the centre, into which a little salt solution had been previously allowed to flow, in order to wash out the last trace of alkaloidal solution upon injection.

ACONITINE ON BLOOD PRESSURE, RESPIRATION, AND PULSE OF WARM-BLOODED ANIMALS.

CATS.

The anæsthetic chiefly employed was ether, and full, though not excessive, anæsthesia was maintained throughout the experiment by constant administration from the ether bottle described in a previous paper. The body of the animal was placed in a metal box, the temperature of the water enclosed in the double walls being kept at about 60° Fahr., the movable lid being heated in the same manner. Injections of dilute solutions of aconitine were made under the skin of the abdomen.

Tracheotomy was performed, and the animal either respired spontaneously, or artificial respiration was carried on by means of the tracheal cannula. Exposure of one carotid, and insertion of a cannula which was subsequently connected with the blood pressure recording apparatus, preparation of the vagi, and, when necessary, of the splanchnic and sciatic nerves, was made in the usual manner.

The apparatus used was mainly that described and figured by us in a previous paper (' Phil. Trans.,' B, 1893). Registration was made by the mercurial manometer and Ficks' kymograph (straight or hollow-curved spring). In addition, when it was considered essential to record the movements of auricle and ventricle, the heart was exposed by resecting three ribs on the left side, or by removal of a portion of the sternum with the anterior extremities of the ligatured ribs on both sides, and the organ was brought slightly forward without dragging, by stitching the divided pericardium to the edges of the wound. Fine threads were attached to the ventricle (by stitching) in as non-vascular a part as could be found, about mid-way between apex and groove, and 1·5 centim. to the left of the junction of the ventricles; and to the auricle by ligaturing the extremity of the appendix, the threads being attached to the levers of recipient tambours, which stood in pneumatic connection with registering tambours. The sufficiency and accuracy of this method was controlled by experiments in which simultaneous registration of intracardiac pressure was made.

Excessive Lethal Dose.

A large cat of 3300 grams, brought to be destroyed on account of its ferocity, received ether, and, as the effect of the anæsthetic was declining, ·0013 gram of aconitine was administered hypodermically. (This proportion is very nearly ·0004 gram per kilo.) After the development of dyspnœa, first accompanied by motor excitement and then by collapse of motility, the lethal effect followed in 45 minutes.

Post-mortem.—The engorged heart pressed tightly against the pericardium. The right ventricle was pulsating at base, the auricles both beating feebly. On puncturing the ventricles, they beat actively for about 80 seconds, but their movement then became arrhythmic and fibrillary in character.

In the absence of artificial respiration, anæsthetised animals, which are the subjects of blood pressure experiments, appear to offer less resistance to aconitine. Thus an injection of ·0005 gram aconitine was fatal to a cat of 2850 grams in 34 minutes (nearly ·000182 gram per kilo.). In the experiment about to be recorded, an animal of 3000 grams received a dose of ·00013 gram, and subsequently a lethal dose of ·000518 gram, in all ·000249 gram per kilo. Death ensued 37 minutes after the second dose (for both doses the proportion is nearly ·00025 gram per kilo.).

CAT of 3000 grams etherised. Placed in warm box. Usual preparation of carotid and vagi. Thermometer beneath skin of thorax.

Time.	Blood pressure.	Pulse.	Respiration.	Temperature.	Notes.
minutes.					
5	136	151	23	38·7	(A$_1$).
6	..	..	..	..	Tie and cut right vagus.
10	126	174	28		
26	131	..	..	..	Injection ·00013 gram aconitine hypodermically.
31	..	170	23		
44	131	169	24	36·4	
57	127	170	29	36·2	
68	127	166	30	..	Injection ·000618 gram aconitine.
73	126	150	11		
79	..	..	..	..	Great variation in blood pressure with series of imperfect systoles, also slow cylinder A$_2$, and A$'_2$ on slow cylinder.
81	114–90	168			
83	100–5	166	36	..	Urgent respiratory movements, though thoroughly anæsthetised.
85	115	131			
90	114	136–246	12	..	Pulse altering and reforming —becoming very irregular. (A$_3$) with imperfect coordination.
92	106–82	256	6	35·8	Pressure falling, heart very irregular. (A$_4$.)
93	63–12	A few irregular compound beats—heart stops during tracing.	..	..	Artificial respiration is succeeded by fresh gasping, which accompanies failure of heart.

Post-mortem.—All heart much dilated. Left ventricle twitching. Left auricle beating fast and fully. Lungs congested.

This does not stultify the statement that death in an animal *not* artificially respired is respiratory. Forcible insufflation ensuring oxidation of blood causes some action of respiratory centre to persist.

The main points in this experiment are the early though slight fall of blood pressure, succeeded by a much more powerful action in the same direction 55 minutes after injection of aconitine. (This fall after lethal doses is usually seen in from 40 minutes to 60 minutes.) The characteristic phase, that of great and rapid pressure fluctuations, commences just after the fall develops. (These variations may amount to 40–50 millims. of mercury, and it has been noticed that for a short time the pressure may be raised to a higher level than the original. Such fluctuation has been described as occurring in dogs and rabbits by the majority of investigators
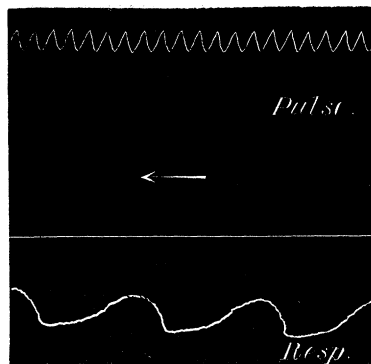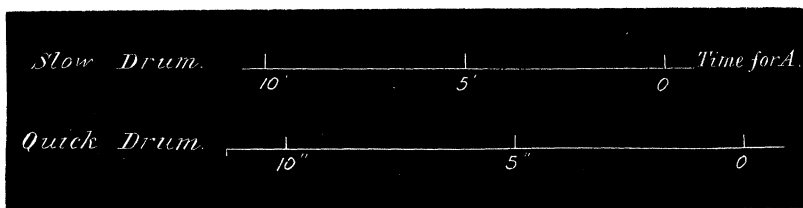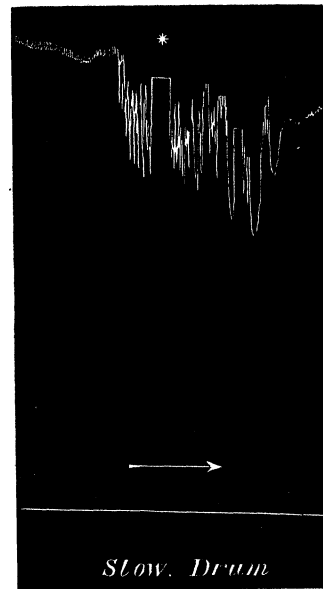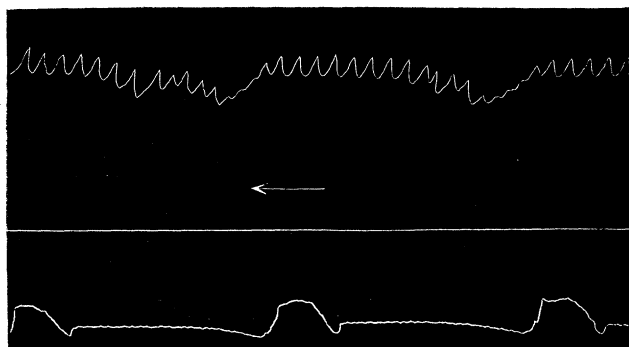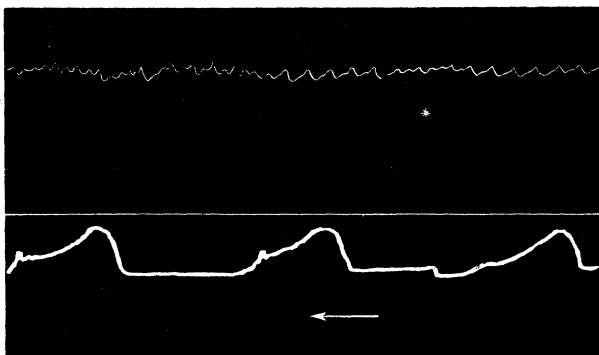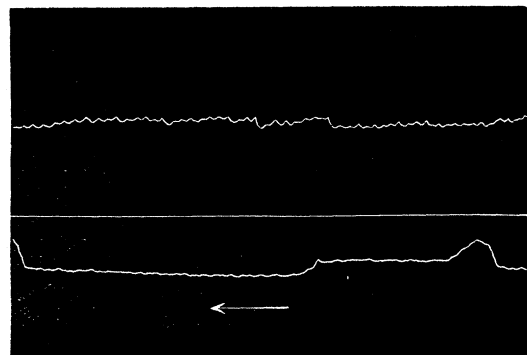
Fig. A₁.

Fig. A′₂.

Fig. A₂.

Fig. A₃.

Fig. A₄.

Description of these and later tracings on pp. 308 and 311.

who have tested aconitine upon these animals.   Vaso-motor changes, cardiac accele-ration or vagus effect have been severally represented as causal, but many authors offer no explanation of the phenomenon. The conclusions arrived at from the experiments under consideration will be stated later on.)

Many changes in the pulse, characterised in the main by great irregularity, though with occasional periods of steady action, are witnessed, a very high rate, 250 per minute being attained : the rapid beat is, however, due to a systole which is only partial in character, and the blood pressure soon yields.

Respiration, accelerated at first, declines rapidly 60 minutes after injection, and is reduced to three or four movements in the minute, the long pause being in the expiratory position.   Although some slight gasping was witnessed when the blood pressure underwent the final fall, this seemed to be a mere residuum of vitality of the respiratory centres.   Artificial respiration was employed too late to cause a marked prolongation of life.   Failure of respiration, which is regarded as the primary cause of death, intensifies and accelerates the cardiac abnormality and collapse.

(If, in place of keeping the body of the animal warm by the method mentioned, a double roll of wadding is fixed round the trunk without further protection against loss of heat, it is found, after administration of aconitine :

1. That the body temperature (both subcutaneous and rectal) suffers a much greater fall.
2. That there is a reduced tendency to cardiac arhythmia and delirium.   The heart, further, never attains the high rate of speed usual when the body temperature is less reduced.
3. That the respiration is relatively more affected than the heart, and its suspension becomes, therefore, even more obviously the cause of death.)

Pulse.

The pulse, soon after aconitine injection, usually shows a transitory acceleration amounting to from two to six beats per minute.   But this change is inconspicuous compared with the marked slowing which accompanies the ensuing extensive fall in pressure, and which may amount to from 10 to 20 per cent. of the total pulses.   (In the case of an animal merely wrapped in wool, the fall is fully 30 per cent.)   It is after this time that irregularity usually becomes apparent.

The appearance of this fault is suggestive of a missed beat, but some indication of an abortive systole, following rapidly upon the effective systole, is frequently detectable.   During expiration especially, there are often two or three imperfect systoles (fig. A_2), which permit a great drop in pressure.   Such changes accompany the development of the phase of acceleration, with fluctuation of pressure.

Many varieties of pulse are now from time to time developed, but even the most

irregular of these may suddenly yield for a brief period to a regular action.*   As the total number of effective systoles is increased during the latter phase, the blood pressure rises.

The final fall of pressure is accompanied by an extremely rapid and irregular pulse (aconitine delirium), which only occasionally indicates a distinct and operative systole of the ventricle; this may last to the end (A_4), or, exceptionally, a more regular rhythm is taken up by the exhausted heart immediately before its arrest.

Such are the chief points which are noticed in a simple pulse tracing—more is to be learnt by studying the movements of the heart itself.

Relationship of Auricular and Ventricular Action.

It may be stated here that simultaneous registration of right and left ventricles has shown that so closely do these sympathise with one another, that deviations from the normal, occasioned by aconitine, occurring in one, may be safely implied in its companion.   The same may be said of the relationship of right and left auricles.
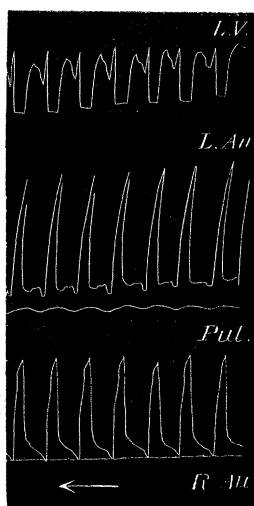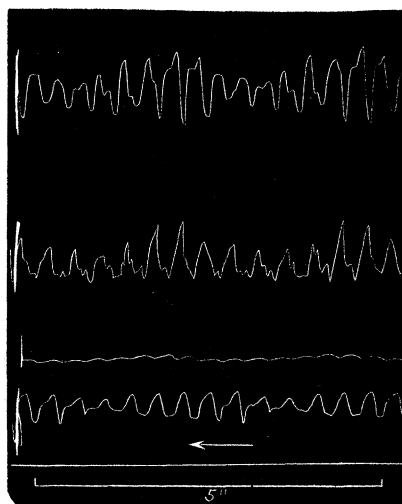
Fig. B₁.

Fig. B₂.

Fig. B₁ shows, before aconitine, left ventricle (top line), left auricle (second line), pulse (third line), and right auricle (fourth line), all 128 per minute.

Fig. B₂ shows, after aconitine, the left ventricle and pulse 180, the two auricles 162 per minute.   (These tracings are taken in the absence of artificial respiration.)

In the early phase of acceleration, and during the subsequent slowing after aconitine, the ventricles show the usual sequence to the auricles in their action.

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* Registrations of the pulse of the aconitinised dog and rabbit, given by LABORDE and DUQUESNEL ('Des Aconits,' etc., Paris, 1883), may be consulted.

Even in the commencing irregularity and the development of the characteristic fluctuations in blood pressure, this sequence is but little disturbed.

As poisoning progresses, the irregularity of the auricle seems to be exaggerated by the ventricle, so that a very abnormal pulse results. Thus in C_3 there is at first auricular acceleration, (226) with slow diastolic relaxation, accelerated ventricular

Fig. C$_1$.
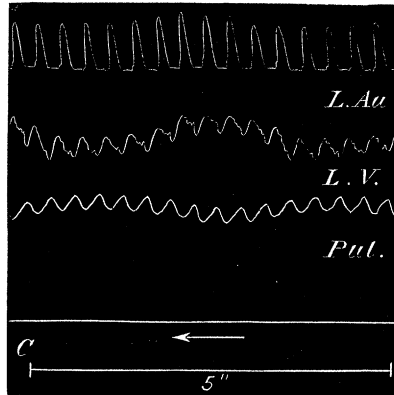
Fig. C$_2$.
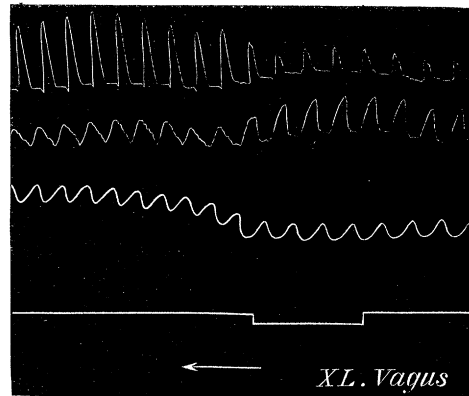
Fig. C$_3$.
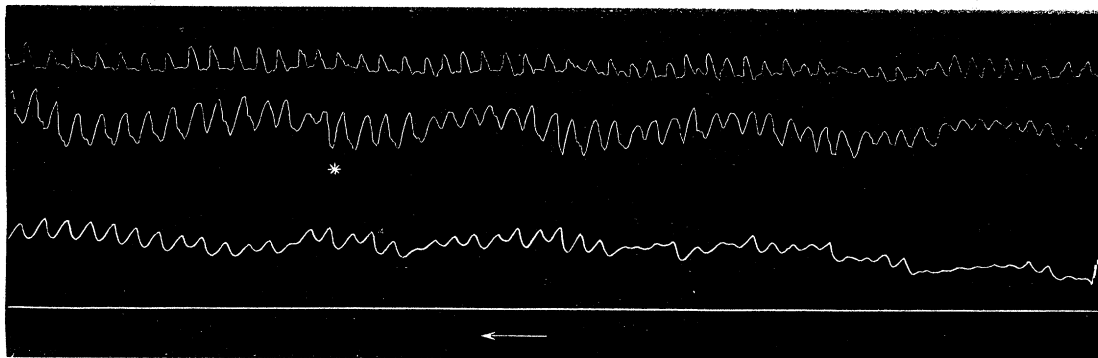
action, (226) with imperfect diastole and systole, and a resulting feeble slurred arterial impulse with very low pressure. Then follows great irregularity in auricular rhythm, and at (*) a reduplicated ventricular beat, the second systole being almost coincident with the premature auricular effort, and the pulse showing only a slight corresponding wave as the pressure drops in sympathy. When, towards the end of the tracing, the auricle steadying itself, beats more slowly, and relaxes thoroughly, the ventricle sympathises, and a steady pulse at once puts up the blood pressure.

Again, in fig. D$_2$, it will be seen how slight a variation in auricular rhythm is construed by the ventricle into an abnormal beat, the intra-cardiac pressure closely corresponding. The top line here records left auricular, the middle line the left ventricular wall movement, whilst the lowest is obtained from the interior of the left ventricle by means of a sound passed down the carotid artery. The heart was

in all respects regular, (D₁) before aconitine was administered. It will be observed in D_2 that the second or reduplicated ventricular beat is practically synchronous with the hastened auricular, and the tracing is suggestive of the possibility that there is a propagation upwards of a premature ventricular beat (as McWilliam* has shown to be possible), which precipitates the action of the auricle. The alternative theory would involve an almost instantaneous transit of impulse from auricle to ventricle, and its equally rapid conversion into a ventricular contraction which raises the intra-cardiac blood pressure sharply. This point cannot be decided on the evidence available. D_3 is the record of the heart's action after a further advance in aconitine action has interfered in the sequence of the ventricle (260), upon the auricle (188), and will be referred to again.

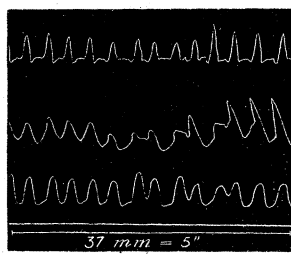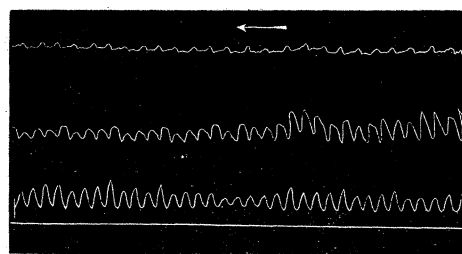Fig. D₁.   Fig. D₂.   Fig. D₃.

So far, changes of rhythm have been considered in which the ventricle mainly follows the lead of the auricle, but, later in the phase of fluctuation, there is a tendency for the ventricle to dissociate itself from the auricle, and to follow imperfectly, or even strike out a line of its own. If this new ventricular rhythm holds the relationship of 2 to 1 of the auricle, as it often does, then a regular (though of course very rapid) pulse is caused, but the pressure is fairly maintained. In fig. E_2 it is seen that such is the case, and it is interesting to note that as the ventricle accelerates to 216, the auricle, which was before 156, slows to 108, as if making an adaptation in order to carry on the circulation. Thus in E_3, the auricle has accelerated to 160, the ventricle to 320. At this stage the movement of the ventricle is very feeble and imperfect, and if a close study is made of the tracing, it will be seen that a reduplicated ventricular beat is associated with those elevations of blood pressure which from time to time occur; that is to say, an approximation to the auricular rate most distinctly favours the circulation. At such times both auricle and ventricle slow to some extent.

Attention may also be directed to D_3, in which intra-ventricular pressure is recorded at a time when the auricle is beating 188, and the ventricle 260, in the earlier part of the tracing, and at the rate of 3 to 4 in the later part. It will be noted that every fourth ventricular beat is here stronger than the three preceding
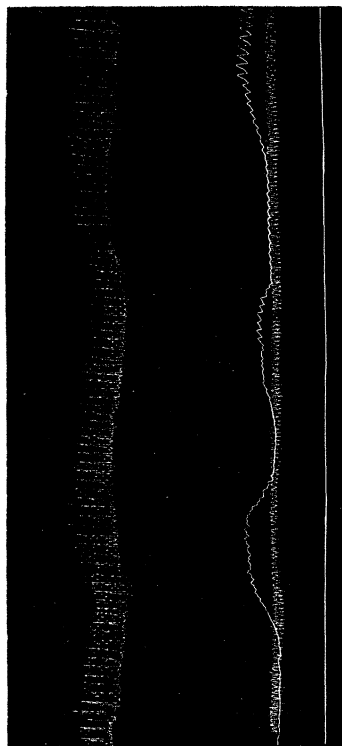
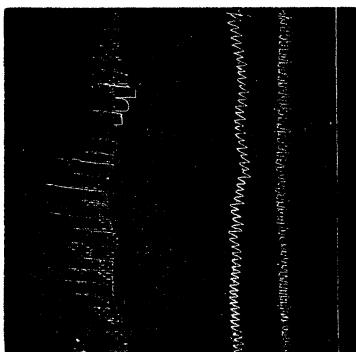* 'Journ. of Physiology,' vol. 9.

Fig. E₃.
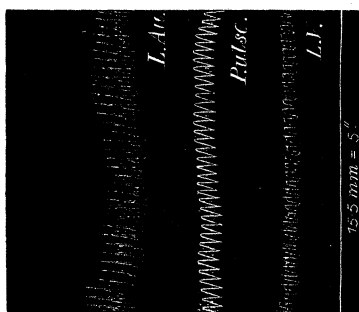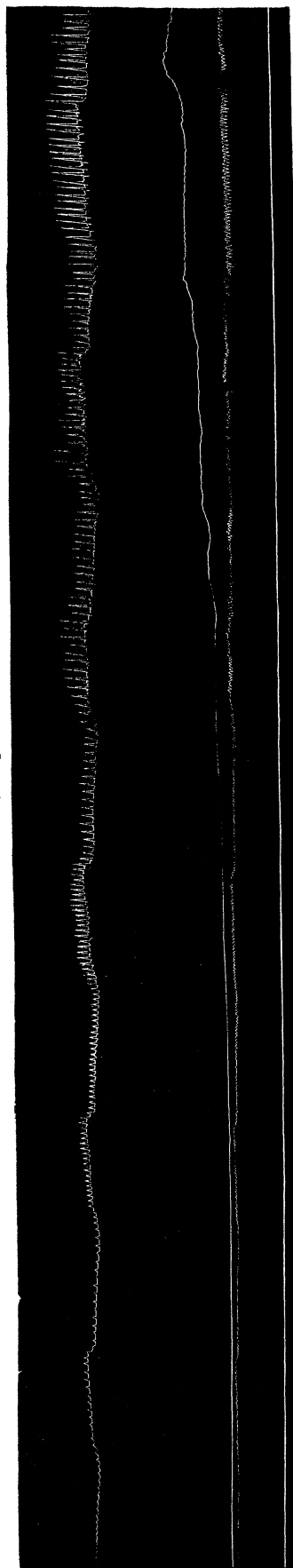

Fig. E₂.

Fig. E₁.

Fig. E₄.

it, and this is clearly the beat which comes in normal sequence to the auricular action. Such a condition, causing great confusion in the mechanism of the circulation, interfering with the coronary supply, permitting occasional regurgitation, must favour a considerable fall in pressure.

It is to these and parallel changes in the rhythm of the auricle and ventricle towards one another that the characteristic effect of aconitine is mainly due. Several of the bodies included in the research, as pseudaconitine and benzaconine, show interesting variations in this relationship.

In the last stage, E_4, the auricle, accelerated and irregular, has a rhythm of 144, whilst the ventricle, acting without regard to it, yields 408 contractions. Whilst the auricle is still beating with considerable force, the ventricle is yielding little more than a rapid series of twitchings, incoordinate and delirious in character ; these fail to force the blood outwards, and the blood-pressure falls rapidly (this condition is also well illustrated by the pulse in A_4). The auricle does not share in this tumultuous action. It has already been mentioned that just before ceasing, the heart may exceptionally revert to a more steady and uniform rhythm ; in most cases ventricular sequence and coordination are both lost.

Influence of the Vagi.

Speaking of the influence of aconitine on the cardiac vagus terminations, BÖHM and WARTMANN* say that they have seen both retention and loss of activity. PLÜGGE† believes that a gradually developing failure of function follows aconitine. LEWIN‡ has seen a transitory excitation, preceding paralysis of the vagus, and more than one observer has spoken of a rise of blood pressure, following stimulation.

That the vagus roots are early stimulated by aconitine,§ so that the blood pressure is reduced by the slowed pulse, is demonstrable by the acceleration with rise of pressure following section of the nerve trunks. Thus, in fig. C_2, the heart which had been slowed from 180 to 146 per minute by ·0001 gram aconitine, administered 30 minutes before, accelerates, the auricle contracts more vigorously, and the pressure rises upon section of the left vagus (the right having been already divided).

It was found that doses of aconitine, so large as to be rapidly lethal, do not entirely paralyse the vagus terminations within the heart until delirium appears, some degree of action being retained up to that time. After smaller lethal doses,

* Op. cit.

† VIRCHOW's 'Archiv,' vol. 87.

‡ 'Exp. Unt. über die Wirkung des Aconitines.'   Berlin, 1875.

§ Since this section was finished and type-written a paper has appeared by MATTHEWS ('Journ. of Exp. Med.,' III.), discussing the action of aconitine on the dog's heart. (This paper is referred to by CUSHNY in a communication about to appear, of which he has kindly sent us the MS.) The inhibitory centre in the medulla is stated to be stimulated in the first instance, and to this the slowing of the heart is due. MATTHEWS has also seen an independent rhythm of auricles and ventricles.

the result of stimulation varies. Thus, during the phase of irregularity in pulse and pressure, especially at its later stage, peripheral vagus stimulation, as well as section of the nerve, may be consistently without any effect upon the aconitine phenomena, or an apparent variation in result, a stimulation operative one minute proving inoperative the next (as observed also by Böhm with Wartmann),* may be present.

Occasionally not a fall, but a rise of pressure follows stimulation. (This has been seen in dogs by the observers just named.) These irregular results merit special consideration, and some of them are illustrated by the following experiments :—

Stimulation of Vagi before and after Aconitine.

Etherised Cat ; usual preparation of vessels ; heart exposed ; movements of left auricle and left ventricle recorded ; vagi separated from sympathetic in neck, and divided. On stimulation, the right vagus (coil 12) reduced pressure by 49 millims., the left (less active) by 43 millims. Aconitine ·0003 per kilo. injected hypodermically.

15 minutes ; stimulation, coil 12 ; right vagus, fall of 35 millims. ; left vagus, 31 millims.

40 minutes ; right vagus, fall of 26 millims. ; pulse slowed by one-half.

60 minutes ; right vagus, fall of 26 millims. ; pulse slowed by one-third.

95 minutes ; no response to stimulation at 12 centims. ; approximate secondary coil to 8 centims. ; right vagus, fall of 23 millims. ; left vagus, fall of 18 millims. At this time, the heart became irregular, the blood pressure fluctuating greatly. Stimulation of both vagi, coil 3 caused a rise of pressure.

100 minutes ; auricle 216 ; ventricle 168 ; before stimulation pressure and pulse very fluctuating and irregular. Stimulation ; left vagus coil 3 (F_1), auricle and ventricle both 152 at end of stimulation. Pulse strong; impulse distinct ; pressure greatly raised.

110 minutes ; the heart regular ; both auricles and ventricles 163 ; pressure raised ; stimulation of left vagus, coil 3 ; slowed auricle to 135, and ventricle to 147, a great fall in pressure resulting.

120 minutes ; no registrable result follows stimulation ; heart's action very irregular ; auricle and ventricle differ in rhythm ; pressure, 35 millims. Inject, ·01 gram atropine (as sulphate) into femoral vein.

128 minutes ; fig. F_2 ; the ventricles are beating in due sequence to auricle 209 ; the pressure has risen by 13 millims.

* 'Exp. Unt. über die Wirkung des Aconitines.' Berlin, 1875.

Fig. F₁.
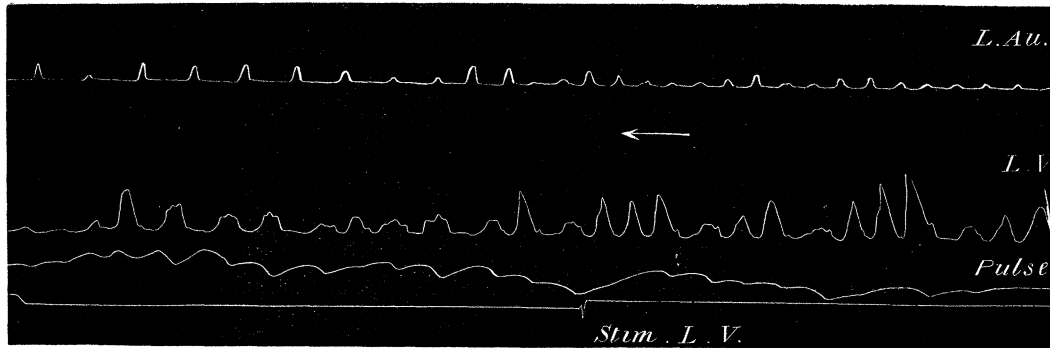
Fig. F₂.
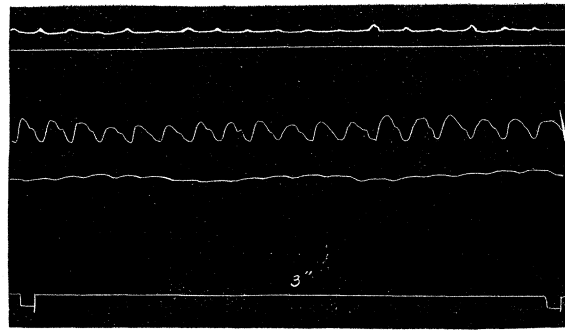
The main points here are :—

1. The reduction of disparity between auricular and ventricular rhythm, the auricle being greatly slowed, the ventricle slightly. As a result the beat of the latter becomes more effective, and the blood pressure rises.

2. The heart for a time having become steady, and the pressure elevated, vagus stimulation causes a greater slowing of the registrable auricular than of the ventricular systoles, and the resulting dislocation favours a great fall in the blood pressure.

3. Atropine acting as the vagus stimulation had done, favours steady ventricular sequence.

After aconitine, the vagus retains a stronger hold of the auricle than it does of the ventricle, though that hold is progressively weakening. Having in view the reduced tendency to asequence of ventricular upon auricular action, due to aconitine, it is easier to understand why vagus stimulation has different results at very short intervals of time. Supposing sequence to be interrupted, the stimulation so adjusts the difference that order is temporarily restored, and the blood pressure will rise, even if the pulse be slowed ; on the other hand, if sequence is more disturbed (as by a greater proportionate slowing of the auricle than of the ventricle), then a fall

of blood pressure results. It is also possible that whilst stimulation may be operative in causing a readjustment in the speed of auricle and ventricle, the pressure may be unaltered, so that if activity of the peripheral vagus mechanism were judged of only by a fall of pressure resulting, the conclusion would be inevitable that there was evidence of entire suspension of function.

In this connection an experiment may be referred to, in which no change of blood pressure, but an acceleration of both auricles and ventricles, followed stimulation. After aconitine, the auricle was beating 240, the ventricle 264, when stimulation of the right vagus (coil 5) caused acceleration of both by 24, i.e., to 264 and 288 respectively. No change in blood pressure resulted, probably from the fact that the influence of acceleration was cancelled by a less favourable sequence of ventricular upon auricular contraction.

Though the experimental evidences adduced may not offer an explanation of all the phenomena seen on stimulating the vagus after aconitine, it is believed that they cover most of them, and that they imply not merely changes in the vagus peripherally, but a variation in the reaction of the heart chamber walls at the time of stimulation.

Rapid failure of the strength of the systole of which the ventricular wall is capable, occurs during the later stages of aconitine action, while the auricular failure is much less marked. Though auricular regularity is largely affected, genuine incoordination has not been witnessed after aconitine. It may, however, be present as a pathological condition, and is then, in my experience, invariably associated with great irregularity of the ventricle. In the experiment from which the tracing G is taken (no toxic

Fig. G.
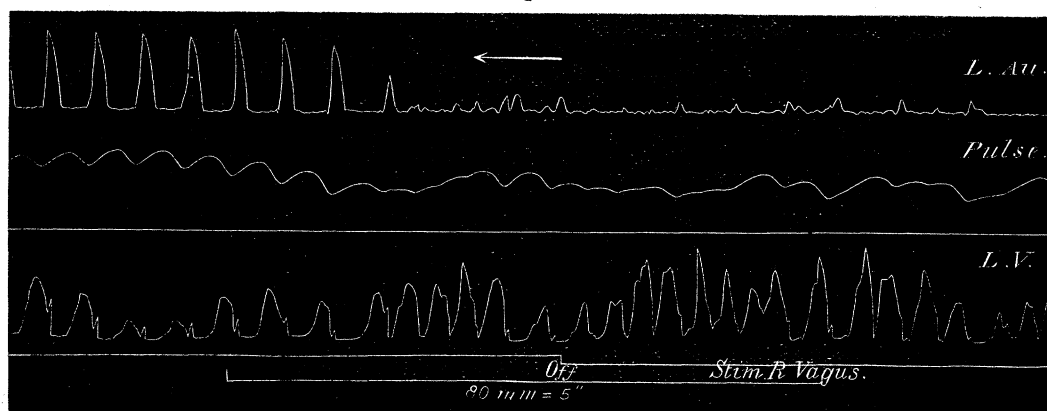
substance having been administered), every stimulation of the vagus produced so active an incoordination of the ventricular systole, that hardly an indication of a general shortening of the appendix is produced. Here the ventricle follows the auricular lead with great faithfulness, and resumes its normal action so soon as the auricle has done so. The auricle seems here to originate the ventricular incoordinate action, but after aconitine this arises spontaneously.

The Vaso-motor Centre and Peripheral Vaso-constrictor Nerves.

The splanchnic nerves retain a considerable degree of activity during the progress of aconitine poisoning, so that up to the commencement of the final stage of inco-ordination, faradisation raises the pressure. It has been observed that such a stimulation may, for some time after its discontinuance, modify the irregularity of the accelerated aconitine heart ; and as this follows vagotomy, it appears to point to a regulation by increased pressure exerted within its chambers, upon the organ itself.

Stimulation of the cord separated from the medulla, brings vaso-constrictor nerves into action. Stimulation of the sciatic nerve after double vagotomy, except at the very termination of poisoning, causes some rise of pressure, but this effect is often small when compared with that before aconitine. (This test, however, must be considered as only partially reliable in presence of a poison which itself acts upon sensory nerves.)

In advanced poisoning, closing of the trachea ceases to raise the blood pressure. Whilst, therefore, the peripheral vaso-constrictor apparatus is not markedly affected by aconitine, the centre is undoubtedly ultimately depressed by it. (NUNNELEY,* from an examination of the frog's web, was led to the conclusion that no peripheral vaso-motor effect was produced by aconitine.)

The following notes are taken from an experiment in which a cat of 3210 grams received ·000777 gram of aconitine. It shows that with such a hyper-lethal dose, the splanchnic, stimulated peripherally, may retain its activity to a large extent up to the final stage of poisoning. For purposes of contrast, the result of an occasional vagus stimulation is also given. The preparation after etherisation was the usual one, except that the splanchnics were exposed, artificial respiration being, of course, employed.

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* ' Roy. Soc. Proc.,' vol. 18, 1870, p. 46.

Time.	Blood pressure.	Pulse.			Notes.
		Before.	During.	After Stimulation.	
minutes. 8	millims. 133–73	171	87	208	Stimulation of left vagus 10·5 centims.
11	139–154	165	..	..	Stimulation of splanchnic coil 10·5 centims.
15	..	..	..	..	Injection of ·000777 gram aconitine.
20	122–131	..	..	..	Stimulation of splanchnic.
26	114–70	134	74	168	Stimulation of left vagus 10·5 centims.
38	91–136	104	216	(?)	Section of right vagus ·5 (the left already cut).
45	100–70	150	96	192	Stimulation of left vagus 10·5 centims.
47	76–86	186	..	192	Stimulation of splanchnic 10·5 centims. Pulse, which was accelerated, becomes didrotic
49	46–16	96–252	..	..	There is a sudden change in rhythm of pulse from slow to very rapid, with great irregularity. Splanchnic stimulation inoperative.
51	..	..	..	..	Death.

It will be seen in this experiment that though death occurred in 36 minutes after the injection of aconitine, 6 minutes and 4 minutes respectively before death the vagus and the splanchnic were both capable of exercising their usual effect, and further that such a great rise of pressure followed sections of the vagus as seemed to indicate a powerful influence exerted by aconitine on its roots. This acceleration, which followed section, was only of brief duration.

Antagonism of Atropine.

Fig. H₁.
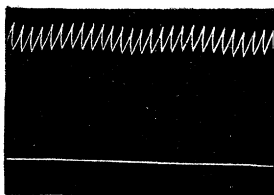
Fig. H₂.
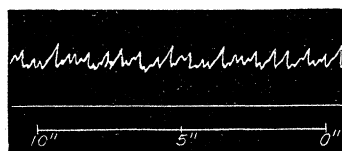
Fig. H₃.
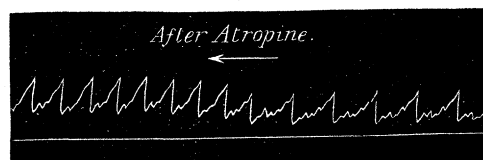
Fig. H₄.
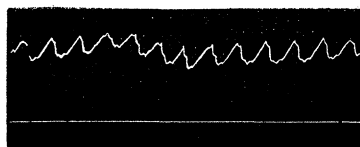
Fig. H₅.
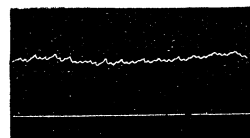
It was found that the specimen of aconitine under examination was actively antagonised by atropine.

A short abstract of an experiment will make this clear.

ETHERISED Cat of 2600 grams in warm box.   Usual preparations.

Time.	Blood pressure.	Pulse.	Notes.
minutes.	millims.		
0	128	68	(Fig. H_1.)
0	..	..	Inject ·00026 gram aconitine.
65	..	..	Acceleration with great irregularity.
69	48–70	184–240	Very irregular and stormy (H_2). Vagus stimulation slows.
72	..	..	Blood pressure falling rapidly. Inject ·015 gram atropine by femoral vein.
78	53	..	Pressure rising. Pulse shows regular powerful systoles, with twitchings intervening (H_3). Vagus stimulation, no effect.
137	74	63	Fairly steady pulse (H_4). Inject ·00025 gram aconitine.
161	76	..	Pulse steady. Inject ·00029 gram aconitine.
181	60	81	Pulse steady. Inject ·00039 gram aconitine.
188	60–66	78	Great irregularity of heart. Partial relaxation in diastole.
200	60	108	Heart feeble and irregular.
205	..	..	Inject ·0005 gram aconitine.
216	52	156	
224	56	228	Very rapid and irregular pulse (H_5).
226	49	264	Pressure failing.
227	..	304	Sudden failure of heart.

In this experiment, which lasted nearly four hours after the administration of the first dose of aconitine, atropine promptly reduced the toxic action, and no less than ·00143 gram of aconitine was subsequently administered (making, with the initial injection, ·00172 gram, or many times the lethal amount) before the action of the antagonist was overcome.

The irregularity of the heart was greatly reduced by the antidote, and the pressure raised to a slight extent.

This result is in conformity with experiments made upon the frog's heart, excised or *in situ*, which go to support the contention of RINGER with MURRELL,[*] that for frogs atropine and aconitine are antagonistic. BÖHM and WARTMANN,[†] however, state that in warm-blooded animals atropine neither suspends nor disturbs the aconitine action. While bearing in mind the result of the preceding and other experiments performed upon cats, it is impossible to unite with this view.

[*] 'Proc. Roy. Soc.,' 1870.
[†] *Op. cit.*

Atropine does not prevent the acceleration of the aconitised, mammalian heart, but it averts the very rapid and feeble action during which the ventricle only partially contracts on its contents, and it tends to approximate the speed of ventricle to that of auricle when this is disordered. In this detail, its action is often similar to the effect of vagus stimulation.

Finally, it reduces the tendency to arhythmic or delirious breaking down of the systole, which is the precursor of death in simple aconitine poisoning. Even if the latter symptom has appeared, an intravenous injection of atropine has been seen to avert the fatal issue. The tracing (H_3) certainly indicates abortive systoles after atropine, but an effective systole occurs at regular intervals.

Résumé of the main points in the action of Aconitine on the circulatory system of Cats.

1. That, after a slight acceleration of pulse, a slowing follows, which is accompanied by reduction of blood pressure.

2. Great fluctuations of blood pressure are associated with many varieties of auricular and ventricular action, such as one, or a series of imperfect systoles of the ventricle; irregularity in rhythm of auricle with increased irregularity, though sequence, of ventricle; asequence of ventricular action upon auricular, frequently having the form of two or three ventricular beats to every registrable and effective auricular systole; or there may be a marked independence of rhythm of auricles and ventricles, alternating with periods of sequence which favour a steadier pulse and elevated blood pressure. The ventricles ultimately develop a delirious condition, in which the auricles do not participate. The auricles sympathise in their action one with another, and the ventricles have the same relationship, but the action of right auricle and ventricle outlasts those of the cavity walls on the left side.

3. The vaso-motor centre is affected later than the respiratory, and though its activity is ultimately much reduced, the splanchnic nerves, their terminations, and the arterioles they control, are excitable till the end of the poisoning.

4. The vagus is at first stimulated centrally, then reduced in activity peripherally, even to the extent, in cases of long-continued action of aconitine, of paralysis. Short of this, its stimulation may reduce pressure, or raise, or leave it unaffected. In most of such periods of paradoxical action, it is found that a divergent action upon auricles (which are more markedly under the control of the nerve) and ventricles, is the explanation. There is, however, an occasional absence of response, shortly followed by a return to reaction, which is suggestive of an intermitting excitability of vagal terminations.

The vagus has no power to control the delirium of the ventricle at the termination of poisoning. A strengthening of the beat of the heart follows vagus stimulation after inhibitory action has disappeared.

ACTION OF ACONITINE ON GUINEA-PIGS.

The characteristic symptoms are : some irritation at the seat of injection (greatly reduced by free dilution of the aconitine solution), grinding of teeth, salivation, a movement like retching, occasional squeaking (apparently due to involuntary contraction of the trunk muscles), weakness, expecially of the legs, the movements becoming scrambling and uncertain, dyspnœa steadily increasing, the number of respirations after preliminary increase becoming greatly reduced, whilst the movements are more laboured and gasping. The sphincters tend to relax. Towards the end, the respiration is reduced to a mere expiratory jerk. Exceptionally in the course of action of aconitine, spasmodic extension and retraction of the legs, almost at regular intervals, may be witnessed. The animal loses all power of voluntary movement, the eye reflex disappears, and the breathing ceases quietly, or temporary recovery occurs.

The left ventricle, if examined the moment after death, is engorged, twitching and fibrillating, but not contracting.

The auricles beating very rapidly (about 270 in succeeding case). They may continue to beat for 12 to 15 minutes post mortem.

Sub-lethal Dose.*

10.30.   NORMAL Guinea-pig of 907 grams.

Minutes.

0	Injected ·000104 gram per kilo., at once a little squeaking and starting.
20	Retching movement ; much salivation ; and some stomach contents extruded.
28	Great salivation ; quiet ; no retching, but " hunching" ; dyspnœa.
50	Great salivation. (This saliva is strongly alkaline to litmus. It was not found to produce an aconitine action when injected into frogs).
60	Weak ; hind legs are specially affected.
100	Acute diarrhœa ; still salivated.
220	Not so weak ; is beginning to eat ; still an occasional squeak.
240	Normal.

Lethal Dose.

Eight days later, the same animal had ·000123 gram per kilo., of aconitine, which proved fatal.

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* This dose is occasionally lethal. For discussion on this point, see note on page 268.

Minutes.

0	Injected, under skin of side.
15	Weak ; retching and hiccough-like movement.
38	Paresis of hind legs ; great salivation and retching.
73	Squeaking ; seldom attempts movement ; hunching ; dyspnœa.
83	Occasional jerks ; sits still ; breathing a little laboured.
98	Legs powerfully extended, and after 4 seconds drawn up. This movement repeatedly seen at intervals of 15 to 20 seconds. Breathing laboured ; grunting.
108	Dyspnœa more marked ; no spasm.
126	Much grinding of teeth.
148	Dyspnœa marked ; loud expiratory grunt ; each time mouth gaping ; cutaneous sensation much reduced ; does not get off back or side ; heart easily felt ; cannot be counted ; excessively rapid ; head still raised, and is the only part of the body moved ; expiration reduced to jerk in epigastrium.
168	Expiratory squeak ; no sensation ; heart very feeble ; lying on back ; pupil dilated.
278	Unconscious ; breathing as before.
303	Breathing gently arrested.

Heart engorged on right side ; left side in intermediate state ; twitching ; auricles beating very rapidly ; lungs slightly engorged.

The lethal dose per kilo., body weight, in two early experiments, gave the results :

$\cdot$000112 per kilo. . . . . . . not lethal.

$\cdot$000138 per kilo. . . . . . . lethal.

Later experiments showed that the lethal point lies between $\cdot$000112 per kilo., not lethal (experiment not quoted) ; and $\cdot$000123 per kilo., lethal.

Respiratory failure is the actual cause of death, but it is followed closely by failure of the circulation. The heart is indeed so much involved by aconitine that it ceases, if artificial respiration is instituted only at the moment of respiratory suspension. If instituted earlier, a delay in the lethal action of the alkaloid results, free oxidation of the blood reviving the heart to a limited extent.

ACTION OF ACONITINE ON RABBITS.

(Chiefly with regard to Respiration and Temperature.)

The animals were placed in a double-walled, lidless box of large size, perforated in the sides, containing hay and food. This was kept about five feet from the fire, so

that a moderate warmth of 15° to 16° C. was maintained within the box. Respiration was, if possible, counted without touching or removing the animal from the box.

On rabbits aconitine produces a train of symptoms not dissimilar to those seen in the guinea-pig. There is slight local irritation at the seat of injection; the salivation is a transitory condition, arising in 15 to 20 minutes after injection, and usually terminating 12 to 15 minutes thereafter. (This saliva has been collected in considerable quantity, and administered to frogs without any evidence of irritation, much less of alkaloidal poisoning, being produced.) A grinding movement of the jaws makes its appearance before any dribbling of saliva is observed; shifting position of feet, as if footing were insecure; occasional hunching and swallowing movement, with strident cry, sluggish pupil, with evidence of progressive weakening of control over the limbs; occasionally there is intermittent spasm, with passing loss of consciousness, dilated pupil, insensitive cornea. In this state death may result, or recovery follows, the breathing accelerating, consciousness returning, and the animal regaining the use of its limbs to the extent previously possessed. The respiration has been specially studied in rabbits after aconitine. The respiration of the normal rabbit is, often without apparent cause, or under excitement or exertion, accelerated to a surprising extent, becoming superficial or comparable to the panting of a dog, and it will often be seen to show a CHEYNE STOKES character. Young rabbits breathe more rapidly than those full grown.

Whatever the character of respiration has been, whether superficial at 120 or 140 per minute, or deeper and of half that number, the first effect of aconitine, in any dose, is to cause acceleration. This time of excitement is short, and is succeeded by a rapid reduction in the speed of respiration, the CHEYNE STOKES variation disappearing; whilst, if the dose be a large sub-lethal one, distinct evidence of dyspnœa makes its appearance, such as excessive movements of the nostrils and muzzle, throwing back of the head, and in severe poisoning, occasional strident respiration, with depression of lower jaw. The chief reduction in speed of respiration occurs in 40 to 50 minutes after injection, and thereafter the dyspnœa abates to some extent, the animal breathing more rapidly.

After a lethal dose all of these symptoms are present, and accompany a great slowing of the respiratory movements, which may progress till death occurs, or exceptionally, yield to a temporary acceleration of feeble character.

If the dose is only a fraction of the lethal amount, the depression is not so pronounced, and the recovery occurs without evidence of urgent dyspnœa. The return takes place gradually to the normal, but the breathing remains for a considerable time of the deep type; the superficial or panting respiration being entirely absent. The fluctuating CHEYNE STOKES respiration also disappears till the effect of aconitine has otherwise passed off.

Projections of the modification in the speed of respiration following various doses of aconitine are shown in Diagram A, which is compiled from the following experiments :—

No. 1 received aconitine in the proportion of ·00014 gram per kilo., with lethal result.

No. 2 received ·00010 gram per kilo.

No. 3 received ·0000927 gram per kilo.

No. 4 received ·0000612 gram per kilo.

Diagram A.
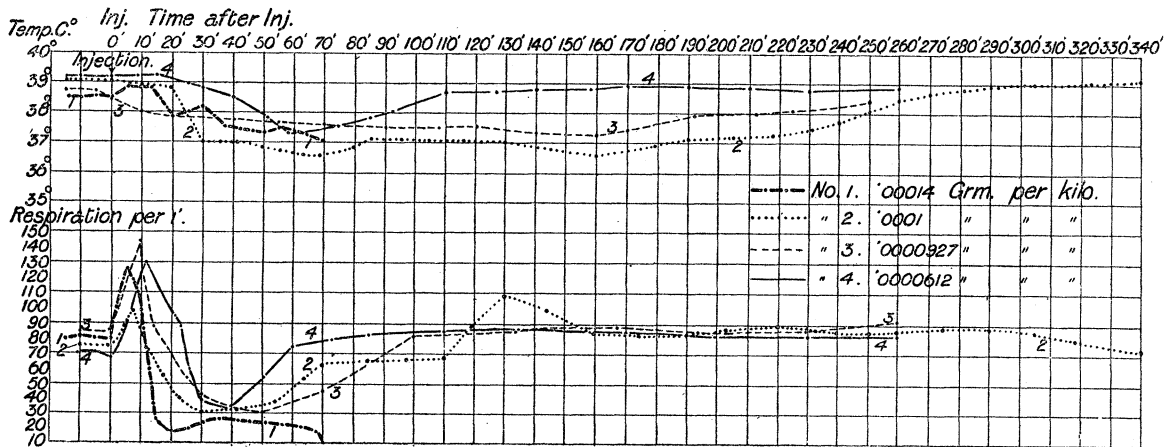
Diagram B shows the contrasted effect of aconitine upon a rabbit sheltered from cold (as described above), and a second, exposed to a lower temperature. A large sub-lethal dose, proportioned to ·000125 gram per kilo., body weight, was given to each. Both of these animals had received aconitine before.

Diagram B.
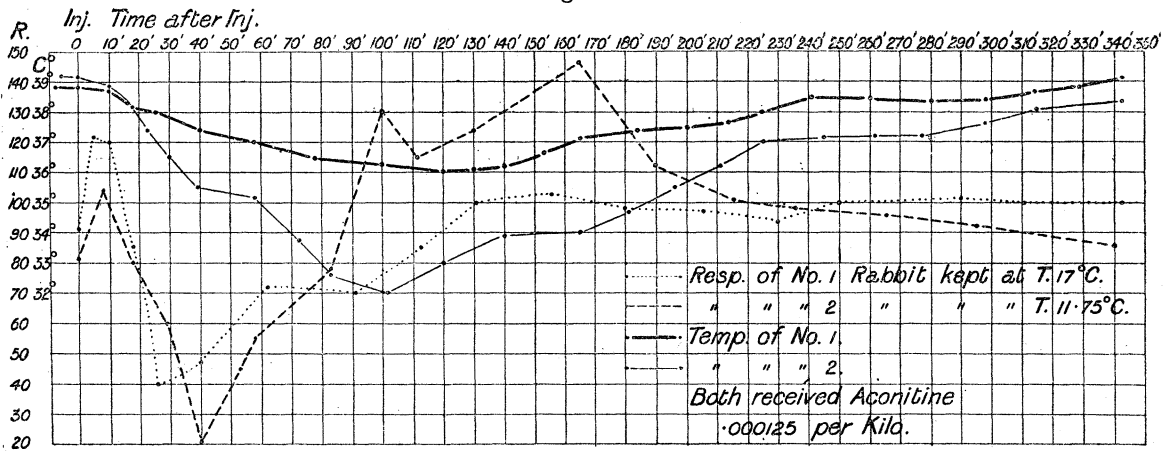
(In blood pressure experiments performed upon cats and rabbits, in which the animals were very partially protected from loss of heat by wrapping them in wadding, it was found that a fall of 8 to 10° C. was commonly produced after a slowly-acting lethal dose of aconitine.)

Aconitine on the Respiration of Narcotised Rabbits.

Ether, chloralamide, or urethane were used in these experiments.   Records were obtained with a Marey's double chest tambour, or with a diaphragm needle.

Under deep etherisation, the quickening of respiration after aconitine, so usual under other circumstances, is less marked, or absent.   Slowing soon appears; the longest pause is inspiratory in character, and the respiration closely simulates that after vagotomy in the unpoisoned animal.   Scarcely any change follows section. If the dose is sub-lethal, acceleration follows slowing; if lethal, arrest of respiratory movement ensues.   This arrest does not imply complete paralysis of the respiratory centre, for, if vigorous artificial breathing is practised, the centre resumes its slow and laborious work, but soon suspends action again.   (Needless to say, death would have followed if aid had not been afforded.   The same phenomenon has been seen in frogs without optic thalami; respiration, very slow, was rendered four times as rapid by inflation of the lung.)   This failure occurs whilst an irregular, and in the main falling, blood pressure obtains, and the remnant of cardiac energy soon disappears if artificial respiration is withheld.   The phrenic nerve responds to electrical stimulation after death.

(As a result of employing oxygen inhalations, it has been found that the respiratory centre is more rapidly aroused than when atmospheric air alone is used.   Irregularity of the heart does not seem to be modified by oxygen, though the ventricle seems to contract more powerfully, some elevation in the general blood pressure resulting.)

Summary.

These facts point to the lethal effect of aconitine upon cats, guinea-pigs, and rabbits being primarily due to respiratory failure, which is in agreement with the conclusions of HARLEY,[*] MACKENZIE,[†] and MURRAY.[‡]

It has been more than once stated how closely circulatory failure, which BÖHM and WARTMANN[§] regard as primary, follows respiratory arrest.   Artificial respiration, if begun sufficiently early, prolongs life, though not to the extent alleged by LEWIN.[||]

The primary increase in respiration after aconitine may arise from stimulation of medullary centres, as well as of the sensory endings of the vagi in the lungs, for it appears to some extent if vagotomy has been performed.   A subsequent depression is produced at both points, the centres remaining, however, sensitive to a certain extent to the stimulation of venous blood, whilst their paralysis may be postponed for a

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[*] 'St. Thomas's Hospital Reports,' vol. 5, p. 145, *et seq.*

[†] *Op. cit.*

[‡] *Op. cit.*

[§] *Op. cit.*

[||] *Op. cit.*

time by artificial respiration of air or oxygen. It is interesting to note the disappearance of the slight panting movements of rabbits, as of the mimetic movements of the hyoid of frogs, leaving only the slow and laborious discharge of the centre from time to time.

As the effect of aconitine passes, the centres become more susceptible to the stimulation of insufficiently oxidised blood, and acceleration results.

Action of Aconitine on Temperature.

Although the temperature of aconitised animals used in simple blood pressure experiments has been referred to, it has been borne in mind that these were so completely sheltered from heat loss, that the effect of the alkaloid was, to a large extent, masked. The average reduction for the rectal temperature was $1°·1$; for the subcutaneous temperature $0°·825$.

In order to obtain more exact information, a long series of thermometric observations upon aconitised rabbits were made. At the same time the respiration was closely examined.

The temperature was in all cases taken in the rectum. Great uniformity was obtained in the graduation of the effect in proportion to the dose administered, provided the animals were kept at the medium temperature indicated.

A slight primary rise, of temperature, $0°·75$ C., may follow a dose one-sixth of the lethal amount, the temperature returning to the normal in the course of an hour, and thereafter, for a short time, being sub-normal.

Larger doses may cause a slighter and more transitory rise, but it is speedily succeeded by a fall.

(The extensive rise of $3°·3$ F., stated by MACKENZIE[*] to precede a considerable fall, has not been observed in the course of these experiments.)

It is from 10 to 20 minutes after injection that the fall appears, proceeding rapidly at first, and then declining gradually till the minimum is recorded. This point is reached usually in 50 to 70 minutes after injection, but after large doses a secondary fall is frequently witnessed, which may reach as low a point, 145 to 160 minutes after injection. A return towards the normal, more rapid after smaller than larger doses, ensues, and the original level may practically be attained in 2 to 4 or 5 hours, according to dose and surrounding temperature. The temperature may, however, remain some tenths of a degree sub-normal for many hours, or, on the other hand, it may become super-normal to a similar extent.

If the dose is lethal, and death takes place rapidly, fall of temperature is not extensive.

In the case recorded (No. 1, Diagram A), the heart immediately after death showed twitchings of the left ventricle, whilst the corresponding auricle was beating

[*] 'St. Thomas's Hospital Reports,' vol. 5, p. 145, et seq.

very rapidly. The right side of the heart was greatly distended with blood. The left ventricle was, however, in firm systole.

Should the conditions be so far modified that, whilst one animal is kept at the medium temperature of 17° C., a second, receiving a like proportionate dose of aconitine, is kept in an atmosphere cooler by several degrees, the effect of the drug on the latter is found to be much more powerful as regards general toxic symptoms, motor depression, dyspnœa, and fall of temperature.

Diagram B illustrates this point. The animal kept at a constant temperature of 17°·5 C. received aconitine at the rate of ·000125 gram; the animal kept at 11°·75 C. received the same proportion. The total fall of temperature in the former was 2°·8 C., in the latter 7°·3 C.

It will be observed from Diagram A that the fall of temperature in the main follows respiratory slowing, the minimum point of the latter being reached 20 minutes to 40 minutes, or even longer, before that of the former.

The acceleration of respiration distinctly anticipates the return towards the normal temperature. If such a rise is long absent in the body heat after respiration has quickened, auscultation will, in all probability, reveal considerable weakness, irregularity, or both, of the heart's action.

Further, the disorder of circulation directly reducing oxidation, whilst favouring increased loss of heat from the surface, contributes to the fall of temperature. The two experiments last referred to confirm the observations upon guinea-pigs made by one of us (C.) in conjunction with Dr. T. L. BRUNTON.*

Repeated Administration of Aconitine.

If a rabbit receive, day by day, such a dose of aconitine as was found, on first administration, to cause a well-marked reduction of temperature, it is observed that, concurrently with the repetition a steadily lessening effect is produced. There is, therefore, established a certain degree of tolerance towards the drug, neither respiration nor temperature being influenced so powerfully as before. There is clearly a limit to this acquired tolerance, and it is also evident that full susceptibility is re-established if the use of the alkaloid be intermitted for six or seven days.

Summary on Lethal Dosage.

Lethal Dose of Aconitine on Warm-blooded Animals.

Cats.—In these animals, as in all others, administration of aconitine was made hypodermically.

A non-etherised animal of 3300 grams succumbed in 45 minutes to a dose of ·0013 gram (= ·0004 gram per kilo.).

* "Modification in the Action of Aconite produced by changes in the body temperature." 'St. Bart.' Hosp. Reports,' vol. 22.

Etherised animals :—A dose of ·00065 gram proved lethal to a cat of 2050 grams in 34 minutes (in this case there is less resistance to the drug than in the one preceding it, as the proportion per kilo. is only ·000312 gram).

Another etherised animal of 2410 grams succumbed to ·000324 gram aconitine in 3 hours. The proportion here is ·000134 gram per kilo., and it may be accepted that this constitutes a lethal dose, though it is, perhaps, slightly excessive. Only an approximate value is claimed for these figures, as the estimations were not made under the most desirable circumstances.

Rabbits.*—The exact lethal dose has been precisely determined at ·000131 gram per kilo., body weight. Whilst this is certainly lethal, a smaller proportion may occasionally prove so.

Guinea-pigs.—The dose was found to lie between ·000112 and ·000123, and a final experiment seems to place it at ·000120 gram per kilo.

These results may be contrasted with WAGNER's and LÜBBER'S† respectively. They mention the following as lethal doses per kilo. :—

Cat .   .   .   .   ·00025 (W.),   ·00013 (L.).
Rabbit .   .   .   ·00035 (W.).
Frog   .   .   .   ·00035 to ·0004 (W.),   ·0003 (L.).

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* [June, 1898.—Although this dose of aconitine may be regarded as the proportion which is lethal in all conditions under which an animal is likely to be examined, excepting possibly when the drug has been administered for some time in increasing doses, yet, amongst animals selected at random, a lethal action will, with increasing dosage, begin to appear when ·000085 gram per kilo. is reached. If rabbits are employed which have been feeding freely, and which have not had aconitine previously, it will be found that the majority succumb to ·00011 per kilo. The reasons for this appear to be threefold:— 1. The degree of tolerance which a series of administrations of aconitine given daily, or every second day, produces, is absent. It is impossible to speak with certainty yet, as to the extent to which tolerance may be developed in this manner. In one instance a rabbit very nearly succumbed to the first dose of aconitine (·00009 gram per kilo.); it subsequently received progressive doses on five alternating days, and then survived a proportion of ·00013 gram per kilo. 2. An animal which has been feeding heavily up to the time of the experiment will have the stomach loaded as well as the appendix, the contents, according to weighings made, amounting to as much as one-fifth or one-sixth of the entire body weight. If only a light meal is given overnight, the weight of ingesta will be down by 80 to 120 grams in the morning. In one full-grown animal there was a total variation through 250 grams in ten days, the diet having been without limit, except with the restriction just mentioned on two occasions. It is evident that the calculation of the dose must vary in such cases, and always to the disadvantage of the animal with loaded viscera. 3. The distended viscera not only lead to a dosimetric excess, but they produce a more serious condition of dyspnœa than would in usual course follow from a given dose of aconitine, and so materially aid the toxic action of the poison. All these points considered, whilst retaining the absolutely lethal dose at ·000131 p.k., it is necessary to qualify this statement by adding that to the great majority of animals taken at random, ·00011 gram proves lethal. (These observations apply in large degree to guinea pigs as well as to rabbits.)]

† 'Beitrag zur Toxikolog. des Aconitines.'

ACTION OF ACONITINE ON FROGS.

Specimens of *R. temporaria*, which had been kept in the laboratory for some days previously, were employed. The area of injection, except when otherwise stated, was the dorsal lymph sac.

Lethal Dose.—Estimated in June and July, the lethal dose is ·000035 gram for a frog of 25 grams weight—or 0·0014 per kilo. Small frogs tolerate a slightly larger proportionate dose of aconitine than larger animals. The lethal dose is relatively reduced in very hot weather, or in animals artificially warmed, whilst winter animals show a slightly increased resistance towards aconitine.

HARNACK[*] and MEUNICKE,[†] using MERCK's aconitine, estimate the lethal dose for frogs at $\frac{1}{30}$ of a mg.

Action of a Hyper-lethal Dose of Aconitine Hydrobromide.

By "hyper-lethal" is meant an amount distinctly above, or largely in excess of the barely lethal amount.

Minutes.

0 Frog of 17 grams (of which left leg vessels had been ligatured under ether) received ·001 gram aconitine; at once quiescent; position contorted; no reflex.

2 Springs three or four times; all reflexes; eye protruded.

3 Great gaping.

5 If legs extended, they are slowly drawn up.

7 No active movement; circulation in web is moderate.

$7\frac{1}{2}$ Reflex disappeared.

$8\frac{1}{2}$ Voluntary extension of leg.

On decerebrating, there was no movement of limbs, but when the cord was destroyed all limbs and muscles of trunk moved freely. The minimal irritability of the ligatured leg was to indirect (sciatic) stimulation 22·5 centims., for the muscle 18 —on the open side, the figures were 19 and 18 respectively.

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[*] Quoted by RICHET, ' Dictionnaire de Physiologie,' art. "Aconitine."
[†] ' Berlin Klin. Wochensch.,' vol. 1, p. 43.

Lethal Dose.

Minutes.

0   Into dorsal sac of frog of 20 grams injected ·00004 gram of alkaloidal solution. The animal at once assumes position with head low ; fore-arms arched over head ; phalanges incurved above eyes ; reflex suspended.

2   Suddenly relaxes position ; powerful and repeated springing.

5   Springing continued ; froth covering plate, sides of funnel and, in part, body of animal.

12   Springing occasional ; position of trunk is twisted and unnatural ; responds irregularly to stimulation.

17   There is occasional voluntary movement ; head is low and trunk seems collapsed.

25   All respiratory movements ceased, but reflexes are present in degree.

35   Legs drawn up, but only after several stimulations.

40   Drawing up of legs is only partial, and often after lapse of 2″ or 3″ after stimulation ; corneal reflex faint.

45   Reflex ceased.

56   Voluntary movement ceased.

110   Circulation scarcely moving in web ; vessels dilated.

202   Heart stopped.

220   Post-mortem ; a large dark pouch or sac over lower half of ventricle anteriorly filled with dark blood ; ventricle only responds by a feeble movement at the base to stimulation ; the auricles beating ; movement of limbs on destroying cord.

(B) *Sub-lethal Dose.*

FROG of 17 grams.

Minutes

0   Received ·000020 gram aconitine in dorsal sac.   At once powerful springing, accompanied by frothing.

3   Active movement suspended ; lies with one leg extended, and the limb is not withdrawn on touching ; leaps round in circle, and again pauses.

7   Gaping frequent ; springs ; escapes ; rests with head distinctly inclined to one side.

22   In sitting position ; eyes open ; movement steady ; no fibrillation.

33   Gaping ; is anæsthetic, but reflex present.

47   Sits with mouth wide open ; list of body over to one side.

65   Springs occasionally, but movement clumsy, and may alight, and thereafter lie with one leg partly extended.

98   Position high, stiff and peculiar ; body and head on one side ; there has been

Minutes.

no attempt to move during the last 20 minutes ; eyes partly closed ; reflex movement very irregular and much reduced when present.

134 Eyes open ; crawls a step or two ; circulation in web is moderately good.

189 Gapes ; no respiration during observation of 3 minutes ; quiet.

285 Arms are more paralysed than legs ; a good reflex occasionally follows stimulation or extension of hind leg ; gapes when touched ; circulation better ; heart beating 38 ; impulse is weak and irregular ; slight voluntary movement occasionally seen.

All symptoms persisted with little variation till—

400 Respiratory movements resumed.

430 Breathing rapidly ; head twisted upon trunk to one side ; all reflexes ; movements sprawling.

Next day normal, except for œdema under skin of thighs.

Duration of Effect of Aconitine.

The longest duration of effect witnessed after a dose of aconitine, nearly lethal in amount, is briefly noted below.

March 1st.—A frog of 26 grams received ·000031 gram of alkaloid in solution. The usual symptoms followed. In 24 hours there was a faint reflex twitch, but no actual movement of limbs ; no voluntary movement ; circulation in web slow and irregular ; respiration almost suspended. Up to the 4th day, there was little variation in these conditions, but at this time, reflex was a little stronger, and respiration, though faint, and occasional, was returning. During this day, as well as the 5th and 6th, the animal lay free, covered with moistened filter-paper, its respiration being recorded meanwhile. On the evening of the 6th day, voluntary movements were witnessed. Up to the 8th day, it seemed apathetic and averse to movement, but on the 9th day was practically normal.

Such a prolongation of symptoms is never witnessed after distinctly sub-lethal doses, for in 48 hours after injection, the animal is approaching, or has already reached, the normal.

Aconitine after Arrest of Circulation to One Leg.

A FROG of 19 grams received ether, and under anæsthesia the vessels of the left limb were ligatured.

Minutes.

0 Upon recovery, it received ·00005 gram aconitine.

8 Excited springing is still present ; great frothing ; reflex withdrawal of both legs.

14 Quieter ; the left leg is steadily, right, irregularly, withdrawn.

Minutes.

24   Moves both legs spontaneously, but no reflex from the right.

40   Spontaneous movements occur but rarely.

50   Still slight spontaneous movement; no reflex from right; in left there is prompt reflex, the frog moving away.

60   Spontaneous movement very seldom.

62   Spontaneous movement ceased.

70   Circulation only just moving in right web; animal does not move spontaneously; reflex from left to itself.

75   Reflex from left is gone; no circulation.

The figures to be noted here are :—

> Reflex goes from unligatured leg in 24 minutes.
>   ,,   ,,   ,, ligatured   ,,   75   ,,
> Spontaneous movement ceases in   62   ,,
> Circulation ceases in   70--75   ,,

Largely Diluted Solutions.—Solutions of aconitine up to ·00025 gram per cub. centim. are distinctly irritant in the first instance, and to this irritation the initial contorted position, with reflex inhibition and some part of the subsequent excitement, is referable ; for, if largely diluted solutions (though lethal in respect to the total alkaloid contained) are substituted, these symptoms are absent, or greatly reduced in degree.

Action of Aconitine on uninjured Frogs and on Frogs deprived of Brain and Medulla.

In all cases, the preparation was made from 18-20 hours before the experiment was performed.

The chief difference between the reaction of normal and brainless frogs, lies in the comparatively slight motor effect after injection in the latter, for though a few extensions of the legs are usual, the protracted springing and minor movements of the limbs, as well as the contortions of the trunk, are not present. The period of initial quiescence or inhibition after injection, so usual in the uninjured animal, is but slightly represented, or altogether absent in the brainless animal. As in the former, this effect immediately succeeds injection ; the question is mainly of local sensory stimulation rather than of absorption, though this rapidly follows. The result of stimulation of sensory perceptive centres is for the time masked by that of inhibitory, which are again involved after absorption has taken place. An " overwhelming " dose of aconitine may cause such prolonged inhibition that, absorption occurring during its prevalence, such complete poisoning results that no further movement of the limbs is witnessed. This is, however, exceptional. Poisoning proceeds more

slowly in the brainless than in the uninjured animal, the reflex in the former being longer preserved. RINGER and MURRELL* have observed the much earlier disappearance of reflex in normal animals; for, whilst after very large doses they saw reflex disappear in 4 minutes, in brainless frogs it lasted 40 minutes. They believed that aconitine abolishes reflex through some action exerted upon the brain, and they unite with LIEGOIS and HOTTOT† in the surmise that the sensory perceptive centres are powerfully depressed by the alkaloid. If this were the sole reason, one would anticipate that reflexes would reappear immediately after their disappearance in the aconitised frog upon decerebration; but this has not been found to be the case (the primary inhibition immediately after injection is, however, removed by destroying the brain).

It may be stated at once that with the aconitine employed, such wide differences in time between failure of reflex in the uninjured and decerebrated frogs respectively have not been seen.

The following average is obtained from five experiments. In each of these, two small frogs of equal size, 12 to 17 grams, one normal, the other decerebrated, received doses of aconitine varying from ·00075 to ·00120 gram. The larger dose is fifty times the lethal amount. The average time between injection and disappearance of reflex was, in the normal, 9 minutes 40 seconds; in the decerebrated, 15 minutes 28 seconds.

In only two of the normal frogs was there much movement, as the stage of inhibition was rapidly merged in that of poisoning of the tissues, but in these two cases the reflex disappeared much before it did in the companion brainless animal, in which only a few extensions of the legs had occurred.

The idea suggested itself that the usual powerful springing, as well as the active movements already described of the trunk of the normal frog after receiving aconitine (and witnessed by RINGER and MURRELL after large doses), must greatly promote the rapid absorption of the poison from the dorsal lymph sac, and its diffusion through the tissues. In the brainless frog, on the other hand, the movement is comparatively transitory, and cannot influence the speed of absorption to nearly the same extent. A simple experiment demonstrated that if movement was enforced upon the brainless frog, poisoning proceeded distinctly more rapidly than if the animal remained quiescent.

Experiment.—Two long and insulated wires were attached to the skin of the abdomen of a brainless frog (No. 1), and connected with the secondary coil of a Du Bois Reymond's inductorium. The first spontaneous movement having subsided after aconitine injection, an opening single induction shock was admitted steadily (30 per minute) so as to cause contraction of the abdominal muscles, and slight extension of the legs. This movement, insufficient in itself to produce marked

* 'Journal of Phys.,' vol. l.
† *Op. cit.*

fatigue, was kept up as long as movement usually occurs in a frog in which the brain has not been disturbed.

A control frog (No. 2) of the same weight, in which the brain had been destroyed, was poisoned with a similar dose of aconitine. After a short struggle, movement ceased.

In No. 1 frog   .   .   heart ceased in   64 minutes.
No. 2   ,,   . .   ,,   ,,   ,,   84   ,,
No. 1   ,,   . .   reflex   ,,   ,,   68   ,,
No. 2   ,,   . .   ,,   ,,   ,, 111   ,,

This experiment has been repeated with modifications, and it yields as a constant result that increased movement accelerates poisoning, and to this in measure the more rapid abolition of reflex in the uninjured than in the brainless animal is attributable. A central inhibition must be held answerable for the rest.

Of the symptoms of aconitine poisoning by lethal doses, there are some which, though characteristic of the alkaloid, have not been followed further, owing to the already extensive scope of the present research.

Stimulation of the central perceptive centres (though these are subsequently depressed), perhaps also of motor areas, may be the cause of the repeated springing movements, which differ in both character and degree from the simple and transitory movements of brainless animals. The frothing developed during active movement, and which we unite with RINGER in thinking is not produced to an equal extent by the same amount of movement from any other cause, is toxignomonic of aconitine, and implies increased, possibly altered, secretion.

The remarkable and grotesque positions assumed, such as unsymmetrical disposal of limbs, torsion of head, arching of trunk, are highly characteristic of aconitine, and are absent in the brainless animal. The asymmetry of the limbs of the two sides, occurring in an animal which is usually so symmetrical, is interesting as existing when voluntary movement, and even some degree of reflex, is present. Depression of cutaneous sensory nerves is therefore not the whole explanation, though this may become contributory; it is more likely that the musculo-sensory nerves and their connected perceptive centres are depressed.

Repeated gaping is probably indicative of excitement about the roots of the hypoglossal nerve.

As a feature of the toxic action of lethal doses, twitching or fibrillation was witnessed in about 18 per cent. of all experiments in otherwise resting muscles. Larger doses are more apt to provoke this condition, and especially to do so near the seat of injection. After spontaneous movement, twitching, as a transitory condition, may be developed in the muscles which have been in action.

Action of Aconitine on the Frog's Heart.

Although the frog's web may be examined, and an approximately correct opinion formed therefrom as to the capacity of the heart for maintaining the circulation, yet the actual condition of the organ can be only imperfectly recognised so long as the thorax remains unopened. The effect of aconitine has been watched upon the heart *in situ* after removal of the sternum in brainless frogs, and also upon the excised organ.

Speed and Rhythm of Heart.—Ascertained by inspection. The animal was placed in the dorsal position upon moistened filter-paper which also lined the covering funnel. The temperature was observed, and as far as possible kept constant.

Summary of Results.—Hyperlethal and lethal doses ·002 to ·00008 gram of aconitine are followed for a time by acceleration, with regular sequence of auricular and ventricular beats, but this soon yields to an incoordinate movement of the ventricle in which the auricle does not sympathise. Blood pouches or sacs, which may remain at the same spot or shift repeatedly, appear in the myocardium. Whilst during incoordination the number of effective systoles is greatly reduced, the number of attempted contractions (s. v. v.) is much increased, the effort of some part or other of the ventricular wall being almost continuous. Whilst one portion contracts, another relaxes, so that a condition prevails in which satisfactory systole or diastole are alike impossible. It is in the lulls occurring in this tumultuous or delirious state that an effective diastole, followed by a systole or a group of systoles, may appear. Before arrest of the heart a more regular rhythm with a greatly enfeebled systole supervenes; the muscle substance is now usually engorged and dark, less frequently it is comparatively anæmic ; blood pouches may, or may not, be present; the discharge of blood from the organ fails. The speed of arrest is in direct proportion to the dose.

When to frogs of from 20 to 24 grams, doses of ·00003 to ·000008 are administered, a primary acceleration occurs, varying from 4 to 10 beats per minute. This is, however, transitory, and a relative slowing succeeds. After the smaller dose, there is no further change than the gradual return to the normal rate, but incoordinate action, often associated with pouching, follows the larger. This coordination may disappear and reappear several times in the course of an observation.

Examination of the web during incoordinate ventricular action shows that at this time there is serious interference with the systemic circulation ; it is often difficult to realise that the feeble and oscillating movements of the corpuscles are the only result of the tumultuous action of the distended and incessantly moving ventricle.

Doses of ·0000025 gram and less, usually produce a slowing of from 2 to 4 beats per minute. It is difficult to say when the limit is reached at which aconitine ceases to act, for even a quarter of the smaller amount may often prove operative.

The more rapid the speed of the heart under examination, the more pronounced is the retardation occasioned by these minute doses of aconitine.

(A) *Lethal Dose.*

FROG of 22·5 grams.   Pegged ; heart exposed ; heart beating steadily 23 per minute.   (Observed 15 minutes.)

Minutes.

0   Inject ·00006 gram of alkaloid into dorsal sac.   A short struggle followed injection.

3   Heart 24.

5   Heart 27.

10   Heart 30 ; every second systole is imperfect, and occurs before the diastole is complete ; second systole rapid, heart becoming very pale.

20   Heart 29 as above ; there is good circulation in web.

30   Heart 29 ; much less blood circulating ; on auricular systole a distinct pouch on anterior ventricular wall, but this is obliterated in ventricular systole.

35   Heart 28 ; diastole imperfect.

40   Heart 30 ; ventricle wall more relaxed, but empties itself very imperfectly.

42   Sudden increase in strength, and great accession of circulating blood, as observed in web.

50   Heart 30 ; great irregularity of ventricle.

60   Heart 30 ; every fourth or fifth beat the ventricular wall is distended in part (pouching) with blood ; it then undergoes a series of tumultuous churning contractions, the blood being driven from one part of the muscle substance to another, no effective systole occurring.   During this condition the circulation in the web is greatly reduced, and occasionally suspended.

80   Heart 29 ; is very irregular.

100   Heart 28 ; regular contraction appears.

120   Heart 17.

140   Heart 11.

165   Heart—auricles beating 18 regularly ; ventricle, which is permanently pouched, gives only a feeble movement to every fourth or fifth auricular beat ; no circulation in web.

195   Auricle 18 ; no circulation in web.

Hours.

23   The next morning the auricle is beating once per minute ; the ventricle quite insensitive.

Sub-lethal Dose (large).

HEART exposed of pegged frog of 25 grams.   After it had been observed for 20 minutes, and was found to be beating steadily at 18 per minute.

Minutes.

0   Injection of ·000016 gram aconitine into dorsal sac.

5   Heart 20.

10   Heart 23 ; heart appears to dilate imperfectly.

15   Heart 24 ; not much blood circulating.

20   Heart 28 ; only part of ventricle contracts.

25   Heart 30 ; a little tendency to pouching on anterior surface midway between auricular and ventricular groove and apex.

30   Heart 28.

35   Heart 28.

40   Heart 25.

45   Heart 23.

50   Heart 21.

55   Heart 20.

95   Heart 20 ; only small part of ventricle dilates and contracts.

180 Heart 20 ; the systole seems rather to drive to another part of the ventricle than to contribute to circulation, which is seen in web to be very imperfect.

Hours.

12   Auricles beating steadily 20 ; incessant churning movement of ventricle ; one part of muscular wall contracting and driving blood into another part ; which again contracts and expels contents ; there is corresponding reddening and blanching of muscle.   It is impossible to estimate number of true systoles.

21   Heart occasionally irregular.

34   Less irregular ; slight pouching on anterior surface of ventricle, and towards the apex.   It is at this position that pouching usually occurs.

Minute Dose.

BRAINLESS frog of 23 grams.   Heart beating 44, and 20 minutes later 44.

Minutes.

0   Inject ·0000026 gram aconitine.

10   Heart 43.

24   Heart 42.

32   Heart 40.

44   Heart 40.

60   Heart 41.

83   Heart 42.

105 Heart 43.

115 Heart 43.

Progress of Toxic Action Illustrated.

The float cardiograph which registers the back to front diameter of the ventricle, the organ being *in situ*, was employed to illustrate progressive poisoning. (The circulation proceeds naturally, destruction of the brain and exposure of the heart being the only necessary preliminaries.)

11.24.   BRAIN and medulla destroyed in frog of 32 grams.   Heart exposed.   (The ventricular float, resting on anterior surface of the wall, did not change position during the experiment.)   Stimulation through the ventricular substance is occasionally administered in the course of spontaneous contraction.

Minutes.

0   Heart 36 per minute.   (Fig. I_1.)

0   Inject into dorsal sac ·00004 gram aconitine.

4   Heart 43.   (Fig. I_2.)

7   Heart 39.   (Fig. I_3.)

10   Heart 30.   (Fig. I_4.)

14   Great irregularity ; rapid and imperfect action, interrupted by an occasional powerful systole.   The smaller beats are empty systoles, no blood being expelled from the ventricle.   (Fig. I_5.)

16   Heart 57 at first ; it then passes into an incoordinate churning condition, during which stimulation does not cause a coordinate systole.   (Fig. I_6.)

40   Heart 27·5 per minute ; reflex from legs going.   (Fig. I_7.)

48   Heart 19 ; reflex gone ; heart responds to single induction shocks. (Fig I_8.)

Stimulation of Vagus and Venous Sinus after Aconitine.

Minute doses of aconitine produce a slight stimulation of the inhibitory mechanism within the heart and so produce a slowing.   The control of the *vagus* over the cardiac rhythm is only impaired after aconitine has produced marked acceleration of the heart, and even then by increasing the stimulation a slowing, or an arrest, may be produced.   During the period of asequence of the different portions of the heart with incoordinate action of the ventricular wall, the vagus may lose its inhibitory action whilst its trophic effect—strengthening of the beat—persists.   Further, at this time the aconitine "block" may be temporarily removed by vagus stimulation. Thus if the sinus is beating more frequently than the auricles, and the auricles than the ventricle (conditions of usual occurrence after aconitine) this stimulation may induce a regular sequence which persists for a short time.

Experiment.—In a heart poisoned by aconitine *in situ* the organ beat as follows :—S. (sinus), A. (auricles), V. (ventricle).—S., A. ; S., A. ; S. ; S., A., V. ; S., A.

(Left vagus now stimulated). .   S., A., V. ; S., A., V. ; S., A., V.

(Stimulation suspended) . ,   ,   S., A., V. ; S., A., V. ; S., A. ; S., A. ; S.
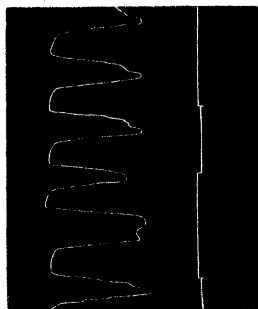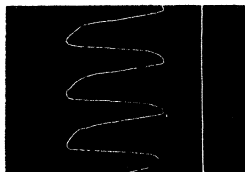
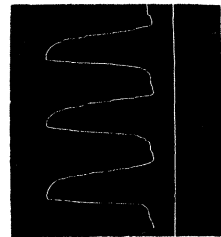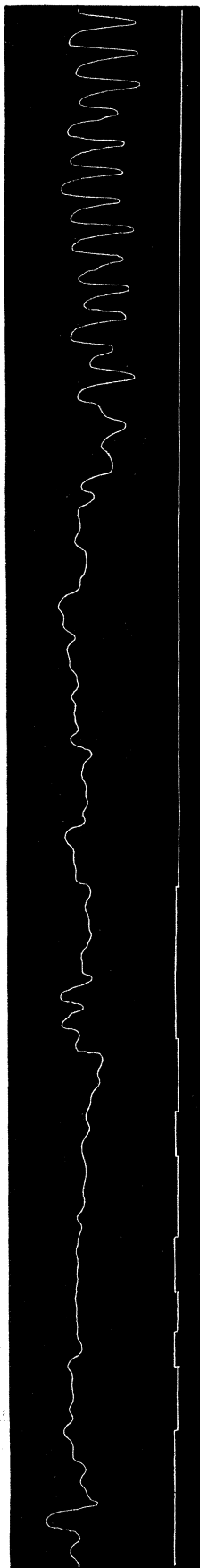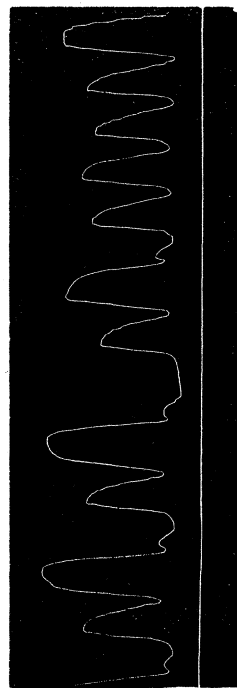Fig. I₄.

Fig. I₃.

Fig. I₂.

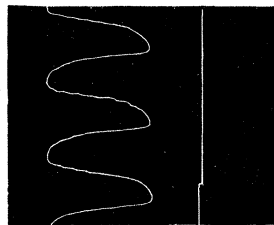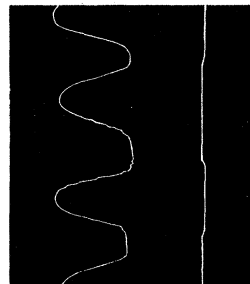Fig. I₁.

Fig. I₆.

Fig. J₁.

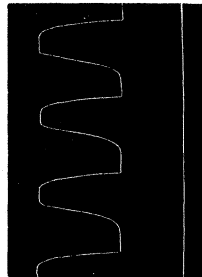Fig. I₈.

Fig. I₇.

Fig. I₅.

Fig. J₂.

Usually the last obvious effect which stimulation produces, after spontaneous movement of all parts of the heart has almost ceased, is to cause two or three contractions proceeding in due sequence from sinus to ventricle.

Inhibition of heart movement, by stimulation of the *venous sinus* after aconitine, is much more difficult to abolish than is vagus action. After the vagus has ceased to inhibit the sinus still arrests the organ. Ultimately, if the dose has been carefully adjusted, the sinus stimulation may be negative in result. Finally, after cardiac arrest, this may start two or three contractions proceeding in the normal directions. Whilst aconitine abolishes the inhibition both of vagus and venous sinus, it is clear that a tendency to sequential beating, and even to an excito-motor effect, may be temporarily developed from stimulation after inhibition has disappeared. These excitable elements retain a share of function, therefore, when action of inhibitory elements has been suspended.

Circulation of Aconitine Solution through Excised Heart.

For these experiments, KRONECKER's perfusion apparatus was made use of. The circulated fluid was RINGER's solution, to every 100 cub. centims. of which ·2 gram of defibrinated, and subsequently inspissated, bullock's blood had been added. This fluid after filtration was found satisfactorily to maintain the nutrition of the heart and preserve its contractile power.

Perfusion experiments with the apical half of the ventricle have not produced the incoordinate systole which is so characteristic of lethal and large sub-lethal doses of aconitine. The result of such perfusions has been to show a greater speed of spontaneous contractions with an apparent increase of irritability of the portion of the organ examined, followed by a failure in the strength of systole, and its gradual extinction.

Only exceptionally as a result of aconitine perfusion has the characteristic incoordinate action of the ventricle been observed. In such cases, the ligature was tied at the auriculo-ventricular groove, and there was probably an auricular remnant in relationship with the ventricle. Such doses as ·00001 gram aconitine cause an acceleration and subsequent slowing of the spontaneously-beating ventricle, the passage into diastole being more gradual than in the normal heart ; then follows a steady decline of strength of beat, the systole becoming weaker, but the dose has to be repeated several times before the ventricle ceases to beat spontaneously. Thus, after circulating ·0000745 gram of aconitine in the course of two hours, an occasional spontaneous beat was witnessed, and the heart contracted to electrical stimulation by a feeble systole. There is frequently observed a bigeminal beat after circulation of aconitine. This beat, which is often the connecting stage between acceleration and slowing, is well shown in the tracing J_2, taken two minutes after the circulation of ·000026 gram aconitine, dissolved in 10 cub. centims. perfusion solution, had

terminated.   It will be observed that during acceleration every second beat becomes progressively feebler until, at the end of the tracing, a mere hindrance to the diastole following the active systole remains.

If a cannula is inserted into the inferior cava, and tied at the position of the first Stannius ligature, a weak aconitine solution, circulated by this means through the heart, and escaping by a cannula in the aorta, causes disturbance of sequence between ventricle and auricles with some degree of incoordination in the ventricular wall.

Antagonism of Atropine and other Active Principles towards Aconitine.

The antagonism of atropine towards aconitine has been clearly indicated by RINGER,* but he points out that though the heart poisoned by aconitine has its excitability to stimulation restored, and its spontaneous rhythm to some extent reinstated by atropine, the beat remains impaired in force.   He infers an antagonism, exerted in part on the myocardium, and arrives at the same conclusion as that independently arrived at by LANGLEY,† viz., that displacement of one drug by another having a stronger affinity for cardiac tissue, is the probable interpretation of the phenomenon.

BÖHM and WARTMANN‡ did not witness this antagonism in mammals.

LANGLEY asserts that the muscarine arrest is not suspended by aconitine.

MURRAY§ speaks of an antidotal action of digitalis.

BÖHM and WARTMANN saw the aconitine heart in mammals slowed by digitalis, but no elevation of blood-pressure resulted.

The observations in the present research were limited to a few experiments with reference to the antagonism of atropine, digitaline, and the alkaloids associated with aconitine, viz., benzaconine and aconine.

Atropine is the most powerful and certain antagonist of the bodies examined in this series.   If administered to a brainless frog in anticipation of, or simultaneously with aconitine, it is found to limit, without altogether hindering, the acceleration of the heart caused by the latter, to reduce or, if the dose is successfully adjusted, to prevent, the occurrence of incoordination already described, and finally, in part, to prevent the exhaustion of the myocardium.

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* 'Journ. of Physiology,' vol. 2.
† 'Journ. of Physiology,' vol. 1.
‡ 'Verh. d. Phys. Med. Gesellsch. in Würzburg,' 1872.
§ *Op. cit.*

FROG of 27 grams.   Brain destroyed.   Heart exposed.   Heart beating 31 per minute.

Minutes.

0	Inject ·002 gram atropine (under skin of right side).
19	Heart 28.
25	Heart 27.
27	Inject ·0001 gram aconitine (under skin of thigh).
41	Heart 32.
59	Heart 35. Systole good.
72	Heart 32.
94	Heart 23. Paired beats; no incoordination; circulation in web good.
118	Heart 20.
152	Heart 20. No impairment in reflex of legs.
187	Heart 19.
224	Heart 18. Steady action; reflex prompt.

Hours.

25	Heart 40. Circulation steady; reflex good.
48	Heart 38. ,, ,, ,, ,,

In this experiment, though acceleration and slowing were witnessed, no incoordination occurred. A control frog of equal size, which had been prepared in the same way and received the same dose of aconitine, showed sacking and incoordination of the heart in 45 minutes, and failure of reflex.

As regards the recovery of the heart arrested by aconitine, our experience coincides with that of RINGER and MURRELL, in that atropine causes a return of excitability, and even of rhythmical contraction, but the beat remains impaired in force.

Neither digitalis nor digitaline appeared to avert incoordination, but both seemed to delay or hinder to a limited extent the subsequent failure of the myocardium.

Benzaconine, both when given in anticipation through the normal channel of the circulation, and by perfusion of the excised heart, retarded the development of aconitine effect, but no distinctly lethal dose of the latter was rendered non-lethal by this agency.

Aconine showed a more pronounced effect, the lethal effect of a dose of aconitine (nearly twice the lethal amount) being averted by previously administering large doses, up to ·014 gram of aconine. In such cases, free acceleration and subsequent slowing, with some incoordination, was witnessed.

PEGGED Frog of 27 grams. Exposed Heart.

Minutes.

0   Heart beating 25 per minute.

0   Inject ·0065 gram aconine.

23   Heart 27 ; excellent circulation.

27   Inject ·0000603 gram aconitine.

36   Heart shows bigeminal beat ; 40 per minute. The second beat occurs before full diastole has taken place.

56   Heart 38 ; filling well ; steady.

67   Heart 33.

84   Heart 28.   There are phases during which the ventricle does not dilate, and systole is abortive.

98   Heart 14 ; both auricle and ventricle show steady sequence; excellent circulation.

110   Heart 22 ; every second beat is feeble or abortive.

126   Heart 11 ; auricle beating 22 ; all reflex is gone.

160   Heart 10 ; auricle beating 20 ; the second auricular beat falls just after ventricular systole, and is not followed.

274   Heart 10 ; the heart is beating irregularly, but circulation in web is fair.

Hours.

23   There is much churning movement, but occasionally a good systolic phase occurs ; no reflex.

$47\frac{1}{2}$ Heart 33 ; regular systole ; good dilatation of ventricle ; circulation in web good ; no reflex.

$71\frac{3}{4}$ Heart 32 ; circulation good ; steady; ventricle fills well ; reflex has returned.

(The late occurrence of aconitine action is of interest here.)

This experiment gives a fair example of the incomplete antagonism of aconine towards aconitine ; it indicates a strengthening of the myocardium by the former. But whilst the lethal action of aconitine was preserved by giving aconine in anticipation, the attempt to recover the aconitine heart by the perfusion of aconine solution failed, and therefore the antagonism of the weaker alkaloid appears to be even less perfect towards aconitine than that of atropine. (For a description of the action of aconine on the frog's heart, the section dealing with this alkaloid must be consulted.)

Summary of Action of Aconitine on Frog's Heart.

1. Even after destruction of the central nervous system, some slowing follows minute doses of aconitine.   This effect appears to be reduced by atropine.

2. The acceleration which may be the first effect of large doses is accompanied by reduced activity of the cardiac vagus, but by a heightened excitability of motor

elements (including the myocardium) group beating, increased excitement on distension and to electrical stimulation are observed.

3. A sequence of auricle upon sinus and of ventricle upon auricle (or blocking of impulses) shows disorder of elements upon which propagation of contractions depends. Further, the expansion of a systolic wave in the ventricle becomes imperfect, and perhaps retarded, so that some parts are entering into contraction whilst others are passing into relaxation, the result being incoordination. This is not necessarily due to a direct action on the myocardium, for it does not seem to arise when only the apical half of the ventricle is employed. This condition (probably from induced exhaustion) may alternate with a phase of steady action. Blood sacs are indicative of a local relatively feeble, or suspended, action of the myocardium. There is no clotting of blood within the ventricular wall.

4. The myocardium is ultimately reduced in excitability and may fail altogether to respond to stimulation, especially when circulation has ceased and oxidation has thereby been interrupted.

5. Vagus and venous sinus stimulation become inoperative, the former much before the latter in the course of aconitine poisoning. After the inhibitory effect has disappeared, the vagus may still, on stimulation, favour a strengthening of the systole and a return towards the normal sequence, which has been interrupted by aconitine. The last visible effect of stimulation is usually excito-motor towards the quiescent or almost quiescent heart. After this stage has passed direct stimulation will still rouse the myocardium to a slight response.

6. Partial antagonism is exerted by atropine and aconine towards the disorder occasioned by aconitine.

Aconitine on the Respiration of Frogs.

As frogs survive prolonged interference with pulmonary respiration, provided the circulation is continued, the manner in which drugs modify or abolish respiration, together with the period of its suspension, and manner of resumption, can be studied in these animals with peculiar advantage and facility.

The respiratory movements of the frog are necessarily observed at two points ; the *hyoid*, which is alternately protruded and retracted, the movement being superficial and extensive, and the *flank*, which is in degree distended in inspiration, and in degree collapses in expiration. Only the major or more extensive movements of the hyoid are associated with ventilating side movements due to entrance of air or its exit from the lungs, though the minor movements may be contributory to oxidation by ventilating the vascular buccal cavity.

(For a discussion of normal movements and their relationship to one another, reference may be made to the recent researches of MARTIN,* and of SHERRINGTON,†

* ' Journal of Physiology,' vol. 1.
† *Ibid.*, vol. 12.

illustrated by the graphic method, and to their criticism of the antecedent work in this department of physiology.)

For graphic purposes, quiescence of the animal is necessary, and the normal frog is available with certain precautions, or the decerebrated animal may be used. With regard to the latter, MARTIN states that the character of the breathing, if modified, is not rendered markedly abnormal by the operation involved.

In these experiments, normal and unbound frogs were occasionally made use of, placed upon damp cork, often with the addition of an upright wall of cork in front of

Fig. A.
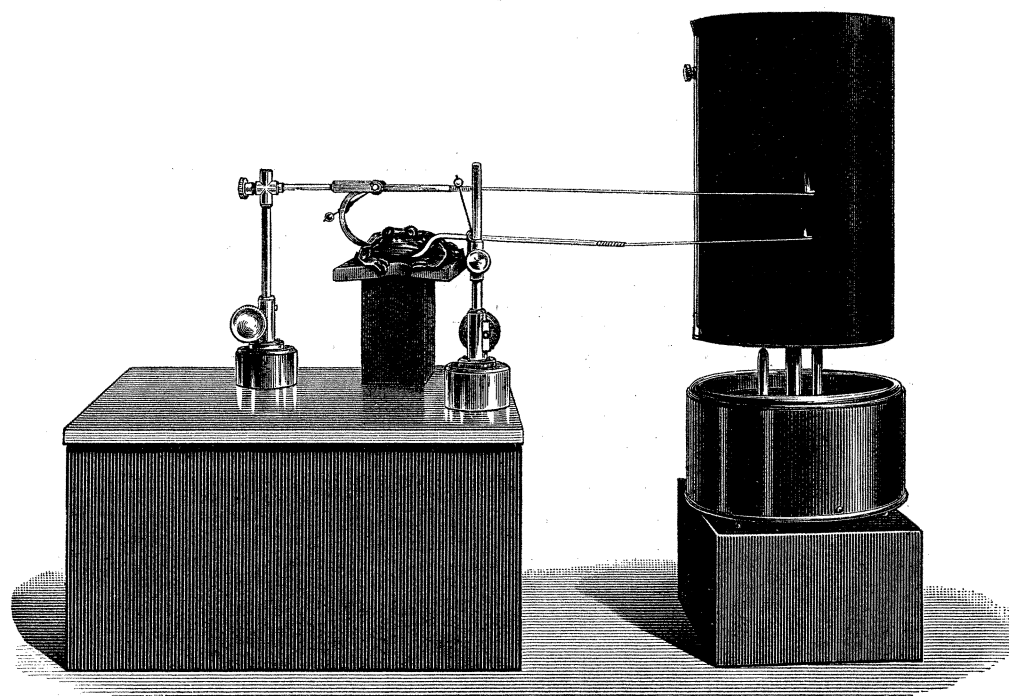
the animal. Should the animal prove restless, there is not the objection to controlling it which observers have supposed. If two loops of tape are run through a piece of sheet cork, so that each of them may pass over foot, leg, and thigh, on the right and left sides respectively, a very slight degree of traction will usually suffice to keep the animal sitting in a normal position, and without causing it inconvenience. If it begins to move, it easily liberates itself, but often it is content to remain, if the cork upon which it is placed is kept moist. After resting upon this board for a few minutes, the respiratory movements in the great majority of cases are identical with those of a perfectly free frog.

The levers which were designed with the object of registering the respiratory movements have answered this purpose so satisfactorily that it has been thought worth while to represent them in a figure, fig. A. They are made of aluminium and straw, and are provided with rod and ball counterpoises which admit of the finest

adjustment of balance, so that the lever will just follow, and no more, the movement of hyoid or side. The pillar of each lever stands on a heavy base of metal, and is capable of elevation by means of a rack and pinion.

Frequently no movements but major movements are executed by the hyoid, each being associated with a side movement.

Fig. K.
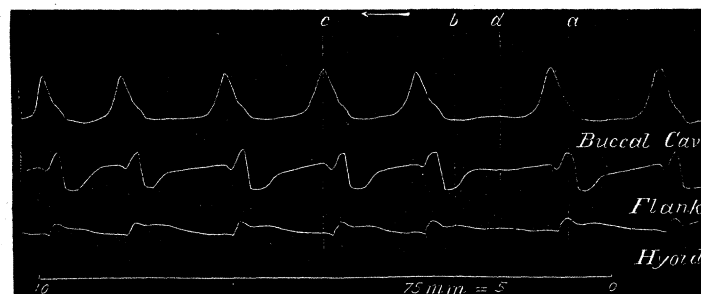
In order to make clear the relationship of these movements, a tracing of dyspnœa is given (K), which is taken from a frog deprived of the cerebrum and optic thalami; the bottom line is from the hyoid, the middle from the flank, and the top line is the record of positive pressure in the buccal cavity. This is obtained by passing a fine conical cannula from the buccal aspect through the tympanum, and connecting it with a small registering tambour, the rise of the lever of which indicates an increase in positive pressure. (When not in use, the outer mouth of this tube is closed with paraffin, in order that respiration may be effectively carried out.)

(This method is a more satisfactory one than interference with the nostrils, and although some degree of dyspnœa is produced, the animal breathes with the mouth closed.)

The coincidence of movements will be recognised by allowing verticals to fall at intervals. Thus—

(a) Maximal protrusion of hyoid—corresponding with expiratory impulse of side due to flank contractions—commencing elevation of pressure in buccal cavity.

(b) Maximal protrusion of side (inspiration), corresponding with arrest of protrusion of hyoid ; absence of pressure in buccal cavity. The glottis is now closed.

(c) Maximal pressure in the buccal cavity ; commencing expansion (inspiratory) of side ; retraction of hyoid.

(d) One of the mimetic or minor movements of the hyoid is recorded as a faint wave ; during this, the passage of the side into inspiration is delayed, and there is a slight increase of intra-buccal pressure.

The following is a summarised statement of the most obvious effects of aconitine upon respiration in the frog :—

Sub-lethal Dose—·000015 gram administered to a frog of 34 grams caused in sequence—

1. An almost complete equalisation in the number of hyoid and side movements (equivalent to an acceleration of side movements).
2. An increased extent of the movements.
3. A slowing of both hyoid and side movements (42 per minute for former).
4. An increased tendency to extensive movements of inflation and emptying of side.
5. A return to the normal 190 minutes after injection.

·00003 gram caused—

1. Reduction of hyoid with increase of side movements.
2. The development of more energetic movements of inflation and partial collapse of the lung than had existed before.   During full inflation, the hyoid yields only minor movements ; in expiration, its movements are more frequent than those of the side.
3. Entire stoppage of respiratory movement between the great expiratory efforts ; this stoppage may last for from 1 to 10 minutes, according to the stage of action.

FROG of 28 grams, sitting free (fig. L_1).   Respiration, side 68, hyoid 162 ; gentle movements of slow inflation, and collapse of side are present.

Minutes.

0   Inject ·000029 gram aconitine.

3   Respiration, side 84, hyoid 116 (L_2).

9   Passing into *inspiration*, side 60, hyoid 60 ; great inflation of lungs ; into *expiration*, side 48, hyoid 108 (tracing L_3).

19   There are long pauses in inspiration, followed by rapid emptying of lung and refilling; hyoid movements are active during these phases.   No hyoid or side movement is observed between these (L_4).   The hyoid rests in protrusion, the side in inflation.   Movements of the hyoid are about an axis which is nearer to the retracted than protruded position.   Through the ensuing night, the movements of the hyoid and side were recorded (L_5) upon a cylinder, rotating 12 millims. in one hour.   From 6 to 9 movements per hour occurred, the lungs tending to revert to the expiratory position.   Recovery was complete in two days.

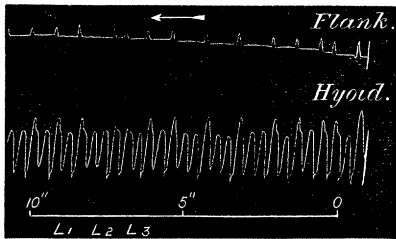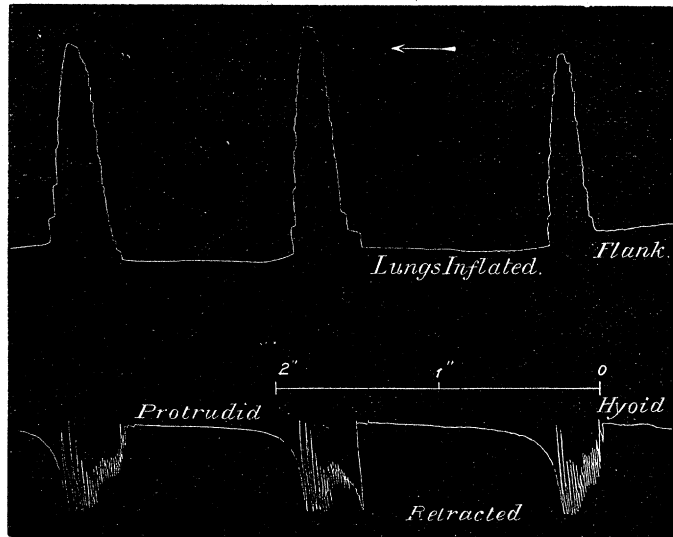The return of respiration is by the gradual reinstatement of rhythmical side movements.   In fig. L_6, the returning (26 hours) rhythm is established ; hyoid movement
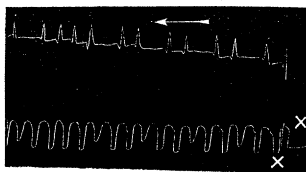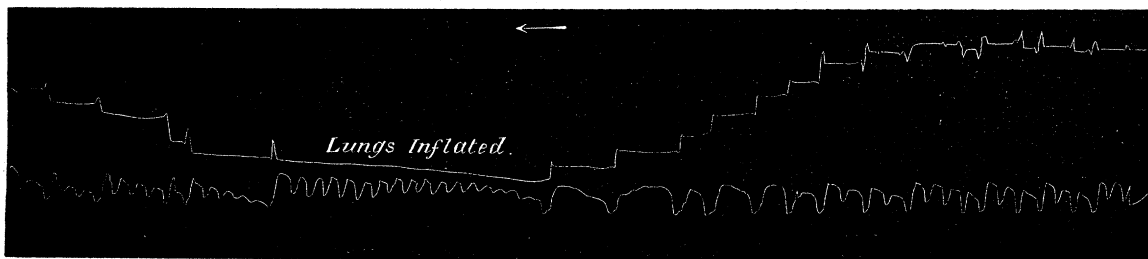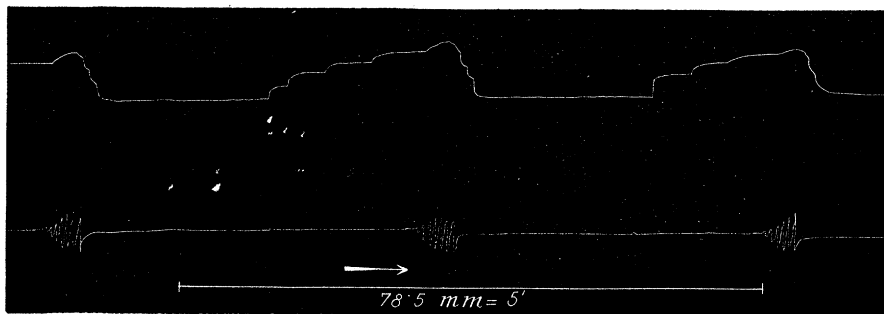
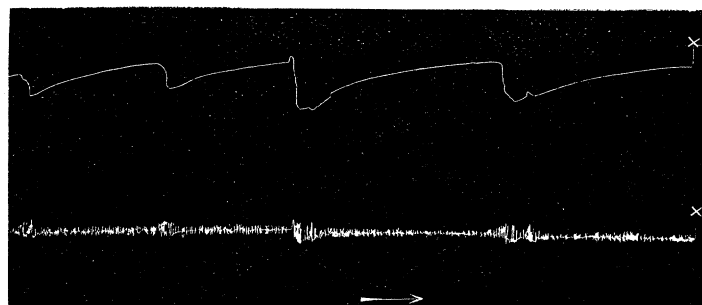Fig. L₁.

Fig. L₄.

Fig. L₂.

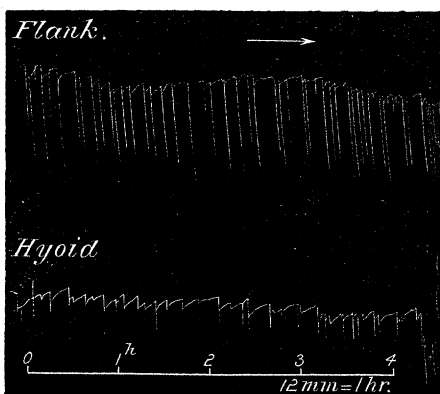Fig. L₃.

Fig. L₆.

Fig. L₅.

Fig. L₇.

is registered only at the completion of emptying of the lung, and during subsequent inflation of the lung, but soon after it participates actively in the emptying (L_7).

Recovery of respiration after a deeper degree of poisoning must be referred to. The tracing M is taken from a frog of 28 grams, which had an almost lethal dose (·000032 gram of aconitine), and the abolition occurred much as in the last-quoted experiment, but more completely.

Fig. M_1.
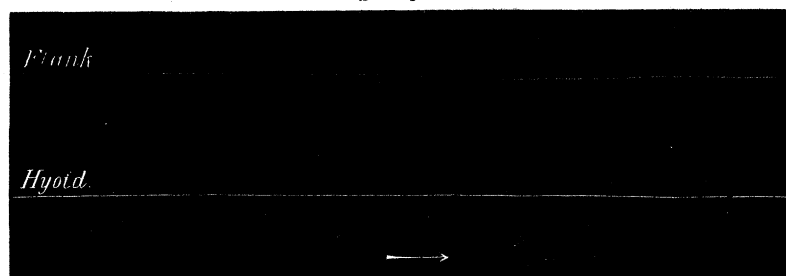
Fig. M_2.
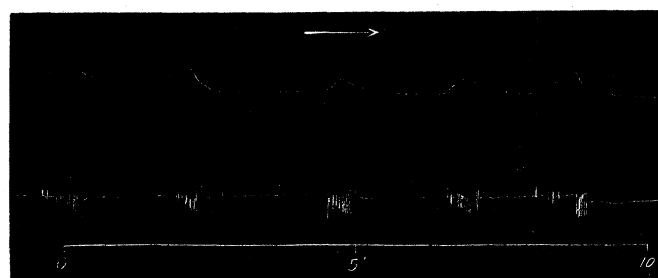
In 19 hours, there is a single faint hyoid protrusion, about every 20 minutes, with a barely perceptible movement of the side. In 42 hours, evident waves are seen (M_1) in the side and hyoid, these waves recurring 24 times in an hour. Only one movement of the side, which could be supposed capable of ventilating the lung, was recorded during 7 hours.

67 hours. There is rhythmical expiratory movement (M_2), associated with hyoid activity, the body tending to become more inflated.

80 hours. There is continuous hyoid activity, minor movements being present. The side movements are steady; a temporary inflation of the lung is followed by gradual expiration. The CHEYNE STOKES phenomenon of respiration, which SHERIDAN points out as occurring in newly decerebrated frogs, is present here in developed form.

Though to superficial observation aconitine may appear readily to abolish respiratory movement in frogs, it will be seen from these experiments that a slight degree of rhythmic discharge of the controlling centres occurs when the general appearances point to an almost lethal effect. The disappearance of the minor or mimetic movement of the hyoid, and the increase of the important major and side movements, seem to indicate a certain urgency in the respiratory needs of the animal; but when long pauses of side and hyoid occur between phases of expiration and inspiration, a

depression of the probably linked central respiratory apparatus may be assumed.   In most experiments a faint rhythmical movement of the hyoid at long intervals was seen to outlast any registrable or appreciable movement of the side.   Such movements are evidence of a residue of activity in the respiratory centres, periodic in development, but not contributory to gaseous exchange in the lung.

If these results are contrasted with those obtained from the rabbit, we find a relative increase in side movements in the former, with acceleration of respiration in the latter.   Later, there is slowing in both ; the panting movements of the rabbit and the mimetic hyoid movements of the frog disappear, but at the stage when respiration becomes too feeble for the oxidation of blood of the rabbit, the animal dies ; whilst the frog lives on, its centres still discharging feebly, or becoming entirely inactive, until the gradual elimination of the drug permits the resumption of their activity.

Action on the Spinal Cord, Motor and Sensory Nerves, and Skeletal Muscle of Frogs.

The vigorous movements following injections of strong solutions of aconitine into the dorsal sac are mainly due to the irritant action upon sensory nerves, for freely diluted solutions do not cause such an effect.   These movements favouring absorption rapidly bring the alkaloid into direct relationship with the central nervous system. The direct action of the poison, though causing a passing stimulation of perceptive and motor centres, is ultimately depressant towards them, whilst limb reflexes become irregular and uncertain.

The reduced activity of sensory nerve terminations is the main cause of reflex failure which occurs whilst spontaneous movement is still possible.   It is only after largely hyperlethal doses, such as those used by RINGER with MURRELL,* that rapid abolition of reflex with direct poisoning of the cord is witnessed.

The employment of simple lethal doses enables one to study more closely the share in reflex failure which is due to cord and sensory nerve terminations respectively.

The experiments made confirmed the observation (LIEGOIS with HOTTOT,* RINGER with MURRELL†, and others), that voluntary movement outlasts reflex in a limb open to the action of the poison, but it must be added that voluntary movement has been frequently seen to disappear before the abolition of reflex in a limb protected from the local action of the poison.   In a word, the cord is but little affected in its reflex function by aconitine administered in moderate lethal doses.

Small pegged brainless frogs were employed, one limb being sheltered from the action of the poison by a preliminary ligature of vessels.   Acid solutions of various strengths, 1–500 to 1–800, served to elicit the reflex, the time of which was estimated in the usual manner by the beats of a metronome.

* 'Jnl. de Phys.,' 1861.

† Op. cit.

When large sublethal doses are used there may be for a few minutes a slight acceleration in the speed of reflex, but this phase is at most very transitory.

A retardation in withdrawal of the unligatured foot then becomes apparent, and rapidly develops, whilst the protected foot is withdrawn promptly from the acid solution. This maintains so long as the reaction of the legs to their own immersion is considered; but if the acid solution is strong, 1–500, a cross reflex ensues on immersion of the protected foot, *i.e.*, flexion of the unligatured and unstimulated leg, the withdrawal being much more rapid than that of direct reflex.

FROG of 25 grams. Pegged 24 hours. Ligatured vessels passing to left limb. Sulphuric Acid—1 to 700. Reflex time taken by metronome beating half seconds. Room temperature = 50° F. (The figures represent time of withdrawal of the legs from immersion of toes on side to which the heading refers.)

Time.	Left.	Right.	Notes.
minutes.	seconds.	seconds.	Diagram C.
0	3	3	This estimation is the same whether immersion is of one or both together.
0	..	..	Inject ·00003 gram aconitine into dorsal sac.
1	..	..	At once washing movements of legs at seat of injected poison.
3	3	2·5	
4	..	..	Quiescent.
5	3	..	
10	3·4	4	
15	3·5	3·5	
20	3·75	4·75	
25	3·75	4·75	No movement of body.
30	4	6·5	
35	4	8	
40	4	7·5	
50	4	10	Touch reflex sharp; very difficult to examine web.
55	4	10	
65	4	10	
75	4	10	
85	4	9	
95	4	10	
105	4	9	
115	4·5	10	
125	4·5	10	Out.
135	4	..	Twitch in 8 seconds not out.
155	4	..	Twitch not out in 12.
165	4	..	Acid was strengthened to 1–500.
175	1	12	To self immersion.
175	1	1·5	From left immersion only.
215	1	0	To self immersion.
	1	1·5	From left immersion only.

The dose is a sublethal one, but it is sufficient to reduce, and finally to abolish, peripheral sensation, except for prolonged stimulation. The cord, whilst showing a slight reduction in reflex activity, is not materially impaired in function throughout.

Diagram C.

————— Right Leg Unligatured.   ·········· Left Leg Ligatured.
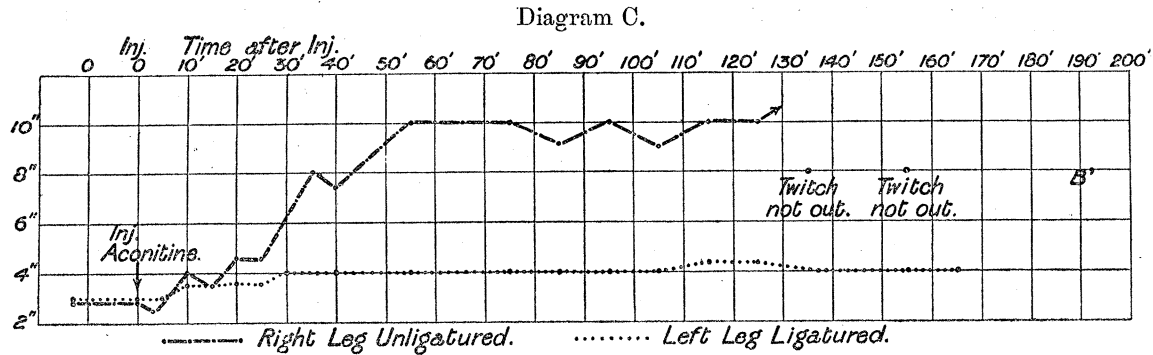
In experiments during which the cord is exposed for a considerable time to the action of aconitine, an impairment in reflex function is witnessed, and yet, after this impairment has advanced to abolition, destruction of the cord, or injection of strychnine, will occasion powerful movements of the hind limbs. The motor ganglia are still excitable, and it is, therefore, probably the sensory cells which are mainly involved.

MACKENZIE's experiments upon mammals, in which he stimulated the posterior columns of the cord when sensory paralysis appeared complete after aconitine, led him[*] to believe that there was no marked action on the cord.

Action of a Lethal Dose of Aconitine on Reflex.

PEGGED (brainless) frog of 22·5 grams. Vessels to left leg ligatured. Reflex ascertained as before to 1–700 acid.

Time.	Left.	Right.	Notes.
minutes.	seconds.	seconds.	
0	2·5	2·5	
0	..	..	Inject ·00007 gram aconitine into dorsal sac.
3	..	..	The short preliminary excitement has quite disappeared.
4	2·5	2·5	
6	2·5	2·5	
9	3	3	
16	3	3·5	
26	3	3·5	
37	3	4	
40	3·5	6·5	Circulation in web varies, but it is distinctly impeded.
54	4	9	
60	4	..	Not out in 30 seconds, though twitch at 25 seconds. Circulation only just moving.
62	..	..	Circulation ceased.
64	5	0	
74	7	0	
79	0	0	Ventricle pouched at apex; insensitive; a uricle occasionally gives a feeble beat.

* 'Practitioner,' 1878.

A depression of the reflex function of the cord is observable, but even after this dose (double the lethal amount) reflex on the protected side outlasts the circulation by 12 minutes, and commencing impairment of the circulation by 34 minutes.

An experiment of RINGER's was repeated as follows :—

Experiment A.—In two frogs, each weighing 28 grams, the brain was destroyed, and the left leg vessels of one of them (No. 1) ligatured. Into the dorsal sac of No. 1, ·00008 gram of aconitine was injected, whilst from No. 2 the heart was excised. Room temperature, 55·50°.

minutes.

No. 1. Circulation ceased in right web in 47.

       Reflex   ,,   left foot ,, 101.

No. 2. Reflex   ,,   legs   ,, 102.

The time elapsing in No. 1 between failure of the heart and left reflex is 54 minutes, whilst it is 102 minutes in No. 2. Even allowing for a progressive interference with the circulation in No. 1, and an accompanying impairment in activity of the cord, there is still sufficient evidence of depression occurring, which cannot be considered as merely secondary to heart failure.

It has been observed that in such contrast experiments as these, destruction of the cord of frogs just after the cessation of reflex produced much more marked movements in the aconitised frog than in the unpoisoned animal from which the heart had been removed.

This indicates a relatively greater persistence of activity in the motor ganglia of the anterior columns in the former, and as it has been shown that brain impulses travel to the legs at a late stage of poisoning, the aconitine action may probably be located in sensory elements of the cord which thereby cease to be accessible to ordinary stimulation. It has been indicated that strychnine will still cause spasm in both legs after reflex failure.

We unite with LIEGOIS and HOTTOT[*] in recognising an earlier effect of aconitine upon the medulla than upon the cord ; a distinct impression being produced upon the former with doses which are practically inoperative towards the latter. It appears, however, after deep poisoning that the medulla may recover some degree of function, as evidenced by return of faint respiratory movements before the return of ordinary reflex.

Sensory Nerve Terminations.

In auto-experiments, a persistent numbness of tongue, lips and soft palate, with feeling of uncomfortable roughness and swelling (though none actually existed), followed the tingling occasioned by dilute solutions of aconitine. (After the first

* *Op. cit.*

effect, the sensation on lips, tongue, and palate is comparable to that produced by hastily drinking a cup of very hot tea.)

The powerful and rapid effect of aconitine upon sensory nerve terminations in the frog's skin has been sufficiently dealt with in the preceding sections.

Stimulation is produced immediately upon administration which acts so energetically that, for a brief period, there is inhibition of reflex movement; this condition yields after lethal doses to active movements which persist when the depression in function of sensory nerves is far advanced.

It has been shown that the primary failure of reflex manifestations is owing to the depression of sensory nerve terminations in the skin, although ultimately, as a sequence to large doses of aconitine, the cord is involved. Small doses produce a depression of peripheral sensory nerves, whilst leaving the cord practically unaffected. It may be that sensory nerve terminations in muscle, as well as their related centres, share in this depression, and that to this, the asymmetrical disposal of the limbs and the grotesque position assumed by the frog poisoned by aconitine, may be largely owing.

Aconitine on the Motor System (central).

After the injection of aconitine, there is produced in both brainless and normal frogs, a certain degree of movement, always much greater in the latter than in the former. (The direct irritation of aconitine may be greatly reduced by injecting the solution under the skin by the tendo Achillis of a leg, the sciatic nerve of which has been previously divided under ether. The primary inhibition is also avoided by this proceeding.) The extension of the legs is exceptionally vigorous, and even quasi-spasmodic, when contrasted with the free movements of volition of the animal; it occurs often with considerable regularity, and is preceded by a general contraction of the trunk muscles, which may impart a hunching appearance. There is much in the form the movement takes which is suggestive of stimulation acting upon central motor apparatus directly, and the greater prominence and persistence of such movements in the uninjured than in the brainless animal, suggest that the motor cerebral centres are involved, and may even continue to discharge at a time when sensory perception has passed into a state of depression.

When large, sublethal doses of aconitine have been used, and the spasmodic stage has passed, an occasional movement of the body and limbs has often been seen to be intimately associated with the discharge of a portion of the air from the lungs, and the admission of fresh air.

This movement (though such an idea scarcely conforms with accepted views of the frog's respiration), might possibly be held indicative of a central recognition of imperfect oxidation, translated into a movement favouring ventilation of the lung.

Motor Nerves.

The majority of observers have obtained negative results regarding the action of aconitine upon motor nerves, the statements of Aschscharumow[*] and Weilland,[†] and later of Gréhant[‡] and Plügge,[§] that a depression is produced, having been denied by Böhm with Wartmann,[||] Guilland,[¶] and others. Langaard[**] saw paralysis of motor nerves after that of the cord.

That a primary hyper-excitation may often be detected, was pointed out by Mackenzie.[††] Many observers accept muscular fibrillation as an indication of such a condition.

Fibrillation is frequently produced by doses which do not largely exceed the lethal amount. It occurs as a transitory and local phenomenon, chiefly in the neighbourhood of the injection, but it may also be developed by movement.

The action upon motor nerves and their terminations was tested by destroying the brain, ligaturing the vessels passing to one of the legs, and placing the sciatic nerves, prepared for a part of their course in the thigh, upon silk threads, and testing the minimal irritability before and after the injection of aconitine by raising and stimulating the nerve from time to time. The ligatured leg furnished a control to the other, in which the vessels were open to circulation. (In some experiments, the nerves were divided at their origin from the cord, but the result remained the same.)

After overwhelming doses ('0015 gram of aconitine), impairment in irritability of the nerve on the poisoned side, amounting to from 2 to 9 centims. in position of the secondary coil, was witnessed.

The result uniformly arrived at when doses of twice the lethal amount and downwards were used, was that with the exception of a slight primary increase of irritability on the poisoned side, the courses of minimal excitability on the two sides were coincident. No impairment of function on repeating stimulation was detectable.

(See also following paragraph on "Ability of Muscle to perform Work.")

* 'Journ. de Phys.,' 1861.

† Eckhard's 'Beiträge,' vol. 3.

‡ Referred to by authors.

§ Virchow's 'Archiv,' vol. 87.

|| Op. cit.

¶ 'Archiv. de Physiolog.,' 1875.

** 'Archiv f. Pathol. Anat.,' vol. 79.

†† Op. cit.

FROG of 35 grams. Pegged. Left arterial vessels ligatured, and main vein divided; normal stimulation. The figures indicate distance of secondary coil from primary.

Time.	Left.	Right.	Notes.
minutes.	centims.	centims.	
0	26	28	
(20 mins. 0 later)	25·5	27	Inject well-diluted ·00009 gram aconitine into dorsal sac.
13	26	27·5	There has not been any spontaneous movement.
23	26	27·5	
41	26·5	29	Heart somewhat incoordinate; slowed.
53	25·5	28·5	
71	25·5	27	
81	..	..	Circulation moving in right.
88	26·5	26	
111	26·5	26	
216	26	25·5	

Irritability after Cardiac Arrest.

The assertion has been made that the irritability of motor nerve terminations, and, in all probability, of muscular tissue, is so much exalted by aconitine that increased irritability is to be observed after cardiac arrest, and until reaction ceases. This was tested by poisoning brainless frogs with aconitine after ligation of the leg vessels upon one side, and examining the irritability of nerve and muscle from time to time till reaction ceased.

Again, with the object of testing the effect of aconitine in a larger dose than could reach the limbs through the medium of the circulation, perfusion under pressure of the vessels of frogs was practised. In all cases, frogs in which the brains had been destroyed were used, and the vessels passing to one leg were securely ligatured. After perfusion, the frogs were carefully preserved in a cool place, surrounded and covered by filter paper moistened with salt solution.

Poisoning.—Doses of from ·000038 to ·00006 gram were used. In each of four experiments, the irritability of the nerve as evidenced by the production of a minimal muscular contraction on electrical stimulation, was slightly increased on the protected side, as contrasted with the poisoned side, and this condition remained till reaction ceased. The muscle was subjected to the same test, but it was not found that the cessation of contraction upon the protected side (usually on the fourth day after poisoning) occurred any sooner than on the poisoned side. The figures in the table indicate the position of the secondary coil at which contraction occurred.

PEGGED frog of 24 grams.   Poisoned by ·00006 gram of aconitine.

22 hours.		46 hours.		70 hours.		74 hours.		88 hours.		100 hours.	
Protected.	Poisoned.	Protected.	Poisoned.	Protected.	Poisoned.	Protected.	Poisoned.	Protected.	Poisoned.	Protected.	Poisoned.
N. 14	11	13·5	8·5	3·5	2·5	0	0	11	9	0	0
M. 16	5·16	16	15·5	15	14	12	11·5				

No prolongation of irritability referable to a lasting excitation of muscle or motor nerve terminations is referable to aconitine, given in the amount specified.   Perfusion of aconitine up to ·002 gram yielded parallel results.

FROG of 28 grams.   Brain destroyed.   Left vessels ligatured.   Perfusion of aconitine in phosphatic salt solution through the systemic vessels under pressure. At the end of the circulation through the aorta of ·00324 gram aconitine, destruction of the cord occasioned well-marked movement of both legs.

1 hour.		25 hours.		48 hours.		71 hours.		95 hours.		106 hours.	
Ligatured.	Poisoned.	Ligatured.	Poisoned.	Ligatured.	Poisoned.	Ligatured.	Poisoned.	Ligatured.	Poisoned.	Ligatured.	Poisoned.
N. 28	26	14	0	8	0	0	0	5	3	2	0
M. 14	14·5	15	12·5	13	11·5	11	8				

These results are not uniform with MACKENZIE'S,* nor yet with RINGER and MURRELL's,† for these observers found a greater persistence of vitality (and of irritability) in the poisoned than the unpoisoned muscles, but after the smaller amounts of aconitine employed in these experiments, the irritability of the un-poisoned nerve was slightly greater than the poisoned, whilst that of the unpoisoned muscle was equal to, or slightly greater than that of its poisoned companion.

* 'Archiv f. pathol. Anat.,' vol. 79.
† Op. cit.

The Muscle Curve.

WIELAND* stated that aconitine produced marked prolongation of the muscle curve, relaxation of the muscle being much retarded; such an effect, in fact, as is associated with veratrine.

BUCHEIM and EISENMENGER† also spoke of a considerable variation from the normal condition.

These observations have not been supported by MURRAY,‡ nor by BÖHM with WARTMANN,§ who believe the curve to be unaffected by aconitine. It has been found that, whilst the curves produced by single and repeated stimulations of protected and poisoned companion muscles are usually, to all intents and purposes, identical, occasionally there is a deviation from the normal, attributable to aconitine.
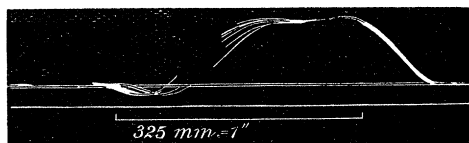
Fig. N_1.

Fig. N_2.

Fig. N illustrates the reaction of two muscles taken from a frog of 22·5 grams. This frog had been poisoned (after pegging, and ligature of the vessels to the left leg) by ·00019 gram aconitine. The heart ceased in 47 minutes after injection; the reflex from the left leg in 67 minutes. Though the reaction of the poisoned muscle to direct stimulation (fig. N_2) is slightly more energetic than that of the control (fig. N_1), there is no essential difference in the character of construction.

Exceptions to Equality of Curves.

Twice out of the series of experiments, which included eighteen observations, it has been noticed that every induction shock developed a fibrillation and twitching of the poisoned muscle, and, as a result of this, the curve was considerably lengthened, relaxation being retarded.

It might be considered that in such cases the muscle curve is essentially different from the normal, but it is rather to be regarded as a condition in which the true curve is masked for the time being by the hyperæsthetic state of the muscle nerve preparation.

* *Op. cit.*

† " Ueber den Einfluss einiger Gifte," &c.: ECKHARD'S ' Beiträge,' 1870.
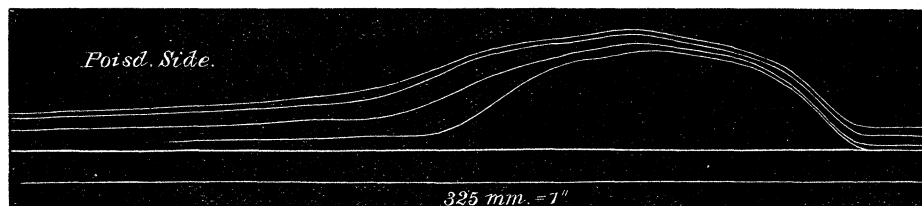
‡ *Op. cit.*

§ *Op. cit.*

Fig. O₁.

Fig. O₂.

Fig. O, 1 and 2. Pegged frog of $26\frac{1}{2}$ grams. Left leg vessels ligatured. Inject ·0001 gram aconitine. The heart ceased in 60 minutes. Contrasted stimulations of poisoned, O₂, and unpoisoned, O₁, muscles repeatedly stimulated by single opening induction shocks. The aconitised muscle shows fibrillary twitchings on receiving each stimulation. Axial weight 10 grams. Lever amplifies seven times. Direct stimulation.

	Greatest altitude of curve from abscissæ.	Length of curve (time).
	millims.	seconds.
Ligatured	7·5	0·12
Unligatured	16·5	0·167

It will be observed that repetition of contractions causes a rapid increase in length of curve of the poisoned muscle, as well as an imperfect return to the abscissæ in the rest interval.

Excepting this rare variation from the normal result, there is no toxignomonic curve associated with the contraction of the muscle of the aconitised frog, its character being in general in close correspondence with that of the unpoisoned muscle.

In the next section, attention will be drawn to other forms of curves which occasionally result from the immersion of the muscle in aconitine solution ; but these variations have never been witnessed as an element of the general toxic action of the drug.

Ability of the Muscle to perform Work.

Single induction stimulations were given at regular intervals, either by a metronome or by a revolving arm, which moved two mercurial keys in such a manner as to permit only opening shocks to pass to the muscle or nerve, or else a series of short faradic stimulations were admitted.

(a.) *Doses up to twice or thrice the lethal amount.*

Stimulation of Nerve.—Stimulation of the nerve on the poisoned side, when the secondary coil is approximated within the limit of maximal contraction, is found to produce a series of contractions equal to, or somewhat less powerful and sustained, than those produced by the muscle on the side of ligature.

The altitude of the tetanic contraction, under weights varying from 10 to 20 grams (axial), is slightly lower on the poisoned side, and there is greater tendency for partial relaxation to occur, though a clonic breaking down of the tetanus has not been observed.

Direct Stimulation.—The doses indicated above in no way limit muscular activity. The maximal contraction to an opening shock, or to a faradic current of longer or shorter duration, is as ample and as well-sustained as on the protected side ; in a small majority of experiments it is even slightly increased. This increase only amounts to 2 to 4 millims., even when the lever employed amplifies 11 times.

V. 3.   FROG of 27 grams.   Pegged.   Vessels to left leg securely ligatured ; ·000077 gram of aconitine was administered, and examination took place immediately after arrest of the ventricle.   Stimulation is (1) by a single induction shock, 24 times per minute, followed by short tetanising currents of ·25 second, delivered at the same rate.   Lever 11.   Weight, 10 grams, axial. Fig. P.

	Min. irritability.	Maximum contraction of induction shock.		Maximum contraction, tetanic.	
	centims.	millims.	centims.	millims.	centims.
Poisoned . . .	N. 23·5	27	(12)	53	(12)
	M. 13·5	32	(7)	60	(7)
Ligatured. . .	N. 32·5	25·5	(12)	58	(12)
	M. 11·5	32	(7)	60	(7)

The extensibility of the unpoisoned muscle is obviously greater than that of the poisoned.

(b.) *Overwhelming Doses* (i.e., *thirty to fifty times the lethal amount*).

The poisoned muscle, though contracting well at first, begins to fail in response to stimulation when the protected nerve muscle preparation is still active ; in other words, exhaustion is more readily induced. This remark applies more strongly to the muscle indirectly than to that directly stimulated.

Fig. P.
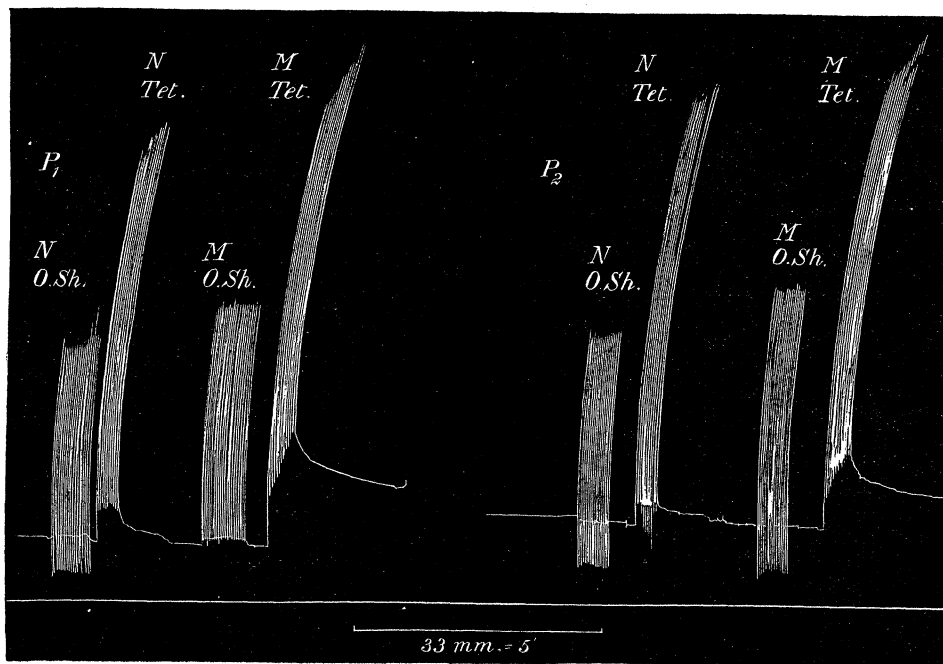
Immersion in Aconitine Solution.

In order to test the local action of very large quantities of aconitine, the plan of immersing nerve muscle preparations in dilute alkaloidal solutions was followed.

Employing the special air- and water-tight chamber described in the 'Phil. Trans.'* a normal nerve muscle preparation was subjected to the local action of measured amounts of aconitine, added to the solution employed in the perfusion of the separated heart, as this serves well to maintain the vitality of nervous tissue; to the control nerve muscle preparation placed in a second chamber, the perfusion solution alone was added. When the addition of ·0026 gram of aconitine is made, powerful movement of the muscle, accompanied by fibrillation, may at once result, or on the other hand, fibrillation may be absent till stimulation has been administered. The ultimate effect of this relatively strong aconitine solution in reducing irritability of muscular and nervous tissue is illustrated by the following experiment.

The muscle nerve preparations from frog of 29 grams were placed in muscle chambers with 40 cub. centims. of blood and phosphate solution. The figures relate to the minimal irritability of muscle and nerve :—

* B, Vol. 184.

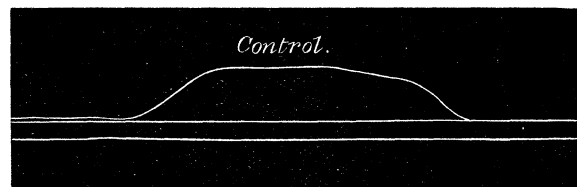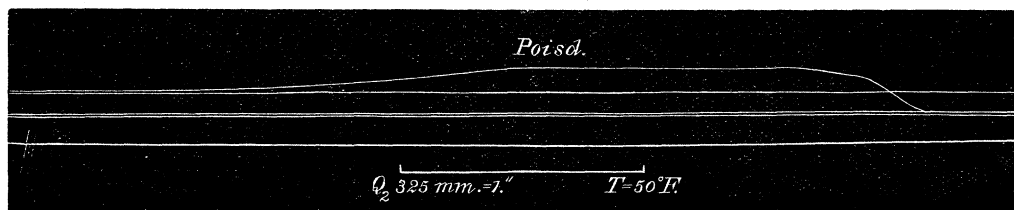| Time.	Left leg.	Right leg.	Remarks.
minutes.	millims.	millims.	
0	N. 32·5 M. 20·5	N. 33·5 M. 20	After repeating with like result, add ·0025 gram aconitine to the chamber holding the preparation from the *left leg*.
11	N. 32 M. 20	N. 32.5 M. 20	
20	..	..	It was noticed that the muscle in the left chamber relaxed very slowly after stimulation, and fibrillary twitchings were observed with the naked eye (fig. Q_2). Curve taken (fig. Q_1), of the right muscle.
46	N. 34 M. 21·3	N. 33 M. 20.5	
95	N. 34 M. 21		
132	N. 32 M. 21	N. 32 M. 19·5	
145	N. 31 M. 21	N. 32 M. 20·5	
175	N. 5 M. 18·5	N. 32 M. 20	
186	N. 3 M. 18	N. 32 M. 20·5	
200	N. 1 M. 18	N. 32·5 M. 20	
215	N. 0 M. 18	N. 32 M. 20·5	
275	N. 0 M. 16		
320	N. 0 M. 10	N. 32 M. 21	
420	N. 0 M. 8	N. 32·5 M. 21	The poisoned muscle now yields a very feeble contraction.
440	N. 0 M. 6·5	N. 32 M. 20·5	
hours. 10½	M. 0		
23	N. 0 M. 0	N. 30 M. 21	

Fig. Q_1.

Fig. Q_2.

The sudden fall of excitability of the nerve was succeeded by complete failure within 4 hours, and whilst the muscle resisted the action of aconitine longer, it will be seen that it finally succumbed within 10 hours of immersion.

The curve (Q_2) obtained from the poisoned muscle 20 minutes after immersion, shows that an effect not by any means unlike that of veratrine is producible by aconitine, but a comparatively strong solution is requisite for its causation. (Fig. Q_1 represents the control contraction.)

As has been already mentioned, fibrillation with arhythmic twitching of portions of the muscle, giving rise to a total shortening, may follow immersion spontaneously, or may be noticed first of all upon stimulating either the muscle or nerve. During fibrillation, which lasts with variation in intensity for from a few seconds to a minute, stimulation was almost, or entirely, inoperative in producing co-ordinate shortening of the muscle. Relaxation with regular response to stimulation ensued. Although contact of the solution was repeated after each group of contractions, the spasmodic condition was seldom witnessed more than twice in the course of an experiment, nor was it reproduced by immersing in a still stronger solution of aconitine.

Beyond this incoordinate movement, the prominent and progressive effect of aconitine in these experiments is to reduce the irritability and contractility of the muscle. This is seen more markedly after indirect than after direct stimulation.
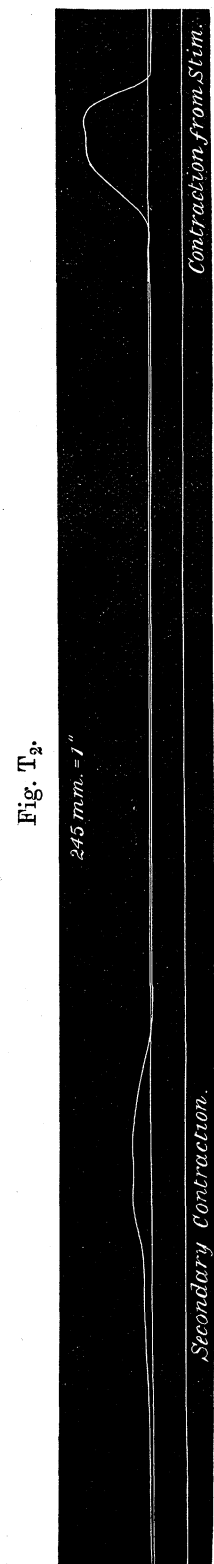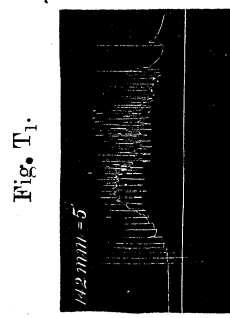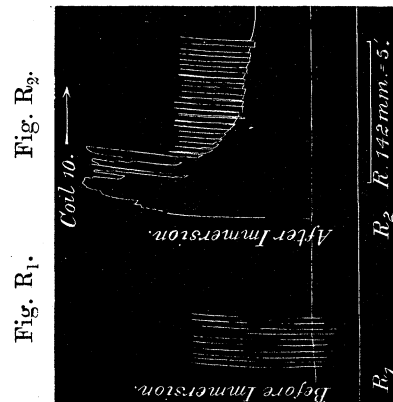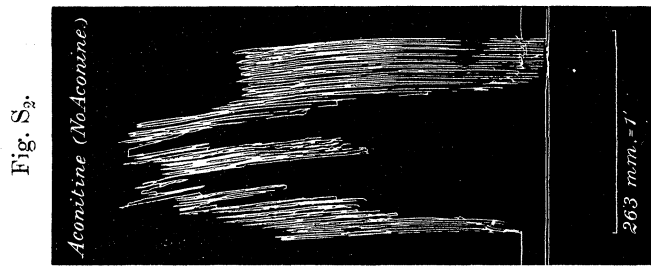
The following experiment will serve to demonstrate the points alluded to :—

GASTROCNEMIUS with sciatic of frog of 27 grams, placed in water-tight chamber, and stimulated directly and indirectly by opening induction shocks at the rate of 20 per minute. Lever 9 ; weight 10 grams axial. Fig. R.

Minutes.

(11.35)   0   Height of contraction from stimulation of N. = 25 millims. ; from M. = 25 millims. R.

(11.40)   0   Admit 40 cub. centims. perfusion solution containing ·0026 gram aconitine into the chamber.

4   Remove fluid, and stimulate the nerve as before. R_2. Fibrillation with great shortening and occasional relaxation occurs, but after 10 stimulations have been given, a more steady response is obtained, though contractions are followed by incomplete relaxations of the muscle.

17   Fibrillation quite absent. Contractions measure 20 millims.

35   The passive shortening of the muscle is gradually relaxing.

55   Contractions 18·5 millims. occur in regular series. Though the solution has been steadily applied, except when stimulation was in progress, there has not been any return of fibrillation. R_3.

Stimulation of the muscle as well as of the nerve causes the same phenomenon, a similar number of fibrillary spasms in each case being produced.

Fig. S₂.

Aconitine (No-Aconine.)

263 mm. = 1'

Fig. S₁.

Aconitine after Aconine.

Fig. R₃.

Coil 6.

Fig. R₂.

Fig. R₁.

Coil 10.

After Immersion.

Before Immersion.

R. 142 mm. = 5'.

R₂

R₁

Fig. T₁.

142 mm. = 5'

Fig. T₂.

245 mm. = 1"

Contraction from Stim.

Secondary Contraction.

Abolition of Fibrillation.

Fibrillation is not produced by aconitine if the frog from which the nerve muscle preparation is taken has been poisoned by curare, by benzaconine, or by aconine.

(These alkaloids do not materially interfere with the passive shortening which may develop in the muscle repeatedly stimulated after treatment with strong solution of aconitine.)

Experiment.—Brain destroyed of frog of 26 grams, and the vessels of the left leg securely ligatured.

Aconine ·032 gram was injected into the dorsal sac. Twenty minutes after reflex had disappeared from the left leg, the right leg giving active direct and cross reflex, two nerve muscle preparations were made from the legs. These were placed in the muscle chambers containing RINGER's perfusion solution with blood. After testing, the left nerve highly active, the right quite paralysed, a series of contractions of normal character were taken from the two muscles. The addition was now made of ·0025 gram aconitine to the fluid from each chamber, and the poisoned solution brought into contact with the muscle. The tracing, S, is taken from the sheltered gastrocnemius, and is the only example of fibrillation obtained during this experiment. This fibrillation was, however, very active, and lasted for nearly two minutes. Not a trace of fibrillation followed the application of aconitine solution to the aconitised muscle before abolition of irritability occurred in 150 minutes.

The picture of the non-aconised muscle when aconitine fibrillation has developed is, the difference in structure considered, suggestively like the churning incoordinate movement of the heart ; both are accompaniments of physiological impulse, and both may disappear, giving place to normal action for a time, and then recur. But curare does not prevent this cardiac incoordination, nor does aconine altogether, though it seems capable of reducing it.

There is one other, and that a rare effect of the local action of aconitine, to which it seems necessary to refer. It has only been seen twice in the course of over twenty immersion experiments, and takes the form of a secondary spontaneous contraction, occurring at an interval of ·5 second or more after relaxation of the aconitine muscle. A parallel effect* has been witnessed after veratrine, and an action not altogether dissimilar after lead.

The tracing will show the nature of this contraction (fig. T, 1 and 2). In the experiment from which it is taken the small secondary contraction alternated with the strong contraction succeeding stimulation. (T_1 shows contractions recorded slowly, T_2 the muscle curve.) This rare condition has never been seen as a result of the general toxic action of aconitine, but it is within the bounds of possibility that such an effect may be so produced.

The question of deviation of the muscle curve from the normal is largely one of the

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* BRUNTON and CASH, 'Journal of Physiology,' vol. 4.

amount of alkaloid locally present in the tissues, but this is not the sole factor, for it is evident that contraction, or muscular exercise up to a certain point, favours these departures, and it may therefore be that changes chemical or thermal produced by such activity may play a part in connection with the alkaloid.

ACTION OF ACONITINE ON OXIDATION BY VEGETABLE PROTOPLASM.

The method followed is that used by Dr. BRUNTON and one of us (C.) some years ago, when the depth of blue colour struck between guaiacum and potato protoplasm after the latter had stood in contact with certain alkaloidal bodies was taken as the gauge of increased or reduced oxidation produced by such bodies.*

It is now found that the admixture of ·00125 gram (or more) of aconitine with 5 cub. centims. of protoplasm for 10 minutes, causes a marked reduction in the oxidising power of the latter, but half this amount of alkaloid interferes but little with the reaction when contrasted with that of protoplasm alone.

It may here be stated, for brevity, that aconine (·01 gram) and diacetyl-aconitine (·005 gram) (especially the latter) both interfere with oxidation when subjected to the same test.   Benzaconine (·00645 gram) has a parallel effect.

Summary on Action of Aconitine on Respiration, Nervous and Muscular Systems.   With Lethal Dose.

Respiration.—Aconitine stimulates the respiration at first.   This is evidenced by an increase in number of flank movements, and a decrease in mimetic (hyoid) movements.   Discharges from the linked centres then occur at longer intervals, and greater variations in lung volume result than are witnessed in the normal frog.

It is conjectured that the suspended action of sensory nerves in the lung (analogous to that occurring in mammals) contributes to this effect.   The periods of entire quiescence lengthen whilst the movements become feeble and finally cease.   Faint hyoid (non-ventilating) movements outlast those of the side, and these are also the first to reappear as a stage in the re-establishment of respiration.

For a time during recovery, as well as in progressive poisoning, the hyoid centre is stimulated to action only during the active flank movements, but when the effect of aconitine is relaxing hyoid movements may proceed without intermission (the mimetic movements having reappeared) the flank centre still exhibiting a long interval rhythm.

The phenomena during recovery follow in an approximately inversed order to that attending development of aconitine effect.

Central and Peripheral Nervous System.—Stimulation of the medulla and of motor cerebral areas are early produced and are accompanied by powerful (but transitory)

* ' St. Bart's. Hosp. Reports,' vol. 18.

exaltation of sensory perception, at first indirect, and then, on absorption of aconitine, direct in character. Early motor symptoms may be marked by an inhibitory motor effect, which is specially developed by large doses of concentrated solutions. This may be seen immediately after injection as a result of sensory nerve stimulations. Motor centres in the cord are possibly stimulated at first, but reflex function is preserved excepting after very large doses at a time when peripheral sensory structures are strongly depressed.

Longitudinal conduction of motor impulses from the brain occurs after reflex manifestations have been much reduced, showing that these paths remain open, whilst very large doses poison every part of the nervous system. The experiments quoted show that motor nerves are relatively unaffected by smaller amounts.

Sensory nerve terminations are temporarily stimulated and then strongly depressed in function, whilst motor nerves are unaffected except by large doses. Skeletal muscle shows fibrillation after aconitine in relatively large amount has had access to it, but such a result is hindered by previous employment of bodies which depress motor nerve terminations (such as curare, aconine, &c.).

Skeletal Muscle.—Any change produced in the muscle curve is attributable to a form of fibrillation or an asynchronous contraction of muscle bundles which is especially developed in the muscle stimulated to contraction, and which has not been poisoned by aconine, curare, &c. There is no evidence of a lasting increase in irritability of nerve terminations or muscle fibre being produced by aconitine; the changes observed indicate rather an opposite tendency. The capacity for work is not affected by small and moderate doses.

Lethal Dose.—It is impossible to state a lethal dose for aconitine which is applicable to all times of year, the variations in toxicity as already observed by RINGER being considerable in seasons not widely separated. Thus, whilst in March non-spawning frogs, which had been in the tanks for a few weeks, succumbed with few exceptions to a proportion of ·000586 gram per kilo., vigorous summer frogs in July not infrequently recovered after doses having a smaller proportion than ·0014, and during a cold May recoveries were occasionally seen up to ·00135 per kilo. It will be seen from reference to the lethal dose obtained from observers using *R. esculenta*, that the resistance here appears to be much less towards aconitine. Even granting a high receptivity of *R. esculenta*, it is not a little surprising that observers have found the toxicity of aconitine to be practically equal per kilo. body weight of frog and rabbit respectively. From these experiments it may be stated in general terms that towards the unit of weight of a summer frog, aconitine has only one-tenth ($\frac{1}{10}$) of the toxicity that it has towards the unit of the tissues of the rabbit.

ACONITINE.—ILLUSTRATIONS.

Fig. A₁. Record of carotid pulse (FICK) above, and of respiration (rise in inspiration) below, taken before poisoning.

Fig. A₂. As above, taken 51 minutes after a small and 11 minutes after a lethal dose of aconitine.

Fig A₂'. Shows pressure on slowly-moving surface when change occurs in rhythm and fluctuation of pressure commences.   (A₂ is taken at *.)

Fig. A₃. 22 minutes after lethal injection.

Fig. A₄. 24 minutes after lethal injection.   Falling pressure, with great irregularity.

Fig. B₁. Tracing from unpoisoned exposed heart.   Left ventricle (top line).   Left auricle (second line).   Carotid pulse (third line).   Right auricle (fourth line).   All levers move up in systole.

Fig. B₂. After aconitine.   Left ventricle and pulse 180, the two auricles 162 per minute.

Fig. C₁. Left auricle (top line).   Left ventricle (second line).   Pulse (third line).   Before aconitine.

Fig. C₂. Section of left vagus and rise of blood pressure.

Fig. C₃. After irregularity has developed.

Fig. D₁. Left auricle (top line).   Left ventricle (external) (second line).   Intra-ventricular pressure (third line).   Taken before injection.

Fig. D₂. 35 minutes after aconitine—lethal dose.

Fig. D₃. 50 minutes after aconitine.   Rhythm of auricle and ventricle differs.

Fig. E₁. Left auricle (top line).   Carotid pulse (second line).   Left ventricle (third line).   Before poisoning.

Fig. E₂. After aconitine.   Auricle beating one to two of ventricle.

Fig. E₃. Still later, great fluctuation in pressure and changes of pulse.

Fig. E₄. Final fall of pressure.   Death.

Fig. F₁. Left auricle (top line).   Left ventricle (second line).   Carotid pulse (third line).   Stimulation of left vagus (the right is already cut).   After aconitine.

Fig. F₂. After atropine.   Heart steadied.   Vagus paralysed.

Fig. G. Left auricle (top line).   Pulse (second line).   Left ventricle (third line).   Incoordination of heart (auricle and ventricle) from vagus stimulation, with recovery.   No poison administered.

Fig. H₁. Pulse before aconitine.

Fig. H_2. Pulse 69 minutes after aconitine.   Strong aconitine action.

Fig. H_3. 6 minutes after injection of atropine.

Fig. H_4. 65 minutes after atropine.   Pressure rising.

Fig. H_5. Great acceleration and irregularity after repeated large doses of aconitine.

Tracing taken with float cardiograph of movements of frog's ventricle *in situ*.

Fig. I_1. Before aconitine.

Fig. I_2. 4 minutes after injecting ·00004 gram aconitine into dorsal sac.

Fig. I_3. 7 minutes after injection.

Fig. I_4. 10 minutes after injection.

Fig. I_5. 14 minutes after injection.

Fig. I_6. 16 minutes after injection.

Fig. I_7. 40 minutes after injection.

Fig. I_8. 48 minutes after injection.

Fig. J. All ventricle on KRONECKER's perfusion cannula.   Tracing taken after perfusion with RINGER's solution and dried blood.

Fig. J_1. 2 minutes after circulating ·000026 gram aconitine.

Fig. N_1. Muscle curve (repeated stimulation by opening induction shock) of gastrocnemius which had been protected by ligature.

Fig. N_2. Muscle curve taken from gastrocnemius on side open to aconitine.
Lever, X 5.   Weight, 10 grams axial.

Fig. O_1. Unpoisoned.

Fig. O_2. Poisoned muscle.
The frog had received ·0001 gram aconitine.
Lever and weight as in N.

Fig. P_1. Series of contractions to opening induction shock and then to faradic current (1) of nerve, (2) of muscle, of ligatured side.

Fig. P_2. Series of contractions to opening induction shock and then to faradic current (1) of nerve, (2) of muscle, of unligatured side.
The frog had received ·000077 gram aconitine.
Lever, X 11.   Weight, 10 grams axial.

Fig. Q_1. Curve of gastrocnemius immersed in normal solution.

Fig. Q_2. Curve of gastrocnemius immersed in normal solution, after addition for 20 minutes of ·00026 gram aconitine.
Lever, X 5.   Weight, 10 grams axial.

Fig. R. Single induction shocks applied to muscle.

Fig. R_1. Before ⎫
Fig. R_2. After ⎬ soaking in aconitine solution.

Fig. R_3. 55 minutes after first application of aconitine.
Lever, X 5·5.   Weight, 10 grams axial.

Fig. S₁. Aconinised muscle exposed to aconitine.
Fig. S₂. Non-aconinised companion muscle exposed to aconitine.
    Single induction shocks.
    Lever, X 9.   Weight, 10 grams axial.

Fig. T₁. Contraction of muscle soaked in aconitine solution and stimulated by a series of opening induction shocks.
Fig. T₂. One of these contractions showing secondary twitch recorded on rapidly-moving surface.
    Lever, X 5.   Weight 7 grams axial.

Respiration of Frog.

Fig. K. Coincidence of respiratory movement of hyoid and side with changes of intrabuccal pressure.
    Top line—The curve rises as pressure increases in buccal cavity.
    Mid line—Side movement.   Distension of side (inspiration), curve falls.
    Lowest line—Hyoid movement.   Hyoid protruded, the curve rises.
        The references a, b, c, are explained in the text.

Normal Respiration of Frog.

Fig. L₁. Upper line, side—Curve falls as side passes towards inspiratory position (distension).
    Lower line, hyoid—Protrusion of hyoid is represented by rise of curve.
Fig. L₂. 3 minutes after injection of ·000039 gram aconitine.
Fig. L₃. 9 minutes after injection.
Fig. L₄. 19 minutes after injection.
Fig. L₅. 7-11 hours after injection.   Tracing on cylinder moving very slowly— 1 hour = 12 millims.
Fig. L₆. 26 hours after injection.   Reviving respiration recorded on medium cylinder.
Fig. L₇. 27½ hours after injection.   Shows a further phase in process of recovery.

Fig. M₁. Registration as above.
    Feeble waves of respiration 42 hours after ·000032 gram aconitine.
Fig. M₂. Returning respiration 67 hours after injection.   Long pauses during inflation of lung.
Fig. M₃. 80 hours after injection.

Diagram A. Action of aconitine on temperature (upper group of curves) and on respiration (lower group of curves) of rabbits.   The amount of aconitine administered is calculated per kilo. of body weight.

Diagram B. Action of equally proportionate doses of aconitine on two rabbits

(temperature above, inspiration below), one kept at a temperature of 17°C., the other at 11·75°C.

Photograph of double levers for registering respiratory movements of hyoid and flank of frogs.

Diagram C. Projection of time of reflex withdrawal of feet (vessels on left side ligatured ; on right, free) of brainless frog poisoned with aconitine.

SECTION II.—DIACETYL-ACONITINE.

Solutions of the hydrobromide of the strength of ·05 and ·005 gram per cub. centim. were prepared from time to time for examination.

When tasted, solutions occasion an impression of bitterness, this being succeeded by tingling and slight numbness, especially of the tongue, lips, and velum, rapidly developing and persistent in character.

ACTION UPON CIRCULATION AND RESPIRATION OF WARM-BLOODED ANIMALS.

CATS.

The main effects during the development of action of diacetyl-aconitine are—a steady fall of blood pressure, progressing with less marked interruption than is seen after aconitine, though 40 to 50 minutes after injection large waves—non-respiratory in character—appear, and for a time mark the decline of pressure. The pulse after small doses shows an initial stage of slowing (which may amount to as much as 30 per cent. of the total), but this effect is of short duration, and may scarcely be seen if the dose has been large. Acceleration with declining strength of auricular and ventricular systoles is a constant phenomenon, and this may progress, with a corresponding fall of pressure, until death takes place. An aconitine-like effect may, however, develop in advanced poisoning, a dislocation in the sequence of ventricular upon auricular action making its appearance, the ventricle usually becoming the more rapid of the two. When sequence is much disturbed, the lethal effect is hastened by the fall of blood pressure. Immediately before death, however, a reversion of the normal rhythm may be observed. (This aconitine-like action has been witnessed in exactly one-half of the experiments performed with diacetyl-aconitine, but it is neither so persistent nor so extensive in its variations as when due to the parent alkaloid.)

Action on the Vagus.

The initial slowing may be reduced by double vagotomy, but when the stage of acceleration has developed, this proceeding has little, or an entirely negative, result. The peripheral vagus is capable—the strength of stimulation being increased—of

producing slight slowing throughout, if incoordination is not developed.   In the latter eventuality, reaction varies as it does under aconitine, and apparently for the same reasons.

Fig. 2.
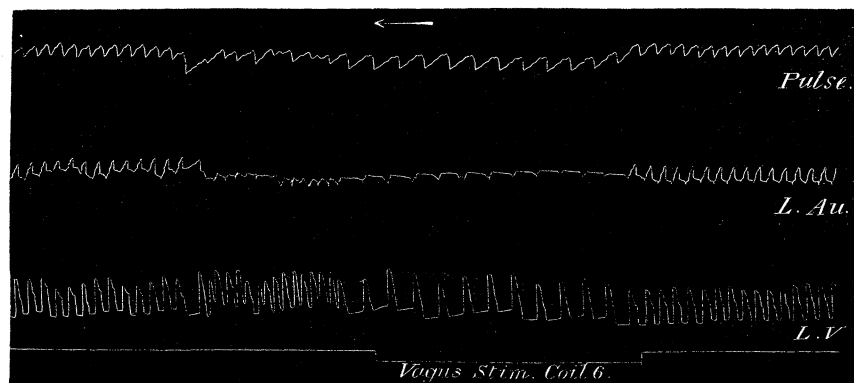
It has been twice noted in cases of poisoning which had not previously shown incoordination that this condition supervened on vagus stimulation, or immediately after stimulation had ceased, the pulse becoming very irregular.   In one of the two cases (fig. 2) an incoordination of the chamber walls was developed in this manner and persisted to the lethal termination.

Vaso-motor Apparatus.

The vaso-motor centre is not put out of action by diacetyl-aconitine, excepting when the heart becomes incoordinate.   Stimulation of the central sciatic after division of the vagi, and suspension of artificial respiration (1, b), cause some rise in pressure, and at the periphery the same result is obtained by stimulating the splanchnics.   If the ventricle has lost its proper sequence, little effect follows such stimulations, probably in part because it is masked by the disadvantageous conditions under which the heart is working.

Respiration, which may be transitorily accelerated, is soon markedly depressed, the last evidence of activity usually disappearing some minutes before the final fall of blood pressure.   When respiration becomes so imperfect as to threaten the life of the animal, the employment of vigorous artificial respiration not only tides over the danger, but causes the appearance of stronger respiratory movements and an improvement in the general blood pressure.   Section of the vagi when the respiration has become much slowed is negative in result.   It is evident that the heart not only suffers primarily from the action of the drug, but secondarily from imperfect oxidation of the blood.   Experiments in which, the thorax being unopened, respiration proceeds spontaneously, show respiratory failure to be the primary cause of death.   Artificial respiration, especially when oxygen is used instead of atmospheric air, reanimates the centre and raises the blood pressure for a time.
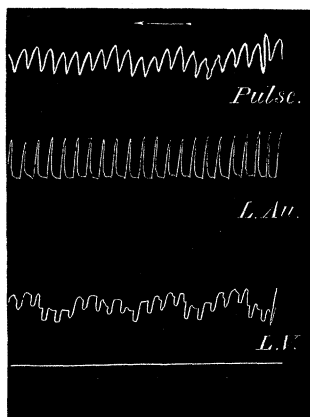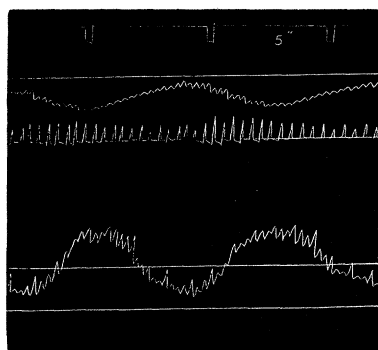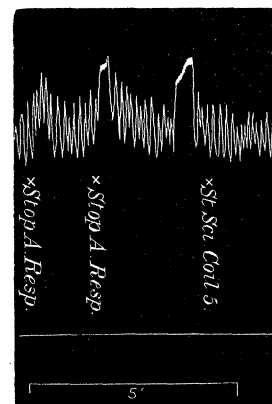
Fig. 1, *a*.

Fig. 1, *b*.

Fig. 1′, *b*.

(For descriptions of these tracings and later, see p. 329.)

EXPERIMENT. Cat of 2910 grams. Etherised. Placed in warm box. Left vagus, left sciatic, and left splanchnic nerves divided and on electrodes. Left auricle (mid line) and left ventricle (lowest line) connected with tambours by threads (the upstroke indicating systole). Cannulas in carotid artery (top line) and trachea. Artificial respiration.

Time.	Blood pressure.	Pulse.	Notes.
Minutes.			
0	105	112–60	Vagus stimulation slows heart to 60 (fig. 1, *a*).
0	..	..	Injected ·01 gram diacetyl-aconitine.
7	98	118	
15	87	128	
17	..	118	
49	92	110	Pressure declining steadily.
61	74	100	
71	74–53	114–72	Stimulation of vagus causes fall of pressure.
84	51	129	Section of right (remaining) vagus.
87	51	133	Acceleration does not raise pressure.
99	53	..	Inject ·005 diacetyl-aconitine.
108	50	134	Sciatic stimulation causes rise of 8 millims. and splanchnic stimulation of 10 millims.
117	..	..	Stopping artificial respiration raises pressure by 16 millims. (fig. 1′, *b*).
121	45	132–120	Large respiratory waves. Vagus (Coil 4) slows heart to 120.
151	40	..	
159	40	{ Auricle . . . 149 Ventricle . . 222 Carotid pulse . 222 }	Auricle and ventricle incoordinate (fig. 1, *b*). Last respiratory movements.
162	32	{ Auricle . . . 135 Ventricle . . 192 }	Pulse not registrable.
167	..	..	Dead.

Lethal Dose (Cats).

Only an approximate estimation can be made, the experiments having had reference to blood pressure and pulse, and necessitating the use of an anæsthetic.

A dose of ·00515 gram per kilo. proved lethal 68 minutes after the second and larger portion had been administered. A dose of ·004 per kilo. is sub-lethal, the blood pressure rising and the respiration accelerating within 3 hours of its injection.

DIACETYL-ACONITINE ON RABBITS.

After injection of a large sublethal dose, there is produced early, though not extensive, salivation, weakness of the limbs, ataxia, with occasional starting and retching or hiccough-like movements. Slowing of the respiration is constantly present, and is coincident with the paresis of the limbs. Very pronounced dyspnœa is seldom produced by sub-lethal doses. The fall of temperature, which commences about twenty minutes after injection, reaches its greatest extent an hour later, and thereafter slowly returns to the normal. After a large sub-lethal dose (·004 gram per kilo.) the temperature remains subnormal for four or five hours. The weakness and ataxia disappear before the temperature regains the normal, respiration meanwhile accelerating.

Lethal Dose.—There is early salivation. Paresis commences in the hind limbs and extends forwards. The temperature falls rapidly. The respiration declines to five or six efforts per minute; before death it usually accelerates and becomes dyspnœal and spasmodic in character, long pauses occurring between the individual acts. The pupil dilates and is insensitive some minutes before death, but intermittent insensibility may occur, as after aconitine.

Post-mortem.—Blood-stained œdematous fluid is present in bronchi, trachea, and mouth. The lungs show patches of ecchymosis on surface. The heart is dilated and filled with dark blood; it is slightly sensitive to stimulation.

Faradisation of motor nerves appears to be followed by diminished response.

The *lethal dose* of diacetyl-aconitine towards rabbits is in the proportion of ·0042 gram per kilo. body weight.

Experiment—Sub-lethal Dose.—A large sub-lethal dose of ·004 gram per kilo. produced (in brief) (Diagram 1).

Minutes.

15 Salivation.

25 Weakness of limbs, head tends to sink. Slowed respiration with occasional hiccough-like movement. Fall of temperature.

40 Movements uncertain and ataxic. Tendency to roll over on side.

80 Greatest reduction of temperature and slowing of respiration.

Later. Although recovery commenced at this time, in 120 minutes there was still

some ataxia, and in 240 minutes a trace of this was still recognisable. Temperatures and respiration were still slightly subnormal.
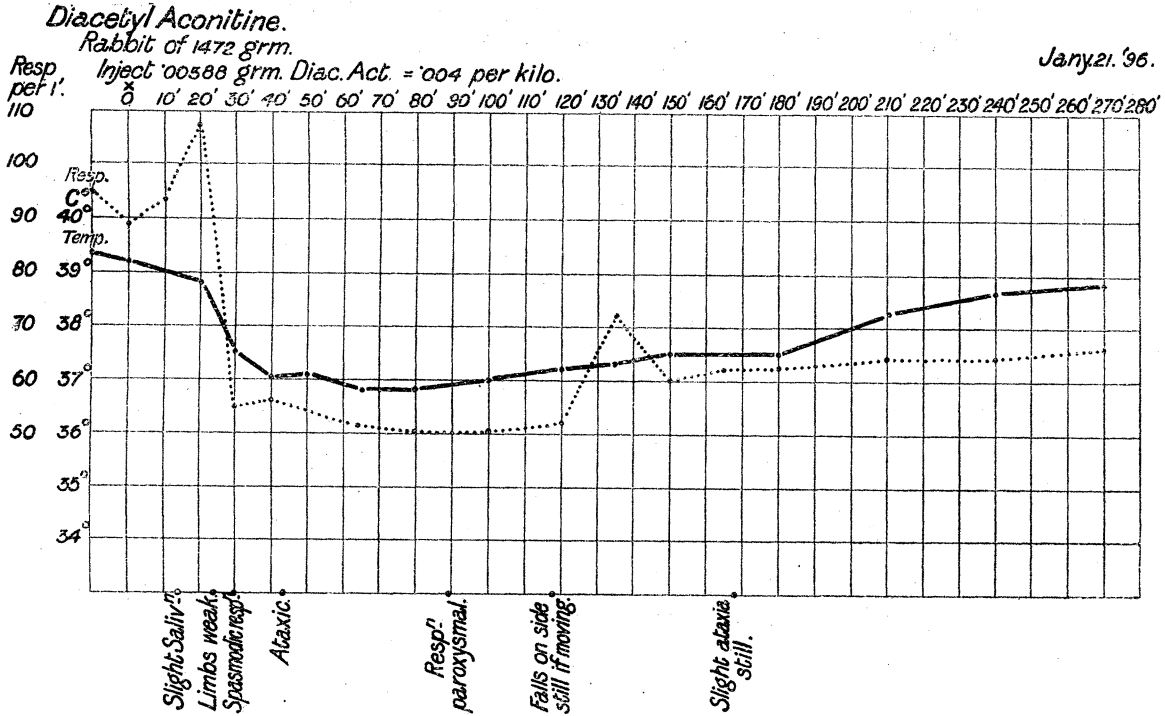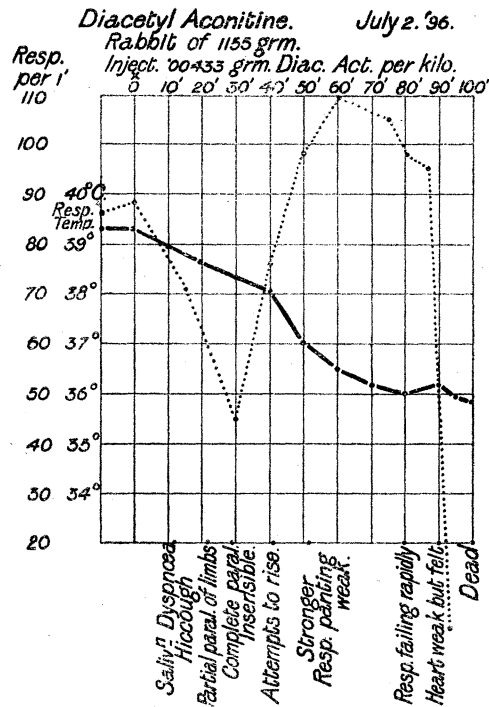
Diagram 1.

Diagram 2.

2 s 2

Lethal Dose.

A large animal received the alkaloidal salt in a dose proportionate to ·004329 gram per kilo. (Diagram 2.) The rectal temperature was 39·3° C., and the respirations about 110 before injection. Temperature in box, 19° C.

Minutes.

13	Salivation. Dyspnœa, with an occasional hiccough-like movement.
18	Great slowing of respiration, gasping, long expiratory pauses. Heart's action good. Head tends to sink. Weakness of all limbs.
25	Dyspnœa marked. Much paresis. Pupil dilated and for a minute corneal reflex lost.
30	Corneal reflex. Attempted movement.
40	Breathing now accelerating. Temperature 38·2° C.
50	Makes an occasional attempt to rise, but cannot. Temperature 37° C. This condition with slight variations persisted to
70	Breathing greatly accelerated. Head thrown back.
80	Temperature 36° C.
90	Respiration greatly slowed and increasingly feeble. Insensible.
96	Respiration very faint and occasional. Heart impulse feeble.
100	Dead.

Post-mortem.—Blood-stained œdematous fluid at mouth and filling trachea. Lungs engorged and several large patches of ecchymosis seen towards base. Heart auricles pulsate occasionally. Left ventricle responds by feeble movement to induction shock. Movement of leg on stimulating sciatic nerve is subnormal.

Note.—The condition of ecchymosis beneath the pleura was recognised in each of the cases in which this alkaloid was lethal to rabbits. It was not present in animals which had been artificially respired.

Temperature of Rabbits.

It will be noted that there is a considerable reduction of body temperature by diacetyl-aconitine in these experiments, and even after smaller doses some fall is apparent.

In the following table the first two results are from the experiments just recorded.

(1.) A dose per kilo. of ·004329 gram caused a fall of 3·3° C. in 90 minutes.
(2.)   „   „   ·004   „   „   „   2·7   „   80   „
(3.)   „   „   ·00277 „   „   „   1·3   „   80   „
(4.)   „   „   ·00184 „   „   „   0·5   „   95   „

Reduced oxidation from the changes produced in circulation and respiration are

the most evident causes of this fall, but depressed muscular activity must be contributory to some extent.   Enveloping the body in wool may reduce the fall of rectal temperature by ·2° to ·3° C.

DIACETYL-ACONITINE ON GUINEA-PIGS.

A dose of diacetyl-aconitine proportionate to ·00417 gram per kilo. was lethal in 70 minutes.   The chief symptoms were chewing, with (occasionally) salivation, weakness of limbs (especially of fore), passing into complete paralysis, the animal being quite limp when taken up.   Respiration slowed, and becoming laboured and dyspnœal, slight spasm before death.   Pupil incompletely sensitive at times, or actually insensitive.

. A *sub-lethal* dose of ·00215 gram per kilo. caused some paresis of limbs in 50 minutes, occasional chewing movement, but no salivation, acceleration at first of the respiration, with little, if any, slowing.

RÉSUMÉ OF RESULTS OF EXPERIMENTS ON WARM-BLOODED ANIMALS.

General Symptoms.—The symptoms occasioned in warm-blooded animals bear a general resemblance to those of aconitine, the much lower toxic properties of diacetyl-aconitine being held in view.   Salivation is distinctly less after the latter, whilst the spasmodic movements of aconitine (hiccough, retching, and starting) are less prominent.   The development of motor paralysis in the limbs and neck is, however, more marked, whilst recovery from the toxic action is relatively slower than after aconitine.   The spinal cord, motor nerves, and probably also the muscular tissue, are more affected by a proportionate dose of this derivative than by the parent alkaloid.

Circulation.—A more uniform and gradual weakening of the heart action is occasioned by diacetyl-aconitine, and death may occur without a marked asequence of ventricular upon auricular action, one of the most constant of aconitine effects. On the other hand, asequence is produced, though in a less accentuated form, in about 50 per cent. of experiments made.   The vagus endings in the heart are not invariably completely put out of action, though the restraining power upon rhythm is materially reduced.   Vagus stimulation has occasionally a tendency to cause a tumultuous and incoordinative action of auricles and ventricles, in which the former seem to be first involved.

Respiration.—Breathing is promptly affected by diacetyl-aconitine, slight acceleration in rhythm being succeeded after lethal doses by a rapidly developing slowing with dyspnœa.   When this phase is fully developed vagotomy does not increase the slowing, as the pulmonary vagi are out of action.   Respiratory movements become feeble before death ; the speed may gradually and steadily decline or there

may be a transitory acceleration before the final arrest. There is no dyspnœal spasm when respiration fails. Although slight stimulation occurs at first, the respiratory centre is powerfully depressed subsequently. Whilst the phrenic and other nerves innervating respiratory muscles are excitable to electrical stimulation at death, it appears that reaction is to some extent reduced, so that a peripheral failure may accompany the central.

Nervous System.—A temporary and intermittent loss of consciousness, with dilated pupil and failure of conjunctival reflex, may be witnessed occasionally, not only after lethal, but after large sublethal doses. Such a state arising, as it does, after respiratory embarrassment, and being frequently relieved by artificial respiration, is probably mainly due to insufficient oxidation of the higher centres. Depression of the medulla is preceded by less stimulation than is associated with the action of aconitine. After transitory excitement of the cord the reflexes are weakened, though peripheral depression of nervous elements, especially sensory, makes it difficult to say how far the effect is central. The failure of attempted movement is suggestive of possible impairment of longitudinal conduction, but the same difficulty in discriminating exists here also.

Sensory nerve terminations are depressed in action, whilst motor nerves after large doses are probably involved to a slighter extent. The cardiac terminations of the vagi are reduced in activity whilst vaso-constrictor nerves are almost unaffected.

Temperature.—The fall of temperature which follows diacetyl-aconitine bears relationship to the dose, amounting to nearly 3° C. after large but sub-lethal quantities. This fall is but slightly reduced by enveloping the body in cotton wool, and it appears, therefore, to be due less to loss of heat than to reduction in oxidation.

Oxidation.—It has been already stated that diacetyl-aconitine interferes with protoplasmic oxidation.

Lethal Dose.—For cats this is below ·00515 per kilo., but above ·004. For rabbits it is ·0042 per kilo., and this proportion is also lethal to guinea-pigs.

DIACETYL-ACONITINE ON FROGS.

The *lethal dose* for frogs (*R. temporaria*) calculated for the kilo. body weight is ·039 gram.

General symptoms of *lethal* dose. After injection there is slight excitement with transitory hyperæsthesia. Body movements are at times somewhat spasmodic in character. Gaping usually present. If the vessels to one limb are ligatured previously, reflex is found to persist longer in it than in the poisoned or open limb. A short series of feeble tetanic spasms, occurring some hours after injection, usually terminates reflex manifestations.

A *sub-lethal dose* occasions some excitement at first, followed by lethargy and ultimately by inability to get off back into ventral position. Reflex is impaired or abolished. The breathing is slowed and may be suspended. The heart, after at first accelerating, beats slowly, and for a time with decreased force.

Experiment.—The vessels of the left leg of an etherised frog of 20 grams were ligatured ; on recovery :—

Minutes.

0   Injected into dorsal sac ·001 gram of diacetyl-aconitine.

10   Increase of movement and respiration—a little hyperæsthesia.

15   Movement moderate. No frothing.

20   Quiet, position low. Lethargic. If roused, crawls rather than hops. Heart impulse moderate. Respiration failing.

25   Cannot get off back. Gaping. Side collapsed, feeble hyoid movement, none of flank. A slight occasional movement chiefly on side of ligature. Reflex very uncertain.

35   Faint reflex mainly on ligatured side. Highly lethargic. No movement attempted. No respiratory movement.

40   Some fibrillation seen in leg muscle on open side.

51   Went into a weak imperfect tetanus which was twice repeated, all reflex disappearing thereafter.

Post-mortem.—Heart in diastole, full of dark blood. No blood sacs in ventricular wall.

Duration of Effect.—A barely lethal dose may prove fatal only in 24 hours, when feeble spasms appear and the heart gradually fails. If the dose is sub-lethal recovery is generally complete—except for slight residual motor weakness—within 36 hours.

Action on Frog's Heart.

Heart poisoned (1) *in situ*, and (2) by perfusion of the organ.

(1.) Large doses of diacetyl-aconitine arrest the heart in diastole, whilst smaller amounts permit of its continued action after respiration and reflex have quite disappeared. There is frequently omission of every second ventricular systole, the sequence being normal after the alternate auricular beat. The tendency to sacking within the ventricular substance (so characteristic of aconitine) is but rarely seen after this derivative, but an incoordinate vermicular movement, especially in the neighbourhood of the base, is frequent. The heart is at first accelerated and then slowed.

Experiment.—The heart was exposed in a pegged frog of 18·5 grams, and after several observations had been taken at intervals, was found to be beating at 32–33 per minute.

0 minute. Injected into dorsal sac ·001 gram of diacetyl-aconitine.

5 minutes, 33·5 beats ; 10 minutes, 38·5 beats ; 20 minutes, 35 beats ;

37 „ 20 „ 45 „ 20 „ 60 „ 18 „

75 „ 16 „ 90 „ 14 „

    (At 75 minutes and 90 minutes the auricle was beating twice the speed of the ventricle.)

151 minutes. Heart stopped. Could not be roused to a systole by stimulation, but a feeble wave passed over the basal portion of the ventricle. Atropine—locally applied—did not cause any recovery.

(2.) Perfusion of the excised organ (tied on the cannula at the auriculo-ventricular groove) with dilute solutions of diacetyl-aconitine, at first increases excitability, favouring spontaneous beating, when this has not been aroused by simple nutrient solution and especially promotes " group beating." Such groups show some variations amongst themselves, but the tendency to incomplete diastole always becomes more marked as the individual group develops. The retardation in the diastolic phase outlasts this stage of motor excitement and reaction to stimulation is reduced during its occurrence to the phase of full relaxation. The heart is " refractory " during all other times. A condition of distinct irregularity is induced on further circulation, marked by some imperfect systoles, recalling somewhat the condition of the mammalian heart. This may yield to a rapid vermicular movement, often proceeding from two foci in alternation, at the base of the ventricle, or an occasional more coordinate, but incomplete, systole with very retarded diastole may ensue. The excitability of the myocardium to electrical stimulation is greatly reduced. At this stage the heart may be slowly recovered by circulating RINGER's solution with blood, both aconine and atropine apparently promoting the restoration of a more general systole. If the circulation of diacetyl-aconitine is carried further, there is an arrest of the organ, from which revival has not been obtained by circulating with digitalin, atropine, or ammonia. The myocardium appears to be permanently injured. (If only the apical half or two-thirds of the ventricle is perfused, some acceleration results on adding diacetyl-aconitine to the circulating fluid and there is diastolic retardation, but group beating and incoordinate movement have not been observed.)

The characteristic group beating indicates a preliminary excitement of motor elements uncontrolled except by the occasional supervention of fatigue. The rapid return of the circulating solution from the tube of the manometer to the heart, is itself a stimulant to the ventricle to contract again, and this probably explains why the heart poisoned *in situ* rarely exhibits this phenomenon to a marked extent. The retarded diastole, or it may be prolongation of a partial phase of systole, occurs under all conditions of examination. Sometimes it is suggestive of a second or induced systole of a part of the ventricular wall, resulting from the first contraction, and the refractory condition of the ventricle at this time is not inconsistent with this

explanation.   Incoordination which frequently succeeds, is probably of a closely related nature, diastole and systole proceeding simultaneously, in the different fibres of the myocardium.   If the incoordinating ventricle is steadily stimulated at intervals, it occasionally happens that a coordinate systole is elicited which persists for a time.   It is interesting to note that diacetyl-aconitine is less toxic towards the myocardium than towards skeletal muscle, the heart continuing to beat spontaneously in a manner, when the merest twitch may be all the response of which the stimulated gastrocnemius is capable.
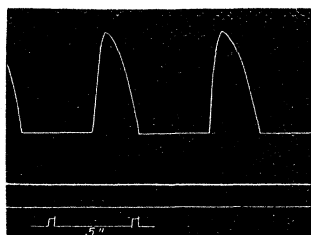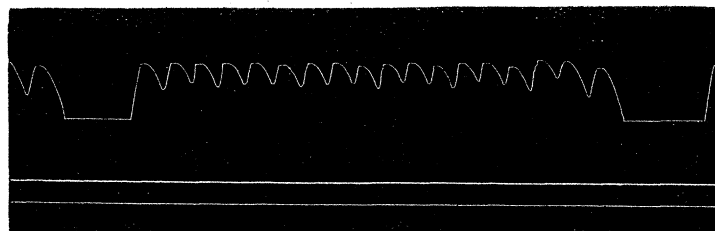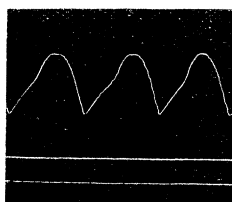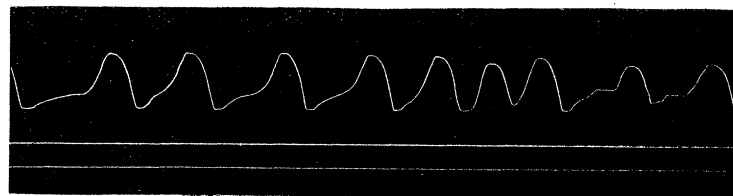
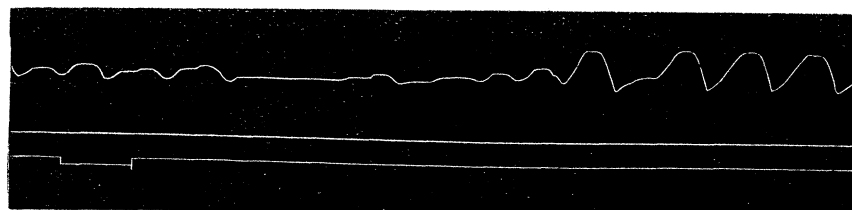Fig. 3a.

Fig. 3b.

Fig. 3c.

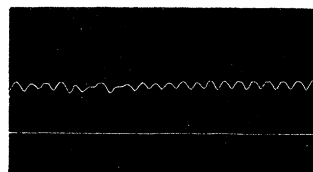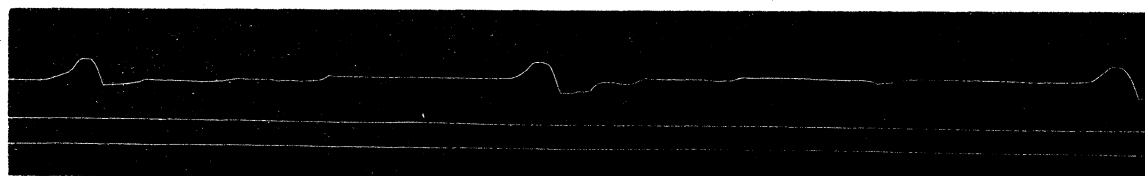Fig. 3d.

Fig. 3e.

Fig. 3f.

Fig. 3g.

Experiment.—Heart of 28 gram frog on cannula, ligatured at auriculo-ventricular groove. Circulated RINGER's solution with blood, 10 cub. centims. Occasional spontaneous beats occur, but most of those recorded originate in stimulation. (Fig. 3$_a$.)

Minutes.

22   During last 22 minutes ·0001 gram diacetyl-aconitine circulated. This condition lasted for 20 minutes. (Fig. 3$_b$.)

38   After circulation of ·000175 gram in all. (Fig. 3$_c$.)

113   ·0004 gram has now been circulated. (Fig. 3$_d$.)

120   ·00068 gram   ,,   ,,   ,.   (Fig. 3$_e$.)

125   ·001 gram   ,,   ,,   ,,   (Fig. 3$_f$.)

151   ·0015 gram circulated. Diastole is very imperfect, and systole only partial. (Fig. 3$_g$.)

The heart recovered gradually on circulating 40 cub. centims. of normal perfusion fluid in 40 minutes; but a tendency to group beating and to imperfect dilatation was still recognisable.

Vagus and Venous Sinus Stimulation after Diacetyl-Aconitine.

Ample proof has been obtained of the fact that in lethal doses which do not act too rapidly, a decline, and ultimately, a complete suspension in vagus activity, may be induced by this derivative. The sinus also yields, but at a later stage than the vagus termination within the heart.

The general results of stimulation of these structures are so similar to these produced by aconitine that reference may be made to the section dealing with this body.

Atropine.—Has some effect in accelerating the slowed heart, and in restoring contraction of the heart arrested by diacetyl-aconitine. Thus, in one experiment, after arrest of the organ by ·0025 gram, local stimulation produced only a lasting tache upon the ventricle, but within six minutes of the local application of a minim of a ·5 per cent. solution of sulphate of atropine the venous sinus and then the auricles began to beat, and finally the ventricle joined in due sequence. The contraction, however, remained feeble.

Action on Frog's Respiration.

There is at first slight acceleration of respiratory movements both of hyoid and flank after diacetyl-aconitine. This gives place to extensive side fluctuations, the period of maximal inflation being associated with slowing of the hyoid movements, or with the occurrence of false or mimetic movements. Finally, all movement of the flank disappears, that of the hyoid becoming faint and grouped; but even after it also has disappeared as a spontaneous manifestation, a slight nip of the skin may provoke

a short series of movements. After a large dose respiration may remain in abeyance for 12–16 hours or longer. This pause is broken finally by hyoid movement, and the phenomena make their appearance in reversed order until normal respiration is re-established.

Fig. 4$_a$.
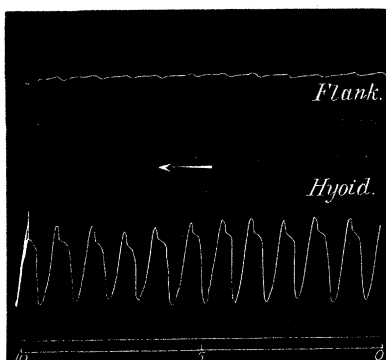
Fig. 4$_c$.
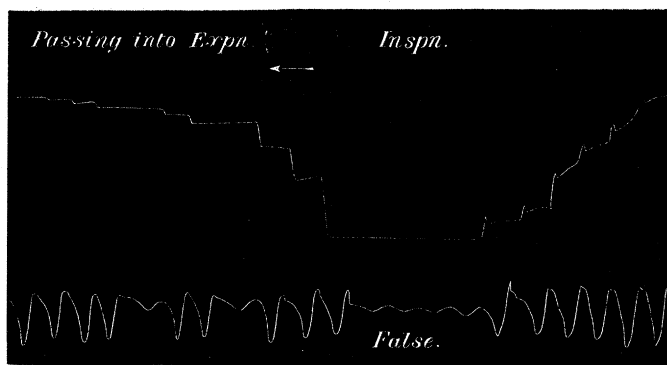
Fig. 4$_b$.
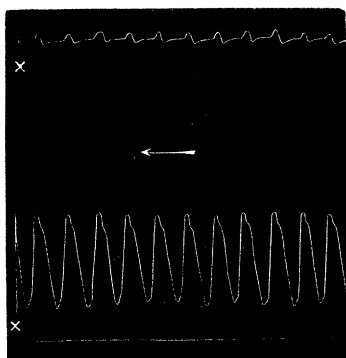
Fig. 4$_d$.
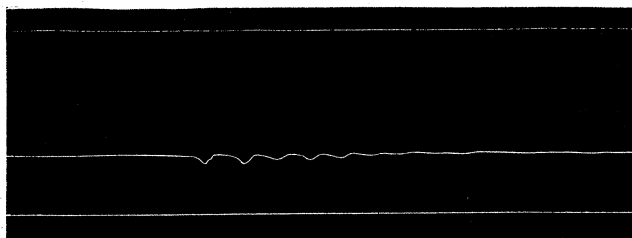
Experiment.—Normal frog of 24 grams. Slightly restrained by tapes passed round legs. Normal sitting position.

Minutes.

  0   Respiration flank (very faint), 67 ; hyoid, 67 per minute.   (Fig. 4$_a$.)

  0   Injected ·0005 gram diacetyl-aconitine into dorsal sac.

 12   Flank, 75 ; hyoid, 75.   (Fig. 4$_b$.)

 36   ,,   ,,

123   ,,   ,,   48 true.   (Fig. 4$_c$.)

227   ,,   ,,   (Fig 4$_d$.)   Stim. foot.

Later. Five hours after injection a record was commenced on a very slowly moving drum (12 millims. in one hour). The tracing commences 11 hours after injection, no genuine respiratory movement occurring till 8.15 the next morning (17 hours after

injection), when an occasional hyoid movement appeared.   The flank began to move late in the morning, and the breathing became normal within 34 hours.

Fig. 4e.
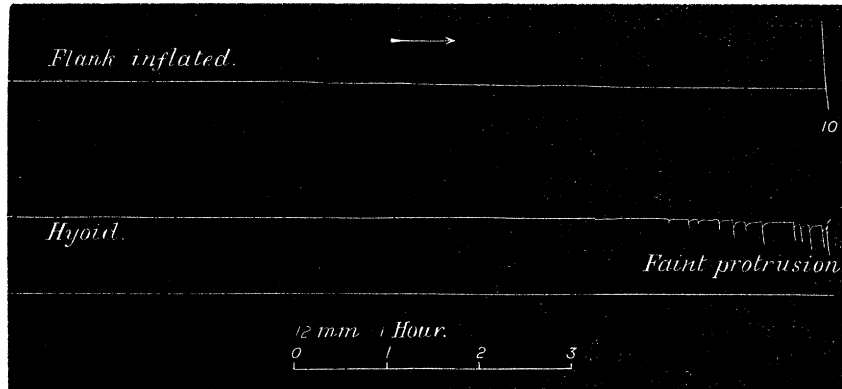
On Reflex Movement.

(Ascertained in usual manner by immersing toes in acid solution.)

Experiment.—(Sub-lethal dose.)   Pegged frog of 23 grams.   Some hours later ligatured all vessels of left leg.   Acid, 1–800.   Feet immersed separately.

Time.	Left.	Right.	Remarks.
minutes.			
0	2·5	2·5	Steady for three observations.
0	..	..	Inject diacetyl-aconitine, ·03 per kilo.
5	2·5	2·5	
10	..	..	
15	..	..	
20	3	4	
25	4	4	
30	4	4	
35	3·5	4	
40	3·5	4	
60	3·5	4	
70	4	5	
80	4·5	6	
95	6	8	
115	9·5	17·5	
125	12	0	After reaction had failed to acid, tactile reflex was elicited for 24 hours. A further injection of the alkaloid at that time caused the development of tonic spasm, and all reflex disappeared.
140	13	0	

It will be noticed that whilst the drug eventually acts upon the spinal cord, it is more energetic with regard to peripheral structures.   This is more clearly seen when a larger dose has been employed.

Experiment.—(Lethal Dose.)   (Diagram 3.)   To a frog of 32 grams, in which the brain had been previously destroyed and the vessels of the left leg ligatured, a dose of ·003 gram diacetyl-aconitine (or ·0937 gram per kilo.) was administered after the reflex time had been ascertained with 1–750 acid solution.   All reflex failed to this stimulation on the open side in 55 minutes, whilst reaction remained steady at 4 seconds on the left.   The acid was now increased in strength to 1–500, and after two withdrawals had been elicited on the right side, reflex ceased whilst response continued in 2–4 seconds in the companion limb.

Diagram 3.

————Poisoned side.   ·········Protected side.
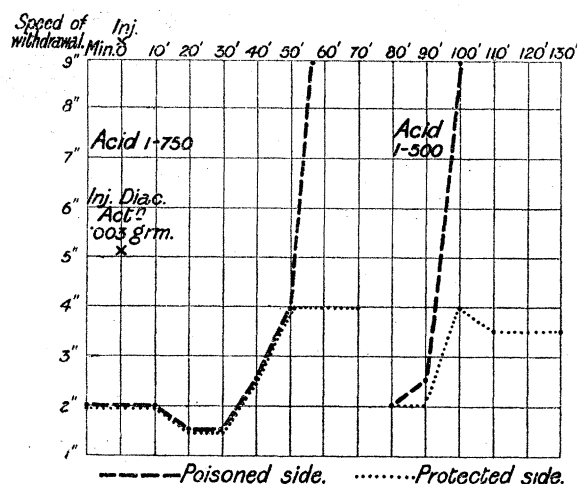
Whilst some reduction in reflex excitability of the cord is produced by diacetyl-aconitine, the ultimate occurrence of a tetanoid spasmodic condition, in the majority of cases, shows that this function may be aroused, and also demonstrates a ready longitudinal conduction of the cord.

On Nerve and Muscle (Irritability and Work).

As a result of gradual poisoning by a large dose of diacetyl-aconitine after exclusion of one limb from the circulation, it is found that the irritability of both nerve and muscle (especially the former) undergoes a marked reduction when contrasted with the nerve muscle preparation to which the poison has not had access. This reduction may proceed to entire or almost entire abolition of reaction.

From the frog which had been the subject of the last reflex experiment detailed, two nerve muscle preparations were made and tested simultaneously in the course of 10 minutes.   The minimal irritability on the two sides was as follows :—

Ligatured side, N. 21 centims., M. 19.   Open side, N. 10·5 centims., M. 14.

The few twitches which were elicited in order to obtain these figures so completely

exhausted the poisoned nerve and muscle that only a few contractions of 2–3 millims. (fig. 5) could be subsequently obtained even to faradisation, and even after an interval of rest had been permitted, no revival occurred. The companion preparation meanwhile responded vigorously to single induction shocks, and yielded a powerful and sustained tetanus on faradisation.

Fig. 5

Fig. 6.
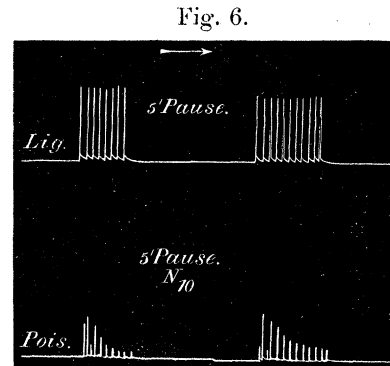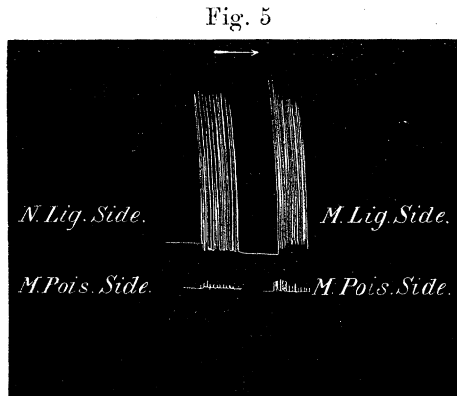
If a distinctly *sub-lethal* dose is used, a slight increase in excitability is occasionally observed as a transitory condition, more usually a reduction amounting to 2–4 centims. (position of secondary coil) for the nerve, and 1–2 centims. for the muscle.

Whilst response to stimulation is good at first, on repetition whether of opening induction shock or faradisation, a rapid decline, especially on the part of the nerve, is witnessed. Rest does not appear to have the same reinstating influence here, as in the case of some of the alkaloidal products which remain to be discussed. Fig. 6, nervous stimulation (upper line ligatured side, lower line open side) shows this failure after diacetyl-aconitine.

Fig. 7a and 7b.
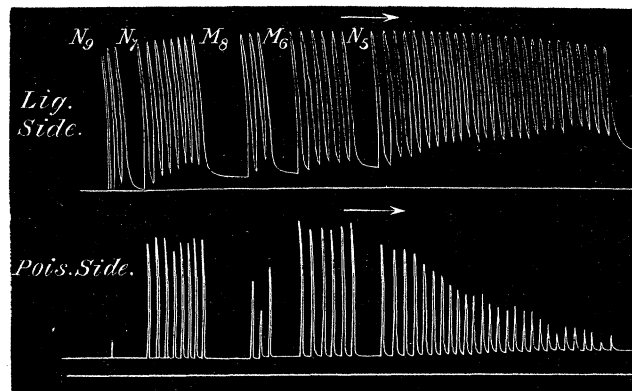
Experiment.—A brainless frog, in which the vessels of the left leg had been ligatured, received a large sub-lethal dose of diacetyl-aconitine. When the toxic effects had become well developed, two nerve muscle preparations were made and

simultaneously tested with regard to irritability and performance of work. Lever X 5 ; weight axial, 10 gram. Fig. 7 gives result of tetanising.

	Ligatured.		Poisoned.	
Minimal irritability.	N. 24 centims.	M. 12·5	N. 20·5	M. 12
Altitude of contraction to single induction shocks	10 millims.	10	5 { Reduced to 1·5 in 9 stimulations }	9·5
Altitude of contraction to series of short faradisa-tions	18	18·5	16 { Rapidly declines on repeating }	18·5
	(Fig. 7*a*)		(Fig. 7*b*)	

Immersion of Muscle Nerve Preparation in Solution of Diacetyl-Aconitine.

Experiment.—Made two companion nerve muscle preparations, and transferred them to small covered glass dishes, each containing 8 cub. centims. of RINGER's perfusion solution with blood. After 30 minutes immersion, tested minimal irritability, the result is given in centimetres (distance of secondary coil from primary).

Time.	No. 1.	No. 2.	Remarks.
minutes. 0	N. 39 M. 28	N. 38·5 M. 28	
0	..	..	Add ·0025 gram diacetyl-aconitine to No. 2
55	N. 39·5 M. 28	N. 38 M. 28	
90	N. 37 M. 27	N. 31·5 M. 24	
130	N. 35 M. 27	N. 19 M. 20	
175	N. 31 M. 25	N. 2 M. 11	(One faint twitch at)
250	N. 28·5 M. 25	N. 0 M. 4	
320	N. 24·5 M. 21	N. 0 M. 0	
hours. 24	N. 5 M. 14	N. 0 M. 0	

In another experiment the addition of ·025 gram of diacetyl-aconitine abolished reaction of the sciatic nerve for every stimulation in 58 minutes.

It is evident that there is considerable and rapid depression of the function of motor nerves as well as of muscular contractility by this alkaloidal derivative, in both respects there is considerable divergence from the effect produced by the parent alkaloid.

No method has been found as yet for restoring contractility in the muscle which has ceased to react after poisoning *in situ*, or by immersion in diacetyl-aconitine. No rigor is induced.

Summary of Main Effects of Diacetyl-Aconitine on Frogs.

General Symptoms.—Much less stimulation is produced of higher perceptive and motor centres in the first instance by diacetyl-aconitine than by aconitine, whilst subsequent reduction in voluntary movement and in reflex are more marked effects. The late appearance of a moderate or feeble general tetanus is characteristic.

Circulation.—Acceleration, often associated with group beating followed by slowing, the diastole being retarded, is observed in hearts poisoned *in situ*, and also when the whole ventricle is subjected to perfusion. The accelerated heart is primarily slowed on vagus stimulation, and during spontaneous slowing this result is also produced, stimulation of the venous sinus arrests the heart; further, the slowed heart is accelerated by atropine. The ultimate effect of diacetyl-aconitine is to abolish inhibition of vagus and, later, of sinus venosus. Atropine acts as a partial antagonist to this derivative. Incoordination of ventricular action though occasionally is less frequently seen than after aconitine. The heart may continue to beat spontaneously at a time when skeletal muscle has practically ceased to react, but, ultimately, at a time when the myocardium is still excitable by stimulation, contraction ceases. Further perfusion destroys the irritability of the myocardium also, and both atropine and aconine may fail to restore it. At an earlier stage both bodies assist recovery.

Respiration.—There is only a very slight stimulation of respiration, and this phase may be readily lost in the depression which rapidly supervenes. Hyoid movements become slower, and for a time large inflations of the flank are witnessed which alternate with expulsion of air. Spontaneous hyoid movements, though outlasting those of the flank, are abolished at last, but for a time the centre may be brought to discharge by sensory stimulation, though no true ventilation of the lung occurs. Breathing is arrested with the lungs moderately full of air. After the suspension has existed for some (6–20) hours, according to dose, the hyoid begins to move at intervals; some hours later the flank begins to associate itself with these movements, and finally respiration is restored.

Nervous System and Skeletal Muscle.—After a transitory and trifling stimulation

of the medulla its function is rapidly depressed. Whilst reflex activity of the cord shows some impairment, there is a tendency to tetanic spasm later in the course of poisoning, but before abolition of reflex, which seems to indicate subsequent excitement. Sensory nerve terminations are early depressed by diacetyl-aconitine, a similar effect occurring later on in motor nerve terminations, and, still later, in skeletal muscle. Rapid exhaustion of the motor nerve and muscle follows repeated stimulation (if poisoning is extensive), but some degree of recovery occurs when an interval of rest is permitted. The occurrence of tetanus, the powerful effect on motor nerve and muscle, are amongst the actions of diacetyl-aconitine which separate it from the parent alkaloid.

Lethal Dose.—The lethal dose is ·039 gram per kilo. body weight.

DIACETYL-ACONITINE.—ILLUSTRATIONS.

Fig. 1. (*a.*) Record of carotid pulse (top line). Left auricle (second line). Left ventricle (third line). The upstrokes in the two latter indicate systole. (Quick drum.)

(1'*b.*) Blood pressure after ·015 gram diacetyl-aconitine (108 minutes after ·01, and 9 minutes after second dose of ·005). Both vagi divided. Effect of suspension of respiration shown on two occasions. (Slow drum.) Also stimulation of the sciatic (central end, coil 5).

(*b.*) Taken 51 minutes after last. (Levers and speed of drum as in (*a*).)

Fig. 2. Arrangement of levers as in 1. Vagus stimulation (coil 6). Record taken 120 minutes after injection of diacetyl-aconitine, ·004 gram per kilo.

Fig. 3. (*a.*) Perfusion of ventricle (ligatured at groove) of frog with 10 cub. centims. RINGER's solution, to which dried bullock's blood had been added (·1 per 50 cub. centims.). Stimulation operative at 9 centims.

(*b.*) During last 22 minutes circulation of 10 cub. centims. of the above with ·0001 gram diacetyl-aconitine.

(*c.*) 38 minutes after first administration of poison, ·000175 gram has now been circulated.

(*d.*) 113 minutes after first administration of poison, ·0004 gram has now been circulated.

(*e.*) 120 minutes after first administration of poison, ·00068 gram has now been circulated.

(*f.*) 125 minutes after first administration of poison, ·001 gram has now been circulated.

(*g.*) 157 minutes after first administration of poison, ·0015 gram has now been circulated.

Stimulation is now inoperative beyond 4 centims.

Fig. 4. (*a.*) Respiration of normal frog. Flank lever above moves up in expiration. Hyoid below moves up in protrusion.

(*b.*) 12 minutes after injection of ·0005 gram diacetyl-aconitine.

(*c.*) 122 minutes after injection. A phase of great inflation of the lung illustrated.

(*d.*) 227 minutes after injection. All spontaneous respiratory movement has ceased. Record of response by hyoid movements to stimulation of leg.

(*e.*) Record on slow cylinder (12 millims. per hour) of flank (above) and hyoid (below). The side is in position intermediate between inflation and collapse. (Commenced 11 hours after injection.) It is during the last 2 hours only that hyoid movement recurs.

Fig. 5. Reaction of normal nerve (8 centims.) and muscle (3 centims.) recorded on upper line and of deeply poisoned (diacetyl-aconitine) nerve and muscle (lower line) to single induction shocks delivered every second.

Fig. 6. Reaction of normal nerve (10 centims.) to series of single induction shocks, repeated after interval of 5 minutes' rest (upper line) and of moderately poisoned nerve similarly tested (lower line).

Fig. 7. Series of short (1·5 seconds) tetanising stimulation delivered to nerve (N) and muscle (M) on ligatured side (upper line) and on poisoned side (lower line).

Diagram 1. Diacetyl-aconitine (large sublethal dose) on temperature (black line) and respiration (dotted line) of rabbits.

Diagram 2. Diacetyl-aconitine (lethal dose) on temperature (black line) and respiration (dotted line) of rabbits.

Diagram 3. Diacetyl-aconitine on reflex (frogs), open side (black line), protected side (dotted line).

SECTION III.—BENZACONINE.

Solutions of benzaconine of an equal strength to those of aconitine having been found inoperative, a proportion of ·0324 gram of actual alkaloid per 1 cub. centim. was prepared in the form of an aqueous solution of the hydrobromide.

The non-irritant properties of this salt permitted its use in such strength without further dilution.

When tasted, the solution produced the impression of a " pure bitter "—no tingling or numbness ensuing.

ACTION UPON CIRCULATION AND RESPIRATION OF WARM-BLOODED ANIMALS.

Blood Pressure.

A slight rise of pressure amounting to 2–3 millims. of mercury, follows a medicinal dose of benzaconine, and may appear also as the first result of large doses.

After such a dose as ·02–·25 gram per kilo. administered hypodermically to an etherised cat, a steady fall of pressure soon develops. This fall progresses till the pressure is reduced to about 50 millims. of mercury, at or near this point the decline becomes much more gradual.

Eventually the level of 20–30 millims. is reached, the action of the ventricle being very slow, but regular in character. This pressure may be maintained for an hour or longer before death occurs.

The prolonged action of the heart, only capable of maintaining a very low pressure in the blood vessels, is characteristic of this alkaloid.

The low level to which the pressure is reduced after the lethal dose, is broken in a large proportion of experiments (4 out of 10) by a more or less regular series of temporary reductions of blood pressure to within a comparatively short distance of the abscisse. This reduction is attributable to a temporary failure of auricular and ventricular action, whilst a sudden resumption of activity terminates the depression, reinstating the pressure which persists until the commencement of another failure.

These phases may be repeated many times (in one experiment their recurrence was witnessed for over two hours). They are succeeded by a very low, but slowly declining pressure which is devoid of this peculiar form of reduction. In those cases in which intermissions were not interrupted, a steadily, though very slowly, progressing fall of pressure took place.

Pulse.

A pulse acceleration (4–6 per minute) follows medical doses and appears for a time after larger amounts. There is, during the early stage of decline to and maintenance of low pressure, a considerable slowing of the pulse, not generally associated with any irregularity. The form of pulse as recognised by touch or recorded by Fick's kymograph, changes, the systolic impulse being firm and ample, whilst a retardation in the decline of tension is frequently accompanied by the development of dichrotic and multiple waves, indicative of a change either cardiac or vascular in its nature.

Elucidation of the slowing and peculiar form frequently assumed by the pulse after benzaconine necessitated the inspection and registration of movements from the walls of the heart. The plan followed was that already described in connection with aconitine. The slowing is found to show the following variations, and in a single experiment it is usual for all these to be manifested at one time or other.

(1.) During the first phase (chronologically) of slowing after benzaconine there is a regular sequence of ventricular upon auricular action.

Fig. a_1.
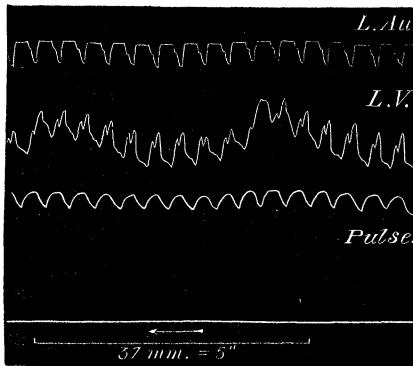
Fig. a_2.
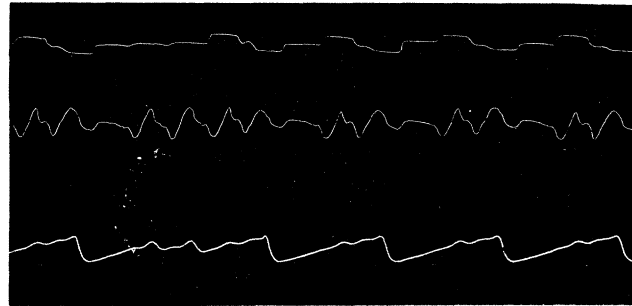
Fig. a_3.
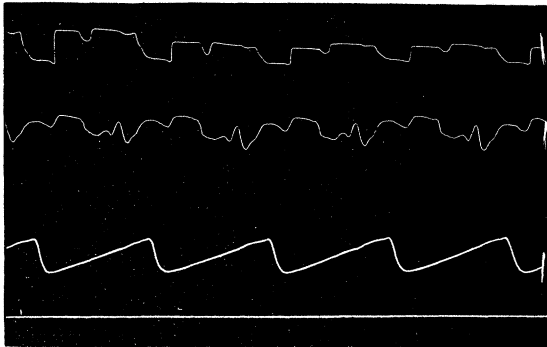
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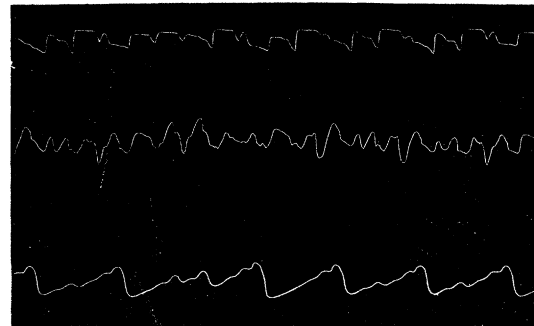
(For description of these tracings and later, see p. 362.)

(2.) In the second phase the pulse rate is greatly slowed, and frequently it will be observed that only one systole of the ventricle is fully effective in every three or four contractions. The partial systoles may, however, cause a check or a small positive wave during the decline of pressure (fig. a 1–4). The ventricular contraction is distinctly prolonged in character. The same may be said for the auricular action, and it is clear that there is a close correspondence (a_3 a_4) between an auricular cycle commencing with a free contraction and terminating with a fair relaxation (minor phases of relaxation and contraction intervening) and the slow carotid pulse. Partial contractions and relaxations of the auricle though having sequence in the ventricle are not of any great value in supplying the ventricle with blood for its expulsion.

(3.) The third chief type of slowing, highly characteristic of benzaconine, occurs when the ventricle steadily refuses every second auricular impulse, but its own beat is regular and productive of a steady slow pulse.

This condition is illustrated by the experiment from which fig. *b* 1, 2, 3 is taken, it persisted without intermission for fully two hours.

Fig. b_1.
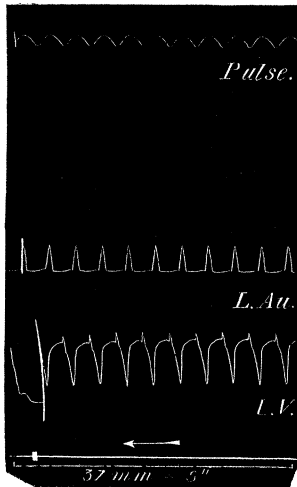
Fig. b_2.
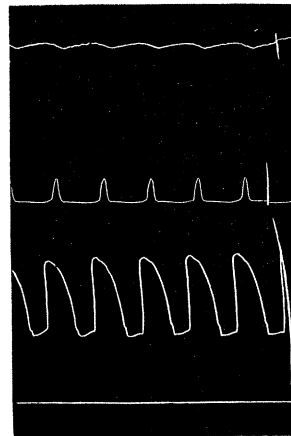
Fig. b_3.
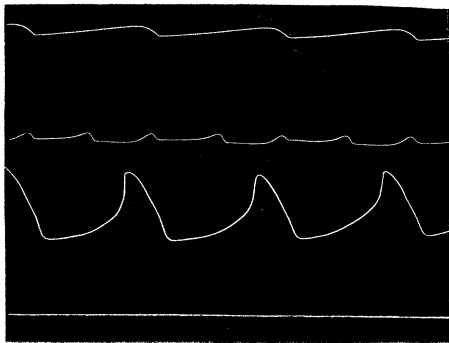
Fig. b'_3.
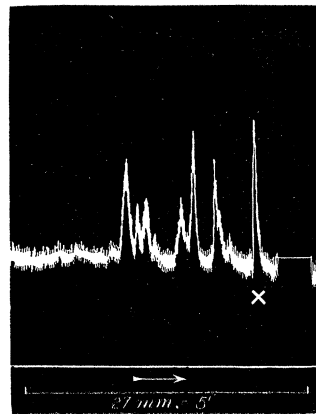
Temporary Arrest of Systole.

The intermittent reductions of pressure referred to are occasioned by a transitory arrest of the heart. In this arrest the walls of all the chambers of the heart participate.

The ventricle ceases before the auricle, and the latter is the first to spontaneously resume contraction.

On section of the vagi during this slowing or arrest, no acceleration or rise of pressure is seen.

CAT of 2720 grams placed in warm box. The temperature carefully maintained throughout. Cannula in carotid. Left vagus divided. Right vagus on thread. Temperature rectal and subcutaneous (side).

| Time.	Blood pressure.	Pulse.	Respiration.	Notes.
minutes.	millims.			
7	112	156	31	Rectal temperature 35·4. Side temperature 35·1.
16	113	158	..	Injected ·0408 gram benzaconine hypodermically.
22	116–80	168–114–174	..	Stimulation left vagus (peripheral) 8 centim. 10 seconds.
27	84	153	21	Rectum 35·4. Side 35.
53	67–20	124	28	
63	63	117	26	
68	..	..	..	Rectum 35. Side 34·7.
77	55	108	19	
89	..	..	..	Inject hypodermically ·028 gram benzaconine.
90	40	54		
104	45–50	54–96	..	Rectum 34·8. Stimulate. Side 34. Left vagus. Coil 8. Undoubted rise and acceleration.
125	50–14	..	..	Pressure suddenly fell; in 3 minutes began to rise. Rigor.
130	40	55	10	Gasping.
141	..	..	..	Heart again stopped.
154	50–16	..	..	Rectum 34. Another great fall. Side 33·6. During this section of vagus (right) no effect.
157	44	55	12	
164	66–10	..	..	Fall; kept down 2 minutes. Palpation employed.
171	58–13	..	..	Fall. Rose in 2 minutes. Palpation.
175	52	50	12·5	Systole long maintained.
179	..	53	12·5	Respiration very irregular and laboured.
188	54–19	..	..	Fall lasted 140 seconds. After this gradual failure of pressure. The natural respiration having failed, artificial respiration employed.
198	30	52	..	Stimulation of peripheral sciatic followed by much reduced contraction of gastrocnemius.
203	10	15	..	Rectum 34·2. Side 32·8.

Death 188 minutes after first injection.

In the experiment just recorded only comparatively few pauses of the heart occur, but they may return periodically for at least two hours.

The pause terminates spontaneously, and is in fact not promoted by palpation, either of the chest wall or of the heart itself. Death has not been seen to occur during this pause; it results usually after the phase of intermission has passed.

The character of the arrest and resumption of action has been observed directly by removing a portion of the chest wall while the record from the carotid was being taken.

The following figures are taken from an experiment (c) (Mar. 3, 1893).

CAT of 2950 grams.   Etherised in warm box; vagi and splanchnics prepared. Artificial respiration.

In the course of 179 minutes there were recorded 41 such intermissions with spontaneous recovery.

In many of these intermissions the pressure fell below 10 millims. of mercury. Minute inspection was made possible by freely exposing the heart, and notes were dictated whilst the registration was continued. Details of the 37th and 38th pauses are as follows :—

	(37th) Pressure.		Heart.	
(c'_3.)	Fell from 27 millims. to 7 millims.	0 minutes.	Ventricles ceased contracting.	
		45 ,,	Auricles ,,	,,
		90 ,,	,, began	,,
		93 ,,	Ventricles ,,	,,

	(38th) Pressure.		Heart.	
	Fell from 25 millims. to 6 millims.	0 minutes.	Ventricles stopped.	
		40 ,,	Auricles ,,	
		75 ,,	,, first pulsation.	
		80 ,,	,, second ,,	
		105 ,,	,, began to beat steadily.	
		108 ,,	Ventricles commenced action.	

The ventricle was in absolute rest in diastole.

Whilst the entire arrest of the heart during the 37th and 38th intermissions in this experiment can be vouched for from direct inspection, it is highly probable that on the other many occasions in which fall of pressure to a few millimetres and absence of registrable pulse occurred, the same complete arrest was produced.

It is conceivable that in some of these pauses a systole, so feeble as not to have

reached the carotid, and therefore incapable of moving the delicate spring of Fick's kymograph, may have been present, but even this would constitute a virtual arrest of the circulation for the time being.

Previous course of the experiment illustrating temporary arrest of heart's action.

The original pressure (fig. c_1), was 119 millims. ; the pulse rate was 126 per minute (fig. c_1).

At 0 minute, injection was made hypodermically of ·0245 gram benzaconine per kilo.

At 40 minutes, injection of ·0162 gram benzaconine.

At 65 minutes, the pulse was 110 per minute (fig. c_2).

At 211 minutes, the first arrest of the pulse with fall of pressure was registered.

At 213 minutes, the pulse was 64 (fig. c_3).

At this time the vagus was still feebly active ; the splanchnic distinctly so. The phases of intermission of the pulse with fall of pressure now began to alternate with temporary spontaneous recoveries, during which the heart contracted powerfully and regularly.

The following table gives the approximate time of recurrence of the pulse failure, and in some instances, when the pulse was recorded by Fick's kymograph (clamped off from the mercurial manometer), the exact time of absence of pulse. When the measurement is taken from the slow cylinder it is only of approximate value.

The speed of recurrence of the phases described is taken from the same experiment. At the time the record commences, 192′ after the first injection of benzaconine, the vagus is still feebly active. The splanchnic is distinctly so ; the vaso-motor centre responds moderately to sensory stimulation.

Fig. c_6.
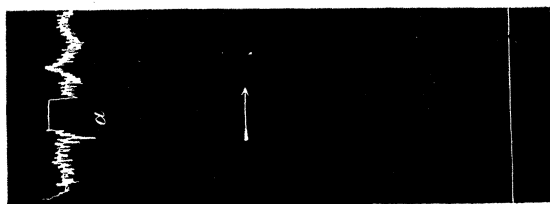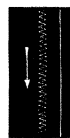
Fig c_4.

Fig. c_5.

Fig. c_3.

Fig. c_1.

Fig. c_2.

Fig. c'_3.

37 th. Intermission.

Fig. c'_2.

2'0 after injection. 18 th. to 25 th. intermissions.

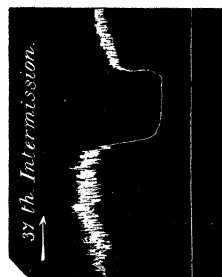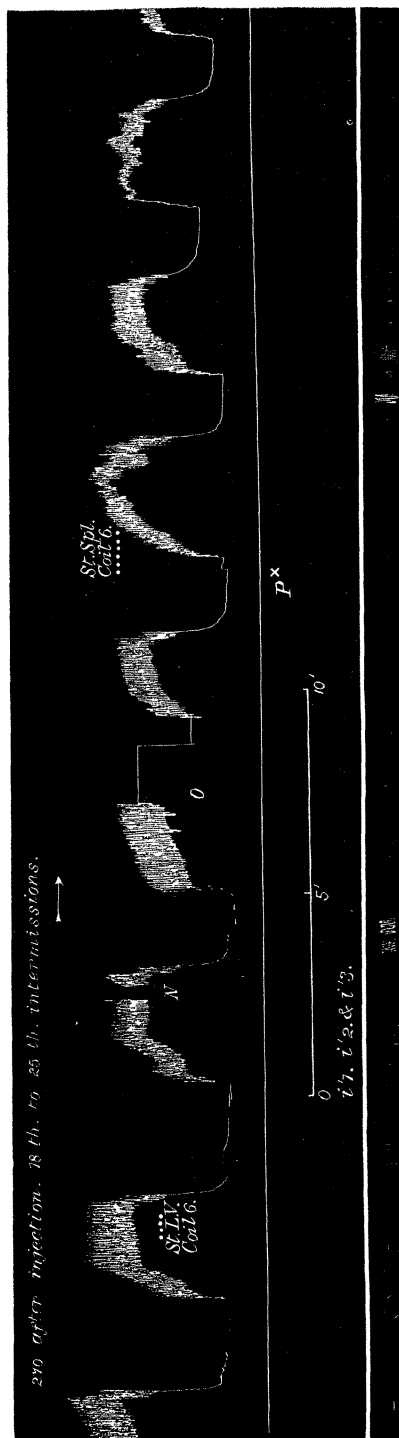St. Spl.
Coil 6.

St. Lv.
Coil 6.

$P^\times$

Fig. c'_1.

α

Time of experiment after injection.	Number of fall recorded.	Approximate time from last fall.	Pressure.		Pulse and remarks.
			Before.	During.	
minutes.		minutes.	millims.	millims.	
211	1	..	40	25	
214	2	3	41	23	
218	3	4	..	..	
222	4	4	..	..	No pulse for 50 seconds.
224	5	2	..	..	
228·5	6	4½	..	..	No pulse for 55 seconds.
232	7	3½	43	16	Pressure rose to 50 on stimulating splanchnic.
234	8	2	..	..	Pulse on rise 37.
237·5	9	3·5	..	..	
242	10	4·5	..	..	No registrable pulse for 58 seconds, but a slight occasional wave seen (see fig. c_4).
243	11	1	..	..	Arrested for 20 seconds.
245	..	..	..	..	Vagus stimulation slows heart between pauses.
249	12	6	..	..	No absolute arrest.
252	13	4	..	..	Arrest for 15 seconds (see fig. c_5).
254	14	2	..	..	Injected ·0026 gram atropine.
257	15	3	43	29	Splanchnic stimulation as fall began raised pressure rapidly to 59 millims.
263	16	4	..	..	
266	17	3	..	..	No pulse for 2 minutes.
271	18	3	44	9	No pulse for 2 minutes 10 seconds. Fig. c'_2 begins. Pause.
276	19	3½	41	9	Heart beat 54 just after vagus. Stimulation inoperative.
281	20	3¾	37	8	No pulse for 90 seconds.
286	21	..	33	·18	No pulse for 65 seconds (see fig. c_6).
290	22	4	34	9	Vagus stimulation inoperative. Splanchnic active.
294	23	4	37	9	
298	24	4	35	14	
302	25	4	31	9	
304	26	2	..	..	
311	27	7	26	8	
316	28	5	..	..	Pulse during rise is 35.
321	29	5	35	11	
324	30	3	..	..	
329	31	5	33	9	
335	32	9	..	..	
341	33	6	..	..	
347	34	6	..	..	
351	35	4	30	11	
356	36	6	..	..	
362	37	6	..	..	Fig. c'_3. Inspection. Arrest of ventricle for 93 seconds.
368	38	6	..	..	Ditto ditto 108 seconds.
372	39	4	..	..	
375·5	40	3·5	..	..	
381	41	5·5	23	6·5	
387	..	6	..	..	Pressure 21. Pulse 37 in groups of threes.
390	Death.				

Death took place not during an arrest, but immediately after the rise had commenced, and before it developed.

When the action of atropine is induced, the fluctuation or phase of spontaneous arrest and recovery still maintains, and it does so in face of the complete paralysis of vagus endings.

Clamping the tracheæ has no effect on the pressure, the pressure declining to 0.

Close examination of the pulse during the commencement of an intermission shows either a preliminary slowing (fig. c_6, 21st intermission), or an arrest without slowing (fig. c_4, 10th intermission).

The resumption of rhythm is gradual in all.

Not unfrequently there is a grouping of beats (2 to 3 to a group) before arrest.

Example of a short pause, with precedent slowing, is given in fig. c_5, taken from the 13th arrest.

Effect of Benzaconine on Vagus Terminations.

During the early fall of pulse rate, section of vagi causes a fractional but only temporary recovery of speed, but this is not maintained and the pressure soon recedes to the original level.

Though impairment in the activity of the stimulated vagus is observable when a decided fall in pressure has taken place, it is only in advanced poisoning that entire failure of its action is witnessed. Should poisoning proceed without the temporary suspensions of cardiac action just described, a faint vagus effect is generally obtainable until the pressure has fallen to within a few millims. of the abscissa, but should intermissions occur, the vagus ultimately becomes incapable when stimulated by reducing the pressure. Whilst stimulation of the vagus still slows the heart, a marked acceleration of rhythm often succeeds. Atropine neither prevents the extraordinary slowing of the heart nor the occurrence of intermissions, this increase in the effective systoles being followed by a rise of pressure.

Effect on Vaso-motor Centre and Vaso-constrictor Nerves.

Even when the pressure has fallen to a very low level, occasional waves of increase may make their appearance spontaneously (fig. b'_3), and these may be simulated by the effect of strong stimulation of the central end of the sciatic nerve, the vagi being cut. (See last elevation in figure (×), produced by this cause.) The vaso-motor centre is, however, only active to a limited extent, and with a prolonged low pressure its action disappears. Its failure contributes to the low pressure.

The *splanchnic nerves* are at no time completely paralysed by benzaconine, although the effect of stimulation undergoes great reduction. During cardiac intermissions no elevation of pressure from their excitation is possible, but as soon as the heart has recommenced some elevation of pressure takes place.

2 x 2

Manner of Action on Heart.

Granting a slight primary depression of the medulla, the question arises : How does benzaconine affect the heart ? The impaired action of the vaso-motor centre contributes to the fall of pressure, but the coincident slowing of the pulse is due to an effect within the heart, and to this the fall is mainly due. It occurs when the vagi are divided, and is not prevented by atropine. Though it might otherwise simulate a condition of inhibition, these facts point rather to a depression of the intrinsic motor apparatus, whilst the walls of the heart chambers retain a large share of their contractile power. In advanced poisoning there is therefore produced the extraordinary condition of a very slowly acting heart, which seems capable of continuing its action for hours, whilst the blood pressure amounts to only a few millimetres of mercury.

Beyond this, however, there is a tendency to a block in the passage of certain impulses from the auricle to the ventricle, whilst the ventricle itself (during one stage) fails to develop a normal propulsive systole in a comparatively large proportion of its efforts at contraction.

The low blood pressure and the leisurely action of the auricles conduce to a slow filling of the ventricle, and so the stimulation to systole usually derived from distension is reduced.

Lastly, there may be absolute suspension, with spontaneous resumption of rhythmical effort on the part of both auricles and ventricles, pointing to more or less intermittent depression and restoration to activity in the elements concerned in rhythmical contraction of the several parts of the organ. They almost tempt the hypothesis that somewhat the same condition is present here as in the stimulated nerve muscle preparation, removed from the benzaconine frog, in which there is a very marked intermission in excitability.

Action of Benzaconine on the Respiration of Cats.

There is a marked slowing of respiration from the first administration of the alkaloid. Even when given in such small doses as $\frac{1}{6}$th to $\frac{1}{10}$th of the lethal amount this effect is produced in degree. As poisoning progresses, and the blood pressure sinks very low, the breathing undergoes a corresponding reduction, but the individual respirations are deepened, the chief pause being in the expiratory position of the chest wall, but the respiratory centre is still active, and in those cases in which the heart ceases altogether for a time, gasping appears, but subsides as the low degree of pressure attainable is restored. This result occurs if the vagi have been previously divided. The heart's action, however, outlasts spontaneous respiration. Artificial respiration neither raises the low blood pressure of benzaconine nor hinders the advent of the heart pauses which have been described.

(One result of benzaconine on respiration has been witnessed which is so remarkable that its description cannot be omitted. In the first experiment performed with benzaconine, the warm box was not used, and the temperature of the animal fell in six hours after the injection of the alkaloid to 30° C. The pressure was steady at from 20 to 24 millims. of mercury (*d*, lower line) ; the pulse, which was originally 194, was now 17 to 21 per minute, and the respiration showed an intermission which was astonishing. Groups of inspirations (upper line) occurred every 3 to 5 minutes with great regularity. Between these efforts the chest wall—which appeared to remain in an expiratory position—showed not the slightest movement, excepting on two occasions, when a single inspiration took place.

In order to be sure that no slight movement was escaping the recording apparatus, the tracheal cannula was on two occasions kept clamped for from 3 to 4 minutes, as indicated in the tracing.

The occurrence of the group of inspirations was accompanied by a slowing of the pulse, which fell to 14 or 15 per minute, the beat being perfectly regular in character ; and then occurred a slight elevation of pressure, the heart beating a little faster. The heart outlasted respiration.

This condition appeared to be attributable to the low body temperature, as well as to the benzaconine, for it has never been observed again, whilst preventing the fall of body temperature by using the warm box.

It reminds one strongly of the phenomena of hybernation, during which the respiratory and circulatory needs are greatly reduced.)

Benzaconine on Respiration of Rabbits.

Blood pressure experiments have been quoted in which marked reduction in the speed of respiration followed benzaconine, and these were supplemented by others in which the respiration and temperature of rabbits were observed at the same time.

Small doses, such as ·0052 to ·01075 gram per kilo. (rabbit weight), cause a slight retardation in respiration which has its maximum 60 minutes after injection. An increase of dose causes more distinct slowing, though even with large sub-lethal doses the total effect is not great.

Thus benzaconine at the rate of ·0243 gram per kilo. caused a fall from 80 to 52 per minute.

After a dose of ·0272 gram per kilo. (lethal to rabbits in 30 to 40 minutes) a rapid decline in respiration with, at first deepening, and then weakening of the individual movements takes place. Respiratory failure occurs before cardiac arrest, but artificial respiration has only a feeble effect in postponing the lethal effect.

Benzaconine depresses the respiratory centre without previous stimulation, whilst the vagus also is depressed in function, so that if section is made of both nerves in a
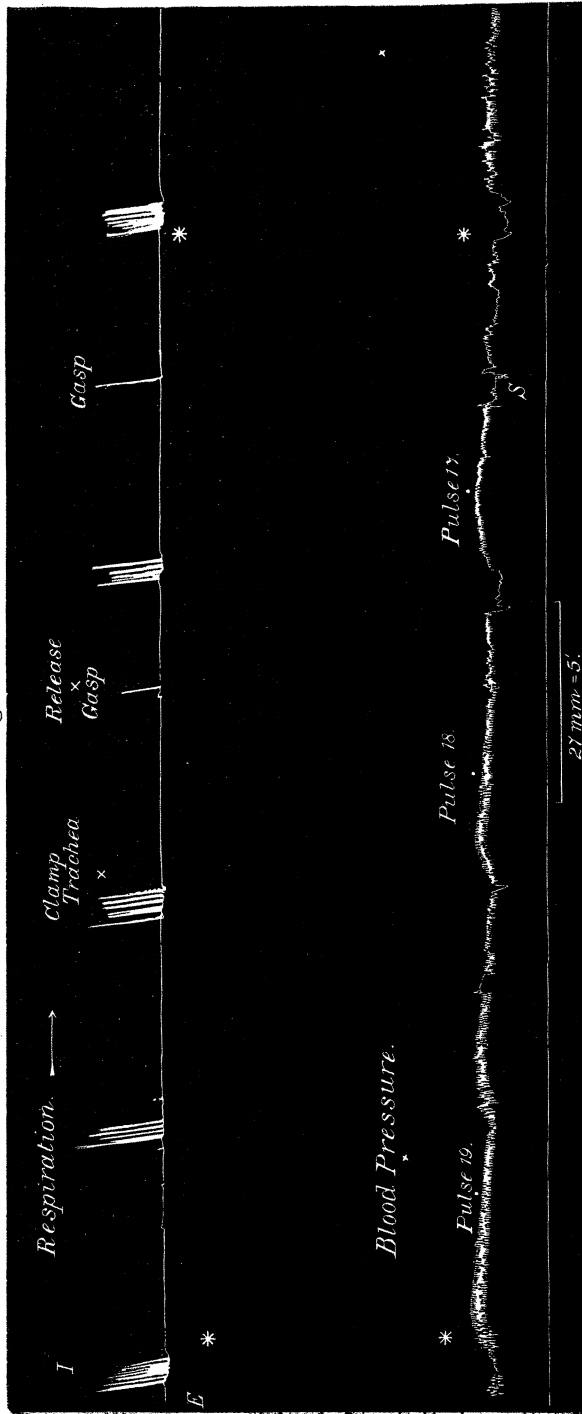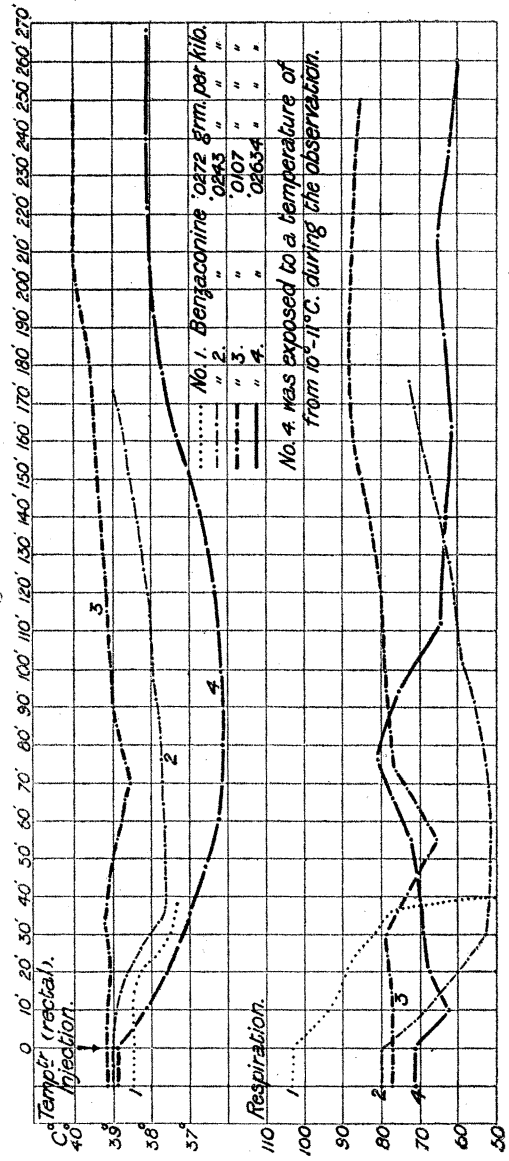
Fig. d.

Diagram a.

narcotised animal after marked slowing has appeared there may be no immediate increase of slowing. The motor nerves innervating respiratory muscles, though still excitable by faradisation, are impaired in function, and no doubt the feeble discharges from the centre proceed to the nervous terminations with increasing difficulty.

Temperature.—Doses of ·0107 gram per kilo. administered to rabbits kept at a temperature of 16° C., caused a reduction of ·5° C. The lowest point was reached 70 minutes subsequent to administration, and the original temperature was regained 30 minutes later, and was thereafter slightly exceeded.

A large dose, ·0243 gram per kilo., caused a prompt fall of temperature amounting in 50 minutes to 1·4° C., and after this a rapid return to the normal occurred, the original point being registered in 145 minutes. A short curve in Diagram *a* shows the course of temperature under a dose of ·0272 gram per kilo. This proved lethal in 40 minutes. The fall amounts to 1·2° C.

Regarding these results it cannot be said that benzaconine has any powerful effect on temperature when in large sub-lethal doses, so long as the animal is sheltered from exposure to cold. Whatever fall is produced is mainly due to the coincident fall of blood pressure, and slowing of pulse and respiration, which have been shown to take place. Benzaconine also opposes protoplasmic oxidation.

During slow poisoning, when exposure to a cool atmosphere is permitted, the remarkable reduction in the activity of circulation is favourable to a great fall of temperature.

An extreme case has been referred to in detailing blood pressure experiments, and a modified effect is shown in Curve No. 4, in which a large sub-lethal dose of benzaconine ·02634 per kilo. reduced the temperature by 2·8°C. in the course of 80 minutes, and in 5h., though the animal was active and vigorous, it was still ·7° C. sub-normal. It is probable that the reduction of movement in such cases of poisoning reduces thermogenesis in the muscles as it appears to do in the case of curare, whilst the slowed circulation, and the increased loss of heat from the surface, all contribute to the fall.

Benzaconine on Guinea-Pigs.

A medium-sized guinea-pig received (an interval of several days intervening) the following doses of benzaconine, in proportion to the kilo. body weight :—

·0170 gram caused merely slight lethargy.
·0238 gram caused the symptoms about to be described.
·0275 gram was fatal.

Large Sub-lethal Dose.

Minutes.

0 A normal animal received benzaconine in the proportion of ·0238 gram per kilo. Respiration 88. Room temperature, 14° C.

5 Slight chewing movement.

10 No salivation. Lethargic.

15 On side ; limp when taken up. Breathing easy. If trying to move in box, rolls over.

26 Respiration is 70. Placed on floor it rolls over to right and left, and legs kick in the air. (The fault is not in volition). No salivation ; starts from sound, otherwise lies still.

36 Body shakes much in attempt to move. Breathes deeply, occasionally a slight expiratory squeak.

51 Lying on side, breathing 59 easy.

105 Rolls over. Fore-feet show more power than hind, which are much paralysed.

135 Paralysis less. Scrambles a step. Kicks if lifted, but limp. Respiration 58. Moves by aid of fore feet.

210 Still sinks with chin on ground. Moves a step or two.

270 Moves chiefly by fore-feet.

325 If roused can run a short distance. Paralysis yielding.

390 Head still tends to sink, but if roused can run smartly.

400 From this point it rapidly recovered.

Lethal Dose.

Ten days after last experiment.

Minutes.

0 The guinea-pig received benzaconine ·0275 gram per kilo. Room temperature, 14° C.

7 Runs actively.

22 Restless and lively.

27 Running suddenly arrested. Is limp.

37 Is nearly paralysed. May run a few steps and then sit rocking and swaying. All reflexes. Tends to assume position flat on stomach with legs out. Legs seem anæsthetic.

47 Lies on back. Very limp. Most movement in head, and a little in fore-legs. No dyspnœa on touching body.

57 Lies breathing faintly.

97 Very limp.

137 Frequent short starts (28 per minute) of body, do not move animal from position. Moves two steps and sits rocking, occasionally squeaks. Feels cold. Rectal temperature, 30° C.

Minutes.

192 Jerking has been constant.

217 Ether inhaled at first increased then abolished jerk ; on recovering, jerk appears first in abdominal muscles, then in ears, and then extends to limbs.

297 Temperature, 29° C. Less jerking, but more paralysis ; moves with difficulty ; seems narcotised ; position of body unaltered ; somewhat anæsthetic.

537 Paralysis of voluntary movement continued, breathing became very faint and slow, death supervened without respiratory spasm.

Post-mortem.—The right heart in partial dilatation, beating very slowly. Left ventricle contracted, scarcely moving. Brain and cord unusually vascular. Stimulation of the sciatic nerve caused contraction in leg muscles. (This reaction appeared to be reduced, but there had of course been no control stimulation before poisoning.)

General Action on Mammals.

Some degree of narcosis is produced ultimately after benzaconine, and is referable to the imperfect oxidation of the blood as well as to a direct action of the alkaloid. The main symptoms indicate depression of the medulla, and an impairment of voluntary control, most marked in the hind-legs at first, less in the fore-legs and neck muscles. How far this is due to a central effect, or how far to a curare-like action upon motor nerve terminations, it is impossible from these experiments to determine, but viewed in the light of experiments upon frogs, the latter is the more probable explanation.

The clonic jerk occurring in guinea-pigs (not in rabbits) is seen at a time when voluntary control of the limbs is much reduced. If it is due to a transitory stimulation of motor elements in the anterior cornua of the cord, its disappearance may be attributed to their subsequent depression in function, or else to advancing loss of activity in the motor nerves at the periphery in association with muscular failure.

ACTION OF BENZACONINE ON FROGS.

(a.) *Sub-lethal Dose.*

FROG of 27 grams.

Minutes.

0 Received 003 gram benzaconine.

12 Springs well ; escaped.

20 Gets promptly off back. Crawls weakly after each effort. Quacks if back touched. Respiration accelerated.

25 Looks inanimate if not roused, no spontaneous movement, but gets off back. Springs if irritated, but makes only two or three efforts, then loses all power of movement

Minutes.

40 Will lie long with legs out. Resumes ventral position if placed on back. Circulation in web excellent. Respiratory movement rare, but provoked by stimulation of hyoid region.

57 No spontaneous movement. Eye and limb reflex are present, the legs being flexed twice, and then for a time reflex is not producible. Reflex outlasts spontaneous movement.

80 Reflex is growing stronger.

90 Position flat, looks dead till stimulated, then legs moved two or three times. Legs drawn up.

110 Still flat in position, but kicks strongly with legs if roused.

150 Gets off back easily.

250 Spontaneous movement now occurs to slight extent.

430 Jumps moderately well, movement a little jerky.

(b.) *Lethal Dose.*

FROG of 25 grams. Ether. Ligatured vessels to left leg. After the effect of ether had passed off, injection of ·00648 gram of benzaconine.

Minutes.

0 No excitement followed the injection.

10 Apathetic, reflexes from both legs. Circulation moderately good.

20 The right leg twice drawn up on touching the right foot, the left also moved. The third stimulation caused movement in the left only. Left reflex good on touching left foot. Slight voluntary movement in left leg and arms ; the latter are less affected than the legs.

30 Left stimulation causes free movement of left and two movements of right, after which right stimulation causes no direct, but only cross reflex. Eye reflex just present. Animal very apathetic.

45 Circulation feeble in web. Eye reflex gone. Right foot is still moved three times to its own stimulation.

65 As above.

85 Right reflex hardly obtainable. Left moderately good. Circulation slow and imperfect.

110 Right reflex gone. Left moderate to itself. Circulation still present in right web. Destroy brain and cord ; on destruction of the latter the left leg is moved, not the right.

Test minimal irritability of nerve and muscle :—

	centims.		centims.
Poisoned nerve	20	Ligatured nerve	18.
„ muscle . . .	9	„ muscle . . .	11·5

Duration of Effect of Benzaconine.

A dose of ·00324 gram to a frog of 24 grams caused abolition of reflex in 125 minutes, the circulation at this time being feeble and respiration to casual observation entirely absent.

24h.   Position flat—looks dead. Two sprawling movements occur to stimulation, but no further reflex obtained. No eye reflex. Circulation improving.

49h.   There is reflex in legs. Eye sensitive. Very apathetic. Lay all day in one position without moving.

72h.   Jumping well, and in all respects normal. (From this frog a series of respiratory tracings were obtained, which will be referred to.)

Benzaconine succeeded by Strychnine and Veratrine.

Brainless frogs, with the vessels to one leg ligatured, received benzaconine in larger and smaller amounts, and at a certain stage in the poisoning strychnine was administered by injection. If the poisoned limb still showed recurrent response, the strychnine tetanus was feeble and recurrent in character, but if reflex had quite disappeared, no reaction followed strychnine. In either case the protected limb gave a firm and sustained tetanus.

On recovering from benzaconine, however, the strychnine effect developed.

If veratrine action is induced after benzaconine, a voluntary or induced movement shows the characteristic tonus of the former poison, but the contraction seems to exhaust the nerve terminations, so that, if repeated once or twice, movement is abolished sooner than it would have been if only a natural contraction had occurred.

The characteristic motor feature in the action of sub-lethal doses of benzaconine is the preservation of a reflex movement which can only be excited for a limited number of times. After its failure, a period of rest favours its reappearance.

Movements of volition cease before reflex, and the animal in which the brain is uninjured has a narcotised appearance—the eyes closed, the body bent forward, and the limbs in any position. It is of interest to note that if one limb of a pegged animal has its vessels ligatured, that limb is drawn up to a flexed position, and returns to it, if gently extended, when the other limbs are in any position as regards the trunk.

That the minimal irritability of the nerve is relatively but little affected will be demonstrated more fully in a later section. As cross reflex from the poisoned leg to the unpoisoned leg exists after the former has ceased to respond itself, it is judged that the primary effect is upon motor nerve terminations, or muscle, or both, and that succeeding this the sensory terminations are affected.

The cord participates primarily but little in the general poisoning, but after large

doses its functions may be suspended, whilst the circulation continues to a sufficient extent to preserve the life of the animal.

Action of Benzaconine on the Exposed Heart (Frog).

Small Dose.

PEGGED frog of 19 grams. Expose heart. Heart beating, 28 —28 —28.

Minutes.

0	Inject ·001 gram benzaconine.		
6	Beating	28.	
28	,,	31.	
46	,,	31.	Circulation very good.
63	,,	31.	
81	,,	30.	
201	,,	30.	Circulation excellent. Ventricles filling amply and contracting powerfully.

25th—next day. Reflex action. Circulation excellent. Beating 30 —30.

Minutes.

0	Inject ·002 gram benzaconine.		
12	Beating	31.	
41	,,	33.	Reflex excellent.
66	,,	35.	Circulation very good.
80	,,	33.	
126	,,	32.	
276	,,	32.	Circulation not quite so active.
356	,,	31.	

Large Dose.

PEGGED frog of 26 grams. Exposed heart. Powerful heart, beating 20 per minute.

Minutes.

0	Inject ·007 gram. benzaconine into dorsal sac.		
7	Beating	21.	Not quite so powerfully ; systole prolonged.
17	,,	20.	Much less action.
32	,,	20.	
47	,,	19.	Feeble and pale. Ventricular wall becomes bloodless in systole, but there is not much blood circulating.
63	,,	16.	
79	,,	17.	

Minutes.

140	Beating	16.	But little blood circulating.
220	,,	18.	
310	,.	24.	Heart pale, flaccid.
343	,,	24.	
403	,.	24.	

24h.—Beating 16.   Auricle and ventricle beat in steady regular sequence, but very feebly.   No circulation.   Tied excised heart on cannula. After circulating the usual blood solution (20 cub. centims.), the two circulations figured were obtained (fig. e).

Fig. e.
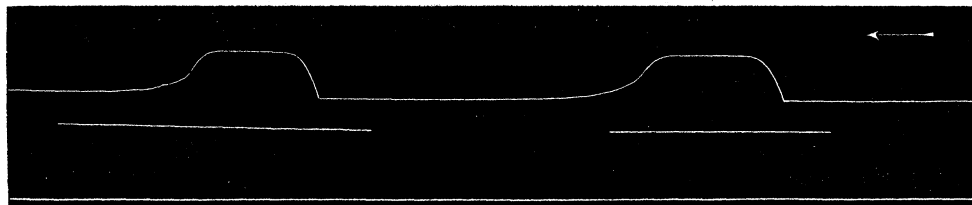
Perfusion of Frog's Heart.

These contractions show a long persistence of the maximum of systole and a marked retardation in the diastolic phase.
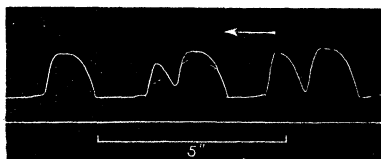
Fig. f_1.   Fig. f_2.
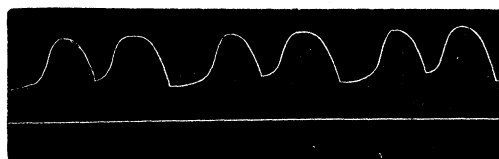
Perfusion of the heart beating spontaneously (fig. f_1) with ·0015 gram of benzaconine, causes a quicker rhythm (fig. f_2), with powerful systole, and a retardation of diastole.

Fig. f_3.   Fig. f_4.

As a further effect, there is produced a long low systole (fig. f_3) with gradual and incomplete diastole, and, as seen also in the case of the heart poisoned *in situ* (e), slowing is produced.   On washing out fully with RINGER's solution, a prolonged, but stronger, systole is recorded (fig. f_4).   The impression made by benzaconine upon the heart is a very enduring one.

Action on Vagus Endings in Heart and on Venous Sinus.

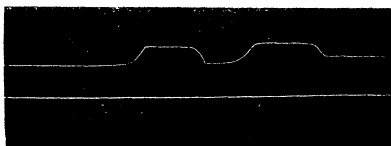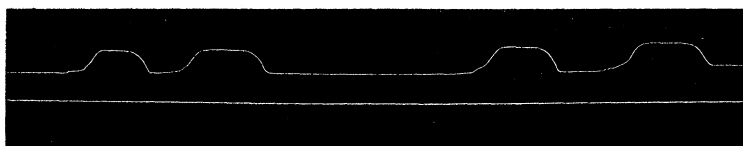Benzaconine does not, until poisoning is far advanced, produce an indifference of the heart to vagus stimulation, though an impaired effect may be observed somewhat earlier. After inhibition ceases, this stimulation may cause acceleration. The stimulated sinus arrests the heart throughout, indeed it has been noted more than once that this stimulation finally arrested the benzaconine heart.

Antagonism of Digitaline and Atropine.

The ventricle which has been reduced by benzaconine to a feeble, and as regards the circulation, almost inoperative, systole is materially strengthened by perfusion with digitaline solution. This is more operative as an antagonist than atropine, which has only a feeble and transitory effect in rousing the benzaconine heart.

General Conclusions.

The main effect of benzaconine on the frog's heart is to reduce the irritability of structures originating contractile effort. The muscular substance, though not early affected, ultimately becomes feeble in its response to stimulation. The very imperfect antagonism of atropine may show that the main cause of slowing and reduced strength of systole after benzaconine does not lie in a stimulation of inhibitory apparatus. As in the case of mammalian myocardium, the character of contraction and relaxation of the frog's heart is modified by benzaconine; prolongation of the systolic phase, and a retarded diastole occurring.

Benzaconine on Frog's Respiration.

After large sub-lethal doses of benzaconine, the respiration may fail altogether, the heart continuing its action. This suspension has been observed to last from 2 hours to over 24, but respiration recommences as motility revives.

The chief features observed in the action of such a dose, are (1) a relative increase in the major or true respiratory movements of the hyoid, which approximate in number to those of the flank, the minor movements being reduced in number; (2) a rapid reduction in the number of the true respiratory movements. Such a reduction, accompanied by failure in strength, may proceed till only a very faint and slow undulatory movement of side and hyoid is registered.

The extensive movement of the side accompanying inflation of the lung and expulsion of its contents, is much less frequently observed after benzaconine than after aconitine, whilst the restoration of respiratory function has less of the rhythmical tendency than is seen after the stronger alkaloid.

It is to be remembered that motor nerves are strongly affected by benzaconine, and that even in presence of some measure of activity in the respiratory centre, the

manifestation of the latter will be liable to reduction, owing to peripheral failure. A large, but sub-lethal dose of benzaconine is followed by entire suspension of respiration, though not for so long a time as after aconine.

Experiment V., 18.   Frog, 23 grams, sitting free.   Levers in position, that on side (above) writes downwards on inflation (inspiration), and hyoid (below) lever rises on protrusion of hyoid.   Card III.   Fig. G.   25 millims. = 5 seconds.

Fig. g_1.
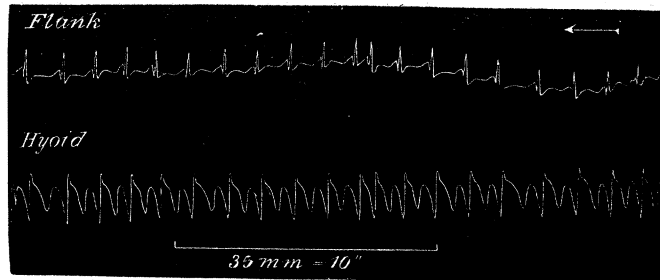
Minutes.

0	Movements of *side* per minute .	48	Panting, with large movements of inflation. A slight impulse of side corresponds to minor or hyoid movements (fig. g_1).
	Major . . .	48	At this time the major movements are relatively more frequent than they were before.
	Movements of *hyoid.*		
	Minor . . .	48	
0	. . . .		Injected ·005 gram. benzaconine into the dorsal sac.
12	Movements of *side* per minute .	33	All minor movements have now disappeared.
	,, ,, *hyoid* ,, ,, . .	33	The hyoid reverts to protruded position, but its elevation, causing depression of the lever, occurs with regularity (fig. g_2).

Fig. g_2.
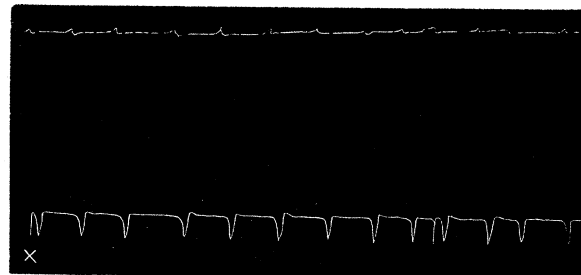
Minutes.

16   Movements of *side* per minute   .   30   The side movements are very feeble,
      „   „   *hyoid*   „   „ about 30   though they show, like the hyoid,
                                                      rhythmical fluctuations in force with
                                                      pauses in between (fig. g_3).

Fig. g_3.
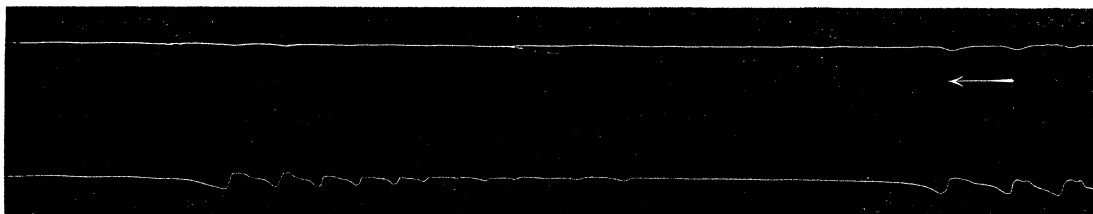
32   One movement of side every   This is reduced to a feeble and ineffec-
      100 seconds (about).   tive wave (fig. g_4).   (15′ cylinder.)

Fig. g_4.

28 m.m. = 1′

35   No eye reflex remains.   Reflex in legs is present.

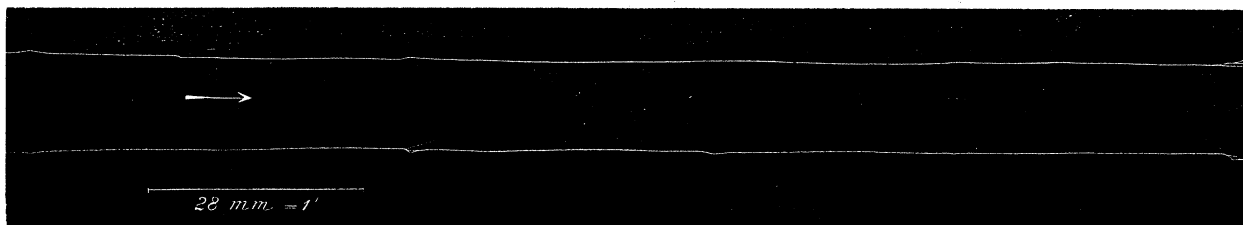50   All reflex movement has disappeared except to strong stimulation.   Respira-
      tory waves are just detectable.

92   Very faint undulatory movements of side and hyoid occur, showing slight
      expiratory and inspiratory phase every 80 seconds.   Stimulation does not
      affect respiratory phenomena.

127   Undulations are still detectable, and have a rate of about one in two minutes.
      From this time, respiratory movements may be said to have ceased.
      Recovery took place.

Total abolition of respiration is much more gradual after a lethal dose of benzaconine than it is even after a medium sub-lethal dose of aconine, and this would be antici-pated if it is remembered how long some evidence of activity is left in the motor nerves of frogs poisoned by the former.   Beyond this point, however, there is considerable correspondence in the effect upon respiration produced by these bodies. Whilst motor nerve endings in the respiratory muscles are early depressed in function, a similar effect upon the respiratory centre checks the origination of respiratory movements.   The linked mechanisms for hyoid and flank respiration are equally involved after the early disappearance of mimetic movements from the former.

Lasting collapse of the lungs may frequently indicate after benzaconine, as after many other poisons, that a lethal effect will follow.

On Reflex Movement.

Reflex in the lower limbs of frogs only outlasts voluntary movement by a short time; exceptionally they disappear simultaneously. Reflex in the fore outlasts that in the hind limbs.

The following experiments were made after TURCK's method upon brainless frogs :—

FROG of 24 grams pegged.   Left vessels ligatured.   Feet immersed separately.
Acid solution 1–1000.

Time.	Left.	Right.	Notes.
minutes.	seconds.	seconds.	
0	1·5	2	
0	1·5	2	
			Inject ·0075 gram benzaconé into dorsal sac.
10	1·5	1·5	
20	2	2	Withdrawal of right leg is slapping and uncertain.
30	2·5	..	Jerked in 2 seconds, not out in 20 seconds; circulation feeble.
40	2·5	..	Circulation barely moving.
60	2·5	..	Jerked in 12 seconds.
80	..	..	Circulation moving very slowly; jerked in 12 seconds.
100	2·5	..	
130	2·5	..	Acid 1–850. Both jerked in 5 seconds, neither out in 20 seconds.
240	1	..	Acid 1–500. First immersion, left, out in 1 second.
390	1	..	Circulation recovering. Left reflex good. Reflex returning in right leg.

FROG of 26 grams.   Pegged.   Vessels to left leg ligatured.   Speed of withdrawal after separate immersion in acid, 1–800.

Time.	Left.	Right.	Notes.
minutes.	seconds.	seconds.	
0	1·5	1·5	Inject into dorsal sac ·0032 gram benzaconine.
5	1·5	1·5	
16	1·5	1·5	Withdrawal feebler than left and rather jerking.
21	1·5	1·5	(1st) 2 minutes on the third immersion jerking in 4 seconds, but not withdrawn, though the left leg (not immersed) is actively moved.
36	1·5	2	Same phenomena as above.
51	1·5	2	Though twitched in 5 seconds, no withdrawal of immersed foot though left flexed.
73	1·5	2	Not out at all though twitched in 2 seconds.
90	1·5	..	„ twitched in 1·5 seconds.
120	1·5	..	Twitched in 2 seconds, not withdrawn though long immersed.

Strengthening of the acid solution, though stimulating the right foot to a few unsustained withdrawals, soon failed to elicit more than the twitching without sustained muscular effort described above.

In time even the twitching ceased, whilst the left leg still responded freely to stimulation ; 5 hours after poisoning the twitch returned in the right leg and gradually power of withdrawal was restored.

The first experiment shows a marked decline in reflex excitability in the poisoned leg, and it also indicates a reduction in the reflex function of the cord. This is referrable to interference with the circulation as well as to a direct action.

(Attention is directed to a side note, viz., that there is an unsustained withdrawal of the right leg, it is withdrawn from the irritant, but at once returned to it. This is explained by the action of benzaconine upon motor nerves.)

The smaller dose administered in the second experiment is not followed by any marked reduction of reflex activity of the cord. The results described indicate a primary and powerful effect upon the motor apparatus on the poisoned side. This proceeds only slowly to total paralysis : there is a long period during which two or three movements are to be elicited from the foot, each response being fainter than its predecessor.

On Sensory Nerves.

That sensory nerves are ultimately affected is undeniable, but this action is produced much more slowly, so that a sensory stimulation to the poisoned foot is followed by cross reflex after direct movement has ceased. Even after the legs have ceased to respond, a slight movement in the arms on stimulating the foot shows sensory conduction to and through the posterior columns of the cord to be existent.

Excitability of Motor Nerves.

It has been already noted that, if reflex is elicited from a brainless frog deeply poisoned by benzaconine, that reflex is frequently powerful for one or two responses, and then diminishes and disappears for a time. Voluntary movement is seen to fail in the same way, the nervous system being intact.

So with indirect stimulation of a muscle nerve preparation ; two or three contractions may occur to feeble stimulations, but thereafter it may fail to respond, or else require a very strong stimulation to provoke response.

After an interval of rest this phenomenon is again observed, and so it is in the separated preparation. Holding this observation in view whilst testing the minimal irritability of motor nerves, as few stimulations were administered as practicable, and it then became evident that in cases of moderate poisoning (the experimental proceeding being the same as described for aconitine) the point of minimal excitability varied but little as between the poisoned and protected sides.

FROG, pegged, of 33 grams.   Left vessels ligatured.   Right free—nerves on threads. The position of the secondary coil from the primary, at which the first contraction occurred, is represented in centimetres in the curve.   (The secondary coil is first approximated and then distanced with regard to the primary, the mean of the two results being taken.)

Time.	Left.	Right.	Notes.
minutes.	centims.	centims.	
0	17·5	18·5	
0	16·5	17·5	Inject ·005 gram benzaconine into dorsal sac.
10	15·5	17	
20	16	17·5	
30	16	18	
40	17	19	
50	18·5	16·5	
60	18·5	16·5	
70	19	16·5	
80	17	16·5	
90	17	16·5	
100	17	16·5	
110	16·5	16	
120	16	15	
140	16	15	
160	15·5	15	
240	16	16	
24th	14·5	14·5	

There is evidence here of a slight temporary increase of excitability after benzaconine, though this is soon lost sight of, and the reaction thereafter is practically parallel with that of the protected nerve.

In cases of still deeper poisoning, especially when the heart showed unusual resistance, stimulation of the poisoned nerve caused contraction in three experiments, at 9·5 centims., 6 centims., and 5 centims. respectively, whilst the companion protected limbs responded at 15, 19·5, and 16 centims.

Excitability of motor nerves is entirely suspended by doses of benzaconine just insufficient to arrest a vigorous heart.   Though all these facts may be demonstrated with the aid of single induction shocks, similar phenomena follow stimulation by faradisation, the muscle yielding a good preliminary contraction, which shows a tendency to break down if stimulation is extended to 2 or 3 seconds.   The subsequent failure of response on repeated stimulation and recovery after a rest pause are both witnessed.

BRAINLESS frog of 24 grams. Leg vessels of left side ligatured. Injected dorsal
sac ·0035 benzaconine. As soon as the reflex was reduced on the unligatured
side to a couple of consecutive movements, companion nerve preparations were
made and tested.

The minimal excitability of the nerve was greater by 1 cub. centim. on the
poisoned side.

Tetanising currents of 1·5 second's duration gave the following altitudes of con-
traction (lever X, 3·5 ; weight = 20 grams axial).

	Millims.		Millims.
Ligatured nerve . . .	22·5	Ligatured muscle . . .	23·5
Poisoned nerve . . .	21	Poisoned muscle . . .	23·5

The tracing illustrates the failure of the nerve.

Tetanus at 15 centims. (Fig. h_2.) Stars indicate where stimulation took place.
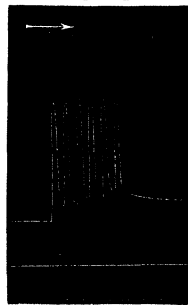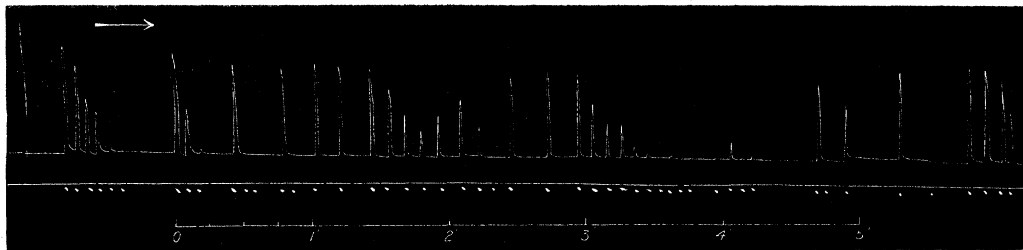
Fig. h_1.

Fig. h_2.

Mins. Secs.

0   0   First stimulation, 21 millims. ; 2nd, 17·5 ; 3rd, 11 ; 4th, 9 ; 5th, 1 ;
            6th, inoperative.

0   45   Three effective stimulations.

1   10   One effective stimulation.

1   35   One   „   „
            Rapid repetition of stimulation at from 10 to 15 seconds causes a single
            feeble response.

Mins. Secs.

5   0   When stimulation is given every 8 seconds there is no response, or only the feeblest twitch, until a longer pause is permitted, and then contractions return.

6   20   First contraction, 20·3 ; 2nd, 17·5 ; 3rd, 15 ; 4th, 10.

The poisoned muscle gives a good and steady series of contractions on repeating stimulation. The protected nerve (fig. h_1) transmits a series of strong contractions to 3 seconds tetanus.

Fig. h_3.
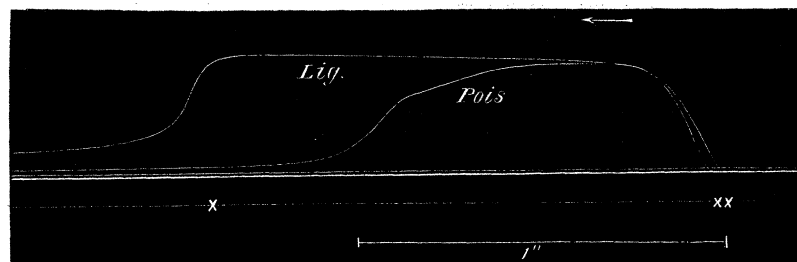
The protected muscle contracts well, stimulation being direct. A contrasted tetanus (first stimulation after 60 seconds' rest) of the poisoned and unpoisoned muscles is given in fig. h_3, both being stimulated from their nerves. It will be observed that though the initial contraction is practically equal, yet the muscle on the poisoned side relaxes whilst stimulation is in progress.

Return of Contractility after Rest.

A time of rest (varying in direct proportion to the degree of poisoning by benzaconine) restores contractility.

If, however, stimulation is repeated during the necessary rest interval, the time of reappearance of contraction may be postponed almost indefinitely. Thus, if the requisite pause interval is from 60 to 80 seconds, a series of three or four stimulations repeated every 30 seconds will delay the return of active contraction until in the end the requisite pause supervenes. If the pause is barely sufficient, only one or two feeble contractions will follow stimulation; if it is longer, a group of five or six, or even more, may be registered. In all cases a rapid decline in altitude is witnessed. In a frog deeply poisoned by ·006 gram benzaconine, in which all reflex except a single slight movement had ceased, a muscle-nerve preparation was placed in the muscle chamber, and stimulations were made by faradising the nerve for 3 seconds. If such stimulations fell within 30 seconds of each other no contraction followed the second and subsequent stimulations. The early part of the tracing (i) shows that the muscle will only yield a single tetanic shortening, unless a rest interval of more than 30 seconds is permitted. When the interval is 1 minute and upwards the ensuing contraction is roughly proportionate to the extent of the precedent pause.

Time from last stimulation.		Height of tetanic shortening produced.
mins.	secs.	millims.
2	0	10·5
0	30	0
1	0	3·5
2	0	12
3	0	14
4	0	16
5	0	23
6	0	23·5

After this point lengthening of the pause did not increase extent of contraction. Practically, therefore, in this case, 5 or 6 minutes' pause was requisite in order to restore the excitability of the nerve end-plates in order to transmit a single (for the time being maximum) tetanising impulse to the muscle.

The points previously mentioned are sufficiently well illustrated in this tracing, and the course of such an experiment is so uniform that the experimenter may foretell the result of his stimulation to a bystander without risk of failure.

In an early stage of poisoning the muscle may react many times to indirect stimulation, but failure of response eventually resulting, a rest time is required to restore contractility. This rest time is shorter than that needed after deeper poisoning.

On the Muscle Curve.

The following experiment illustrates the steady but rapid decline of altitude of the muscle curve, and the restoration after a rest of 3 and 4 minutes respectively.

PEGGED frog of 24 grams, poisoned by benzaconine, ·004 gram. The vessels of the left leg having been previously ligatured. Reflex was still active when the two muscle nerve preparations were made. The stimulation is by a series of opening induction shocks (at 8 coil centims.) delivered at the rate of 49 per minute to the nerve. Lever amplifies 10 times. Fig. k, 1–4. Fig. k_1 results from repeated indirect stimulation of the nerve on the protected side.

Minutes.

0   Poisoned leg. 23 stimulations exhaust contractibility entirely (k_2), the curve becomes lower and longer; it is about 6 minutes since the last stimulation. First contraction, 19 millims.

3   Partial recovery. 10 stimulations exhaust the nerve terminations (k_3). First contraction, 11·5 millims.

7   After a pause of 4 minutes (k_4) the original contraction is high (16·5 millims.) and rapidly relaxes. A quick fall succeeds and after 20 stimulations reaction fails.
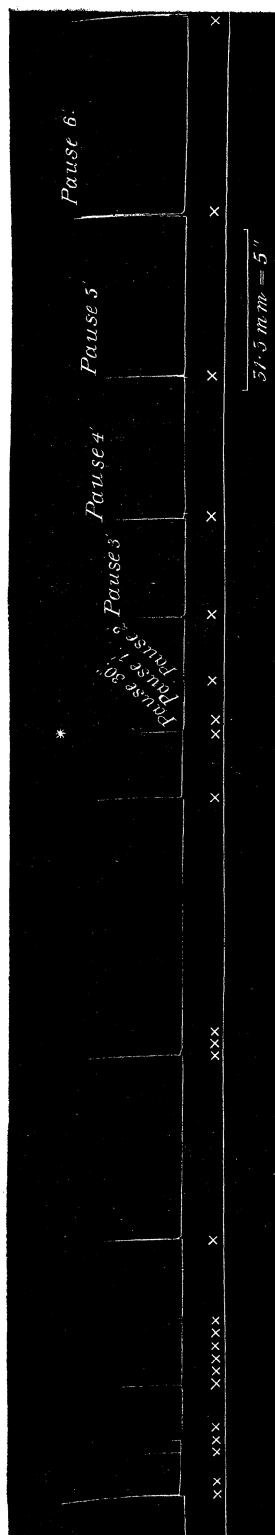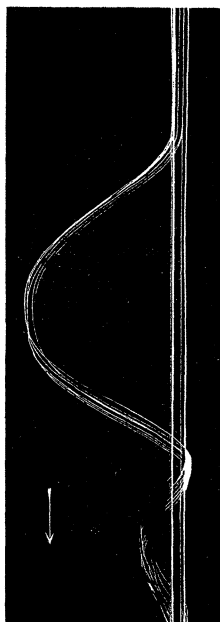
Fig. i.

Pause 6.

Pause 5'

Pause 4'

Pause 4

Pause 3'

Pause 3

Pause 2

Pause 1'

Pause 30'

51·5 m m = 5"

Fig. k₂.

1"

Fig. k₁.

Fig. k₄.

4 after k₃.

Fig. k₃.

3 after k₂.
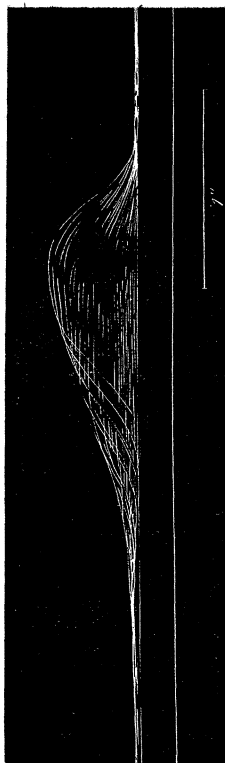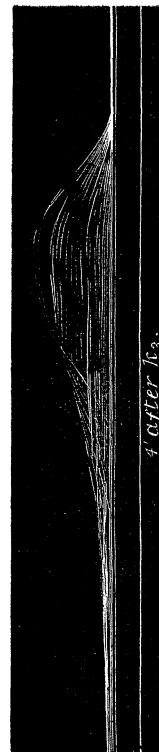
These figures fully illustrate the modification the muscle curve undergoes after benzaconine, evidence of rapid fatigue being shown in the lengthening of contraction and fall of altitude, the residual contraction being also increased.

Exhaustion of motor nerve endings is in part causal to these phenomena, and it is further clear that they are capable of becoming fatigued when they do not transmit an influence, developing a coordinate muscular contraction. This fact, as well as the consideration that they recover when circulation is suspended, seems to show that accumulation of waste products from muscular contraction does not contribute to the failure.

Action on Skeletal Muscle, including Muscle Curve.

Minimal excitability of the muscle tissue is reduced by benzaconine. In seven experiments it was found that the impairment occurred uniformly in 5, the extent being from 1 to 3 centims. (distance of secondary coil from primary). In the two remaining experiments there was equal excitability on the two sides.

Contrasted with the normal or protected muscle, the muscle exposed to the free action of benzaconine is (though responding well at first to repeated single induction or faradic stimulations) unable to sustain its original contraction, a breaking down of tetanus and decline of altitude appearing. This decline is not so abrupt as when the nerve is stimulated, but it is of the same character, for a time interval is needed to restore contractility. This interval is shorter than that necessary after indirect stimulation. As the result of repeated single induction shocks, the curve tends to become slightly longer and distinctly lower. All these points may be demonstrated at an earlier stage of poisoning if stimulation is indirect rather than direct, but it is clear that the muscle substance is rendered—

(1.) Incapable of executing a long series of maximal contractions.
(2.) Liable to a rapid development of fatigue, with complete failure of contraction.
(3.) Capable of recovery after exhaustion by permitting a rest pause.

Experiment.—A brainless frog, in which the vessels of one leg were completely ligatured, received benzaconine ·27 gram per kilo. In 4 hours, the reflex from left leg was strong and repeated. The right was only drawn up once.

Two muscle nerve preparations were made and at once tested. Stimulation was by 2 seconds' faradisation, followed by 3 seconds' rest. Coil, 6 centims. Weight axial, 10 grams. Lever, X 7. Indirectly stimulated the poisoned gastrocnemius gave a single tetanus—no more—to repeated stimulation, the unpoisoned giving a good series, though attended by much passive contraction. After 5 minutes' rest the poisoned muscle directly stimulated (l_2) gave a series of contractions, soon failing,

and on resting for 3 minutes the same result followed, but the failure was even more rapid. The normal muscle shortens rapidly to the repeated strong stimulation (l_1).

Immersion Experiments.

Immersion of 1 . . . . The nerve alone.

,,   ,, 2 . . . . The muscle alone,

was practised in these experiments; solution of ·05 grain to ·5 grain benzaconine per cub. centim. being employed. Without giving details of the results, a summary may be introduced.

(1.) Though a very transitory increase in excitability may sometimes be observed, the only well-marked effect of benzaconine is to depress conduction by the nerve trunk as well as of the motor nerve terminations in muscle.

(2.) The effect on the nerve trunk is only slightly less rapid than on the nerve terminations.

(3.) Muscular tissue is reduced in excitability and in its contractility.

(4.) There is never any evidence of fibrillation on stimulation.

On Peripheral Motor Apparatus.

Though stimulated motor end-plates soon fail to rouse the muscle which still re-acts to direct stimulation, it is evident that the muscle substance itself loses its contractile power when deeply under the influence of benzaconine. Contractile power is regained after a pause, this rest interval being shorter than when indirect stimulation is made. There is no tendency to passive shortening, even under strong stimulation, and in this respect the poisoned muscle (l_2) contrasts with the muscle of the ligatured side (l_1).
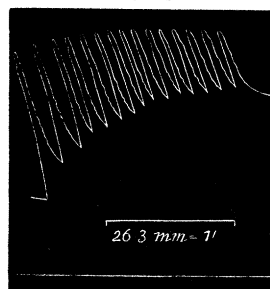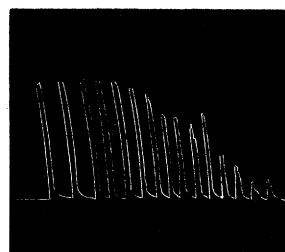
Fig. l_1.

Fig. l_2.

26 3 mm - 1'

Lethal Dose of Benzaconine.

Cats.—Animals which were the subjects of blood pressure experiments, and therefore etherised, furnished the following figures :—

(1.) Animal breathing naturally, ·025 gram (in two doses) per kilo. arrested respiration in three hours.

(2.) Animal artificially respired, ·0245 gram per kilo.

Rabbits.—The fatal dose is about ·0272 gram per kilo.

Guinea-pigs.—The lethal dose is between ·0238 gram and ·0275 gram per kilo.

Frogs.—·284 gram per kilo.

Thus the fact becomes evident that benzaconine is in given dose about 10 times as toxic to the gram of the rabbit as to the gram of the frog.

BENZACONINE.—ILLUSTRATIONS.

Figs. a 1–4. Progressive action of benzaconine on auricle, ventricle, and pulse :—

Fig. a_1. Before injection. Left auricle above. Left ventricle intermediate. Pulse below. (In all tracings movement upwards represents systole).

Fig. a_2. 30 minutes after benzaconine.

Fig. a_3. 45 minutes after benzaconine.

Fig. a_4. 58 minutes after benzaconine.

Figs. b 1–3. Action of benzaconine on auricle, ventricle, and pulse.

Fig. b_1. Before injection. Pulse above. Left auricle intermediate. Left ventricle below.

Fig. b_2. 25 minutes after benzaconine (·022 gram per kilo.)

Fig. b_3. 65 minutes later.

Fig. b'_3. Spontaneous vaso-contractor waves (pulse slow throughout). At X sciatic (central) stimulation.

Figs. c 1–6. Tracings showing carotid pulse before and after benzaconine ; and

Figs. c' 1–3. Pressure before and after benzaconine.

Fig. c_1. Before injection. (Abscisse constant in c_1 c_2 c_3.)

Figs. c_2, c_3. After injection.

Figs. c_4, c_5, c_6. Three arrests of heart. (Abscisse lowered.)

Fig. c'_1. Original blood pressure.

Fig. c'_2. Record of intermissions, 18–25.

Fig. c'_3. Record of intermissions, 37 during inspection.

Fig. d. Slow record of pressure (below) and respiration (above) in advanced poisoning by benzaconine, the body temperature being much reduced.

Diag. a. Rectal temperature (upper line) and corresponding number of respiration (lower line) in rabbits receiving varying amounts of benzaconine.

Fig. e. Contractions of frog's heart after deep poisoning with benzaconine and then circulating 20 cub. centims. blood and phosphate of lime solution.

Fig. f_1. Frog's heart perfused with blood-phosphate solution, spontaneous and induced beats.

Fig. f_2. 2 minutes after circulation of benzaconine ·0015 gram benzaconine.

Fig. f_3. 10 minutes after circulation of benzaconine ·0015 gram benzaconine.

Fig. f_4. 2 minutes after washing out with original solution.

Fig. g_1. Frog's respiratory movements. Upper line—flank lever (moves downwards in protrusion). Lower line—hyoid lever (moves upwards in protrusion).

Fig. g_2. As above, 12 minutes after benzaconine, ·004 gram.

Fig. g_3. As above, 16 minutes after benzaconine, ·004 gram.

Fig. g_4. As above, 32 minutes (slow cylinder).

Fig. h_1. Repeated tetanus from stimulating nerve of ligatured leg.

Fig. h_2. Tetanus from stimulating nerve of slightly poisoned leg. Stars indicate stimulation by faradic current of 1·5 second's duration.

Fig. h_3. Tetanus recorded on quick surface of muscle unpoisoned (outer) and poisoned (inner), both stimulated indirectly.

Fig. i. Tetanic (3 seconds), stimulation (indirect) of benzaconine muscle deeply poisoned. Stars indicate stimulation. A pause of at least 6 minutes between stimulations is necessary fully to reinstate nerve endings. No response if stimulations not separated by more than 30 seconds.

Fig. k_1. Ligatured side. Repeated opening stimulation of nerve. Record on rapidly moving surface.

Fig. k_2, k_3, k_4. Poisoned side. Repeated opening stimulation of nerve. Record on rapidly moving surface.

Three groups of contraction recorded, a rest pause of 3 minutes and 4 minutes intervening.

Fig. l_1. Series of (2 seconds) faradic stimulations followed by 3 seconds' rest of gastrocnemius (directly stimulated) on ligatured side.

Fig. l_2. Series of (2 seconds') faradic stimulations followed by 3 seconds' rest of gastrocnemius (directly stimulated) on side poisoned by benzaconine.

SECTION IV.—ACONINE.

INTRODUCTORY.

Many investigators who have made a study of the pharmacology of aconitine, have also devoted attention to another alkaloid, the so-called "napelline," named by HÜBSCHMANN in 1852. SCHROFF* noted that 1 gram given to a rabbit occasioned chewing, salivation, retching, impaired respiration, uncertain movement, weakness and death. After four times this dose administered hypodermically, death ensued from respiratory failure in 42 minutes. BUCHHEIM and EISENMENGER† state that the "napelline" of SCHROFF produced effects which did not differ materially from German aconitine. Numbness of the tongue, salivation and slowing of the pulse were observed in the case of students taking this preparation experimentally. MURRAY,‡ using TROMMSDORF's preparation, noted in frogs after ·005 gram a paralysis of motility and respiration in which the heart did not share. Motor paralysis rapidly developing and lasting for days, followed injection of ·01 by BUCHHEIM and EISENMENGER, but the muscle curve, though elongated, was not rendered abnormal.

KLEBS found the effects of lycoctonine from *A. lycoctonum* very similar to those attributed by other observers to "napelline," and other descriptions of the action of the lycoctonine of TROMMSDORF, show many points of similarity.

Without further reference in detail to the literature of "napelline," it may be stated that from its recorded effects it is evidently in many instances largely constituted of the alkaloids benzaconine and aconine, together with some admixture of other alkaloids, amongst which aconitine is the most obvious. Actual analysis§ by one of us and F. H. CARR§ of some of these specimens of "napelline" fully confirms the supposition deduced from their action.

This section will be devoted to the pharmacology of aconine which was used in the form of hydrobromide. The doses mentioned refer to the amount of actual alkaloid administered.

As small doses were found to be comparatively inoperative, solutions were from time to time prepared having a strength of ·0648 to ·1296 gram of actual alkaloid per 1 cub. centim.

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* 'Beitrag zur Kentniss des Aconit. Wien,' 1871.

† 'ECKHARD's Beiträge,' 1870.

‡ 'Phil. Med. Times,' 1878.

§ DUNSTAN and CARR, "The Composition of some Commercial Specimens of Aconitine," 'Trans. Chem. Soc.', 1893.

ACTION OF ACONINE HYDROBROMIDE.

Placed upon the tongue solutions give rise to a simple bitter taste, which is not followed by any sensation of tingling and numbness.

On Blood Pressure, Pulse and Respiration of Warm-blooded Animals.

CAT of 2970 grams, etherised, in warm box. One splanchnic on thread, the other already cut. Vagi on threads.

Time.	Blood-pressure.	Pulse.	Notes.
minutes.			
8	108–136	162	Stimulation of splanchnic (coil 10).
15	24 millims. fall	163–106–168	Stimulation of L. vagus after section (coil 10).
24	114	186	
28	..	..	Inject ·0648 gram alkaloid hypodermically.
	114	186	
54	..	168	
65	116	168	Inject ·0648 gram alkaloid.
71	119–91	166–92–159	Slowing as marked as before on vagus stimulation.
80	112	166	
88	110–134	170	Stimulation of splanchnic (coil 10).
109	110	176	Clots removed.
122	108	..	Inject ·0648 alkaloid (or ·065 per kilo. in all).
123	110	180	
142	108–134	164	Stimulation of splanchnic.
164	..	164	
174	110–88	174–102	Stimulation of vagus (coil 10).

During this time no appreciable effect on the rapidity of the pulse or on the blood-pressure is observable, neither are the terminations of vagi or splanchnic in any way affected. The experiment was then terminated by injecting aconitine. The usual phenomena of aconitine poisoning resulted, but there was delay in the development of the toxic symptoms, death taking place 120 minutes after a hyper-toxic dose.

During the development of aconitine action, the splanchnic remained unparalysed. The vagus stimulation failed to cause a fall but reduced the irregularity of the heart for a short time.

Large Sub-lethal Dose.

CAT of 2270 grams etherised in warm box.   Usual preparation of arteries and vagi.

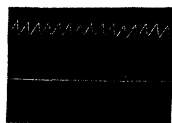Fig. I a.   Fig. I b.   Fig. I c.

For description of these and later, see p. 386.

A brief summary only will be given, fig. I.   (The tracing is taken with FICK's kymograph, the abscisse is not constant.)

Time.	Pressure.	Pulse.	Respira-tion.	Tempera-ture.	Notes.
minutes. 0	154	174	29	36·5	Fig. I a. Stimulation of left (divided) vagus (coil 10) causes a fall of 78 millims.
0	..	..	..	..	Inject ·166 gram of aconine per kilo. hypodermically. (If the lethal dose for cats and guinea-pigs per kilo. are equal, this would represent less than two-thirds of the lethal amount).
20	146	172	26	36·1	
60	144	171	25	..	(I b.)
204	143	181	24	36·6	Stimulation of vagus as before caused fall of 71 millims. (I c.).

It will be seen that practically no effect is produced by this large dose.   The pulse is firm and strong from first to last, and never deviates much from the original rate the pressure is only 11 millims. below the original level, the breathing slightly accelerated, the vagus in full function.

Fig. I d.
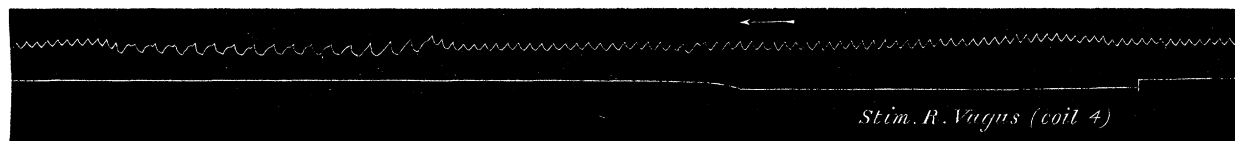

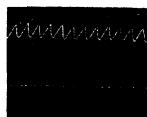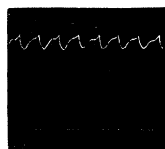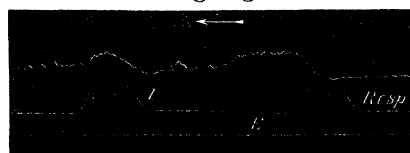Fig. I e.   Fig. I f.   Fig. I g.

In view of the fact that the experiment had lasted considerably over three hours, it may be assumed that a positive strengthening of the cardiac systole had resulted.

At this time it was resolved to test the action of aconitine, as previous experiments had led to the opinion that aconine antagonised the more powerful alkaloid to some extent.   The record of the continuation of the experiments is as follows :—

Time.	Pressure.	Pulse.	Respiration.	Notes.
minutes.				
208	..	..	..	Inject ·0078 gram aconitine.
250	..	..	..	Waves of fluctuation of pressure through 50 millims.
263	118	210	..	Stimulation of vagus causes a rise of pressure, with subsequent slowing (I d).
280	97	104	60	Phase of slowing of pulse.
293	..	..	..	Inject ·0013 gram aconitine.
285	..	243–122	53	Pulse passing from fast and irregular to slow (I e).
319	120–94	288	26	The phase of rapid respiration has passed.
325	..	104	..	Change from fast to slow, but regular pulse (I f).
335	120–92	312	6	Large respiratory movements. The pulse is much accelerated, but not irregular.
352	110–84	348	10	
370	..	282	8	Pulse rapid and irregular (I g).
409	94	380	14	The experiment was here terminated.

Thus 161 minutes after the injection of a hyper-lethal dose of aconitine, and 76 minutes after a further injection, the two together constituting a dose many times the lethal amount for an animal this size, the pressure was still fairly high though the pulse was enormously accelerated and irregular, the respiration being much slowed.   The vagi were paralysed.   From the whole course of this experiment an antagonistic effect of aconine towards aconitine upon the heart may be inferred.   Its action appears to consist rather in strengthening the systole and averting incoordination than in hindering acceleration.   There is, however, a tendency for the pulse to revert to a slow and steady rhythm, instead of breaking down as it would certainly have done, had aconitine, in the stated dose, been administered alone.

Experiment with Lethal Dose.

In this experiment a dose of ·4 gram per kilo. was administered, and would have been fatal (from respiratory failure) but for artificial respiration.   The usual preparation of the etherised animal was followed, and the reaction of left vagus and left sciatic nerves tested.   The animal breathed spontaneously through the ether bottle and the air by-way which was kept open throughout.

A short abstract will be made of the notes of this experiment.

Time commencing with injection.	Blood-pressure.	Pulse.	Respiration.	Notes.
minutes.				
0	138	144	18–21	
0	140–112	144–101	..	Left vagus stimulated.
0	..	..	..	Inject ·4 gram aconitine per kilo.
40	132	138	16	Breathing more superficial.
65	134	139	11	Heart slowed only slightly by vagus stimulation (coil 8).
80	135	141–147	10	On cutting right (remaining) vagus no rise of pressure, but pulse accelerated by 6.
110	136–132	..	..	Stimulate right vagus (coil 6).
143	50	132	6·5	Respiration failing, and pressure follows it.
144	..	..	0	For 20 minutes artificial respiration employed, which at once restores pulse and pressure.
155	130	134	..	
160	..	..	..	No spontaneous respiration, stopping artificial, causes rise of blood-pressure.
176	136	139	11	Spontaneous respiration is now witnessed. Stimulation of either vagus is inoperative. Stimulation of sciatic always occasions rise.
190	137–35	132	..	Respiration again failing, artificial respiration.
220	134–146	140	..	Large non-respiratory waves of pressure. Experiment terminated.

ACONINE ON GUINEA-PIGS.

This alkaloid is relatively inert when contrasted with aconitine. Doses of ·13 gram to medium-sized guinea-pigs caused lethargy with occasional rigor, but no marked paralysis.

GUINEA-PIG of 672 grams. Breathing 60. Kept in box at temperature of 17·5 C.

Minutes.

0   Inject ·13 gram aconine (·193 gram per kilo.).

36   Respiration 58. Runs well. Slight shudder. Head sinks a little.

46   Apathetic. Not anæsthetic.

54   Runs a step if roused. Has shudder and head sinks.

72   Respiration 56. Occasional lurch with rigor. Runs a step or two.

88   No dyspnœa. Respiration 54.

133 No starting or dyspnœa. Has not moved for 30 minutes, but if roused runs well.

148 Has urinated. Eating. Recovering.

Two days after, the animal being perfectly normal, showing Cheyne-Stokes respiration.   Injected ·162 gram (·241 per kilo.).

Minutes.

40   The same symptoms as before have appeared.

48   Has powerful rigors at intervals of 12 to 25 seconds.   Body raised and shaken all over.   Runs a step or two, but is ataxic.   The feet brought down with a " dump."   Body warm.   Has urinated and defæcated.

58   Spasms stronger; occur at intervals of 18 seconds, 3 seconds, 11 seconds, 3 seconds, 11 seconds, 2·5 seconds, 14 seconds, 3 seconds.   No spasm if taken up; no anæsthesia; struggles, chews, runs well if put down.

64   Shudder returns.

98   No marked rigor.   Urinated.

103   Runs freely ; no spasm or abnormality.

Lethal Dose.

Minutes.

0   Guinea-pig of 644 grams.   Respiration, 92.   Temperature, 38° C.   Injection of ·1944 gram aconine (·301 gram per kilo.).

25   Respiration, 84.   A little apathetic.   Head sinks.   Temperature, 37°·6 C.

35   Shudder.   Hind legs weak.   Temperature, 37°·2 C.

43   Respiration, 72.   Distinct shudder—no spasm.   Hind legs much weaker than fore.   A little general anæsthesia.

51   Shudder stronger.   Grinding teeth ; dyspnœa ; though kept in warm box feels cold.

55   Respiration, 16.   Gasping with strident sound and strong shudder.   Temperature, 30° C.

59   Powerful gasping.   Heart 120, good.   Eye reflex going.

65   Breathing fainter.   Eye reflex gone.   No spasm.   Temperature, 36°·3 C.

66   Dead.   Heart, all parts beating.   The left ventricle very feebly.   Right side full.   Right ventricle and auricle much more vigorous.   Lungs normal.

Reaction of gastrocnemius on stimulating sciatic is distinctly impaired.

The actual cause of death here was clearly respiratory failure.

In another lethal experiment the proportion of ·315 per kilo. was effective in 20 minutes.

The amount of the alkaloid at disposal was insufficient for the estimation of the lethal dose for rabbits.

The lethal dose for guinea-pigs, originally located between ·241 and ·301 gram per kilo. body weight (see two experiments quoted), appears from later experiments to be about ·275 gram per kilo.

ACTION OF ACONINE ON WARM-BLOODED ANIMALS.

Summary.

Circulation.—There is no marked variation in the speed of the heart under aconine beyond a slight slowing, which is to some extent reduced by vagotomy. The pulse is firm and the force of the systole appears to be increased.

The blood pressure is steady (except when there is threatened failure of respiration), and very well maintained during prolonged observations. The vaso-motor centre and its peripheral connections are unaffected. The (cardiac) vagus is weakened only by lethal doses of aconine. This weakening does not, however, produce a marked acceleration of the heart. Aconine, to some extent, antagonises the tendency to asequence of the ventricle, and incoordination produced by aconitine.

Respiration.—A marked slowing of respiration follows large doses of aconine (and may proceed to a lethal issue, if artificial respiration be not employed). This is mainly due to depression of the respiratory centres, the discharges from which become less frequent and less energetic. Vigorous artificial respiration may for a time revive the function of these centres. The reduced activity of motor nerve terminations occasioned by lethal doses of aconine is in degree contributory to the respiratory failure.

Nervous System.—The peculiar clonus, with ataxic movement; loss of power in the hind limbs and then in the fore, are attributable in part to an effect upon motor nerves, but it is probable that the origination of motor impulses is interfered with, and their conduction hindered. Entire loss of volition and of eye reflex precede death by a short time only.

Temperature.—A serious reduction in rectal temperature has been observed only in those cases in which respiration is greatly depressed.

Secretion.—There is no increased salivation nor urination.

Lethal Dose.—For cats this is less than . . . ·4   gram per kilo.
        and more than . . . ·166   ,,
    For guinea-pigs it is . . . . ·275   ,,

Post-mortem.—There is some reduction in response to motor nerve stimulation.

The heart shows active contraction in all its parts, excepting in the left ventricle, which is usually in systole. Electrical stimulation is operative in other parts of the organ.

ACONINE ON FROGS.

(1.) *Sub-lethal Dose.*

The symptoms of a large sub-lethal dose are unvarying; they are—increasing torpor, failure of respiration and of reflex in presence of a well-maintained circulation. No

symptom of irritation has been recorded, though there is transitory excitement of respiration.

Sub-lethal Dose.

Frog of 23 grams.

Minutes.

0   Received ·00648 gram of alkaloid in dorsal sac.

15   Spring short ; crouches on alighting—escapes, gets off back.

25   Spring very short, and on alighting may lie with legs out.   Respiratory movements are deep and slow.

40   Has not moved spontaneously since last note.   Lies flat with legs out.   Stimulation of foot causes some movement of all body.   If placed in dorsal position, faint ineffective struggle to rise.

47   On stimulation of foot there is faint twitch, but no withdrawal.

60   Reflex has disappeared, except slight in trunk and eye.   Circulation in web is excellent.

75   As above—lax, and apparently devoid of respiration.

150   There is slight increase of reflex in the legs.

245   After gradual return of reflex, animal crawls a little spontaneously, though legs are drawn up in rather jerky manner.   Circulation excellent.

338   The frog is now normal and mobile.   Springing well and escaping if left uncovered.

(2.) Lethal Dose.

Frog of 20 grams.

Minutes.

0   Injected ·0388 gram of aconine into dorsal sac.

12   There has practically been no movement since injection.   Reflex feeble.

15   Reflex from legs and eye gone.

18   Last trace of respiration disappeared.

20   Circulation in web excellent.

Hours.

24   Not the slightest sign of life, except slow circulation in web.

47   Circulation is very slow.   No sign of vitality otherwise.

72   As yesterday.

84   Circulation ceased.

Duration of Effect of Small Dose.

A dose of ·007776 gram to a frog of 22 grams (·3534 per kilo.) in 58 minutes caused a complete extinction of all reflexes, though respiratory movements were observed. This condition continued for 3 hours, when reflexes began to return, and in 6 hours

the animal was hopping about, though the spring was short and tremulous, and the legs often remained extended for a considerable time.

In 9 hours, the animal was abnormally active, springing repeatedly and often to quite an unusual distance.

Duration of Effect of Large Dose.

Hours.

0   A frog of 20 grams received ·031 gram (1·55 per kilo.) aconine in dorsal sac.

24   Circulation feeble ; no other sign of life.

48   Circulation feeble.

96   Circulation stronger ; no reflex of any sort.

118   Reflex has returned, and animal moves spontaneously.

Respiratory tracings taken from this animal will be referred to later on.

In this case, therefore, recovery occurs after aconine in the proportion of 1·55 per kilo.

Lethal Dose.

The frog just referred to received aconine at the rate of 1·75 gram per kilo. six days after the above experiment terminated, and this dose proved lethal. The lethal dose, therefore, lies between 1·55 and 1·75 per kilo. body weight.

In order to analyse the paralysing effect of the alkaloid, a double ligature was placed round the iliac and femoral vessels on one side of previously pegged or etherised frogs, which then received measured doses of aconine.

FROG of 18 grams. Etherised : ligatured vessels to left leg. After effect of ether had passed :—

Minutes.

0   Injected ·013 gram aconine into dorsal sac.

7   Perfectly quiet. Apathetic. All reflexes—position flat.

12   Reflex feeble from right foot to itself, but good to left.

16   No reflex from right leg to itself, but faint cross reflex to left.

25   All reflex gone from right—left moved once spontaneously.

36   No reflex of any sort from right. Eye reflex gone. Heart action good.

42   No reflex except in left leg.

58   Left leg moved.

60   Injected ·0013 gram strychnine (actual alkaloid) into ventral sac.

64   Left leg moved several times.

69   Left leg in firm tetanus—no other part of body affected. Stimulation of right foot does not cause any tetanus in left. Experiment terminated.

The experiment has been repeated in another form by administering guanidine hypodermically to a brainless frog. After the characteristic fibrillations and twitch-

ings of the muscles had become well developed, the vessels of the left leg were ligatured and ·010 gram aconine injected into ventral sac.

Whilst fibrillation was preserved on the ligatured side, it was abolished in 70 minutes after aconine on the unligatured. Reflex movement gradually reappeared on the right side, and was succeeded 325 minutes after injection of aconine by a return of fibrillation.

Guanidine has a peripheral action on motor-nerve terminations; this experiment shows that its action is suspended by aconine, which paralyses the nervous structures upon which guanidine acts; but, as the action of aconine is transitory, guanidine, which has a prolonged effect, again causes the characteristic fibrillations.

Medium Toxic Effect.

FROG of 26 grams.   Pegged.   Left vessels ligatured.

Minutes.

0   Inject ·00648 gram aconine.

90   Right foot feebly moved on stimulating.

Left promptly moved when itself stimulated.

Moderate cross reflex upon left to right.

115   Right no longer moved from direct stimulation.

Left well withdrawn. Circulation active in right web.

120   Destroy cord : Faintest twitch in right leg.   Strong movement in left.

Stim. pois. N, minimal   7   centims.   At both 4 and 2 centims. gave good series
                                          to induction shock and tetanus.

M,   7   ,,

Lig. N,   21   ,,   Gave excellent series of contractions.

M,   11·5   ,,   Gave excellent series of contractions.

Heart beating 21.   Regular and strong.

The failure of motor nerve terminations is here very marked, the motor phenomena strongly resemble those of curare poisoning.

Action of Aconine on Speed and Rhythm of Heart of Frog.

Medium Dose.

The action of aconine upon the exposed heart of brainless frogs produced a slight slowing which was persistent in character. Neither irregularity nor want of sequence was observed. If moderate doses are administered the ventricular systole remains strong and somewhat prolonged. The excitability of the organ is not materially altered by aconine.

Sub-lethal Dose.

PEGGED frog of 25 grams.   Ligature left sciatic vessels.   Expose heart.   Heart 20. ·
Minutes.

0	Inject aconine ·0077 gram.	
15	20.	Systole very powerful; long maintained.
30	20.	
40	18.	Powerful.
60	18.	
70	16.	Circulation full.
90		
130	17.	Reflex quite gone from unligatured side. Good on the left.
180	17.	
215	16.	
266	16.	

Hrs. mins.

7	10	17.	Reflex in both legs.
9		21.	Circulation full and strong systole.

In a similar experiment a dose of ·02 gram aconine reduced the rate of the heart from 38 to 29 in the course of 36 minutes.   (A normally rapid heart is proportionately more affected than a slow one.)   The administration of atropine, whether hypodermically or locally, did not cause acceleration.

Lethal Dose.   Followed by Atropine.

PEGGED frog of 17 grams.   Expose heart.

Minutes.

0	Heart steady for 15 minutes at 28 per minute.	
	Reflex good.	
0	28.	Inject ·020 gram aconine into dorsal sac.
8	27.	
14	27.	Leg reflex less active.
22	22.	Systole prolonged, diastole retarded.
30	20.	
38	16.	Reflex gone.
40	Inject atropine ·005 gram and apply locally to heart.	
48	16.	
56	13.	
61	14.	
72	12·5.	
80	11·5.	
95	11.	Systole now feeble from atropine.
120	11.	Sequence regular, beat failing, very little circulation.

Vagus and Venous Sinus Stimulation after Aconine.

Aconine produced slowing of the heart when the vagus had failed before injection to produce any inhibition.   If the vagus had proved active, aconine in doses sufficient to put motor nerve terminations out of play did not affect it ; only large sub-lethal and lethal doses were found capable of reducing or altogether suspending vagus action.   No acceleration of the heart followed this action.   Sinus stimulation has been seen in the large majority of cases to retain its controlling effect until the heart stopped beating spontaneously ; after this occurrence its stimulation, or frequently that of the vagus, provoked sequential contraction, lasting for a longer or shorter time.

It appears, then, that the slowing of aconine is not referable to a stimulation of inhibitory apparatus within the heart, which is controlled by the vagus, but that it rather limits the origination of motor impulses by acting upon some mechanism non-identical with the vagal.   The fact that atropine does not accelerate the heart slowed by aconine makes it improbable that this mechanism is that rendered active by stimulation of the sinus venosus.

*Aconine succeeded by Aconitine.*

If a dose of ·008 to ·015 gram of aconine is administered to a brainless frog with exposed heart, and about the time that entire failure of reflex takes place aconitine in dose slightly excessive of the certainly lethal amount is administered, the full train of aconitine symptoms does not follow.   If the dose of aconine is relatively small, the heart accelerates under aconitine, and may even develop the rhythmic churning movement so characteristic of the latter, but this phase passes, and the heart quiets down to a slow steady rhythm with a fairly good ventricular systole.

A larger proportionate dose of aconine may reduce this acceleration, and altogether hinder incoordinate movements, the heart continuing to beat strongly and steadily. The myocardium is not only strengthened in its systole, but the resistance to a sequence of the ventricle upon the auricle is increased by aconine, so that the dislocation which aconitine induces, as well as the incoordination and ultimate failure of the systole, are to a certain extent limited or prevented.   The largest dose of aconitine which has been antagonised is $1\frac{1}{2}$ times the minimum lethal dose.   (As it is not intended in this paper to do more than simply indicate the existence of antagonisms, this point will not be further developed here.)

Perfusion of the Frog's Heart.

The heart of a frog which has received a medium dose of aconine placed on KRONECKER'S cardiograph, and filled with perfusion solution, shows a steady and powerful systole, with some delay in diastolic phase.

Circulation of aconine solution through the excised but unpoisoned heart brings about a well-marked change in the form of the systole. This change is characterised by a powerful contraction long continued, and succeeded by a very gradual passage into diastole. The commencement of the diastolic phase frequently shows an arrest which is suggestive of spontaneous reduplication. Apart from this a tendency to paired systolic contractions is common.

Fig. II. a.   Fig. II. b.   Fig. II. c.
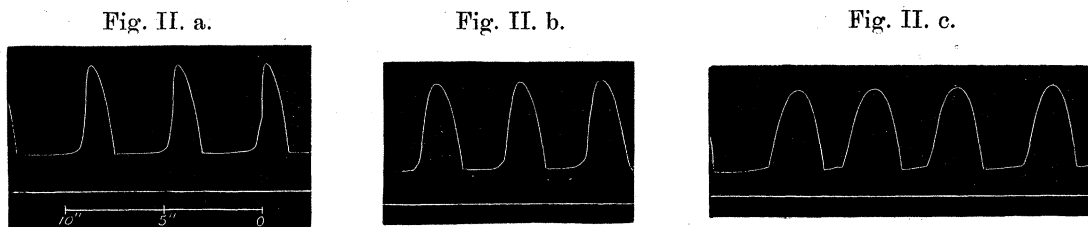
The following experiment illustrated by fig. II. was made with the normal heart of a winter frog kept in the laboratory for some days before the experiment. Laboratory temperature, 48° F. All the recorded beats are spontaneous. The altitude of contraction is given as well as duration of the active ventricular cycle.

Fig. II. d.   Fig. II. e.
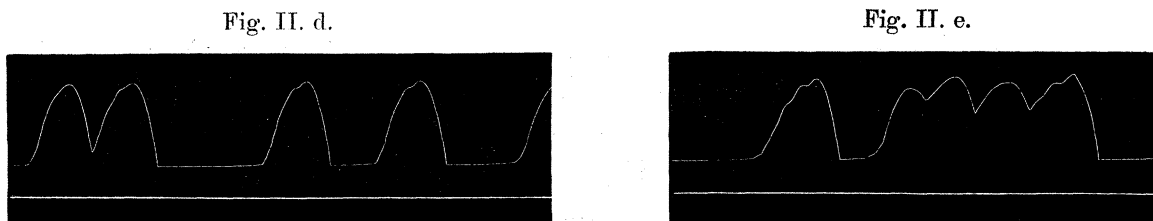
Time.	Altitude.	Duration of ventricular cycle.	Remarks.
minutes.	millims.	seconds.	
0	18·5	1·75	Fig. II. a.
0	..	.	Circulate ·00065 gram aconine.
4	18·25	2·25	Fig. II. b.
7	..	..	Circulate ·00065 gram aconine.
9	16	2·75	Fig. II. c.
13	..	..	Circulate ·0013 gram aconine.
15	16·5	3·25	Fig. II. d.
23	..	..	Circulate ·0013 gram aconine.
27	..	..	A series of contractions without relaxation at first recorded. The single contractions show two notches during passage into diastole.
31	16	3·75	Fig. II. e.
33	16	3·6	

In all ·0039 gram has been circulated in the course of the experiment.

Action of Aconine on the Respiration. (Frogs.)

A small dose of aconine (·0013 gram) causes a slight transitory acceleration followed by slowing and weakening of both side and hyoid movements. Thus, a reduction to the extent of 30 per cent. may be registered in the speed of respiration, but acceleration is observed as the effect of the drug passes off.

(It has been observed that, as a preliminary to respiratory movements which culminate in inflation of the lung, a gentle movement of trunk and limbs takes place. This does not result in any change in position of the body, but immediately afterwards the distension of the lung is seen to have occurred.

This phenomenon, which is also frequently seen after benzaconine, may indicate that muscles are brought into play which do not usually contribute to the respiratory act. It is only seen after minor degrees of poisoning.)

After larger, but distinctly sub-lethal doses, the side movements are rapidly reduced in number and extent, and the large movements of inflation and partial emptying of the lungs are practically absent, though gentle fluctuations may be present for a time. Intermittent hyoid movements outlast those of the side, but they are also reduced in extent and speed, and finally disappear, as in the case of the side. A slow wave-like movement of the floor of the buccal cavity without any active respiratory impulses may occasionally be observed. The return of respiration is heralded by a few gentle movements of the side and hyoid, the lung tending to expand slightly, and this expansion is succeeded by a slow and almost passive reduction in bulk, practically unattended by active movement of either side or hyoid.

Entire restoration of respiration gradually follows.

FROG of 24 grams. Sitting free, and breathing easily.

Minutes.

0 (Fig. III. a.) Side, 72 (about) ; hyoid, 140 per minute.   Inject ·015 gram aconine.

5 (Fig. III. b.) Side, 80 (about) ; hyoid, 156 per minute. The movements are less extensive.

20 (Fig. III. c.) Side, 44 ; hyoid, 54 per minute. The movements are gradual and wave-like.

32 (Fig. III. d.) The side shows gentle slow waves ; the hyoid still has phases of more active movement at intervals. One of these is seen in fig. III. d.

55 Respiration has ceased.

364 (Fig. III. e.) Respiration having recommenced, slow but slight waves of expansion and contraction of lung are seen. The length of the wave given is 4 minutes 15 seconds. Irritation of the foot will now cause respiratory waves, but no movement of foot.

Hour.

30 (Fig. III. f.) Side, 44 (about) ; hyoid, 148 per minute. Animal sitting free and can spring well.
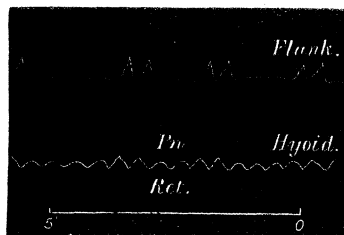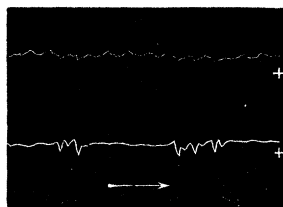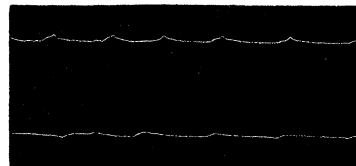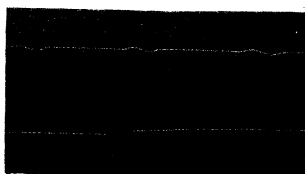
Fig. III. a.

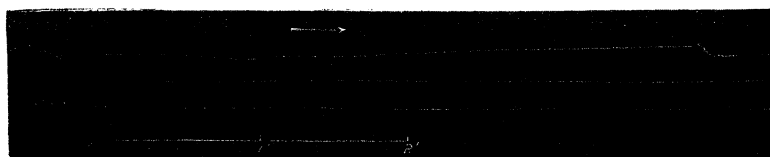Fig III. b..
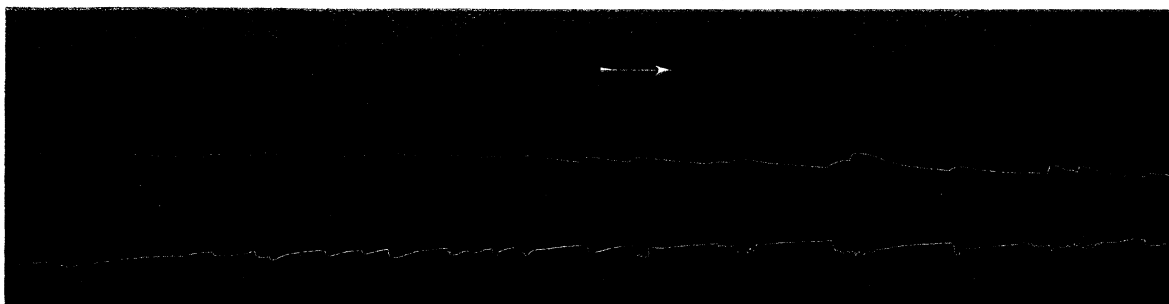
Fig. III. c.

Fig. III. d.
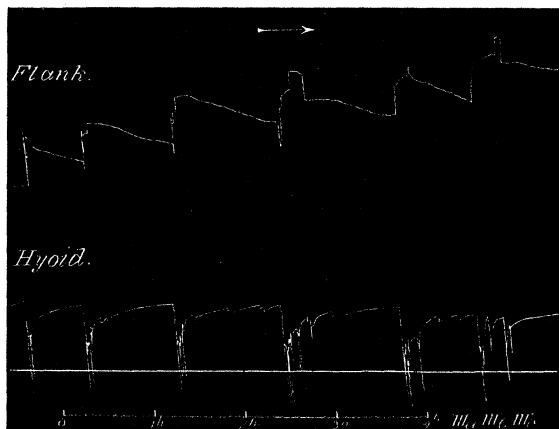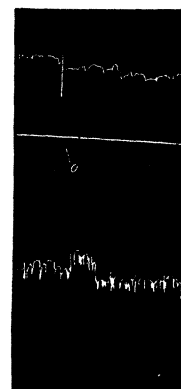
Fig. III. f.

Fig. III. e.

Fig. IV. a.

Fig. IV. b.

Fig. IV. c.

Large doses, as ·016 to ·023 gram, administered to a frog of 24 grams abolish all trace of flank movement within 30 minutes. If the primary effect of aconine is closely watched, it will be seen that some degree of respiratory movement persists for a time after the disappearance of the ordinary reflexes. Thereafter, for four or five days, not the slightest pulmonary respiration, as evidenced by movement, is discernible. The sides do not, however, collapse if the dose is sub-lethal. After such a lapse of time the respiratory movements begin to develop, and finally—usually about a week after administration of aconine—they are perfectly normal.

Records upon a very slowly rotating cylinder, having a horizontal movement of 12 millims. in one hour, have shown that the return has at first the appearance of slow and insignificant undulations of flank and hyoid, the latter being detected first. These recur three or four times in an hour ; an increasing inflation of the side is usually present. There is not much development beyond this point till reflex begins to return, when phases of slow distension of the lung are terminated by a marked partial emptying succeeded by a second distension. The hyoid remains for the most part in a protruded position, but is actively and extensively moved during the partial emptying of the lung. Finally the movements become more frequent, showing briefer phases of rest, and the respiration, as it originally existed, is re-established.

Experiment.—A normal frog of 24 grams* received ·0162 gram aconine. For four days there was no respiratory movement whatever. On the fifth day slight waves appeared, which in the evening developed into a stronger movement (fig. IV. a) On the morning of the sixth day reflexes were still absent, but in the afternoon they were feebly indicated, and powerful movements of the side and hyoid, with intervals of about 80 minutes, were registered late in the evening (fig. IV. b). On the seventh day, though quite free and with all its reflexes, the animal was so apathetic that it sat without movement, the excursions of the side being relatively small, the hyoid active (fig. IV. c) at short intervals. At 4 P.M. the animal sprang off the board and the experiment terminated.

It is interesting to note that the motor nerves of respiration retain their function longer, and, after poisoning, regain it sooner, than is the case with those supplying the muscles of the legs.

Aconine on Reflex.

The experiments were made upon pegged frogs in which the vessels of one leg—the left—were ligatured. The immersion of the toes in acid solution was made alternately.

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* This experiment is referred to at page 372, under " Duration of Effect."

I. 17.—FROG of 25 grams, prepared as above (Diagram 1).

Time.	Left.	Right.	Remarks.
minutes.	seconds.	seconds.	
0	2	2	Acid for testing reflex, 1–650.
0	..	..	Inject ·013 aconine into dorsal sac.
5	2	1·5	
10	2	1 5	
15	2	1·5	
20	2	2	
25	2	2	
30	2·5	2 5	
35	2·5	3·5	Twitch at 2·5 seconds.
40	2·5	..	Twitched in 3 seconds, nearly out in 5 seconds; but the left leg and arms are actively moved.
45	2	..	Not out in 15 seconds, as above.
50	2	..	,, ,, ,,
55	2	..	Nip of right toes causes no movement of right; but slight of arms and left leg.

Diagram I.

——— From leg to which vessels ligatured.
············   "   "   "   "   poison had access.
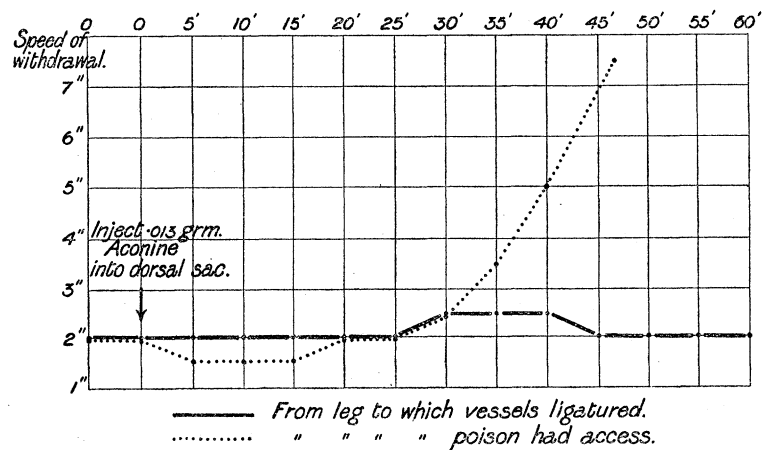
Examination of the gastrocnemius muscle with attached nerve was made at once, when it was found that indirect stimulation caused a mere muscular twitch to the strongest opening induction shock, whilst stimulation of the nerve on the ligatured side caused a powerful contraction.

In another experiment in which ·0162 gram of aconine had been administered in 48 hours, distinct reflex was still obtained from the leg on the side of the ligatured vessels.

The result indicated in these experiments is uniformly obtained. The reflex activity of the cord is not materially altered, but the terminations of motor nerves are markedly depressed in activity by aconine.

On Sensory Nerves.

The reflex phenomena, in the experiment just quoted, indicate that cross reflex is obtainable at a certain period of the poisoning, when stimulation of the unligatured leg has ceased to produce direct reflex action, and, therefore, that at this stage, the sensory nerve is capable of transmitting an impulse causing withdrawal of the protected foot, whilst the leg upon the open side having its motor nerve terminations paralysed, is no longer moved. (It is only in a prolonged experiment that a slight impairment in function of sensory nerve termination is witnessed, and this is probably attributable in part to other agencies, such as the frequent immersion of the toes in irritant fluid.)

Aconine on Motor Nerves.

Periodical testing of the point of minimal irritability of the motor nerve, the terminations of which are exposed to the action of aconine, demonstrates a reduction which makes its appearance in from 40 minutes to 60 minutes after poisoning, by such small doses as ·008 gram, and progresses rapidly thereafter.

In a small proportion of experiments, about 1 in 3, a slight initial increase of excitability has been noticed.

Larger doses impair excitability in a few minutes.

Experiment.—PEGGED frog of 30 grams.   Ligatured vessels of left side.

(The figures indicate the distance of the secondary coil from the primary.)

Time.	Left.	Right.	Remarks.
minutes.	cub. centims.	cub. centims.	
0	19·5	20·5	
0	..	..	Injected ·01 gram aconine into dorsal sac.
10	19·25	20	
20	19·5	20	
30	19·5	21	
40	20·5	21	
50	20·5	18	
60	19·5	15	
70	21	10	
80	20·5	12·5	
95	20	7	
115	19·5	5	
135	..	..	
290	15	3	A faradic stimulation causes, at 3 cub. centims., a feeble pointing of toes only on the right side.

The excitability in this case is slightly increased at first on the open side, but in 50 minutes the curves cross one another, and a rapid decline follows.

I. 18.—PEGGED frog of 25 grams.   Left vessels ligatured.

Inject ·01 gram of aconine, and before reflex had disappeared from the open leg, made nerve muscle preparations from each side, and subjected to stimulation. Lever X4.   Single induction opening shock.

Ligatured leg—N. A good series of 11 millims. each.
    ,,   ,,   M.   ,,   ,,   11·5   ,,   ,,
Poisoned leg—N. A declining series ; the first measuring 5·5 millims.
    ,,   ,,   M. A series better maintained than of the nerve at 8·5 millims.

Tetanising Stimulation.

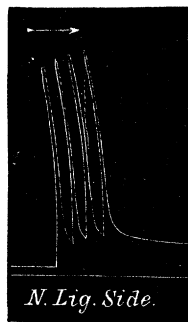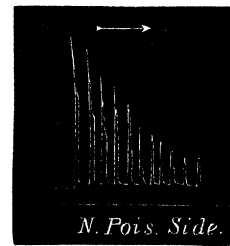Fig. V. a.   Fig. V. b.

Ligatured leg—N. (V. a) 40 millims. well sustained on repetition.
    ,,   ,,   M.   41   ,,   ,,
Poisoned leg—N. (V. b) 31 to 6 millims. in the course of 11 stimulations.
    ,,   ,,   M.   33 to 34   ,,   ,,   ,,   5   ,,

The interesting point in the tetanus of the nerve on the poisoned side (V. b) is the rapid failure of response and the fact that rest permits of some degree of recovery.

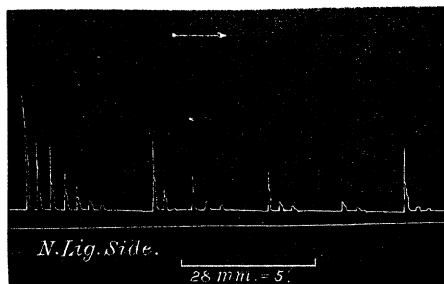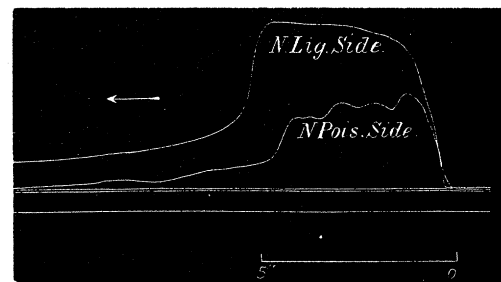Fig. V. c.   Fig. V. d.

This phenomenon is therefore somewhat like that produced by benzaconine, but the recovery is neither so perfect nor so systematic (V. c).   From a tracing taken on

a more rapid cylinder the character of the tetanus obtained from the nerve on the left side and on the poisoned side (V. d), the latter manifesting a clonic breaking down, will be understood.   Though the tetanising current was admitted for not more than 5 seconds, relaxation was far advanced when stimulation was suspended.

Action of Skeletal Muscle.

Minimal irritability was found to be reduced on stimulation of the muscle itself, but only to the extent of 2 or 3 centims. (position of secondary coil).   When the stimulation was delivered of maximal strength, a good series of contractions resulted to single opening shocks, and a powerful succession of contractions to faradic currents.

Some impairment in altitude was recognised in about half of the experiments performed.   In these cases the variation between the tetanic curve of the poisoned and the normal muscle, did not amount to more than 4 or 5 millims. (the lever multiplying 4 times).

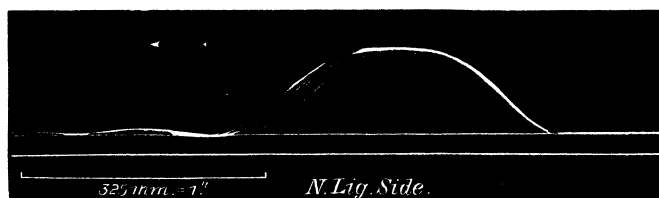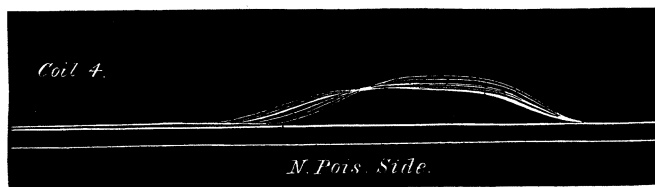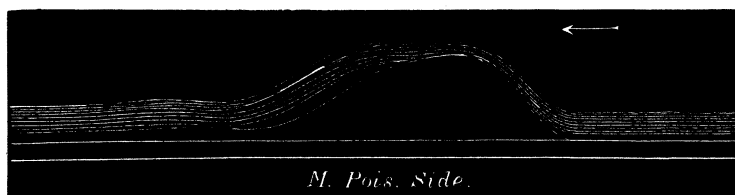## The Muscle Curve.

Fig. VI. a.

Fig. VI. b.

Fig. VI. c.

The muscle curve when taken from the poisoned muscle, indirectly stimulated, is low and tends rapidly to fall in altitude whilst it lengthens at every stimulation (VI. b).   When stimulation is direct a good series is given without such changes.

(In VI. c the close approximation of the secondary coil causes a progressive tonic shortening.) The frog which furnished these curves had received ·008 gram of aconine. There is no fundamental difference in form of the curve which separates it from that obtained from the unpoisoned muscle (VI. a), the latter being identical for direct and indirect stimulation.

Immersion of Nerve and Muscle in Aconine Solution.

A reduction of irritability of both nervous and muscular tissue are produced in an accelerated form upon immersion.

Two muscle nerve preparations of the gastrocnemii of a frog of 27 grams were prepared and immersed in 10 cub. centims. of phosphate of lime solution with blood (see diagram II.).

Diagram II.
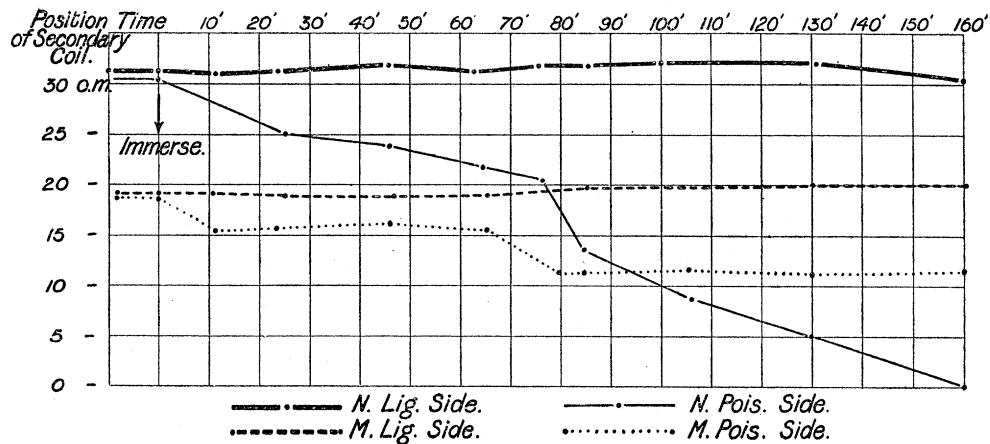
This solution preserves the irritability of nervous tissue very well. (In making a preparation for such a purpose when no graphic registration is desired, it is convenient to retain the femur and remove the thigh muscles except at their origin, at which point a ligature includes them and the sciatic nerve. By this means the nerve is left in the usual condition of extension, and is thoroughly exposed to the action of solutions, whilst the electrodes are easily slipped beneath it.)

Minimal Irritability.

Minutes.	No. 1.	No. 2.
0	N. 31·5	N. 30·5
0	M. 19	M. 18·5
0	..	Add ·0130 gram of aconine
11	{ N. 31 { M. 19	N. 31 M. 16·5
25	{ N. 31·5 { M. 19	N. 25 M. 17
47	{ N. 32 { M. 19	N. 24 M. 16·5
61	{ N. 31·5 { M. 19	N. 22·5 M. 15·75
75	{ N. 32 { M. 19·5	N. 20·5 M. 12
85	{ N. 32 { M. 19 5	N. 14 M. 12
105	{ N. 32 { M. 19·5	N. 8·5 M. 12
130	{ N. 32 { M. 20	N. 5 M. 11·5
160	{ N. 30·5 { M. 20	N. 0 M. 12

The result obtained is a constant one : the motor nerves and their terminations being gradually depressed at first, and rapidly subsequently. The effect upon muscular tissue is also fully apparent. Evidences of such stimulating action of the nerve endings as aconitine produces, are here entirely wanting.

Aconitine fibrillation and twitching is abolished by aconine, or its occurrence is prevented, if the latter be first applied.

ACTION OF ACONINE ON FROGS.

Summary.

Circulation.—The heart of the frog beats vigorously after doses of aconine large enough to abolish reflex and respiration in several animals. The systole remains powerful and maintained, whilst the diastole is to some extent retarded. There is slowing in rhythm, though not to a great extent, except after doses which interfere with the function of the organ. This slowing is not hindered by atropine. The sequence of the ventricle upon the auricles is undisturbed, and it has been seen that the disorder following aconitine is within certain limits antagonised by aconine. This antagonism appears not only to be due to a strengthened conduction of auricular impulses, but also to a stimulant effect produced on the myocardium by aconine.

Respiration.—Respiratory movement is rapidly abolished by medium doses of

aconine though it outlasts limb reflex.   It is last observed as a feeble rhythm of the hyoid.   According to the dose, hours or days elapse before a recurrence of movement, first recognised in the hyoid, is witnessed.   A series of true ventilating movements of hyoid and flank then appears and is repeated at long intervals.   Finally respiration resumes the normal type.

Nervous System.—(1.) *Central.*   The brain and cord are only involved in deep poisoning, but as, owing to peripheral motor paralysis volition cannot manifest itself, it is difficult to judge of the effect even then, unless a limb is sheltered by previous ligature of its vessels from the local effect of aconine.   Under such conditions reflex is elicited from the limb at a time when voluntary movement has ceased, and there is a presumption, therefore, that the higher centres are depressed before the reflex function of the cord is impaired.   This impairment is only witnessed after very large doses.

(2.) *Peripheral.*   Motor nerve terminations are reduced in excitability, or altogether thrown out of action at a time when sensory nerves are unaffected ; ultimately, however, there is a slight reduction in reaction of the latter.   Recurrent excitability in the nerve terminations is witnessed at a certain phase of poisoning.   The curve of the muscle obtained by indirect stimulation is of diminished altitude when contrasted with that of the sheltered muscle ; it falls and lengthens rapidly on repeating stimulation.   Reaction to faradisation (if present) is imperfect in extent and duration.

Muscular System.—The irritability of the aconine muscle is slightly reduced, but it reacts well to stimulation and yields a curve which does not differ materially from that of the sheltered muscle.

Lethal Dose.—The lethal dose of aconine for *R. Temporaria* is slightly less than at the rate of $1\cdot75$ gram per kilo.

ACONINE.—ILLUSTRATIONS.

Fig. I_a. Normal tracing of pulse (FICK) from cats carotid, and respiration (lever moves up in inspiration).

Fig. I_b. 60 minutes after injection of aconine.

Fig. I_c. 204 minutes after injection of aconine.

Fig. I_d. Stimulation of vagus after administration of aconitine.

Fig. I_e. Change of character of pulse.

Fig. I_f. Slow and regular pulse.

Fig. I_g. Pulse becomes irregular and rapid.

This tracing is taken 370 minutes after the injection of aconine.

Fig. II$_a$. Perfusion of normal ventricle of excised heart (KRONECKER).
         The contractions are spontaneous.
Fig. II$_b$. 4 minutes after circulation of aconine solution.
Fig. II$_c$. After further circulation of aconine solution.
Fig. II$_d$. After further circulation of aconine solution.
Fig. II$_e$. After circulation in all of ·0039 gram aconine.

Fig. III$_a$. Normal respiration of frog (unrestrained).
         Upper line (side), lever sinks on inflation.
         Lower line (hyoid), lever rises on protrusion.
Fig. III$_b$. 5 minutes after injection of ·015 gram aconine.
Fig. III$_c$. 20 minutes after injection.
Fig. III$_d$. 32 minutes after injection.
Fig. III$_e$. 364 minutes after injection.
Fig. III$_f$. 30 hours after injection.   Slow-cylinder record.

Fig. IV$_a$. Record of respiration of frog recovering on the fifth day after administration
         of a large dose of aconine.
Fig. IV$_b$. Record on sixth day.
Fig. IV$_c$. Record on 7th day.
         All taken on a very slow (24 hours) cylinder.

Fig. V$_a$. Repeated tetanus (indirect stimulation) from gastrocnemius on side of
         ligatured vessels.
Fig. V$_b$. From poisoned gastrocnemius (nerve stimulation).
Fig. V$_c$. Recurrent indirect stimulation of poisoned gastrocnemius.
Fig. V$_d$. Contracted tetanus of poisoned and unpoisoned muscles, both *indirectly*
         stimulated.

Fig. VI$_a$. Series of contractions to opening induction shock of muscle protected by
         vascular ligature from the action of aconine.   Indirect stimulation.
Fig. VI$_b$. Contractions obtained from stimulating nerve on poisoned side.
Fig. VI$_c$. Contractions obtained from stimulating muscle on poisoned side (coil,
         4 centims.).

Diag.   I. Aconine on reflex (frog).
         Reflex of poisoned leg (dotted line) and protected leg (black line).
Diag. II. Projection of aconine effect on excitability of nerve and muscle.

SUMMARY AND GENERAL CONSIDERATIONS.

The following is a summary of the pharmacological action of the alkaloids :—

ACTION ON THE CIRCULATION.

Aconitine at first stimulates medullary centres slowing the heart ; acceleration follows, auricles and ventricles taking up an irregular and (at one stage of toxic action) independent rhythm. Imperfect systole (especially in the ventricles) develops. Irritability of ventricular wall is much increased. Great variation of blood pressure accompany the preceding phenomena. After great ventricular acceleration, with very imperfect systole, delirium of the ventricles supervenes. The vagus (stimulated) continues to restrain speed of contraction (especially acting upon the auricle), and may favour closer sequence of ventricle upon auricular systole, so as to cause a rise in blood pressure. For the same reason, during a stage of sequence, it may cause the usual effect (fall of pressure). In slow poisoning the cardiac vagus ceases to produce any effect on stimulation. Atropine is unfavourable to the independent rhythm of auricles and ventricles, and also to the ultimate reduction of ventricular action into incoordinate contraction (delirium).

The vaso-motor centre is at first stimulated, but later depressed in function, whilst peripheral splanchnic stimulation is active to some degree throughout poisoning.

Diacetyl-aconitine, whilst producing effects in the main resembling those of aconitine, shows less tendency to cause independent rhythm of ventricles upon auricles. In half the experiments made, a failure of systole occurred without a sequence—in the remaining half an aconitine-like effect was witnessed.

The cardiac vagus is less affected than by aconitine, but its effect on stimulation depends much upon the sequence or non-sequence of ventricular upon auricular action present at the time.

The vaso-motor centre and peripheral vaso-constrictors respond to this alkaloid much as they do towards aconitine, but the stimulation in the early stage of action is less marked.

Benzaconine.—After very brief pulse acceleration, slowing, with reduction of blood pressure occurs, the latter being due mainly to the depression of the motor mechanism within the heart. After a stage of irregularity, during which full diastole of both auricles and ventricles only appears occasionally, a blocking of auricular impulses to the ventricle succeeds, so that a rhythm of 2 to 1 is produced. (After aconitine this state of affairs is largely reversed.) Complete though transitory failure in the production of a spontaneous beat (the ventricles being first involved, then the auricles) is seen in a large proportion of experiments. This is not due to stimulation

of inhibitory apparatus, which is put out of action by atropine, for the phenomenon occurs after atropine. It is referable rather to depression of the motor apparatus. Contraction returns spontaneously, either from spontaneous revival in excitability of this apparatus or from stimulation of the highly venous blood.

The vaso-motor centre, though depressed in function, retains some action, until the very low pressure results which maintains before death.

Vagus stimulation causes slowing, until in a late stage of poisoning, the blood pressure remaining very low, its action fails. After effective stimulation pressure rises beyond the original level from acceleration of the heart and strengthening of the systole.

Digitaline is (of the bodies examined) the most effective antagonist towards benz-aconine.

Aconine is, relatively to the three compounds just considered, harmless towards the heart. At first it stimulates the vagal roots slightly, causing a slower beat. As, however, it strengthens the systole of the ventricle, the blood pressure rises and is maintained at a high level throughout a long experiment. Asequence or disorder of rhythm is not produced, but an antagonistic effect is shown towards aconitine and diacetyl-aconitine. In this action aconine opposes independent rhythm of auricles and ventricles, facilitating the transmission of the normal impulse, and it opposes the tendency to delirium of the ventricle. Only lethal doses reduce the activity of cardiac vagus terminations. The vaso-motor centre is practically unaffected.

The circulation remains active in frogs for days, in entire absence of reflex and respiratory movements.

ACTION ON RESPIRATION.

Aconitine at first stimulates the respiratory centres and the sensory vagal fibres in the lung. Depression rapidly follows, death in Mammals being due to central respiratory failure. The peripheral innervation of respiratory muscles is not inter-fered with.

Diacetyl-aconitine produces a slighter initial stimulation than aconitine. Death results from central failure. Pulmonary œdema is commonly observed in rabbits. Respiratory spasm occurs at death.

Benzaconine does not appear to stimulate either respiratory centres or pulmonary vagus, as do the two former. The centres are depressed from the first; respiratory failure induces death without spasm. To this the reduced action of motor nerves on the respiratory muscles contributes.

Aconine, whilst slowing the respiration from its action upon the centres, also possesses a pronounced curare-like effect upon motor nerve endings in respiratory muscles. No spasm attends death.

ACTION ON THE NERVOUS SYSTEM.

Aconitine in large doses causes occasional loss of consciousness, with failure of conjunctival reflex and dilated pupil. This is not a directly narcotic effect, but is secondary to reduced oxidising power of the blood from circulatory and respiratory impairment. For a time there is evidence of stimulation of motor areas, and especially of the medulla, with its contained centres; to this depression succeeds; reflex centres in the cord are stimulated, and then depressed by large doses. In frogs voluntary movement outlasts reflex. Sensory nerves at the periphery are depressed in function after very transitory stimulation, whilst motor nerves are practically unaffected.

Diacetyl-aconitine produces a stimulation of the medulla, but less in degree than that caused by aconitine. The subsequent depression, especially of the respiratory centre, is well marked, the respiration being relatively more affected than the circulation. The general reflex function of the cord is depressed after preliminary excitement. The action with reference to sensory nerves is the same as that of aconitine, but motor nerve terminations, though they are not powerfully affected, are reduced in activity by diacetyl-aconitine.

Benzaconine causes a lethargic and ultimately semi-narcotised condition, which is referable to low intracranial blood pressure as well as to a direct action upon the cortex. Medullary centres are depressed from the first, whilst the only effect on cord reflex is long obtained in ligatured leg when the poisoned leg is stimulated, sensory nerves being unaffected except in deep poisoning. On the other hand, motor nerves and their terminations are reduced in function, a peculiar intermittency of response following poisoning.

Aconine only produces loss of volition and impairment of conjunctival reflex shortly before a large dose proves fatal. Motility is interfered with, but this is mainly due to a curare-like effect upon motor nerve endings. The respiratory centre is depressed, respiration failing when the heart still beats vigorously.*

ACTION ON OXIDATION PROCESSES.

All the four alkaloids here considered reduce the oxidising power of vegetable protoplasm, aconitine being most and aconine least active. Diacetyl-aconitine is here more energetic than benzaconine.

ACTION ON INTERNAL TEMPERATURE.

Aconitine produces a fall (exceptionally preceded by a slight rise) which develops and increases as respiratory slowing develops, but the minimum is reached (50–70

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* Changes in the electrical properties of nerves brought about by this group of alkaloids have been recorded by WALLER, with material provided by us. 'Proc. Roy. Soc.,' March 12, 1896.

minutes in rabbits) only after a partial recovery of respiration. Exposure to a cold atmosphere increases the fall and delays the recovery. Diminished oxidation produced directly, and through impairment of circulation and respiration indirectly, are apparently causal to the fall.

A dose of aconitine less than half the lethal proportion will cause a fall of nearly 2° C. below the normal.

Diacetyl-aconitine occasions less effect than aconitine on the temperature when the dose bears an equal relationship to the respective lethal doses. This is due to a less vigorous action on heart and respiration. Like aconitine it interferes both indirectly and directly with oxidation.

Benzaconine produces a trifling reduction of temperature until a dose is reached which greatly reduces the pulse and speed of respiration, when a proportionate fall occurs. The reduction of muscular movement tends still further to limit heat production. Proportionately to its toxic dose the effect is not so active as in the case of diacetyl-aconitine.

Aconine is inoperative towards body temperature except in very large doses, which enfeeble respiration and cause a curare-like action on motor nerve terminations. Even then the effect is relatively slight, as the heart remains active, and the vaso-constrictor system is still in play (lethal dose causing death (guinea-pig) in 60 minutes reduced the temperature by 1·7° C.).

ACTION ON SKELETAL MUSCLE.

Aconitine does not in ordinary lethal doses materially affect irritability, capacity for work, or form of contraction of frog's muscle. Exposure to the direct action of aconitine causes fibrillation and lengthening of the muscle curve (an effect resembling slight veratrine action has been described). Fibrillation is abolished by aconine and curare, and is, therefore, not attributable to the action of aconitine directly on muscular tissue, but to a stimulation of motor nerve endings.

Diacetyl-aconitine reduces the irritability of muscular tissue ; the muscle (after poisoning *in situ*) is more readily fatigued, the curve of contraction, therefore, losing in altitude whilst increasing in length.

Benzaconine in large doses produces rapid fatigue, with failure of contractility, which is, however, restored by rest. Contact of strong solutions reduces excitability and capacity for work.

Aconine in doses sufficient to immobilise frogs is inoperative. Larger quantities slightly reduce excitability and capacity for work, but have not the action so characteristic of benzaconine.

Lethal Doses.

The results are stated in decimals of a gram per kilo. of the body weight, and where two figures are given the lethal dose lies between them.[*]

	Cat.	Rabbit.	Guinea-pig.	Frog. (R. Temp.)
Aconitine	·000134	·000131	·00012	$\begin{cases} ·000586 \text{ (March)} \\ ·0014 \quad \text{(July)} \end{cases}$
Diacetyl-aconitine . .	·004–·00515	·0042	·0042	·039
Benzaconine	·0345	·0272	·0238–·0293	·284
Aconine	·166–·4	..	·275	1·55–1·75

General Considerations.

Our study of the pharmacology of these alkaloids has proved that the introduction of two additional acetyl groups into the molecule of aconitine does not create any pronounced variation in the pharmacological action, but results merely in a general weakening of the characteristic action of the parent alkaloid.

Considering next the effect of removing the acetyl group from aconitine, which is seen in the behaviour of benzaconine, we find that the characteristic features of aconitine action are almost entirely annulled. The great toxic power of aconitine has been entirely destroyed, so that the lethal dose of benzaconine for both cold and warm-blooded animals is relatively so considerable as to remove it from the class of poisons in the ordinary acceptation of the term.

In the action of benzaconine on the heart and circulation very little trace of the effects of aconitine can be observed ; whilst after the administration of aconitine the ventricles ultimately beat more rapidly than, and often independently of, the auricles, the opposite is the case in the action of benzaconine. On the heart, indeed, it acts to some extent as the antagonist of aconitine, slowing the heart, especially the ventricles, in opposition to the great acceleration produced by aconitine ; so that in a certain measure it is observed that benzaconine behaves as an antidote to aconitine poisoning, though not so effectively as atropine. This is a point of considerable practical importance when it is remembered that benzaconine occurs to a variable extent with aconitine in *A. napellus*, from which plant the ordinary medicinal preparations are made. The removal of the acetyl group has also abolished the stimulating effect of aconitine on the respiratory centres and the pulmonary vagus. On the other hand in its general action on the respiration and on temperature a certain resemblance is traceable between the depressant action of benzaconine and aconitine. Peripherally benzaconine depresses the activity of motor nerve endings

* See note p. 268.

and in a lesser degree of skeletal muscular tissue, whilst aconitine acts principally upon sensory nerve terminations.

In contrasting the action of aconine with that of benzaconine we are studying the effect of withdrawing a benzoyl group. It has been seen that in removing the acetyl group from aconitine we produce an alkaloid which is no longer a virulent heart poison ; the removal of the benzoyl or benzoic group from benzaconine furnishes aconine, which is so far from being a heart poison that it may be ranked as a general cardiac tonic, and in virtue of this action as the antagonist of aconitine. In a much greater degree than benzaconine it is an antidote to aconitine, so much so that we have found that the administration of aconine is successful in averting in small animals the effect of a lethal dose of aconitine. Amongst the distinctive features in the pharmacological action of aconine is to be noticed a curare-like effect on the motor nerve endings in the muscles, which is not observed with either aconitine or diacetyl-aconitine. No fault of sequence between ventricles and auricles, such as is observed, in opposite directions, after the administration of aconitine and benzaconine can be observed in the action of aconine. Aconine cannot be classed as a poisonous alkaloid, very large doses being necessary to produce death even in frogs.

The results of this enquiry, which has occupied the authors for the greater part of four years, bring out in a most striking manner the almost complete dependence of the extraordinary toxic power and pharmacological action of the aconitine molecule on the presence of the radical (acetyl) of acetic acid, whilst in a lesser degree the action of benzaconine is seen to depend on the existence in the molecule of this alkaloid of the radical (benzoyl) of benzoic acid. The inertness of the alkaloid, aconine, denuded of both the acetyl and benzoyl groups of aconitine, seems to the authors to be one of the most interesting facts in chemical pharmacology. From the practical point of view the authors regard the demonstration of the antagonism of aconine and benzaconine towards aconitine as an important result of this investigation, which, taken as a whole, it is believed, will throw into clearer light the mode of action of the alkaloids of *Aconitum napellus*.