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VIII. *Contributions to the Study of the Connection between Chemical Constitution and Physiological Action.*—Part II.

By T. LAUDER BRUNTON, *M.D., F.R.S.*, and J. THEODORE CASH, *M.D., F.R.S.*

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It is now more than four years since this research was begun, and it has necessitated such a large number of experiments that, if given in detail, they would fill several hundred pages, and, therefore, only a brief account of the results, with details of a few typical experiments, can be given here.

During the time we have been engaged in this research a great deal of work upon the physiological action of aromatic compounds has been done by other observers; but upon trying to collate their results, with a view to arriving at some general conclusions, it appeared that the conditions under which the various experiments have been carried out have differed to such an extent as to render comparison very difficult.

In this research we have endeavoured to perform our experiments as nearly as possible under the same conditions, so that the results should be comparable. We have employed bodies of comparatively simple constitution, so that differences in their physiological action might be readily connected with differences in their chemical structure.

PLAN OF THE RESEARCH.

The plan of the present research to a certain extent resembles that of our former investigations into the action of the compound ammonias.

We have studied :

1st. The alterations in action which occur when an atom of hydrogen in benzene is replaced by haloid radicles.

2nd. The action of the compounds formed when one, two, or more atoms of hydrogen are replaced by alcohol radicles.

3rd. The alterations produced by the introduction of one, two, or three atoms of hydroxyl.

4th. The alterations produced by the replacement of one hydrogen atom by the radicle  $\text{NO}_2$ .

5th. By the replacement of one hydrogen atom by the amidogen radicle ( $\text{NH}_2$ ).

We have also examined the modifications in the action of various members of the series by changes in temperature.

#### GENERAL RESULTS.

The most marked actions of those members of the benzene group which we have examined were exerted on the spinal cord and brain. The action on the spinal cord was indicated by a tendency to tremor and the action on the brain by lethargy.

We observed certain differences in the symptoms, both motor and sensory, caused by various members of the group. We were struck by the fact that the symptoms they cause in Frogs bear a certain resemblance to those produced by certain diseases of the spinal cord in Man. Thus, benzene causes a tremor which seldom occurs but when movement is attempted, and in this resembles the tremor of disseminated sclerosis, whilst monochlorobenzene, moniodobenzene, and also amidobenzene cause the movements to assume a violent slapping character, which reminds one of the movements occurring in locomotor ataxy, a disorder in which the posterior columns of the cord are affected.

#### METHODS.

The methods employed were :—

- 1st. To examine fully the action of the various substances upon the system generally of certain animals (Rats and Frogs being chiefly employed); and
- 2nd. To study their effect in detail upon the brain, spinal cord, nerves, and muscles in Frogs, and on the circulation in Cats.

#### (1ST.) GENERAL ACTION.

In the former class of experiments a known quantity of benzene or its compounds was injected in a state of emulsion into the dorsal lymph sac of a Frog or under the skin of the side of a Rat, and the progress of the poisoning observed.

#### OF EXAMINING THE (2ND, *a*) ACTION ON THE SPINAL CORD.

If it was desired to test the irritability of muscle, spinal cord, and nerve, after the toxic symptoms had developed, the animal was decapitated and the various organs just mentioned were tested in the following manner:—The upper portion of the spinal cord was exposed and stimulated by means of a faradic current of electricity, the electrodes employed having platinum tips terminated by short threads of silk moistened in blood serum and resting upon the cord. The action of the drug upon the excitability of the cord was judged of by the effect which stimulation of the cord had upon the muscles.

(2ND, *b* AND *c*.) ACTION ON NERVE AND MUSCLE.

The action on the cord having been ascertained, a preparation of the gastrocnemius and the sciatic nerve supplying it was made and placed in a moist chamber for examination. The nerve and muscle were then stimulated successively. Contractions resulting from single induction shocks were recorded upon a rapidly moving cylinder, and tetanic spasm of the muscle from stimulation by a faradic current was recorded on a slowly revolving cylinder.

(2ND, *d*.) BLOOD-PRESSURE.

The apparatus employed in the blood-pressure experiments was somewhat complicated, as we endeavoured to arrange it so that we could take a tracing of the mean arterial pressure representing a long time in a small space, and yet obtain at any moment on a more rapidly moving surface such a tracing as would give an actual

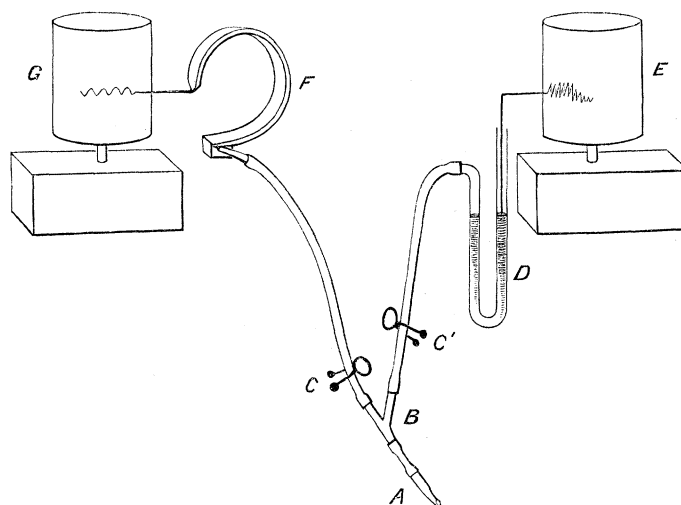


Fig. 1. Diagram to illustrate the apparatus used in registering the blood-pressure, pulse, and respiration.

*A* is the cannula for insertion into an artery. *B* is a Y-tube by which the artery can be put in communication either with a mercurial manometer *D*, or a Fick's kymograph *F*, or with both of them at the same time. *C* and *C'* are two clips by which the communication of either or of both manometers with the artery can be shut off at will. *E* is a slowly revolving cylinder on which the mercurial manometer registers the blood-pressure. *G* is a rapidly revolving cylinder on which the Fick's kymograph registers the pulse beats from time to time, and on which the respiration is also registered.

indication of both the number and the form of the pulse beats and respirations in a given time. This was accomplished by employing a mercurial manometer, which wrote on a blackened cylinder having a very slow speed of rotation (once in the hour), and in addition to this a Fick's spring manometer, which wrote upon a rapidly rotating cylinder. These manometers were capable of being clamped off from each

other, and the system of tubes leading to the Fick's manometer contained a very short length of thick walled india-rubber tubing, in order that the form of the pulse wave might be communicated as accurately as possible to the apparatus.

This may be more readily understood by means of the accompanying diagram.

At any time whilst the experiment was in progress, we were able, by clamping off the mercurial manometer and opening the clamp controlling the connection with the spring manometer, to obtain a tracing of the pulse unmasked by oscillation of the mercury in the former, which we could associate with the slow record by corresponding marks or figures. On the rapid drum we also registered the movements of respiration by means of a Marey's tambour, which was connected with a double tambour applied to the walls of the thorax.

SECTION I.—ACTION OF BENZENE AND SOME OF ITS COMPOUNDS ON FROGS.—  
GENERAL SYMPTOMS PRODUCED.—ACTION ON SPINAL CORD, MUSCLE, AND NERVE.

ACTION OF BENZENE  $C_6H_6$  UPON *Rana Temporaria*.

The general action of benzene on Frogs is to produce :—

- (A.) Lethargy and disinclination to voluntary movement ;
- (B.) Tremor and jerking, which always occur on movement, and sometimes to a slight extent when at rest ;
- (C.) Alteration in the response to stimuli ; and
- (D.) Subsequent paralysis.

The alteration in the response to stimuli observed in Frogs poisoned by benzene consists in :—

- (a.) Increased sensibility ;
- (b.) Diminished local movement ;
- (c.) General diffusion of movement.

For example, when the toes of a normal Frog are pressed very lightly, it generally happens that no movement occurs at all, or only a slight local movement of the foot away from the stimulus. In a Frog poisoned by benzene, such a stimulus produces tremor, not only in the foot touched but over the body generally, while if the foot is withdrawn at all the movement is feeble and tremulous.

*Effect of a Small Dose of Benzene.*

If one minim of benzene be injected into the dorsal lymph sac of a Frog, no marked symptoms are observed for from 15 to 30 minutes. At the end of this time, however, it is noticed that the leg, if gently extended, is drawn up with a tremulous or interrupted movement. This tremor develops further into jerking, which occurs



spontaneously and also whenever active movement, such as jumping or rising from the dorsal position, is attempted. This jerking may be accompanied by general movements of the trunk of a "ducking" or "huddling" character. There appears to be in most cases a temporary but distinct hyperæsthesia. This condition may appear exaggerated by attempted movement provoking tremor of the whole body. There are periods of complete rest between the attacks of jerking.

This is the usual extent of the symptoms exhibited by Frogs of 30 grms. weight receiving one drop of benzene.

#### *Effect of Larger Doses.*

If a larger dose be injected, the inability to perform coordinate movement increases and at length the animal lies with the legs extended, a mere twitch of the toes and fingers only occurring on stimulation of the foot. Later on, the reflex becomes localised to the foot stimulated, and is ultimately lost altogether. The reflex from the eye is long maintained.

Absorption of benzene is slow and irregular, and it has been observed to cause a local rigor of muscle which may hinder absorption.

The heart usually continues to beat after reflex movement has ceased, or if it has stopped it is found to be still irritable.

#### *Action on Individual Organs.*

Destruction of the brain diminishes the jerking because it stops all attempts at voluntary movement; but if the Frog be left for a time till reflex movements are again active, the movements are to a large degree jerking. If the sciatic artery on one side be ligatured the jerking and tremor still occur on that side. This shows that the jerking is not due to a peripheral action of the drug on the motor nerves or muscles, but is due chiefly, if not entirely, to its action on the spinal cord. The jerking may sometimes be less on the ligatured side, but this is, we think, due to the effect of stasis in diminishing the irritability of the nerves and muscles on that side, although we cannot with certainty altogether exclude the possibility of the drug having acted as a peripheral stimulus. In a brainless Frog, which has been slightly poisoned by benzene, if the upper end of the dorsal cord be exposed and stimulated, the consequent contraction of the leg may be found less on the side of the unligatured artery than on the side of ligature, indicating that benzene has had a certain paralyzing effect on the nerves or muscles of the unligatured leg.

At a later period, stimulation of the cord is unattended by any contraction of the leg muscles on either side. This shows that the excitability of the cord is destroyed.

Stimulation of the nerve itself on the unligatured side yields a feebler contraction than on the ligatured, but even in cases of deep poisoning, reaction to some extent is

present. This shows that either the motor nerve or muscle is enfeebled by this poison. Figs. A and A'.

The curve obtained by directly stimulating the muscle is strong, but often—as in the case of indirect stimulation—slightly longer than on the ligatured side. This shows that the muscle itself is somewhat enfeebled. Figs. B and B'.

#### Action of Benzene on Muscle and Nerve.

Decerebrated Frog weighing 22 grms. Iliac vessels ligatured on the right side. 2 minims of benzene injected into the dorsal lymph sac. Examination of the muscles made 4 hours after the injection.

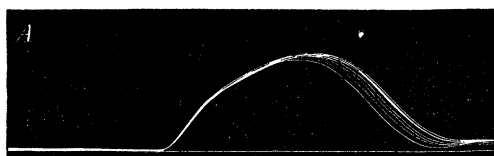


Fig. 2. (A.) Ligatured (*unpoisoned*) leg. Curves obtained by repeated stimulation of *nerve*.

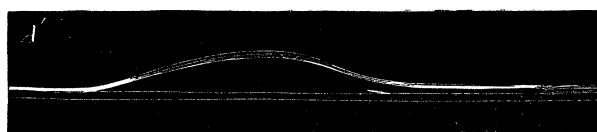


Fig. 3. (A') Unligatured (*poisoned*) leg. Curves obtained by repeated stimulation of *nerve*.

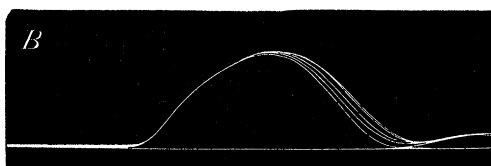


Fig. 4. (B.) Ligatured (*unpoisoned*) leg. Curves obtained by repeated stimulation of *muscle* directly.

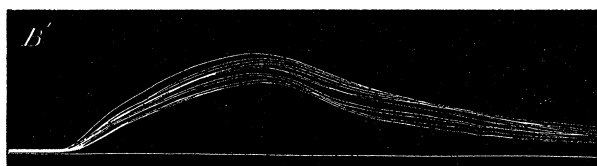


Fig. 5. (B'). Unligatured (*poisoned*) leg. Curves obtained by repeated stimulation of *muscle* directly.  
Time, 44 millims. = 0.1<sup>s</sup>.

The function of the heart is but little affected by benzene subcutaneously administered (Section II.). The chief action of the poison is, therefore, on the spinal cord, though it has some effect upon the muscle substance, and also upon the terminations of motor nerves.

#### *Alterations in the Action of Benzene by Heat and Cold.*

The effect of heat is to increase the symptoms at first and then greatly to accelerate the occurrence of paralysis. Thus, if a Frog be taken about an hour after the appear-

ance of tremor, but while all reflexes are still active, and placed in a hot bath slightly below 30° C., in a short time all reflexes may have completely disappeared, while a control animal subjected to the same experiment still remains active. At a temperature of 30° C. the reflex function of the cord of the Frog is suspended.\*

Cold has no marked effect on the action of benzene, either in the way of accelerating or of retarding its action.

*Experiment.*

FROG Weighing 28 grms. Room Temperature, 63° Fahr.

- 0<sup>h</sup> 0<sup>m</sup>. One minim of benzene injected into the dorsal lymph sac.  
 25<sup>m</sup>. Weaker. Slight tremor on jumping.  
 105<sup>m</sup>. Much tremor on touching. All reflexes. "Ducking" movements. No rigidity.  
 170<sup>m</sup>. Cannot crawl. Draws the legs up with jerking movement. Circulation active. Pigment cells much contracted. Placed in a hot water bath at 29° C.  
 In 10<sup>m</sup> after immersion reflex had entirely ceased.  
 In 15<sup>m</sup> " " the legs were in a condition of rigid extension.  
 After removal from hot water, reflex tremor of the anterior extremities, trunk, and legs occurred on irritating the foot. On touching the eye, no closure of the eye but tremor of fore arms and abdominal muscles occurred.  
 (In benzene poisoning rigidity has been frequently noticed.)

*Result of Examination of Individual Organs.*

Cord still irritable to slight extent. Muscles of thighs and upper part of gastrocnemius in rigor.

(1.) REPLACEMENT OF HYDROGEN IN BENZENE BY HALOID RADICLES.

Haloid radicles do not modify the action of benzene to the same extent as they do that of ammonia,† but nevertheless they do produce certain modifications, and in somewhat the same directions as we found in our experiments on ammonia.

This modification is most marked in the case of iodine, whose compounds with benzene (like its compounds with ammonia) have a tendency to produce paralysis of muscle, of motor nerves, and of cerebral reflexes, without the production of spasm. It appears to possess a depressant action on the heart.

Monochlorobenzene appears to affect the spinal cord greatly, causing spasm, and reflex action is more rapidly affected than after benzene. It diminishes the activity of the circulation, but it does not appear to affect motor nerves and muscles more than benzene.

The bromo- and iodo-compounds appear to differ from benzene and from chlorobenzene in the more powerful paralyzing action which they exert on the cerebrum.

Weight for weight the chloro-compound is the most lethal, then the bromo-, and lastly the iodo-compounds.

\* M. HALL, 'Roy. Soc. Proc.,' 1831, p. 37.

† BRUNTON and CASH, 'Phil. Trans.,' 1884.



We shall now record three experiments selected as typical from others made with monochlorobenzene—the first at room temperature, the second under the action of cold, the third with heat.

*Monochlorobenzene.* ( $C_6H_5Cl.$ )

This substance causes in Frogs weakness, tremor, especially on movement, and inco-ordination of a character which reminds one of locomotor ataxy in Man. The circulation is little affected. The pigment cells are contracted.

*Experiment.*

*Rana Temporaria* of 24 grms. weight.

Nov. 3rd.

One minim of monochlorobenzene was injected into the dorsal lymph sac. Laboratory temperature  $60^{\circ}$  F.

45<sup>m</sup>. After injection. Slight tremulousness, both when attempting movement and when taken up.

87<sup>m</sup>. On stimulation of foot both legs thrown out in a "slapping" fashion, and there is much tremor and twitching of the head, limbs, and trunk. Frog crawls slowly and tremulously. Cannot hop. Kicking with legs is kept up for a long time (once for 20<sup>s</sup>) after stimulation of foot.

100<sup>m</sup>. It cannot crawl; can only draw the legs up with great labour and jerking. Circulation active. Pigment cells contracted to balls.

130<sup>m</sup>. The brain was now destroyed by pegging.

135<sup>m</sup>. Reflex is recovering, and there is slow withdrawal of the foot with great tremor. Tremor and some jerking still occur when no stimulation is applied.

24<sup>h</sup>. Next day it lies with its legs out. Any touch of the foot is followed by tremulous movements of the feet and hands, but no withdrawal of the leg.

On decapitating the animal and opening the lymph sac, it was found to contain some unabsorbed monochlorobenzene. The spinal cord was now destroyed from above downwards till reflex was almost gone. Much of spontaneous tremor now lost, but on pinching toe there was jerking of both legs.

ACTION of Cold.

Cold lessens the action of the substance, reducing the tremor and making the movement slower.

*Experiment.*

FROG of 25 grms.

0<sup>h</sup> 0<sup>m</sup>. One minim of monochlorobenzene was injected into the dorsal lymph sac after exposure to cold ( $7^{\circ}$  C.) for 25 minutes.

21<sup>m</sup>. No tremor, but great lethargy. If taken out, it crawls forward very slowly, drawing the legs up with remarkable slowness.

56<sup>m</sup>. Tremor is now distinct, though modified by the torpor of cold.

96<sup>m</sup>. Distinct tremor to some extent; the frog feels markedly cold.

130<sup>m</sup>. It makes springing movements, but does not change its position. Is much more normal than the Frog (similarly poisoned) at the room temperature,  $60^{\circ}$  F.

- 146<sup>m</sup>. As before. General lurching of the body is frequent.
- 24<sup>h</sup>. All reflexes are present, but slow and tremulous. Jerkings of limbs and lurchings of body whilst sitting still. On stimulating the foot the leg is withdrawn slowly and with a jerking movement. Circulation in the web is slow and unsteady. Vessels are dilated. Pigment cells contracted.

#### ACTION of Heat.

Heat increases the action of the substance, rendering the jerking greater at first, and then rapidly lessening the reflexes, which are restored again by cold.

#### *Experiment.*

#### FROG of 27 grms.

- 0<sup>h</sup> 0<sup>m</sup>. One minim of monochlorobenzene was injected into the dorsal lymph sac.
- 65<sup>m</sup>. Tremor on movement is now well marked.  
Frog was put into a hot bath at 29° C.  
Jerking at first was much increased, but soon became reduced.  
10<sup>m</sup> after immersion reflex is almost entirely gone, but there is still twitching on stimulation of foot. (Control animal remains active.) Seems to recover somewhat when taken out of the bath. It was again placed in hot water at 29° C.
- 20<sup>m</sup>. A slight tremor of the adductors was the only sign of reflex left.  
It was now placed in an ice chamber. Temperature, 7° C.  
In 5<sup>m</sup> the reflex was much increased; some active spontaneous movements likewise occurred.  
30<sup>m</sup> after being placed in the ice chamber, reflex, though slow from cold, was active in all parts.  
Again placed in warm bath.  
In 15<sup>m</sup> all reflex was completely gone. It was now taken out and covered with ice.  
In 5<sup>m</sup> it was endeavouring to shake ice off.  
In 20<sup>m</sup> all reflexes were present; it drew its legs up strongly.  
Sits up well. All reflexes active and without tremor. Crawls well; does not attempt to hop.
- Next morning. After being 15<sup>m</sup> in bath at 29° C. hops and springs well, and has, to a large extent, regained power of movement.

#### *Monobromobenzene.* (C<sub>6</sub>H<sub>5</sub>Br.)

This compound appears to cause more lethargy and less tremor than chlorobenzene.

#### *Experiment.*

#### FROG of 32 grms.

- 0<sup>h</sup> 0<sup>m</sup>. Injected 1 minim of monobromobenzene into the dorsal lymph sac.
- 40<sup>m</sup>. The springs are only a few inches in extent. It hops along the bench if left to itself, but is somewhat lethargic.
- 55<sup>m</sup>. On touching the eye there is a start of the whole body.
- 85<sup>m</sup>. It crawls. It can only spring from 2 to 3 inches at a time unless much roused. There is tremor in the limbs and trunk after a spring. Tremor is also provoked by tapping over the

occiput or along the spine. A squealing sound occurs at intervals which appears to be due to strong contraction of the abdominal muscles, causing expulsion of air from lungs.

- 115<sup>m</sup>. Circulation in the web is slow but general. Eye is prominent. Much tremor in all the limbs and trunk on attempting movement, which is now impossible.
- 180<sup>m</sup>. Leg is drawn up weakly on irritating it. Frog seems, however, to be still hyperæsthetic. Some twitching of the muscles is noticed when movement is attempted.
- 275<sup>m</sup>. Twitching and fibrillation of muscles on attempting movement, and also, but only to a slight extent, when lying still. There is no rigid spasm.
- 24<sup>h</sup>. Cannot hop, but crawls. Very tremulous. Slow withdrawal of extended leg.
- 72<sup>h</sup>. Tremulous on movement, but can take a series of short hops (2-3 inches); no tremor whilst movement not attempted.

#### ACTION of Larger Dose (in brief).

##### *Experiment.*

- 0<sup>h</sup> 0<sup>m</sup>. The brain of a Frog weighing 35 grms. was destroyed by pegging. The left sciatic artery was ligatured. The right sciatic plexus was divided. 3 minims of monobromobenzene were injected into the dorsal lymph sac.
- 45<sup>m</sup>. Very faint reflex on stimulating the left foot by pinching, no other reflex present.
- 80<sup>m</sup>. As at 45<sup>m</sup>. Heart still beating.
- On stimulating the cord there was hardly any movement of left leg, and, of course, none of the right. The curve of contraction on indirect stimulation is somewhat lower and longer from the muscle poisoned by bromobenzene, than from that protected by the ligature.

#### MODIFYING Effect of Cold (in brief).

##### *Experiment.*

FROG of 32 grms. Room Temperature 15° C.

- 7<sup>h</sup>. The Frog was placed in a cold chamber.  
3 drops of monobromobenzene were injected into the dorsal lymph sac.
- 40<sup>m</sup>. The Frog can crawl and hop short distances.

This Frog is much less affected than a control Frog poisoned by the same dose and kept at the room temperature.

#### MODIFYING Effect of Heat.

Heat may temporarily increase movement, but it lessens tremor and hastens disappearance of reflex action.

*Experiment.*

FROG of 33 grms. was kept for 20 minutes at a Temperature of 29° C. 1 minim of Monobromobenzene Injected into Dorsal Sac.

- 10<sup>m</sup>. Temperature maintained. Frog is crawling round the vessel. There is an occasional powerful extension of both legs. Head is "ducked" or depressed for an instant.
- 15<sup>m</sup>. Eye-reflex gone, but the legs are still drawn up if extended.
- 30<sup>m</sup>. Temperature maintained. No withdrawal of the foot, and only slight tremor of the leg on pinching the toe. Circulation is good, pigment cells are distended. (Control Frog exposed to same temperature springs actively.)
- 35<sup>m</sup>. Taken out of bath.
- 70<sup>m</sup>. Reflex is returning. Leg drawn up. There are movements of respiration. Put again into the hot chamber at 29° C.
- 76<sup>m</sup>. Reflex has totally disappeared.

*Condition of circulation, spinal cord, nerve, and muscles.*

The Frog was now decapitated and examined.

Heart was beating. Stimulation of the upper part of the dorsal cord causes moderate contraction of the gastrocnemius. This shows that the conducting power of the spinal cord is not destroyed.

The curves obtained from direct and indirect stimulation of this muscle are good, though the altitude is somewhat reduced and the duration slightly increased.

*Monoiodobenzene. (C<sub>6</sub>H<sub>5</sub>I.)*

Monoiodobenzene causes lethargy with some increase of reflex. Tremor occurs on movement, and spontaneous movements become much less sustained.

*Experiment.*

- 0<sup>h</sup> 0<sup>m</sup>. Room temperature 65° F. Half a drop of monoiodobenzene was injected into the dorsal lymph sac of a Frog weighing 36 grms.
- 35<sup>m</sup>. after injection. Lethargic, but springs well.
- 80<sup>m</sup>. Springs strongly if roused, is torpid.
- 120<sup>m</sup>. Legs are thrown out in a wild slapping fashion, extension is strong, but rather spasmodic.
- 155<sup>m</sup>. On stimulation it gives a few active springing movements, which are tremulous and unsustained, and only move the animal a few inches.
- 195<sup>m</sup>. Is now very tremulous on attempting movement, but not so when resting.
- 240<sup>m</sup>. Still springs 1-2 inches. Very tremulous. Twitching of muscles occasionally noticed. Eyes protruded in breathing.
- 24<sup>h</sup>. Lies on belly. Withdraws legs slowly, but can hardly move; great tremor.
- 72<sup>h</sup>. But little tremor now noticed, can hop repeatedly each movement very short, *i.e.*, 2-3 inches.

*Monoiodobenzene.**Experiment.*

- 0<sup>h</sup> 0<sup>m</sup>. 2 minims of monoiodobenzene were injected into the dorsal lymph sac of a Frog weighing 20 grms.
- 5<sup>m</sup>. Restless. Breathing accelerated.
- 8<sup>m</sup>. Quieter.
- 29<sup>m</sup>. Quiet and lethargic. If roused it is slightly tremulous.
- 43<sup>m</sup>. Reflex is increased. Still lethargic. Spring is short and tremulous.
- 68<sup>m</sup>. Reflex still increased. All movements very tremulous. Legs lie flat on the bench, the position of animal is low. It still draws its legs up if they are extended. When placed on its back, it can move round to the ventral position, but only with great effort.
- 223<sup>m</sup>. Still draws leg partially up, but very tremulously. When placed on its back it tries to get round, but the only result is a twitching of the muscles of the limbs and trunk. Eye reflex still present.
- 278<sup>m</sup>. Condition the same. Heart accelerated.
- 24<sup>h</sup>. No respiration. No reflex of any kind, but when the Frog is placed on its back there is a faint tremor of fore limbs.

In another experiment the brain was destroyed in the first instance, the iliac vessels were ligatured on one side and 2 minims of monoiodobenzene were injected. The cord was destroyed just when the reflex movement of the ligatured leg was disappearing, the unligatured leg had ceased to respond some time before. During the destruction of the cord there was a twitch of the leg, the vessels of which had been ligatured. All the muscles were dark red and injected, excepting those of the ligatured limb. Tetanus of the gastrocnemius on the poisoned side on stimulation of the nerve was weak and broken. The muscle reacted more strongly to direct stimulation, but the contraction still was less active than that of the companion muscle on the ligatured side.

(2.) MODIFICATION OF THE ACTION OF BENZENE ( $C_6H_6$ ) BY REPLACEMENT OF ONE ATOM OF HYDROGEN BY AN ALCOHOL RADICLE.

The introduction of alcohol radicles into benzene in place of hydrogen appears to modify its action in much the same way as one would expect from a general consideration of the properties of the alcohol group, which, as a rule, have a sedative action on the nervous system.

The compounds of benzene with alcohol radicles produce less tremor, less hyperæsthesia, and greater lethargy than the halogen compounds.

The circulation is but little affected by them.

These compounds, like the halogen compounds already discussed, exercise little action on muscle and nerve, but where an effect is observed it is greater on the nerve than on the muscle.



The action of the alkyl compounds of benzene appears to be much more fleeting than that of the haloid compounds, the effect of the former generally passing off in 24 hours, while that of the latter often lasts two days or more.

In the case of methylbenzene,  $C_6H_5CH_3$ , a secondary increase of reflex action is sometimes observed after the reflexes have become greatly diminished and after spontaneous movement has quite disappeared. We have not yet been able to determine whether this is due to a paralysis of inhibitory centres in the brain, or to decomposition of the methylbenzene molecule with liberation in the organism of some product of its decomposition, having an exciting action, or whether it may be due to some other cause than these.

This secondary increase in the reflex action of the cord is of some interest, inasmuch as a similar phenomenon, though much greater in extent, has been noticed by FRASER in the case of atropine. A further analogy between methylbenzene and atropine was observed in one case in which, after reflex action had become greatly diminished, convulsions of the fore legs with a certain degree of gaping and opisthotonos occurred in a Frog poisoned by methylbenzene.

We shall illustrate the action of this drug by the notes of two selected cases of poisoning, in one of which the convulsive symptoms followed the course we have just described.

*Methylbenzene.*  $C_6H_5CH_3$ . (*Toluene.*)

Produces gradual failure of voluntary movement and reflex, accompanied by little or no tremor, occasionally convulsive movements of limbs and trunk occur.

*Experiment.*

FROG of 33 grms. Temperature  $78^{\circ}$  F.

- 0<sup>h</sup> 0<sup>m</sup>. 1 minim methylbenzene was injected into the dorsal lymph sac.
- 27<sup>m</sup>. Rather restless. Head rather dorsiflexed for a few seconds.
- 35<sup>m</sup>. If undisturbed will remain for a considerable time in one position. All reflexes are impaired, especially the eye reflex. Respirations 108 per minute.
- 50<sup>m</sup>. Can spring if roused, but is generally perfectly still; will sometimes lie a considerable time with legs extended.
- 53<sup>m</sup>. Moving about spontaneously.
- 65<sup>m</sup>. Has had several attacks of convulsive extension of fore legs with throwing back of head and gaping, which have resulted in the body being propelled backwards. The left leg is slightly extended, the right quiescent.
- 80<sup>m</sup>. Lies with the legs in any position. Spasm not provoked by touching bell jar covering it, or by striking the bench, but occurs on pinching the foot.
- 125<sup>m</sup>. Circulation in the left web is very active. There is still some spasm in the fore arm. All reflexes are present to some degree, though the eye reflex is much impaired.
- 24<sup>h</sup>. No tremor nor abnormality, except that the spring is short.

*Methylbenzene.**Experiment.*

DECEREBRATED Frog of 32 grms. Right Iliac Artery ligatured. Room Temperature, 69° F.

- 0<sup>h</sup> 0<sup>m</sup>. 2 minims of methylbenzene were injected into the dorsal lymph sac.  
 10<sup>m</sup>. All leg reflexes are present. There is no tremor, Frog draws the leg up well.  
 31<sup>m</sup>. No tremor, it lies with its legs half extended. Both legs are drawn up on touching, but more strongly on the ligatured side.  
 71<sup>m</sup>. All reflexes are gone. Circulation in the left web is decidedly good; the pigment cells are contracted. There is a very faint cardiac impulse still, just causing circulation in right web.

*Condition of Spinal Cord, Nerves, and Muscles.*

Distance of secondary from primary coil, 12 centims. No contraction on stimulation of cord. At 10 centims. there is a twitch of both feet. 8 centims. tetanus of both legs (all tissues divided but the nerves). No contraction to speak of from nerve on the ligatured side, which seems exhausted by the few contractions caused by stimulation of the cord. On direct stimulation of the muscle tetanus occurred at 16 centims.

*Unligatured Leg.*

There is no tetanus from the nerve; muscle tetanus with coil at 13 centims.

This case, therefore, shows relatively little or no affection of muscle. The nervous tissue is evidently the seat of the poisoning.

*Action of Dimethylbenzene. C<sub>6</sub>H<sub>4</sub>2(CH<sub>3</sub>).*

Its action closely resembles that of the compound last described. There is, perhaps, a little more tendency to tremor occasionally manifested. The heart is but little affected. The result of stimulation of nerve and muscle is the same as in methylbenzene. The only result observable on the day after injection is slight lethargy and a less vigorous spring than was executed before the administration of the drug.

*Experiment.*

FROG of 32 grms.

- 0<sup>h</sup> 0<sup>m</sup>. 1.5 minims of dimethylbenzene were injected into the dorsal lymph sac.  
 5<sup>m</sup>. Breathing rapid. Restlessness.  
 32<sup>m</sup>. Spring short and weak, no tremor. Can get off its back.  
 52<sup>m</sup>. Eye protruded, no longer closed on touching. All reflexes are present. Legs drawn up rather jerkily; cannot get off back.  
 72<sup>m</sup>. Still faint twitch on pinching foot. This is often, however, a mere fibrillation, with no true movement of the limb.  
 102<sup>m</sup>. All reflex quite gone. Circulation active. Pigment cells contracted.

*Condition of Cord, Nerves, and Muscles.*

On stimulating the upper end of cord there is a very faint twitch of the legs. Stimulation of the sciatic nerve gives a stronger contraction. Direct stimulation of the muscle causes more vigorous contraction. Heart beating strongly.

After a dose such as 1·5 minims, or even twice as much, has been administered to a medium-sized Frog, recovery usually takes place. In 24 hours, except for a little weakness and lethargy, the animal is scarcely to be separated from a normal Frog. There is no tremor. When equal doses of this and the preceding compound are severally administered to two Frogs of equal size, the action produced by the dimethylbenzene appears to be the stronger.

*Trimethylbenzene. C<sub>6</sub>H<sub>3</sub>(CH<sub>3</sub>). (Mesitylene.)*

This substance appears to be the most active of the methyl compounds which we have investigated. The eye reflex is lost comparatively early, and, after a dose of 1·5 minims, all body reflex frequently disappears within an hour. After the eye reflex is lost, touching the conjunctiva not unfrequently causes movement of the limbs.

*Experiment.*

## FROG of 32 grms.

0<sup>h</sup> 0<sup>m</sup>. Injected 2 minims of trimethylbenzol under skin of belly.

15<sup>m</sup>. If laid on its belly, will lie still with the legs in any position. If put on its back, it may still make efforts to change its position, but they are not persisted in. No closure of eye on touching, but if touched there is extension of both legs. All circulation has ceased in web. No reflex on pinching, but occasionally 4–5 spontaneous extensions.

60<sup>m</sup>. All reflex is quite gone.

*Condition of the Cord, Nerves, and Muscles.*

On stimulating the cord there is feeble tetanus of both legs, which seems rather stronger in the ligatured. On the unligatured side nerve tetanus is moderately good with undulations. Muscle tetanus is less good, probably owing to exhaustion from previous stimulation through the nerve. On the unligatured side both nerve and muscle tetanus are as extensive when commencing as on the ligatured side, but are not so sustained.

(Circulation ceased early.)

The comparatively early cessation of reflex was noticed in almost all cases of poisoning by this drug.

Thus, one Frog of 48 grms. received 1·5 drops and another of 32 grms. 2 drops of trimethylbenzene. Reflex was gone in the former in 80 minutes, in the latter in 60 minutes. (Detailed results of reflex experiments are given in the next section.)

*Ethylbenzene.*  $C_6H_5C_2H_5$ .

This substance is more active in causing paralysis than the methyl or dimethyl compounds; a slight degree of jerking may develop on attempting movement.

If one minim of ethylbenzene be injected into the dorsal lymph sac of a Frog of 30 to 35 grms. weight,

- In 30<sup>m</sup>. The frog appears to be weaker, but, if roused, may give a series of short slapping extensions of legs, which move the animal but a very short distance.
- „ 50<sup>m</sup>. The ability to spring declines; attempts at crawling still occasionally occur. There is increasing apathy. No twitching whilst at rest, but muscular movements are rather jerking owing to failure of centres (nervous). Frog lies with legs out, but still starts if touched. Eye reflex persists as long as limb reflexes.
- „ 100<sup>m</sup>. All reflex usually ceases, that in arms generally outlasting that in legs. Very occasionally a slight spontaneous start of legs occurs after all reflex has ceased.

Sometimes touching the eye may cause twitch of toes when all stimulation of foot is inoperative to cause reflex.

If the iliac artery be ligatured in a brainless Frog, the reflexes may appear rather more strongly on this side, but not invariably so, as often no difference is discernible.

The heart is usually found beating slowly; the ventricle is pale, and contracts imperfectly.

The circulation in the web may, however, cease at the same time as the reflex (as in one case 103 minutes after poisoning).

Stimulation of the cord (brachial) usually gives only a feeble contraction of both legs, not amounting to a tetanus.

In one case, 103 minutes after one minim of ethylbenzene, the cord was completely paralysed. In two other cases, when the poisoning took longer (150 minutes and 154 minutes), and a faint twitch still persisted as reflex, a distinct tetanus was obtained.

If the iliac artery be ligatured on one side and poisoning carried to the abolition of reflex, the tetanus from the sciatic of the unligatured side is usually feeble or very feeble; that of the muscle is much stronger, but still somewhat impaired in contrast with the ligatured side.

In one case, after all reflex had gone, the cord still yielded tetanus without marked alteration in reaction from nerve and muscle on the unligatured side.

## Action of Ethylbenzene on Muscle and Nerve.

Decerebrated Frog. Left iliac vessels ligatured. 1 minim of ethylbenzene injected into the dorsal lymph sac.



Fig. 6. (a) Ligatured (*unpoisoned*) leg. Twenty maximal stimulations of the sciatic nerve gave the above curves. Direct stimulation of the muscle gave similar curves.

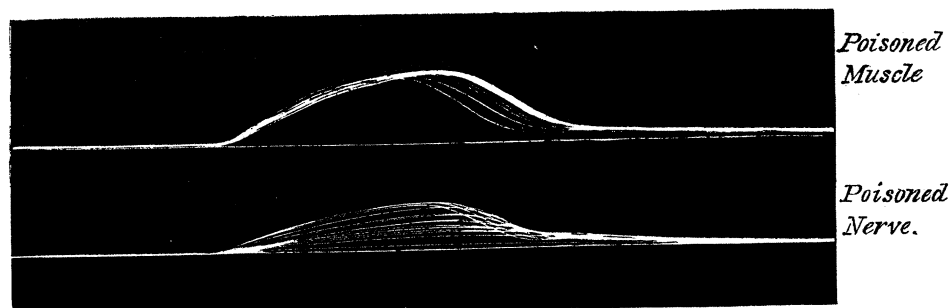


Fig. 7. (b) Unligatured (*poisoned*) leg. Twenty maximal stimulations of the nerve gave the lower of these two series. Twenty maximal stimulations of the poisoned muscle directly gave the upper series.

Time 44 millims. equal to 0.1<sup>s</sup>.

*Experiment.*

FROG of 35 grms.

- 0<sup>h</sup> 0<sup>m</sup>. One minim of ethylbenzene injected into the dorsal lymph sac.  
 43<sup>m</sup>. If touched sharply will spring six or eight times very rapidly. Spring is very short, but often repeated, and gives an appearance of great haste with but little progress.  
 81<sup>m</sup>. Cannot spring, but extension of legs is sharp and slapping; lies with legs out; no tremor or jerking; starts when touched; hyperæsthetic.  
 103<sup>m</sup>. Reflex rapidly failing.  
 140<sup>m</sup>. All reflex quite gone, except slight tremor of foot on touching eye.

*Condition of Cord, Nerve, and Muscles.*

Stimulation of the cord gives a very feeble twitch of legs, but no true tetanus. On stimulation of the sciatic nerve the contraction is stronger, but still weak. Contraction from direct stimulation is very much stronger. Heart beating slowly, systole imperfect.



TABULAR View of the Comparative Action of Benzene and its Haloid and Alkyl Compounds.

Substance.	Motor symptoms.	Time of occurrence.	Circulation.	Mode of administration.	Duration of symptoms.	Post-mortem examination.
Benzene . . . . .	Hyperæsthesia, starting, jerking on touching, and occasionally spontaneously	25 <sup>m</sup> to 30 <sup>m</sup> after injection of 1 minim	Not markedly affected	Injection subcutaneously to vapour	More than 24 hours	Local action—muscular rigor, cord chiefly paralysed. Nerve affected to a lesser extent
Monochlorobenzene . . . . .	Hyperæsthesia, tremor on movement 20 <sup>m</sup> to 40 <sup>m</sup> after injection of 1 drop. Jerking with withdrawal of foot on touching, ending in tremor without withdrawal. Spontaneous jerking is interrupted if the Frog is pegged beforehand. Kicking of the leg continues long after stimulation	20 <sup>m</sup> to 30 <sup>m</sup> after injection of 1 minim	As above	Injection subcutaneously to vapour Introduction into the stomach	Leg withdrawn (in 24 hours) slowly and with jerking movement	Cord generally capable of conducting to some extent. Nerve affected to a lesser extent
Monobromobenzene . . . . .	Hyperæsthesia. Broken movement, tremulousness. Increasing weakness, twitching and fibrillation of muscles on attempted movement, but to a very slight extent spontaneously	As above	As above	Injection subcutaneously to vapour Introduction into the stomach	More than 24 hours	Cord as above. Tetanus from it soon breaks down or yields clonus only. Both nerve and muscle affected to a lesser extent
Monoiodobenzene . . . . .	Hyperæsthesia, but less than in the case with Frogs poisoned by chloride or bromide. Twitching and fibrillation as above. Eye reflex seems to cease sooner	20 <sup>m</sup> to 80 <sup>m</sup> Develops later than others	As above	Injection subcutaneously to vapour Introduction into the stomach	Action does not seem to outlast the bromide or chloride effect. In this, as in others, heat of 29° C. rapidly abolishes reflex after stage of excitement	As above. The nerve and muscle seem to be relatively more affected

TABULAR View of the Comparative Action of Benzene and its Haloid and Alkyl Compounds—(continued).

Substance.	Motor symptoms.	Time of occurrence.	Circulation.	Mode of administration.	Duration of symptoms.	Post-mortem examination.
Methylbenzene . . .	Usually no evidence of hyperaesthesia. All reflexes retained for some time. No spontaneous tremor, movements become weaker, and may be a little broken before reflex lost, but nothing like the weakness, jerking and tremor of the compounds above	30 <sup>m</sup> to 50 <sup>m</sup> increasing lethargy and weakness	Heart's action weak	Injection subcutaneously	Next day is usually lethargic, spring short, but no tremor or jerking observed	If the poisoning be very profound, the cord may scarcely conduct at all. The nerve is rapidly exhausted on stimulation. But voluntary motion and reflex appear to cease some time before conduction disappears
Dimethylbenzene . . .	Symptoms as above, with perhaps a little more tendency to tremor, but this is still insignificant when compared with haloid compounds	30 <sup>m</sup> . Increasing weakness after injection of 1·5 minims. Reflex gone in 80 <sup>m</sup> to 100 <sup>m</sup>	As above	Injection subcutaneously Larger doses than of haloids are needed to produce the symptoms	As in the case of methylbenzene	As above. There is still a weak tetanus from stimulation if poisoning has not been extreme
Trimethylbenzene . . .	Restlessness succeeded by increasing weakness and lethargy. A little tremor present. Eye reflex is usually first lost. Stimulation from touching eye often causes leg movement. Most active of the three methyl compounds	20 <sup>m</sup> after dose of 1·5 minims. Eye reflex and all body reflex ceases in 30 <sup>m</sup> to 50 <sup>m</sup>	Heart often ceases soon	Injection subcutaneously Stronger than above	As above	As above
Ethylbenzene . . . . .	No marked hyperaesthesia. There is increasing lethargy and weakness. No twitching when at rest, but muscular movements are rather jerking. Occasionally a spontaneous start of legs occurs after all reflex has ceased. Eye persists as long as limb reflex	50 <sup>m</sup> after 1 minim attempts at voluntary movement still occur. After 100 <sup>m</sup> all reflex has usually disappeared	Heart ceases about the same time as reflex or soon after	Injection subcutaneously	Shows a little weakness in 24 hours after poisoning	A weak tetanus may be obtained even when all reflex had ceased before examination

## (3.) BENZENE WITH HYDROGEN REPLACED BY HYDROXYL (OH).

The introduction of the hydroxyl group in place of hydrogen increases the tendency to convulsions. These convulsions are due to the action of the drugs on the spinal cord, occur independently of voluntary movement, except when the dose is very small, and continue almost unchanged after destruction of the cerebrum. Slight tremor may occur before destruction of the brain, but is greatly masked by the powerful contractions referred to. Fibrillation to a limited extent is seen after the brain is destroyed. The action of the compounds containing hydroxyl differs with the number of atoms of hydroxyl present and their position in the benzene molecule.

In the case of monoxybenzene (phenol) the substance is identical whichever the carbon atom may be to which the OH group is attached in the benzene nucleus.

Experiments on this substance are so numerous that we have not recorded any here.

*Dioxy- and Trioxybenzene.*

In the case of dioxybenzene there are three substances, ortho-, meta-, and para-dioxybenzene, having the hydroxyl groups in the positions 1:2, 1:3, and 1:4 respectively. The ortho-compound is usually known as pyrocatechin, the meta- as resorcin, and the para- as hydroquinone.

We may anticipate our description of the action of the one of these bodies—resorcin—by saying that its action, though differing in degree, is very similar in kind to pyrocatechin and hydroquinone, as was also clearly shown by BRIEGER\*. When .002 to .003 grm. of the salt dissolved in a drop of distilled water is injected under the skin of the back of a Frog, in two minutes there is a certain amount of jerking observed in all the movements of the animal. This jerking rapidly extends to all the limbs and to the muscles of the trunk, so that in four to five minutes it has become universal. There is an occasional very short pause between the clonic movements, and not unfrequently at the commencement of their occurrence the animal emits a squealing cry indicating the involuntary expulsion of air through the larynx as a result of abdominal muscular compression. There is often gaping of the lower jaw. Reflex movement is increased for a time. Breathing laboured.

If the animal is confined under a funnel or bell jar open at the top the vessel becomes covered internally with foam. In ten to fifteen minutes the jerking movements become continuous, that is to say, not that they alter their individual character, but that they do not show any lasting intermission or rest pauses.

The animal is unable at the maximum of this condition to perform any coordinate

\* 'Arch. f. Anat. u. Physiol.' (Supp.-Band 1879), and 'Centralblt. f. d. Med. Wiss.,' 1880.

movement, whilst at an early period in the action of the drug all attempts at movement at once provoke and increase the clonus.

The jerking stage may last from one to five hours, or even longer. In the case of small doses it continues longer than after larger doses, which tend to cause paralysis. During this paralysis or semi-paralysis the extended legs are no longer drawn up on stimulating, though from a slight thrusting-out movement the reflex function of the cord evidently exists to some extent. There is more reflex activity in the anterior part of the cord than in the posterior part; occasional twitchings of individual muscles or groups of muscles still take place, but these are fainter than before, and scarcely affect the position of the limbs.

Recovery may occur, though it is rare, excepting in the case of large Frogs, after  $\cdot 003$  grm. has been injected; but with smaller doses, before this paralytic condition has developed far, or after it has done so, the return to voluntary movement is often surprisingly rapid, though for some time jerkings and twitchings occur.

More usually the paralysis increases, and the legs remain extended in a semi-rigid condition, when all sign of life has disappeared.

If the dose administered hypodermically is as small as  $\cdot 00025$  grm., very definite symptoms still appear in the case of small Frogs of 15 grms. weight. The power of voluntary movement is retained, but all movements become tremulous and jerking, and there is some tremor and incoordinate muscular contraction when the animal is not making any effort to move. The spring remains fairly strong, and slight hyper-æsthesia is to be recognized.

In the course of seven or eight hours after the injection the animal is again practically normal. We have observed curious variations of reaction of individual Frogs equal in size, and which had been kept under exactly similar circumstances, towards resorcin, one animal appearing sometimes to be readily influenced by half the dose which produced little effect upon another.

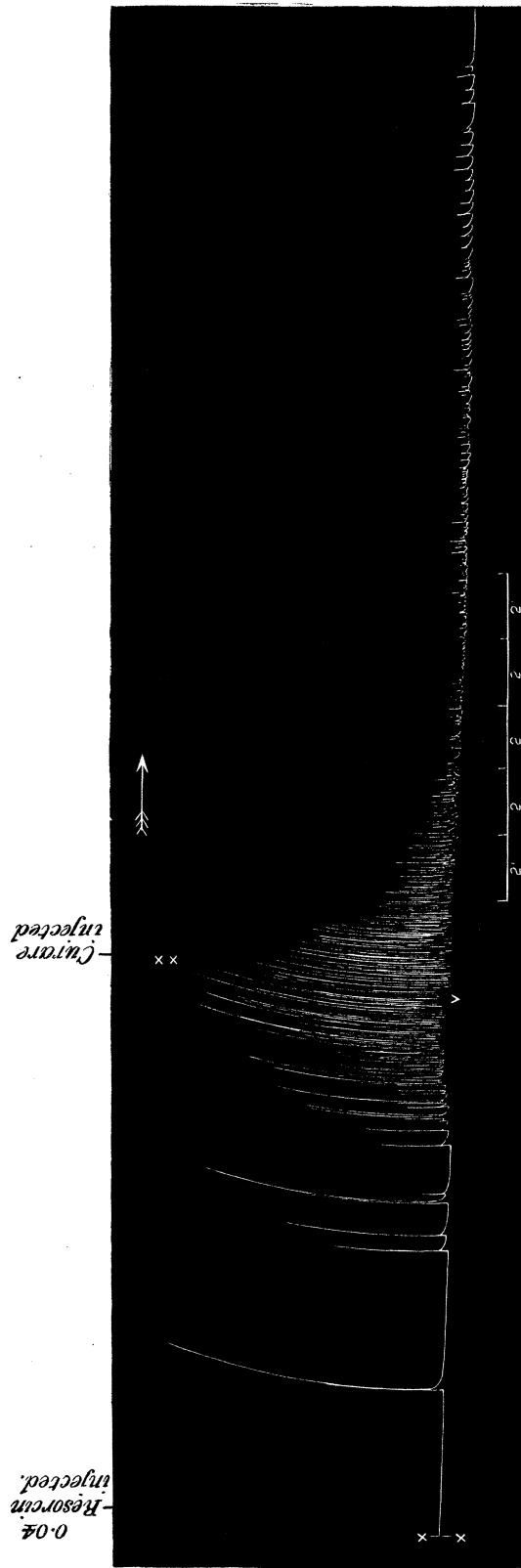
Larger doses than 3 mg. accelerate the twitching and paralytic stage, absorption occurring readily.

Complete flaccidity with loss of all movement takes place. On destroying the brain and upper part of cord there may be total quiescence of all the muscles of the limbs and trunk during the operation, and frequently strong stimulation of the cord also fails to cause contraction. This shows that the power of the cord to conduct longitudinally is destroyed. The heart is generally arrested in diastole, but usually remains irritable, contracting two or three times after each mechanical stimulation.

In advanced poisoning, which has not, however, taken place too rapidly, the function of the motor nerves is much impaired, and frequently that of the muscles also, and direct stimulation produces a stronger contraction than indirect.

The noticeable feature in the poisoning by dioxybenzene is the rapid development of muscular contractions, often occurring at very regular intervals of time, not passing into a tonic or tetanic contraction.

Fig. 8. Action of Dioxybenzene  $C_6H_4(OH)_2$  (1:3), Resorcin, on the Spinal Cord in causing Spontaneous Contractions of the Muscles.



Frog weighing 37 grms. Decerebrated. The left iliac artery was ligatured and then all the tissues of the leg were divided, with the exception of the sciatic nerve. The femur was fixed in a clamp, and the tendo Achillis attached to a lever. At  $\times$  0.04 grm. resorcin was injected in aqueous solution into the dorsal lymph sac. At  $\times$  a large dose of curare was injected in the same way.

All the contractions are spontaneous. After the injection of curare they decline in amplitude from the paralyzing effect of the curare on the spinal cord. Time, 11 millims. = 2<sup>m</sup>. The tracing occupies 45<sup>m</sup>.



## BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION. 569

This movement has its origin in the cord. The action of the drug eventually destroys the power of the cord to manifest increased reflex irritability by tetanic spasm when strychnine is injected, provided that this injection succeeds the full development of the symptoms produced by resorcin. If these, however, are but partially developed, tonic spasm results after strychnine. Curare injected into the dorsal sac abolishes these movements, the disappearance being noted first in the unligatured and later in the ligatured leg.

*Dioxybenzene* 1 : 3. (*Resorcin.*)

## ACTION ON FROG

*Experiment.*

## FROG of 24 grms.

- 0<sup>h</sup> 0<sup>m</sup>. Injected .002 gm. dissolved in salt solution under skin of back.  
 6<sup>m</sup>. Restless. Slight jerking.  
 8<sup>m</sup>. Jerking active and universal on movement.  
 12<sup>m</sup>. Short pauses only between jerking spasms. Frequent squeal. Reflex irritability is increased. Breathing laboured. Gaping.  
 24<sup>m</sup>. Much froth round funnel from constant movement of animal. Twitching and fibrillation of muscles.  
 1<sup>h</sup>. Does not leave position, limbs chiefly in extension. Jerking almost continuous.  
 3<sup>h</sup>. Jerking diminished. More successful effort at spontaneous movement. From this time improvement rapidly occurred.

*Experiment* (in brief).

## FROG of 15 grms weight.

- 0<sup>h</sup> 0<sup>m</sup>. Injected .002 gm.  
 8<sup>m</sup>. Movements are distinctly tremulous. Restlessness.  
 17<sup>m</sup>. Jerking of head, trunk, and limbs, legs flat at side of body, the animal resting on its ventral surface throughout. Froth in jar. Cannot direct spring. This animal is far more affected than a Frog which has received twice the dose of trioxybenzene.  
 37<sup>m</sup>. Legs extended, and if pushed up revert to this position. Also thrust out from time to time. Movements getting feebler, heart still beating. No distinct eye reflex, but on touching eye there is a twitch of the rest of body.  
 67<sup>m</sup>. No eye reflex, legs out. Feebler movement of trunk and leg muscles still continue. Increased by stimulation and by putting in dorsal position. Heart beating.  
 267<sup>m</sup>. No marked change of condition but twitching is now very feeble.

*Experiment.*

FROG of 18 grms.

- 0<sup>h</sup> 0<sup>m</sup>. Injected .003 grm. resorcin into anterior lymph sac.  
 5<sup>m</sup>. Violent jerking. Ducking and squeaking now present (from contractions of abdominal muscles). Frequent extension of limbs. Movement constant.  
 15<sup>m</sup>. All eye reflex is gone. Legs extended, there is twitching of groups of muscles, but the legs are but little moved.  
 65<sup>m</sup>. There are still twitchings of muscles but legs are not moved.  
 120<sup>m</sup>. All jerking ceased, legs appear to be in semi-rigor and yield no response to electrical stimulation.

*Action on the Nerves and Muscles.*—Resorcin is shown, by the rigor which occurs, to be a muscular poison, but it appears to weaken the peripheral terminations of motor nerves before affecting the muscles. This is shown by the following experiments.

If the brain is destroyed in the first instance and the iliac vessels on one side ligatured, reflex movement continues for a time more active upon the side of ligature, and the leg of that side reacts more powerfully to stimulation of the other, than the latter does itself.

The tetanus which the muscle yields on the unligatured side is feebler than on the other, the difference being more marked for indirect than for direct stimulation.

*Trioxxybenzene.*  $C_6H_3(OH)_3$  1 : 2 : 3. (*Pyrogallic Acid.*) (*Pyrogallol.*)

This substance we found to differ decidedly, in its action towards Frogs, from resorcin. But the symptoms produced by it are not merely different in degree, but also in character.

The tendency to the production of spontaneous rhythmical movements, which is so strong in the case of resorcin, is here much less marked. If, after a dose of .003 grm. has been injected an hour, the legs be gently extended, they are still drawn up, though with a somewhat tremulous movement. But little tremor or spontaneous jerking occurs if the Frog is not touched. Even when the brain is intact, there is not the same restlessness but rather a lethargic state, during which all reflexes are preserved for a time and then disappear, the eye reflex and that from the fore limbs being the first to go.

One of the most striking differences between resorcin and pyrogallol is that the former produces severe symptoms at first, from which the animal partially recovers, while the latter produces slighter symptoms at first but afterwards kills. (Thus an animal, poisoned by resorcin, may at first appear as if it would certainly die and yet recovers, while another poisoned with pyrogallic acid, may seem so little affected that one thinks it is in no danger, and yet it will be found dead next morning.)

The function of the cord does not appear to be quite so rapidly and profoundly

affected as in the case of resorcin, but the nerve was equally impaired in function. The muscle curve was usually well maintained but somewhat less extensive than before.

Whilst the immediate effects of the drug are much less marked than in the case of resorcin, it is certain that doses of over  $\cdot 002$ , though acting slowly, produce a highly deleterious effect on nutrition, as after them on the succeeding morning the animal was often found dead.

According to JÜDELL, PERSONNE, and ZEISSER, the death in warm-blooded animals is due in large dose to action on the central nervous system, in smaller dose to the solution which is effected of the red blood corpuscles.

### *Experiment.*

#### EFFECT of a Small Dose of Pyrogallol. Frog of 15 grms. weight.

- 0<sup>h</sup>0<sup>m</sup>. Injected  $\cdot 001$  grm. trioxybenzol. (1 : 2 : 3, pyrogallol.)  
 10<sup>m</sup>. Restless. Movements rather tremulous.  
 15<sup>m</sup>. Springs well. But tremor on movement.  
 35<sup>m</sup>. Reflex is increased. There is no "huddling" movement.  
 65<sup>m</sup>. Is lethargic, but reflex increased. There is slight "squatting" or "huddling" movement occasionally.  
 185<sup>m</sup>. Spring rather short. Lethargic, tremulous on movement, but not when at rest. Reflex increased.  
 300<sup>m</sup>. Tremor less. Decidedly lethargic.  
 Next day, perfectly normal.

### *Experiment.*

#### EFFECT of a Moderate Dose of Pyrogallol. Frog of 15 grms.

- 0<sup>h</sup>0<sup>m</sup>. Injected  $\cdot 002$  grm. pyrogallol into dorsal lymph sac.  
 7<sup>m</sup>. Restless. Movements somewhat tremulous.  
 29<sup>m</sup>. Crawls stiffly and with a little tremor. Springs. Has slight "hunching" or ducking movement of head. No foam in jar.  
 42<sup>m</sup>. Sitting up, springs well, though especially after movement there is tremor and "hunching" with bending of head; closure of eyes, apathetic.  
 72<sup>m</sup>. Crawls stiffly, more tremulous. Very little ducking or tremor when not attempting movement. Reflex is increased, striking bench originates movements. Gets off back with perfect ease. Is apathetic.  
 232<sup>m</sup>. Condition continues much as at last report. It is only on movement that tremor and ducking occur. Spring short. Reflex increases. Is apathetic.  
 353<sup>m</sup>. Crawls well if roused and with less tremor, but is apathetic. No jerking if at rest.  
 Next morning the animal was dead.

*Experiment.*

## EFFECT of a Large Dose of Pyrogallol.

## FROG of 15 grms.

- 0<sup>h</sup> 0<sup>m</sup>. Injected .0075 gm. pyrogallol into dorsal lymph sac.  
 4<sup>m</sup>. Restless. Movements already tremulous.  
 11<sup>m</sup>. If roused makes rapid and violent series of springs, but only progresses  $\frac{1}{2}$ –1 inch at each movement. After movement some involuntary extensions of legs and ducking of head.  
 21<sup>m</sup>. Resting on ventral surface. Rarely starting occurs. Reflex is increased. Is lethargic. Legs drawn up to body, and do not show rhythmical extensions as in case of dioxybenzol. Still springs short distance, but feebly.  
 54<sup>m</sup>. Sits with head raised, and shows but rarely jerking or starting except when roused; can still crawl.  
 Cannot resume ventral position if placed on back.  
 105<sup>m</sup>. Weak, lethargic.  
 160<sup>m</sup>. Ducks and starts if roused. Reflex is increased.  
 275<sup>m</sup>. Cannot get off back. Much jerking if roused.  
 400<sup>m</sup>. Lies on belly, legs drawn up. Attempts to spring, but hardly moves body. Cannot rise from back.  
 Next morning was dead.

*Experiment.*

## ACTION of Pyrogallol on the Spinal Cord, Nerves, and Muscles.

A brainless Frog with vessels ligatured in right leg. About .012 gm. injected into lymph sac. After all reflex had entirely ceased the cord was exposed and stimulated by a faradic current. It was found that at 15 centims. distance of the secondary coil there was jerk of the right leg, and that on approximating the coil to 10 centims. there was distinct tetanus on this side. The left leg, which had been exposed to the action of poison, was not moved till the coil was more nearly approximated (3 centims.). The tetanus of the ligatured leg was distinctly better than that of the unligatured from indirect, and slightly better from direct, stimulation.

(In testing the effect of medullary stimulation, all the tissues connecting the legs with the trunk were divided excepting the sciatic nerves.)

## COMPARISON BETWEEN THE ACTIVITY OF RESORCIN AND PYROGALLOL.

In Frogs the activity of pyrogallol in the production of immediate symptoms appears to be only one-quarter to one-fifth as great as that of resorcin; ultimately, however, it is almost exactly equal in its lethal effect.

## ACTION OF AMIDOBENZENE.

*Amidobenzene.*  $C_6H_5.NH_2$ . (*Anilin.*)

In considering the action of benzene, in which one atom of hydrogen has been replaced by amidogen, we must remember that this substance, viz., anilin, is capable

of being regarded from two points of view: (*a*) as amidobenzene, or benzene in which one atom of hydrogen is replaced by amidogen,  $\text{NH}_2$ ; or (*b*) as phenylamine, *i.e.*, ammonia ( $\text{NH}_3$ ), in which one atom of hydrogen is replaced by phenyl ( $\text{C}_6\text{H}_5$ ).

In correspondence with this constitution we find that we may regard the symptoms produced by it either as those (*a*) of benzene modified by amidogen, or (*b*) of ammonia modified by benzene. Thus we find the symptoms differ from those of benzene and resemble those produced by ammonia, in the tendency to more violent spasm and to greater paralysis of muscle and nerve. They differ from those of ammonia in the fact that the convulsions never assume the form of true tetanus, the tetanic spasm which the ammonia group would produce being broken up, so to speak, by the action of the phenyl.

As contrasted with the compounds already discussed, with exception of the hydroxyl compounds, it will be at once apparent that the accession of symptoms produced by the action of amidobenzene is decidedly more rapid. Within 5 to 7 minutes of subcutaneous administration a distinct muscular twitching with incoordination of movement makes its appearance. The movements, whilst in the main purposeless and frequently confined to one side, have sometimes a regular speed of recurrence, one form of motion being repeated again and again at short intervals. Occasionally the thrusting out and flexion of one leg may cease and the corresponding limb will take up the same action and repeat the movement at a similar rate. Less frequently a group of movements more distinctly coordinate occurs, usually those observed in swimming, and they may persist for several minutes. The eye reflex appears usually to outlast limb reflex.

As the notes of the case quoted show, the longitudinal conduction of the cord is evidently diminished, and the effects of nervous stimulation are relatively to those of direct (muscular) stimulation greatly lessened, though the muscle is itself considerably affected by the poison.

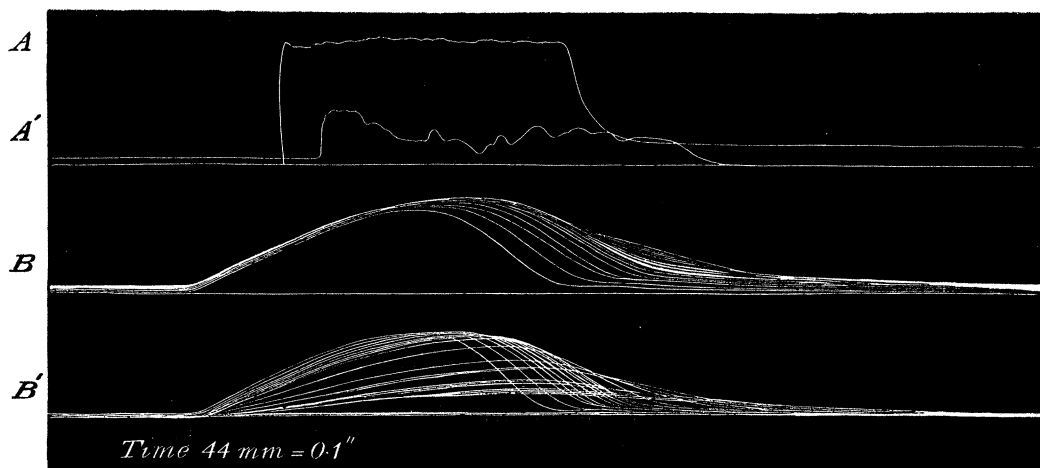
It was evident from the examination of other animals which had not been so completely poisoned, that, even if the initial stimulation of the nerve yielded a moderately good contraction, whether stimulation was repeated once or twenty times per second, the succeeding contractions became feeble and the muscle soon ceased to respond altogether to indirect stimulation.

When decerebration and ligature of the iliac artery had been practised before the introduction of the poison, it was found that reaction of the corresponding limb both to direct and indirect stimulation was stronger than on the side to which the poison had access by the circulation. (Fig. 9, A, A'.)

At the same time tremor was observed in the ligatured leg, evidently as a result of central action of the drug, and the reflex from it was not longer maintained than on the unligatured side.



Fig. 9. Action of Amidobenzene (Anilin) on Muscle and Nerve.



A, tetanus from unligatured (poisoned) leg by direct stimulation for 5<sup>s</sup>.

A' " " " indirect " " (*i.e.*, stimulation of nerve).

B, thirty contractions at intervals of 2<sup>s</sup> from direct stimulation.

B' " " " indirect "

The Frog weighed 30 grms. It was decerebrated; the left iliac vessels ligatured; and 1 minim of amidobenzene injected into the dorsal lymph sac. The examination was made after 2<sup>h</sup>. B and B' were taken before A and A'. The ligatured (unpoisoned) muscle gave on both direct and indirect stimulation a much more powerful and sustained contraction on tetanising, and the curve from single induction shocks did not elongate and fall in altitude as on the poisoned side (B').

### *Experiment.*

#### ACTION of a Small Dose of Amidobenzene. (Anilin.)

##### FROG of 45 grms.

- 11<sup>h</sup> 53<sup>m</sup>. Injected one minim of anilin into the dorsal sac.
- 12<sup>h</sup> 3<sup>m</sup>. Active, but movements are tremulous; occasional quack.
- 7<sup>m</sup>. Head tends to bend forward with jerk. All movements are now very tremulous. Moves round in circle, quacks. No springing spontaneously, but, if stirred, can still spring three or four inches. Breathing more laboured.
- 25<sup>m</sup>. Spasm chiefly in muscles of trunk at present. Crawling movement slow and tremulous; seems to feel ground with feet before resting on them. Still tends to creep round in circle. Can still spring five or six inches with great effort. Legs are drawn up slowly, and there is great trembling on alighting. The body gives a lurch when table is struck, but no tetanus.
- 40<sup>m</sup>. Quiet. All limbs drawn up normally. Seems more sensitive to cutaneous stimulation.
- 1<sup>h</sup> 0<sup>m</sup>. Quiet. Tremor on movement of body. Circumrotation. By rapidly approaching an object towards the eye, tremor of the whole body was produced, with or without a quack.
- 15<sup>m</sup>. Crawling is very slow and tremulous, and occasional spring of three to six inches.
- 2<sup>h</sup> 10<sup>m</sup>. No further symptoms. Crawl very tremulous, but stronger.
- 35<sup>m</sup>. Do. do.
- 3<sup>h</sup> 10<sup>m</sup>. Hops better; is less tremulous.  
Next morning, perfectly normal.

*Experiment.*

## MEDIUM Dose.

FROG of 29 grms. Room Temperature, 63° F.

- 0<sup>h</sup> 0<sup>m</sup>. Injected two minims amidobenzene into dorsal sac.
- 7<sup>m</sup>. Hind legs sprawl, toes spread out. Twitchings in muscles. Appears more paralysed in fore than hind legs. Breathing laboured and accompanied by protrusion of eyes. Leg at once drawn up if extended and gently touched. Striking the bench on which the Frog rests provokes tremor of legs and all body.
- 25<sup>m</sup>. One leg extended, with twitchings and separation of toes, but devoid of rigidity. The other leg and arm only show movements and twitchings, which are incessant. Eye reflex still present. (There is more movement here than in any other of the series.)
- 27<sup>m</sup>. Alternate extension and drawing up of right and left legs, as if in crawling, but no progress is made. All movements are very jerking.
- 33<sup>m</sup>. Extremely active waving of arms; thrusting out of legs and jerking of body set in without any true tetanus, lasted 2-3<sup>m</sup>. After this, slower swimming movements, which lasted 15-20<sup>m</sup>. Thereafter movement (spontaneous) declined.
- 137<sup>m</sup>. Legs yield no reflex now. Arms faint reflex. Eye reflex still present. Occasional spontaneous contractions of muscles of trunk and extremities still occur.
- Examined. There appears a slight coagulation at one part of dorsal sac.
- Tetanic stimulation of cord produces a hardly observable effect. Stimulation of the nerve gives broken tetanus. Faradisation of the muscles gives sustained but small tetanic contraction. The muscle gives a feeble curve.

*Nitrobenzene (Mono).*

We have examined the action of only one nitrobenzene, namely the mononitrobenzene,  $C_6H_5(NO_2)$ .

Its action upon Frogs is that of causing lethargy, with increasing tremor on movement. The power of voluntary movement disappears; touching the foot, however, may cause tremor of limbs.

Even when the Frog shows no reflex of any kind, a series of jerking movements of the legs may be made, apparently spontaneously, and these may be accompanied by muscular fibrillation.

The circulation in the web is slow and feeble, the pigment cells contracted.

Recovery may occur from this condition.

In 24 hours there is ability to crawl for a short distance; the movements, however, are distinctly tremulous.

When the symptoms of poisoning are fully developed, strychnine injected into the

dorsal sac no longer produces tonic spasm, nor anything approaching it, but there is increased tendency to a diffused twitch in response to local stimulation.

When the nitrobenzene is introduced into the stomach the same symptoms are induced, though more slowly than when the injection is subcutaneous.

### *Experiment.*

#### ACTION of Small Dose of Nitrobenzene on Frogs.

After the injection of 1 minim of nitrobenzene into the lymph sac, in—  
15<sup>m</sup> to 20<sup>m</sup>. Movement is tremulous, legs more slowly withdrawn. Occasional starting in limb when lying quiet, but usually no tremor during rest. Occasionally a series of rapid extensions of legs, as in swimming, occur. Reflex decreases till at 80<sup>m</sup> there may be only twitching without withdrawal of foot.

If 2 minims are injected, the symptoms may develop more rapidly. Eye reflex may disappear in 40<sup>m</sup> to 50<sup>m</sup>. It may be outlasted by extension of legs as a reflex act.

#### *Effect of Heat, 30° C.*

In a Frog poisoned by nitrobenzene and kept at 30°, the symptoms were as follows:—

- 5<sup>m</sup>. Tremor well marked.
- 10<sup>m</sup>. If leg is pinched it is thrust out and drawn up. There may be a coordinate kick with both legs. No withdrawal of arms if pinched, but legs are moved.
- 35<sup>m</sup>. All reflex is entirely gone, except the faintest tremor on pinching either of the feet. If taken out and placed on the bench there may be soon slight return of reflex, but this is usually very slight.

#### *Effect of Cold, 7° C.*

- 50<sup>m</sup>. After injection of 1 minim, still hops. Some tremor and slowness in drawing leg up after spring.
  - 80<sup>m</sup>. All reflexes present. Has quite ceased to crawl.
  - 200<sup>m</sup>. All reflexes present. No tremor when not attempting movement.
- From this condition complete recovery occurs.

#### *Effect on the Spinal Cord, Nerves, and Muscles.*

When reflex has almost entirely ceased it is usually found that stimulation of the upper part of the cord causes a very faint twitch in either leg (even if the sciatic artery has been previously tied in one). On the unligatured side indirect stimulation caused a very feeble contraction, if any; direct stimulation a relatively stronger, though imperfect contraction, which becomes rapidly prolonged on frequent repetition of stimulation (fig. 10). On the ligatured side both direct and indirect stimulation yielded good contractions. The chief effect is on the cord, which is markedly paralysed by this drug, especially in its conducting power. Next to this the end plates of the nerves are paralysed, and lastly, the muscular tissue is affected.

## Action of Nitrobenzene on Muscle and Nerve.

Decerebrated Frog weighing 24 grms. Right iliac vessels ligatured. 0.05 c.c. nitrobenzene injected into the dorsal lymph sac. Curves taken 5<sup>h</sup> after the injection.

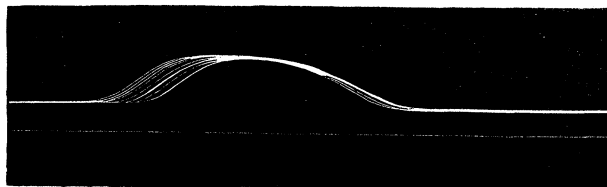


Fig. 10. Muscle of ligatured (unpoisoned) leg. Stimulated by opening shock of induction coil every 2<sup>s</sup>. Curve obtained by stimulation of the nerve was nearly equal to that obtained by direct stimulation.

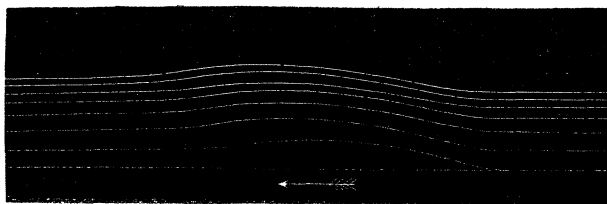
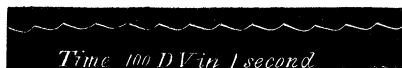


Fig. 11. Muscle of unligatured (poisoned) leg. Stimulated in the same way. The muscle relaxes imperfectly during the intervals between the contractions. There was no response at all of the muscle when the nerve was stimulated.

*Experiment.*

## MEDIUM Dose of Nitrobenzene. Frog of 29 grms.

- 0<sup>h</sup> 0<sup>m</sup>. Injected 2 minims of nitrobenzene into dorsal lymph sac.
- 24<sup>m</sup>. Torpid and slower in movements.
- 34<sup>m</sup>. Rests on belly, does not sit up, crawls and springs, but movements are tremulous and legs not rapidly drawn up. Repeated springing movements.
- 50<sup>m</sup>. All reflexes present, but the leg is drawn up slowly and jerkily. No tremor on movement whilst lying still, except an occasional starting of limb.
- 79<sup>m</sup>. Suddenly executed series of 10 to 12 rapid extensions of legs as in swimming. No eye reflex.
- 84<sup>m</sup>. Sharp twitch of both legs without withdrawal on pinching foot, but no movement of arms or trunk. Very faint reflex of each arm on stimulation of itself. Circulation very active, pigment cells not markedly altered.
- 109<sup>m</sup>. Movements of leg muscles very faint.

*Action on Spinal Cord, Muscle, and Nerve.*

Exposed the brachial cord. Left leg entirely divided except sciatic nerve, no contraction on tetanising nerve or cord. Response to direct stimulation of the muscle was extremely feeble, stronger in the other leg; from which 90 contractions were taken.

## EXPOSURE TO VAPOUR OF THE BENZENE COMPOUNDS.

The original experiments of BRIEGER,\* who showed how readily poisoning in Frogs might be induced by placing the animals in solutions of resorcin and its isomers, demonstrated the fact that by cutaneous absorption these substances are highly lethal. CHRISTIANI† has demonstrated in the same manner the poisonous action of benzol. The literature of pyrogallol abounds with instances of poisoning produced by the application of the drug applied in the form of ointment to the human body. The inhalation and cutaneous contact of the vapour of nitrobenzene have caused poisoning, and anilin when brought into contact with raw surfaces, as in the treatment of skin diseases, and more especially when its vapour has been inhaled, has produced its characteristic poisonous effects. Exposure of Frogs to the vapour of the anilins and their alcoholic combinations has been found by JOLYET and CAHOURS‡ and other observers to cause poisoning.

In confirming these and other experiments, we have found that exposure of Frogs to the vapour of benzene, its haloid compounds, its alcoholic compounds, to anilin, and to nitro-benzene, produces the characteristic symptoms of poisoning with great rapidity and completeness. We introduced Frogs into large funnels, the lips of which were covered with vaseline, so that they fitted air tight upon glass plates. In the neck of the funnel a fragment of sponge was contained, and into this the body to be tested was dropped. There was by this method no actual contact of the substance with the Frog, merely the exposure to the vapour liberated from the sponge.

We will merely quote one or two of such experiments in this place.

*Experiment.*

## ACTION of the Vapour of Monochlorobenzene.

FROG of 15 grms. in large funnel as above described. Temperature 15° C.

- 0<sup>h</sup> 0<sup>m</sup>. Dropped three drops of monochlorobenzene into the sponge contained in mouth of funnel.  
 20<sup>m</sup>. Violent springing alternating with crawling movements, great frothing on sides of funnel. Legs are strongly withdrawn.  
 45<sup>m</sup>. Movements, much less powerful, are jerky and broken.  
 85<sup>m</sup>. All reflexes are jerking. Start of body and limbs on striking bench. Lies still if not roused, legs extended.  
 95<sup>m</sup>. All movement completely gone. *Frog taken out of the funnel.*  
 135<sup>m</sup>. There is a very faint twitch of toes on stimulating fore foot or hind foot. On decapitating, a

\* BRIEGER, 'Arch. f. Anat. u. Phys.,' 1879.

† 'Comptes Rend.,' vol. 56, p. 1131.

‡ 'Zeitschrift f. Physiol. Chemie,' vol. 2, p. 282.



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weak movement of arms and legs occurred. On stimulating the spinal cord, contraction in legs was very imperfect and unsteady. Nerve distinctly impaired in function. Muscle gives feeble tetanus. Heart still beating slowly.

## ACTION of the Vapour of Dimethylbenzene.

The symptoms produced by dimethylbenzene were much less marked, chiefly characterised by motor paresis.

## ACTION of the Vapour of Amidobenzene. (Anilin.)

Anilin caused, after an initial period of excitation, great tremor and twitching, and after exposure to vapour for 40 minutes, the animal hardly possessed the power of crawling. Appearances like those of paralysis agitans.

*Experiment.*

## ACTION of the Vapour of Nitrobenzene.

PLACED a Frog under glass on filter paper. Temperature  $15^{\circ}5$  C.

- 0<sup>h</sup> 0<sup>m</sup>. At upper end of glass, five drops of nitrobenzene dropped on sponge.  
 20<sup>m</sup>. Cannot hop, all reflexes present, but slow and jerky. Breathing rapid.  
 60<sup>m</sup>. *Decerebrate*. Thereafter no spontaneous movement causing tremor occurred, but on irritating foot, withdrawal was very slow and still tremulous.  
 420<sup>m</sup>. All reflex gone from legs. Very weak reflex from arms. Circulation active, strong.

*Condition of Spinal Cord, Muscle, and Nerve.*

Decapitated, prepared upper part of cord and cut through all tissues but nerve of one side. Contraction in gastrocnemius of this side, though not so strong as of the other on stimulating cord. After contraction occurred, fibrillation lasted some time.

Although it may seem almost superfluous after what we have already said, yet we shall now give, in the briefest possible manner, the most prominent results obtained, which may serve to contrast the bodies we have examined.

*Benzene* (aromatic) causes relatively but little tremor, except on movement, and whilst it may for a time increase the reflex function of the cord, in the end it causes paralysis. The central nervous (cerebral) apparatus is somewhat specially affected by *bromobenzene*, whilst spontaneous jerkings, with tremor on movement and increasing lethargy, characterise *iodobenzene*. *Monochlorobenzene* tends to cause more pronounced spasm than the foregoing. There is great tremor, with ataxic movements. The circulation is but little affected.

The *methyl compounds* abolish voluntary movement and ordinary reflex, but sometimes after the ordinary reflex response has disappeared, touching may cause other movements which are not usually induced, as touching eye causing extension of limbs, but no eye reflex (as in case of trimethylbenzene), occasional clonic convulsive movements of limbs and trunk have been observed to occur spontaneously (as in case of methylbenzene). There is more tremor after dimethylbenzene than after methylbenzene. The eye reflex disappears relatively soon.

The trimethylbenzene is distinctly the most active of the three.

*Ethylbenzene* is stronger than methylbenzene in producing paralysis, but not so strong as the trimethyl compound. Some amount of tremor is observable on attempted movement.

*Dihydroxybenzene* meta (resorcin) is distinct from all the others in the spontaneous, rapidly occurring, and somewhat rhythmical movement which it occasions. This symptom, whilst rapid in making its appearance if the dose is small, lasts for a long time before paralysis of the cord ensues.

*Pyrogallol* has not the same tendency to cause clonic spasm, but tends rather to produce a lethargic state with gradual decline of reflex.

*Amidobenzene* causes the most rapid occurrence of motor phenomena, the hydroxyl compound excepted. There is great tremor after a spring. Very active incoordinate movement is made, but tonic spasm is absent.

*Nitrobenzene* causes lethargy with increasing tremor on movement. The reflex is abolished somewhat early, but after this time a series of jerking movements of the legs, perhaps with fibrillation, may be observed.

#### SECTION II.—ACTION OF BENZENE AND ITS COMPOUNDS UPON REFLEX.

An extensive series of observations was made with the view of testing the effect upon reflex action of the various bodies entering into the series under discussion. Decerebrated Frogs, prepared some time previously, were used for this purpose.

Immediately before the experiment commenced, the right iliac artery and vein were ligatured, in order that an estimate might be formed of alteration of reaction originating, not in the cord itself, but in the muscles and peripheral nerve terminations. The foot of the suspended Frog was stimulated by dilute acid of various strengths, from 1 per 1000 to 1 per 6000 (by measure). The reflex was tested every 10, 15, or 20 minutes, according to circumstances, and estimated by means of a metronome beating half-seconds.

The time of withdrawal was recorded, and from the figures obtained the diagrammatic charts were constructed. One difficulty peculiar to the substances under consideration was met with, namely, that from the action of certain of them, a condition of spontaneous jerking was developed, which was aggravated by immersion, even in pure distilled water, at the moment the application was made. This action, which occurs when the foot is very suddenly immersed, but not nearly so much so when gradually, was specially pronounced in the case of benzene, monochlorobenzene, and amidobenzene (anilin). The difficulty was overcome by a more gradual immersion, and by repeating the test until the uniformity of time of withdrawal clearly indicated that this was due to the stimulation by the acid.

On account of the motor symptoms produced by the hydroxyl compounds, we found them unsuited to this form of experiment.

The ultimate effect of many bodies in the series is to render the withdrawal of the foot highly tremulous and jerking. The flexion of the leg is followed by an extension, and this again by another flexion, so that instead of a sustained withdrawal from the irritating acid fluid, the foot is splashed in and out, and the action is continued until the foot is washed with pure water, and sometimes even after washing. After use the animals were placed in the cold and kept moist. The doses employed throughout the series of over 70 experiments were either the  $\frac{1}{36}$  of a cubic centimetre, or exactly double the quantity. The measurement was made in an accurately graduated capillary tube. Twenty-four hours after the larger dose reflex was still active, chiefly in the case of Frogs receiving the moniodobenzene, dimethylbenzene, and benzene, though with the smaller dose it was usually retained, excepting after trimethylbenzene.

*Benzene.*  $C_6H_6$ .

This body in larger dose,  $\frac{1}{18}$  c.c., rapidly lengthens the time elapsing before reflex reaction to acid solutions, which were previously strong enough to cause rapid withdrawal of the foot. The curve which may be obtained by placing verticals, representing the time elapsing before reflex withdrawal of the foot, upon an abscissa, which is divided into equal time intervals, shows a parallel change of responses on the ligatured and unligatured sides, allowance being made for the slower reflex in the former owing to blood stasis. With a smaller dose,  $\frac{1}{36}$  c.c., the failure of reflex is much more gradual; in the experiment from which the curve is formed it varied only from 1.5 second to 7.5 seconds in the course of  $4\frac{1}{2}$  hours. There was no certain indication of shortening of the reflex phenomenon even at an early stage of the poisoning.

We quote the results of two experiments.\*

\* In recording the reflex time we occasionally give two speeds, as 1 second to 1.5 second, indicating at that particular time a withdrawal, sometimes at 1 second, sometimes at 1.5 second. In the figures we have drawn up the mean is given between these numbers.

*Experiment a.* (4.)

FROG of 32 grms., pegged some hours previously.

LIGATURED Right Iliac Vessels. Acid Solution 1-4000 (by measure). Reflex three times tested at short intervals. Injected  $\frac{1}{8}$  c.c. Benzene into Anterior Lymph Sac.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes	seconds	seconds	
0	1.5-2	2.5	
10	1.5	2	
20	3	3.5	Jerking of feet and spreading of toes commenced
40	10	9	Change to 1-2000 acid
50	2.5	2.5	Jerking exaggerated on instant of immersion
60	3	3-3.5	
120	6-6.5	6.5	Legs jerked out sharply, but thrust in again; the movement is exaggerated for some time after falling in water
180	8.9	8.9	

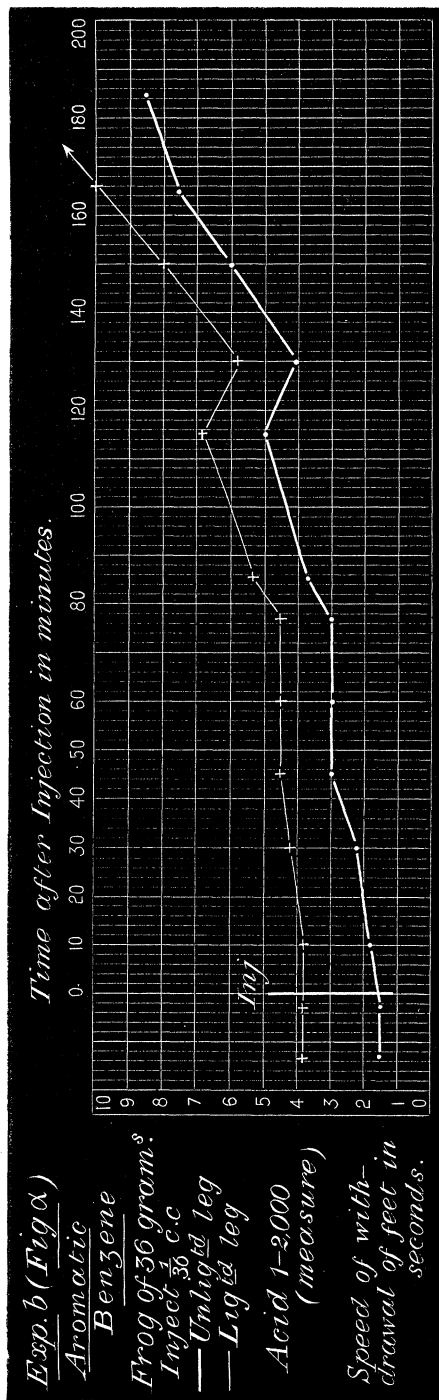
In 24 hours the reflex of this Frog was good, and but slightly tremulous

*Experiment b.* (Fig. 12, a.)

FROG of 36 grms. Preparation as before.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes	seconds	seconds	
0	1.5	3.5-4	Tested four times at short intervals. Acid solution 1-2000
			Injected $\frac{1}{8}$ c.c. aromatic benzene
10	1.5-2	3.5-4	
30	2-2.5	4-4.5	
45	3	4.5	
60	3	4.5	Withdrawal tremulous
85	3.5-4	5-5.5	
115	5	6.5-7	All movements are flapping and unsustained
130	4	5.5-6	
150	6	8	
166	7-8	10	
190	8.5	Not in 20	Next day reflex from both legs was good to mechanical stimulation

Fig. 12.





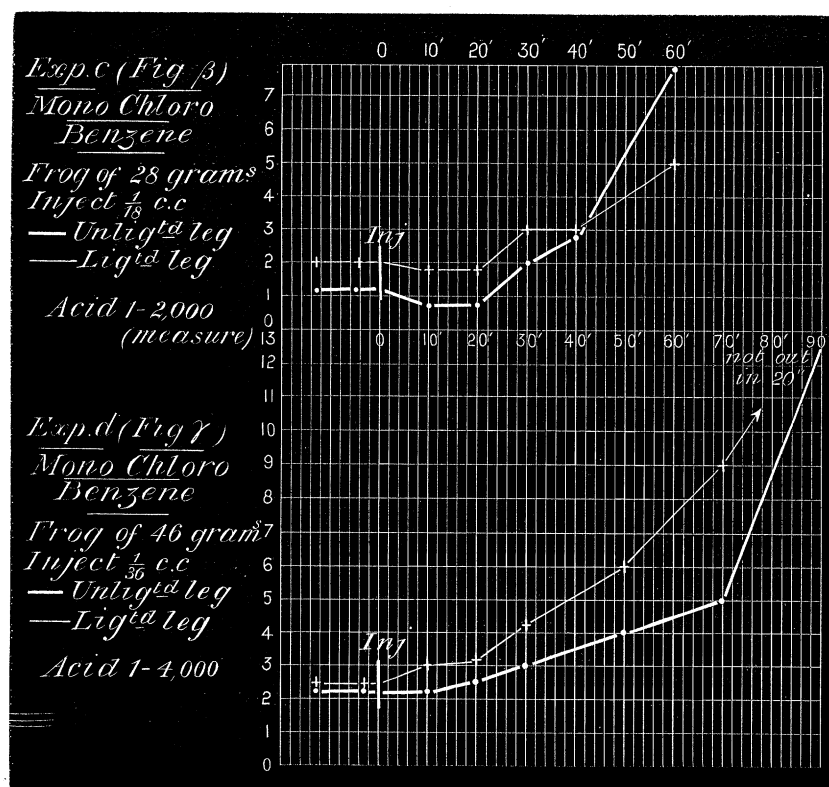
*Monochlorobenzene.*

This compound causes a powerful effect upon reflex ; it is, in fact, one of the most active bodies in the series. In about one-half of the experiments a shortening of the reflex period was produced immediately after injection. The reduction varied from .5 second to 1.5 second, and was never present for more than 30 minutes after the injection had been made. After this temporary reduction, or an alternative equality or slight lengthening of reflex, a very rapid change took place, the period of reflex increasing considerably with every estimation. Spontaneous spreading of toes and jerking of feet and legs were developed in all cases, and this condition was increased by immersion in the acid solutions, and sometimes persisted for a time in exaggerated form after washing with cold water. Immersing suddenly in water caused an active instantaneous jerk. In several experiments the ligatured leg, though as much affected in this respect as the unligatured, was stronger in its reaction, and, spite of diminished irritability from stasis, came to respond by withdrawal more rapidly than the other, indicating a direct paralysing action of the drug on the side of free circulation.

*Experiment c. (Fig. 13,  $\beta$ .)*

FROG of 28 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds 1-1.5	seconds 2	Acid 1-2000 (measure). Tested reflex four times at intervals
Injected $\frac{1}{8}$ c.c. monochlorobenzene into anterior lymph sac			
10	.5-1	1.5-2	Twitching of toes has commenced
20	.5-1	1.5-2	
30	2	3	
40	2.5-3	3	
60	8	5	Twitching of toes and feet active
24 hours. All reflex gone			

Fig 13,  $\beta$  and  $\gamma$ .*Experiment d. (Fig. 13,  $\gamma$ .)*

FROG of 46 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds 2-2.5	seconds 2.5	1-4000 acid. Tested reflex thrice
Injected $\frac{1}{36}$ c.c. monochlorobenzene into anterior lymph sac			
10	2-2.5	3	
20	2.5	3-3.5	
30	3	4-4.5	
50	4	6	Movement broken and tremulous
70	5	9	Active jerking before withdrawal
90	13	Not out in 20 secs.	

On changing the solution to 1-1000 (nothing weaker caused withdrawal), the reflex of the unligatured limb was reduced to 5 seconds, but lengthened again with moderate rapidity to 10 seconds. The ligatured limb yielded no further response. In 24 hours there was feeble reflex on the unligatured side, and in 48 hours this had become moderately active.

*Monobromobenzene.*

The action of this body upon reflex is considerable and moderately rapid, though it is distinctly less than that of monochlorobenzene. There is during the course of the experiment an almost entire absence of the motor phenomena which are so prominent in the former. No distinct reduction in the time of reflex was observed. The curves obtained from the ligatured and unligatured limbs ran fairly parallel. In the experiment quoted the latter at first was slightly slower than the former, but the position became in time reversed.

*Experiment e.* (Fig. 14,  $\delta$ .)

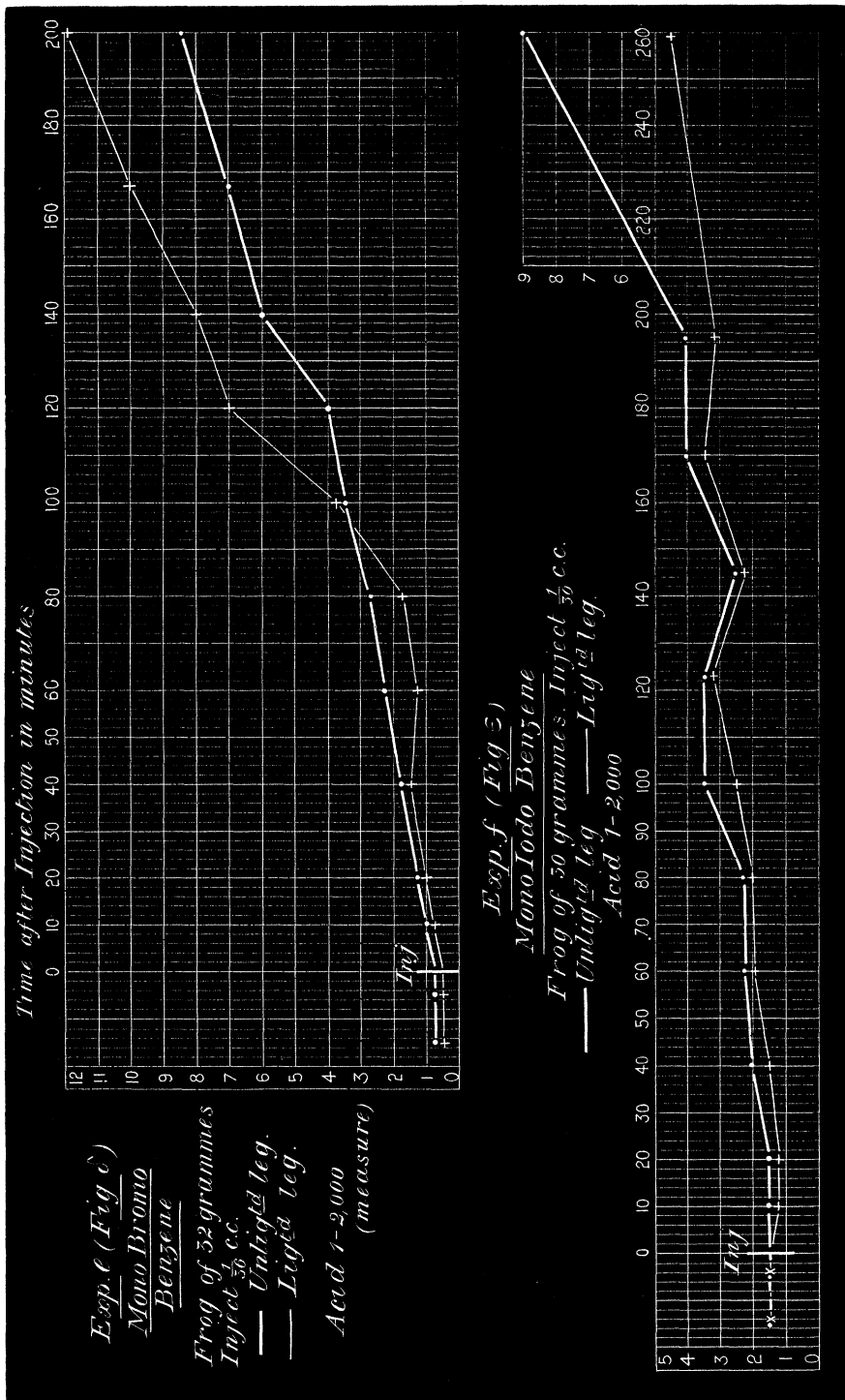
FROG of 32 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds .5-1	seconds .5	Tested thrice at intervals. Acid, 1-2000
Injected $\frac{1}{36}$ c.c. monobromobenzene into anterior lymph sac			
10	1	.5-1	Withdrawal tremulous, but no spontaneous jerking
20	1-1.5	1	
40	1.5-2	1.5	
60	2-2.5	1-1.5	
80	2.5-3	1.5-2	
100	2.5	3.5-4	
120	4	7	
140	6	8	
175	7	10	
200	8.5	12	
275*	12	18	From 1-4000 acid solution
24 hours. Reflex entirely disappeared to all stimulation			
* Not shown in fig.			

*Monoiodobenzene.*

Of the haloid compounds, iodobenzene is the least active upon reflex. Although it does not appear to reduce the reflex period in the first instance, the prolongation caused as a rule develops slowly. In experiments extending to 4 and 5 hours it was found that the ligatured leg, at the conclusion, usually had a distinctly shorter reflex latency than its unligatured companion; from which circumstance a direct effect of the drug upon the terminal nervous filaments or the muscular tissue, impairing their function, is to be inferred. The spontaneous jerkings appear like those caused by chlorobenzene. A persistence of reflex on the day after the experiment appeared more usual than with the other haloid compounds for equal doses to animals of equal weight.

Fig. 14,  $\delta$  and  $\epsilon$ .



*Experiment f.* (Fig. 14,  $\epsilon$ .)

FROG of 30 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds 1.5	seconds 1-1.5	Tested thrice at intervals. Acid 1-2000
Injected $\frac{1}{30}$ c.c. moniodobenzene into anterior lymph sac			
10	1.5	1-1.5	
20	2	1-1.5	
40	2	1.5	
60	2-2.5	2	
80	..	..	
100	3.5	2.5	Withdrawal becoming tremulous on both sides
125	..	3-3.5	
140	2.5	2-2.5	No spontaneous jerking
170	4	3.5	
195	4	3	
260	9	4.5	
24 hours. Moderately good reflex in both legs			

The action of *methylbenzene* is apparently identical with that of the dimethyl compound, which we shall now consider.

*Dimethylbenzene.*

The effect produced by this compound upon the time of recovery is neither rapid nor powerful, and this statement holds even when the larger dose,  $\frac{1}{18}$  c.c., is employed. A reduction of the latency has been observed in a considerable proportion of the experiments made with this drug, and this phenomenon has occasionally been seen to last for 40 minutes. Failing a positive reduction, the speed of withdrawal remains for a time unaffected. When the reflex does begin to lengthen the increase is gradual. There is no spontaneous movement. The reflex after the lapse of 24 hours is good and destitute of tremor.



*Experiment g.* (Fig. 15,  $\zeta$ .)

(The time of reflex was identical for a considerable period in the two legs.)

FROG of 31 grms. Usual Preparation.

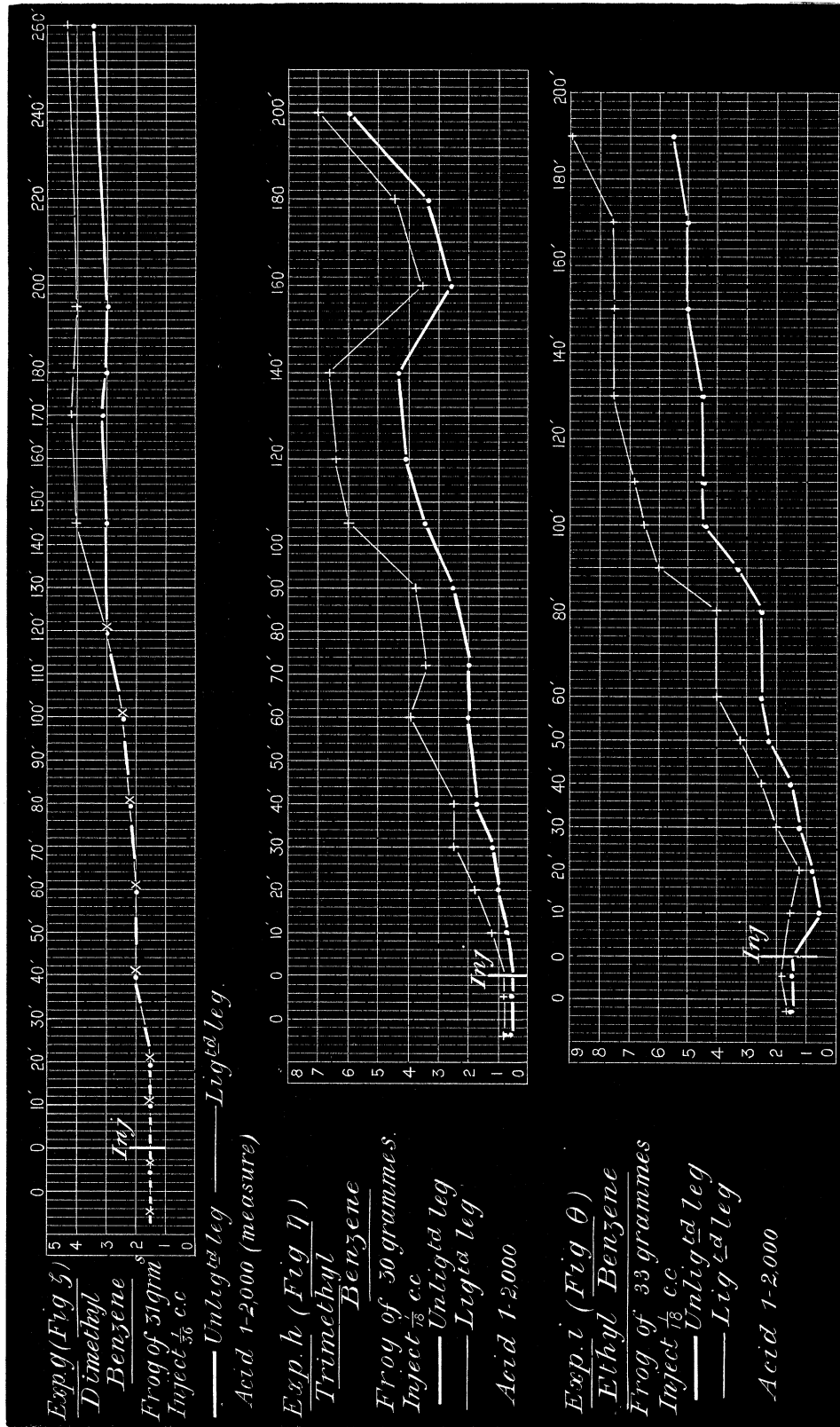
Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds 1.5	seconds 1.5	Tested four times at intervals. Acid solution 1-2000
Injected $\frac{1}{36}$ c.c. dimethylbenzene into anterior lymph sac			
10	1.5	1.5	
20	1.5	1.5	
40	2	2	
60	2	2	
80	2-2.5	2-2.5	
100	2.5	2.5	
120	3	3	
145	3	4	
170	3-3.5	4-4.5	
195	3	4	
260	3.5	4.5	
24 hours. Reflex moderately good, devoid of tremor			

*Trimethylbenzene.*

This compound is markedly stronger in its action upon reflex than the dimethyl compound. No shortening of reflex has been noticed, but a steady prolongation of the time elapsing between immersion and withdrawal of the foot. As a rule, the curves obtained from the ligatured and unligatured legs respectively run fairly parallel, but occasionally the unligatured drops behind the other, as if eventually a direct effect was produced upon the muscle substance and nerve terminations.

In 24 hours after the smaller dose reflex has, as a rule, entirely disappeared.

Fig. 15,  $\xi$ ,  $\eta$ , and  $\theta$ .



*Experiment h.* (Fig. 15, η.)

FROG of 30 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds .5	seconds .5-1	Thrice tested at intervals. Acid solution 1-2000
Injected $\frac{1}{8}$ c.c. trimethylbenzene into anterior lymph sac			
10	.5-1	1-1.5	
20	1	1.5-2	
30	1-1.5	2-3	
40	1.5-2	2.5	
60	2	4	
70	2	3.5	
90	2-3	3.5-4	
110	3-4	6	Well withdrawn. No tremor
130	4	6.5	
150	4-4.5	6.5-7	
170	2.5	3.5	A most distinct acceleration of reflex, regular on every immersion
190	3.5	4.5	
210	6	7	
24 hours. All vitality gone.			

*Ethylbenzene.*

Although the effect produced upon reflex is moderately rapid and extensive when large doses have been administered, with smaller doses the result is much less marked, so that this compound is to be regarded as amongst the feebler in its power of reducing the reflex activity of the cord. As a primary result of its action the time of reflex is usually reduced, sometimes by as much as 1 second. This stage of acceleration may persist from 10 to 30 minutes. Thereafter a lengthening of the period occurs and develops slowly or rapidly according to the dose. There is no protraction of spontaneous tremor and jerking, though the withdrawal of the legs becomes ultimately tremulous.

The day after the experiment, when the smaller dose had been used, the reflex was usually found to be good and unaccompanied by tremor.

*Experiment i. (Fig. 15,  $\theta$ .)*

FROG of 33 grms.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes	seconds	seconds	
0	1.5	1.5-2	Tested four times. Acid 1-2000
Injected $\frac{1}{18}$ c.c. ethylbenzene into anterior lymph sac			
10	1	1.5	
20	.5-1	1	
30	1-1.5	2	
40	1.5	2.5	
50	2-2.5	3-3.5	
60	2.5	4	
70			
80			
90	3-3.5	6	
100	4.5	6.5	
110	4.5	6.5-7	
130	4.5	7.5	
150	5		
170			
190	5.5	8	

In Experiment k, in which a Frog of 38 grms. received  $\frac{1}{36}$  c.c. of ethylbenzene, the time of reflex, when tested with 1-2000 acid, increased in 140 seconds by less than 2 seconds, and in 2 hours later it had increased only one additional half second. The day after the preparation showed good reflex in both legs; no tremor was present.

*Amidobenzene.*

Anilin has considerable power in causing spontaneous movement in a pegged Frog. The movement is spontaneous, but it is exaggerated on dipping the foot into acid solution or even into water. No reduction of the reflex period has been observed. The time occupied in withdrawal lengthens materially, whilst the increased jerking immediately after immersion shows it is a case of slow summation of stimulations centrally rather than of a failure of peripheral motor and sensory apparatus. The curves of response of the ligatured and unligatured legs are very parallel throughout.

If the acid solution used is of the strength of 1-2000, and the amount of anilin injected does not exceed  $\frac{1}{18}$  c.c., reflex may still occur within three or four seconds of the original speed, even after the lapse of three hours.

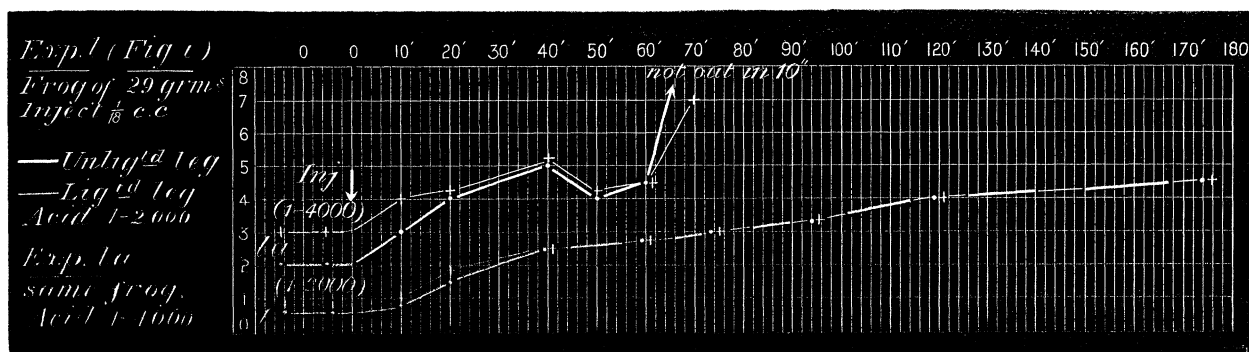
## BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION. 593

*Experiment 1; la. (Fig. 16, c)*

FROG of 29 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes. 0	seconds. .5	seconds. .5-1	Thrice repeated at intervals. Acid 1-2000
Injected $\frac{1}{18}$ c.c. amidobenzene			
10	.5-1	1	Withdrawal tremulous
20	1.5	1.5-2	
40	2	2	Twitching of toes increased even after acid removed by washing
50	2.5	2.5	
60	2.5-3	2.5-3	
75	3	3	Are only just drawn clear of the solution. The ligatured leg is the stronger of the two
95	3-3.5	3-3.5	
120	4	4	Withdrawal very weak and tremulous. Jerking and spreading of toes after washing
175	4.5	4.5	
Same preparation tested at same time with 1-4000 acid solution			
0	2	3	
Time of injection			
10	3	4	
20	4	4-4.5	
40	5	5-5.5	
50	4	4-4.5	
60	4.5	4.5	
70	Not out in 10	7	

Fig. 16, c.





*Nitrobenzene.*

Little or no movement of the reflex frog preparation is observed independently of the stimulation.

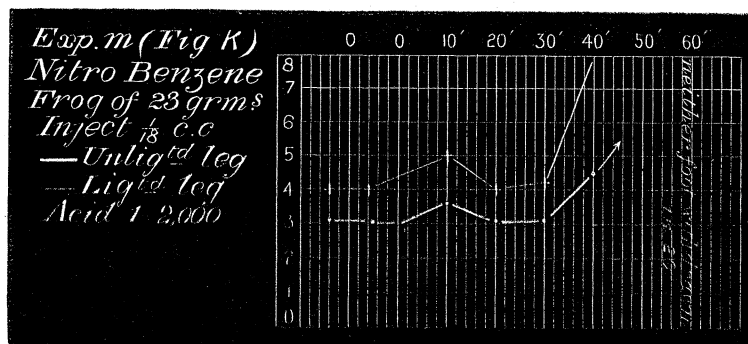
If the dose of nitrobenzene injected is a moderately large one ( $\frac{1}{18}$  c.c. to frog of 23 grms.), great prolongation of reflex is observed usually within an hour. Thus, in the case referred to, in 60 seconds after injection neither leg was removed within 20 seconds, though at 20 minutes the reflex stood at 3 seconds and 4 seconds for the two legs respectively. A dose proportionately much smaller, as in the case quoted ( $\frac{1}{36}$  c.c. to frog of 41 grms.), shows a comparatively slight effect upon the cord, the reflex remaining active, with but little tremor on stimulation. After the smaller dose recovery frequently takes place, so far that reflex next day is good on the side of ligature, and the withdrawal of the protected foot occurs more powerfully on stimulating the unprotected than the withdrawal of the latter itself. It is evident, therefore, that sensory nerves are no more affected than motor, if as much, by the action of this drug, which has a direct effect upon the exposed limb in addition to its action on the cord.

*Experiment m. (Fig. 17, κ.)*

FROG of 23 grms. Usual Preparation.

Time.	Unligatured leg.	Ligatured leg.	Remarks.
minutes 0	seconds 3	seconds 4	Tested thrice. Acid 1-2000
Injected $\frac{1}{18}$ c.c. nitrobenzene			
10	3.5-4	5	
20	3	4	
30	3	4.5	
40	4.5	8	
60	Neither out in 20		

Fig. 17, κ.



*Experiment n.*

FROG of 41 grms. Injected  $\frac{1}{36}$  c.c. Nitrobenzene.

In this experiment reflex on immersion in 1-4000 acid solution became gradually slower, but after 3<sup>h</sup> the ligatured leg was still withdrawn in 4<sup>s</sup> (instead of 1<sup>s</sup> before injection) and the ligatured in 5·5<sup>s</sup> (instead of 1·5<sup>s</sup>).

When a reflex Frog poisoned with nitrobenzene is laid on a flat surface, the legs, if flexed, are not violently extended with jerking and tremor, as in the case of monochlorobenzene, amidobenzene, &c., but are retained in a flexed position.

## SECTION III.—THE ACTION OF BENZENE COMPOUNDS IN CAUSING MUSCULAR RIGOR.

It had been frequently observed that local coagulation of muscle was produced at parts with which the benzene compounds had come into contact ; it seemed advisable therefore to determine whether the activity of these bodies was uniform or whether some were more active than others. With this object in view the compounds were either brought into direct contact with the muscle by filling the muscle chamber already described ('Phil. Trans.,' Part I., 1884) with them, so that the muscle was completely immersed, or else measured quantities were introduced into a muscle chamber which was specially constructed so as to be absolutely air-tight, and thus without bringing the liquid into direct contact to allow of its action during volatilisation upon the muscle.

By the first method it was found that powerful rigor was rapidly induced by all the members of our series. The contrast between the three halogen compounds showed that in the case of—

Monochlorobenzene, the active shortening of the muscle	
30 minutes after application of the drug was . . .	3·1 millims.
Monoiodobenzene, the active shortening of the muscle	
30 minutes after application of the drug was . . .	3·4 „
Monobromobenzene, the active shortening of the muscle	
30 minutes after application of the drug was . . .	2·5 „

In each case contraction commenced within one minute of contact with the benzene compound.

As this method however involved the use of such large quantities of the compounds the series was not completed, but the second plan (*i.e.*, the spontaneous volatilisation of carefully measured amounts of the compounds in an air-tight chamber, into which a muscle had previously been introduced) was followed.

The contrast was made at equal temperatures.

By following this plan it was soon determined that variations occurred between the various benzenes. Shortening of the muscle did not immediately occur as in the case of immersion which has been already described. It was even found that when stimulation of the muscle was practised before and after the admission of the benzene compound, the contraction occasionally remained as powerful for some time under the latter conditions as it was before, but this was always in absence of any material shortening. The variation between the bodies with regard to this as well as to the shortening was, however, considerable. Some proved themselves distinctly more active than others.

When  $\frac{1}{10}$  c.c., exactly measured, of the *halogen* compounds was introduced, it was found that monochlorobenzene was much the most active in causing rigor, then monobromobenzene, and monoiodobenzene was a good deal weaker than either of them.

When the strongest of these bodies (monochlorobenzene) was contrasted with the alkyl compounds it was found to take an intermediate place between methyl-, which is the strongest, and dimethylbenzene which stands next to it; when contrasted with the third of the methyl compounds, trimethylbenzene, monochlorobenzene shows itself itself later in producing shortening, but its ultimate effect is more powerful.

The activity of the methyl compounds is therefore inversely to the extent of methyl substitution in the benzene molecule.

Ethylbenzene is not far removed from methylbenzene in the total effect of the shortening it produces. In each of four experiments the latter was strongest. It is generally quicker in causing shortening than methylbenzene. Ethylbenzene is distinctly stronger than the di- and trimethyl compounds.

With such small quantities as  $\frac{1}{30}$  c.c. of these compounds a very distinct and moderately rapid shortening was induced, as the following figures, illustrative of a few experiments only, suffice to show, the contrast in each instance being between companion muscles of the same Frog at equal temperatures. Two slow drums were employed, having a slightly different speed of rotation.

No. 1	has a rate of	33 millims. in 10 minutes.	Figs. 18 and 19.
No. 2	„	39 „ „ „ „	Fig. 20.

Nitrobenzene and amidobenzene showed themselves much less effective than the other compounds when muscles were exposed in air-tight chambers to their action.

In experiments in which only the  $\frac{1}{30}$  c.c. of these bodies was tested, it was found that after the lapse of 15 hours no shortening nor rigor were observable.

When the muscles were exposed for many hours in the presence of a large amount of these bodies, mononitrobenzene was earlier in producing its effect than anilin.

COMPARATIVE Action on Mnscl. — Rigor.

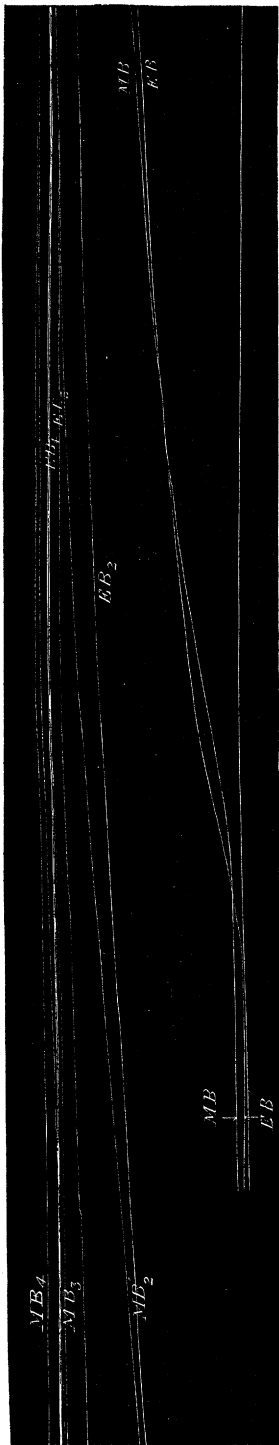


Fig. 18. Ethylbenzene and Methylbenzene.

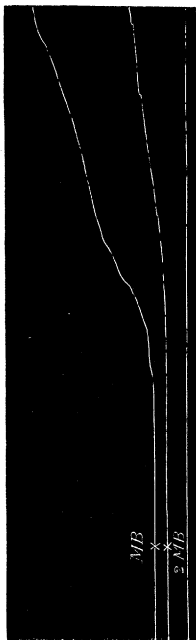


Fig. 19. Methylbenzene and dimethylbenzene.

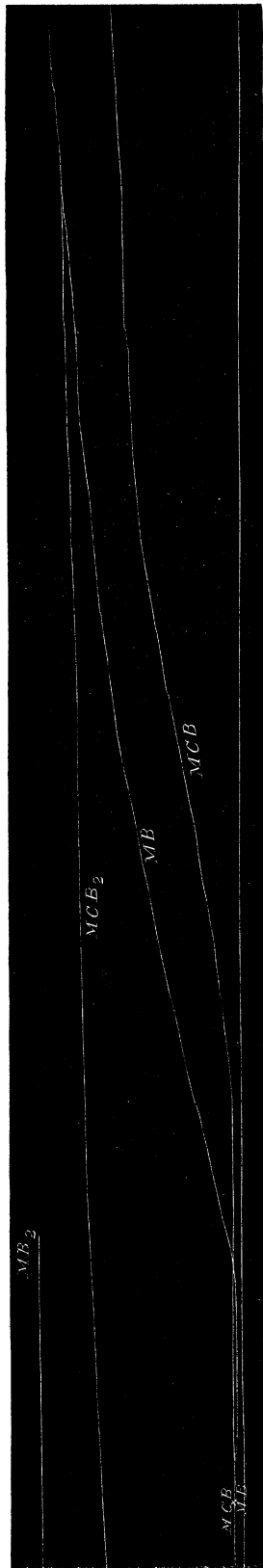


Fig. 20. Monochlorobenzene and methylbenzene.

Substance.	Amount.	Temperature in °C.	Frog's muscle.	Weight.	Time of first sign of contraction.	Contraction.			
						Extent 30 minutes after exposure.	60 minutes.	2 hours 4 minutes.	12 hours.
Monochlorobenzene } fig. 20	c.c. $\frac{1}{30}$	12.75	Triceps . . .	grms. 10	min. sec. 15 0	millims. 1.5	millims. 3	millims. .	
Methylbenzene . . .	"	"	"	"	7 10	2.8	4.2		
Methylbenzene . . .	"	10	Gastrocnemius	10	6 0	4.1			
Dimethylbenzene . . .	"	"	"	"	8 12	2.3			
Methylbenzene . . .	"	12	Gastrocnemius	10	10 0	2.6	5.3		
Trimethylbenzene . . .	"	"	"	"	13 0	8	5.3		
Methylbenzene . . .	"	11.75	Gastrocnemius	10	6 30	2.7	6.1	7	
Ethylbenzene . . .	"	11.75	"	"	9 45	2.5	5.6	6.5	
Ethylbenzene . . .	"	11.25	Triceps . . .	10	9 20	4.3	7.3		
Trimethylbenzene . . .	"	"	"	"	13 20	1.3	4.3	6.7	
Amidobenzene . . .	"	12	Triceps . . .	10	Not in 14 hours				
Nitrobenzene . . .	"	"	"	"	"				No rigor in 14 hours



This result would not seem to point away from the theory which might possibly be advanced, that we have here to do to a large extent with a question of varying volatility between the various benzenes.

The boiling-points of amidobenzene and nitrobenzene are 184 and 209 respectively, and the only body which at all approaches them in the slowness of its action is moniodobenzene, with a boiling-point of 188.

Ethylbenzene, with a boiling-point of 134, comes after methylbenzene (111), but before dimethyl- (146) and trimethylbenzene (163).

#### SECTION IV.—EXPERIMENTS UPON RATS.

Benzene, and the compounds of the benzene series, together with resorcin, were administered hypodermically to Rats, the animals chosen for experiment being as nearly as possible of the same size.

##### *Aromatic Benzene*

Produces lethargy, with some exaggeration, however, of reflex, and occasional spontaneous jerking, with great impairment of mobility.

##### *Experiment.*

- Injected 5 gtt. into right groin.
- 19<sup>m</sup>. Is torpid, but can run easily if roused.
  - 31<sup>m</sup>. Is hyperæsthetic and jerks away, if touched, to another place.
  - 36<sup>m</sup>. Starts if touched. There is an occasional spontaneous jerk.
  - 60<sup>m</sup>. Much less affected than either of the others (nitro- and amidobenzene) examined at the same time.
  - 80<sup>m</sup>. Falls over on one side if touched.
  - 260<sup>m</sup>. Sitting up and beginning to run.
  - 300<sup>m</sup>. Normal.
- Next day perfectly normal.

Small doses of monochloro-, monobromo- and moniodobenzene (2 minims) injected beneath skin of three Rats of equal medium size, caused in each case slight lethargy without any special symptoms. This lethargy continued for from 60 minutes to 90 minutes, after which time complete recovery occurred.

##### *Larger Doses.*

*Chlorobenzene.*—6 minims injected beneath skin caused some tremulousness in movements in 30 minutes. The animal became lethargic, and if not roused remained sitting in corner of cage. It was, however, easily roused by touching or noise, and then ran well, though its movements were somewhat unsteady. This condition lasted

for three hours after administration of chlorobenzene, and thereafter a return to normal took place.

*Bromobenzene*.—After a similar dose of this drug a Rat of equal size became very lethargic, and though sitting up and possessed of all its reflexes, it could hardly be roused to movement.

When recovering it walked slowly with a rolling or rocking movement, its balance appearing uncertain.

*Iodobenzene*.—Was distinctly more active than either of the other haloid compounds (6 minims to animal of equal size to other two).

- 12<sup>m</sup>. After administration it was observed to jerk five or six times in succession, became rapidly weak, tending to sink on its side.
- 27<sup>m</sup>. Resting on side. Very lethargic. All reflexes are present.
- 37<sup>m</sup>. Breathing much accelerated. Rocks as if attempting movement, but lies in any position in which it is placed.
- 2<sup>h</sup> 42<sup>m</sup>. Symptoms are more marked than at the last report. The animal cannot move trunk or limbs. The eye reflex still persists. No tremor. Breathing rapid. The conditions remained much the same till death occurred in 5 hours from failure of respiration.
- Post-mortem. Right heart contains much dark blood. No other special appearances.

Subcutaneous injection of 6 minims of ethyl-, methyl-, and dimethylbenzene respectively, caused a condition of lethargy which lasted from three to four hours. The animal could be roused at any time. No special motor symptoms were produced, but a certain degree of anaesthesia was observable in each instance.

Trimethylbenzene of the same dose caused closely similar symptoms, but terminating in the death of the animal.

#### *Dioxybenzol on Rats.*

0·03 gm. of metadioxybenzol, dissolved in five drops of salt solution, injected subcutaneously into large Rat.

- 3<sup>m</sup>. Shuddering and jerking of body, shaking of head.
- 9<sup>m</sup>. Above symptoms much more marked.
- 12<sup>m</sup>. Still walks, but very ataxic. Breathing accelerated.
- 18<sup>m</sup>. Resting on side and back, cannot rise, all limbs in clonic spasm. Abdominal, thoracic, cervical, and facial muscles also contract sharply at intervals. No fixed or tonic spasm.
- 41<sup>m</sup>. This condition continued until 41<sup>m</sup> after the injection, when jerking became less, and the power of spontaneous movement began to return. Washed face and walked a few paces.
- 51<sup>m</sup>. Reflex is still rather exaggerated, but spontaneous jerking has almost disappeared.
- 80<sup>m</sup>. Quite normal.

Doses of 0·05 to 0·1 were fatal; death occurred from paralysis of the respiratory muscles. The heart appeared to be relatively not much affected, its action outlasting the respiration.

(Pyrogallic acid was not examined in this series.)

*Amidobenzene on Rats.*

Rapidly developing weakness, with jerking and marked dyspnœa, is observed.

Injected 4 minims into right groin.

- 15<sup>m</sup>. Tends to sink on belly. Hind legs weaker than fore.  
 18<sup>m</sup>. Breathing over 200 per minute. An occasional start or jerk is noticed. Can still crawl very slowly, but usually lies with legs extended behind it.  
 57<sup>m</sup>. Is much more affected than the benzene or nitrobenzene Rats.  
 87<sup>m</sup>. A good deal of jerking as it lies, both of fore and hind limbs. Much dyspnœa.  
 107<sup>m</sup>. Breathing very hurried; great dyspnœa.  
 262<sup>m</sup>. Quite insensible; no reflexes. Jerking of limbs at intervals, as 2<sup>s</sup>, 5<sup>s</sup>, 5<sup>s</sup>, 3<sup>s</sup>, 2<sup>s</sup>, &c. Respiration rapid and laboured, 150 per minute. Body not very cold. Breath smells of amidobenzene.  
 342<sup>m</sup>. Died.  
 Only very slight twitch of toes occurred on crimping sciatic.  
 Post-mortem.—Limp; cortex of kidneys and brain surface congested. Right side of heart very full.

*Nitrobenzene on Rats.*

Torpidity, weakness, failure of reflex, absence of motor symptoms. Failure of respiration.

Injected 5 minims into right groin.

- 38<sup>m</sup>. Runs, but is weaker and somewhat torpid.  
 53<sup>m</sup>. Runs a step or two and falls on side, but soon recovers itself.  
 83<sup>m</sup>. Rises with difficulty if turned over on side.  
 130<sup>m</sup>. No marked reflex from body or limbs, but from eye still present. Breathing quiet, not hurried.  
 258<sup>m</sup>. More under influence of drug. Is now profoundly insensible to all stimulation. Breathing and pulse feeble. Surface very cold.  
 358<sup>m</sup>. Breathing slower; no twitching; no reflex; quite insensible.  
 500<sup>m</sup>. Died.  
 Post-mortem.—Lungs congested. Right heart contracted, also left. Kidneys not markedly hyperæmic (in these respects differs from amidobenzene).

## SECTION V. ACTION OF AROMATIC BENZENE AND ITS COMPOUNDS ON PULSE, BLOOD-PRESSURE, AND RESPIRATION OF MAMMALS.

In all cases ether was the anæsthetic employed during the experiments. This was administered from a bottle which was connected with the tracheal cannula by means of a short tube. By turning the stop-cock (Dr. BRUNTON'S\*) with which the bottle was provided, atmospheric air was substituted for ether. The animal was kept thoroughly anæsthetised, but never profoundly narcotised.

*Aromatic Benzene.*

Experiments made with this substance yielded fairly similar results.

The blood-pressure was for some time but little affected (in one instance slightly increased), and the character of the pulse was not materially altered, although it was considerably reduced in frequency.

The respiration showed at first a slight acceleration, but this soon yielded to a

\* 'Brit. Med. Journal.'



*Monochlorobenzene.*

When injected subcutaneously in an emulsionised condition, monochlorobenzene was found at first to raise the blood-pressure and to accelerate the pulse and respiration. The blood-pressure remained high throughout the first two hours, during which time one drachm had been injected (in experiment quoted below). The pulse rate was also increased. Some slowing of the respiration was produced eventually. Whilst large doses injected subcutaneously did not produce more marked action, small doses, in a fine state of emulsion, injected into the femoral vein caused cardiac arrest, respiratory efforts outlasting the heart's action.

After the injection of this drug, ether appeared in one case to have an unusually depressant action on the heart.

MONOCHLOROBENZENE. Cat 5 lbs. Etherised. Cannulæ in Trachea and Femoral Vein.  
Animal in Warm Box.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes 0-20		123	134-162	25
20	Injected 20 minims monochlorobenzene (emulsionised) subcutaneously			
38		132	165	30
60		..	181	
67	Injected 20 minims monochlorobenzene			
77	If anæsthesia is not profound there is considerable tremor of limbs			
85	On giving ether, first a fall, then rise, then rapid fall of blood-pressure to 9 millims. Division of both vagi and artificial respiration caused recovery			
105		168	156	22
120	Injected 20 minims as before			
125	" " "			
140	Clot formed in right carotid which could not be removed. Changed cannula to left carotid. Unusual tendency to clotting throughout the experiment			
158	Pulse somewhat dicrotic	164	124	22
172		..	116	
173	Injected 20 drops (emulsionised) into femoral vein			
178	Heart ceased	..	0	
183	Respiratory effort ceased			

*Post-mortem.*—Heart. Auricular appendix beating actively. Right ventricle in diastole, smelling strongly of monochlorobenzene. Left ventricle in strong systole. Lungs healthy, contain much mucus, but do not, on naked eye examination, show hæmorrhages or infarction. Gastrocnemius contracts well both to direct and indirect stimulation.



*Monobromobenzene.*

Like aromatic benzene and monochlorobenzene this substance (monobromobenzene) was found to act very feebly when injected subcutaneously. Administered in this way some increase of blood-pressure with acceleration of the pulse was produced.

When injected into the jugular vein, very largely diluted, a small dose of 1 to 4 minims caused a slight rise of pressure if the injection was slow, but a fall if it was rapid. The respiration became greatly accelerated, sometimes irregular and gasping. When the pure drug was slowly injected without dilution, gasping respirations succeeded and ultimately complete paralysis of respiration. Even when the pure drug was employed very large doses were injected before death took place. Death was due, in the experiments made, to failure of the heart.

CAT of 8 lbs. Preparation as usual. Injection was made into the Jugular Vein.

Time.	Remarks.	Pulse for 1 minute.	Blood pressure.	Respiration.
minutes				
0	(Fig. 21) . . . . .	144	114	24
25	Injected 1 minim of monobromobenzene, thoroughly emulsified into the jugular vein . . . . .			
60		148	111-115	
83	Injected 1 minim as before, but more rapidly. There is a fall of 18 millims. for a few seconds followed by rise of 4 millims.			
90	Injected 2 minims, shaken up in 3 c.c. salt solution, slowly. Rise of 3 millims., but if injection was made more rapidly there was at once a fall . . . . .		118	
92	Systole well maintained . . . . .	126	110	46
105	Injected 4 drops as before, with a fall of pressure succeeded by a rise (fig. 22). Respiratory curves in blood pressure increased in extent . . . . .			
120	(Fig. 23) . . . . .	144	94	44, rather irregular
130	Injected very slowly 8 drops . . . . . (Injection occupied 9 minutes) . . . . .	..	104	
140	(Fig. 24)	..	82-92	
150	Slow injection of 20 minims in 30 c.c. salt solution yields faint rise of pressure succeeded by gasping . . . . .			
155		140	100	
162		..	110	0
165	Injection of 4.5 minims unsuspended into vein. Succeeded by salt solution. Respiration occasional and gasping. Pause in expiration. 120 minims undiluted in all, injected in 3 doses . . . . .			
175-190	After first dose of 30 minims (fig. 25) . . . . .	131	100-32	5-6
195	Blood pressure falling, vagi are cut. Rise of pressure for few seconds, and the heart ceases . . . . .		43	

*Post-mortem.*—Lungs engorged. Some ecchymosis observed on section. Left heart simply contracted. Right heart dilated. Blood smells much of monobromobenzene. Kidneys congested, but showed no hæmorrhages.

Intestine exhibits peristalsis.

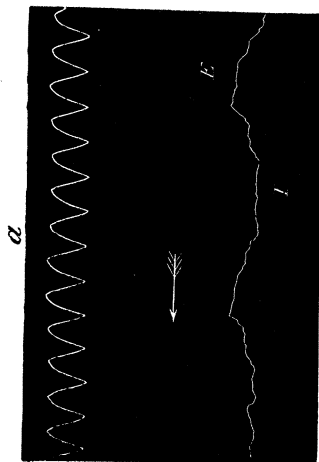


Fig. 21. Quick drum (55 millims. equal to 5<sup>s</sup>). Pulse and respiration. Before injection of monobromobenzene.

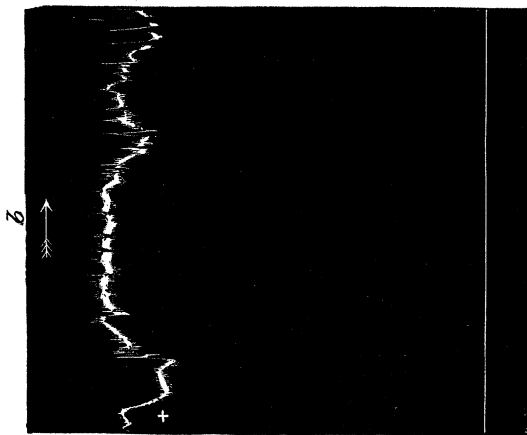


Fig. 22. Slow drum (19.4 millims. equal 5<sup>m</sup> in all experiments). \* Intravenous injection of 4 minims monobromobenzene. Time 105<sup>m</sup>.

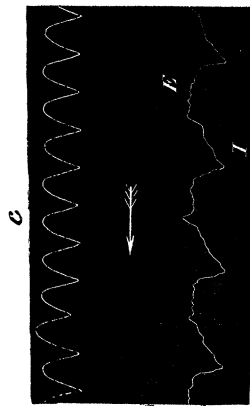


Fig. 23. Quick drum. Pulse and respiration. Time 120<sup>m</sup>.

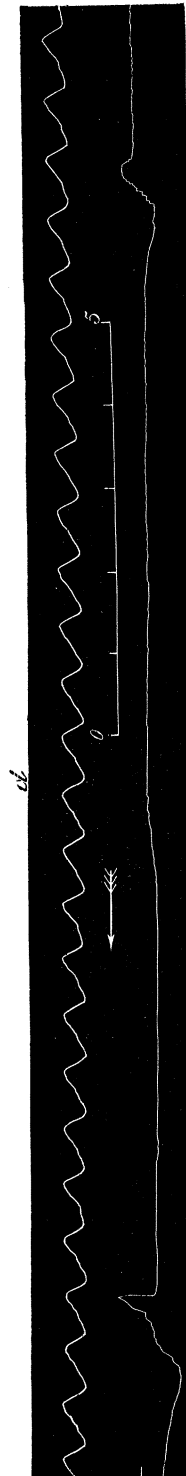


Fig. 24. Quick drum. Pulse and respiration. 140<sup>m</sup>.

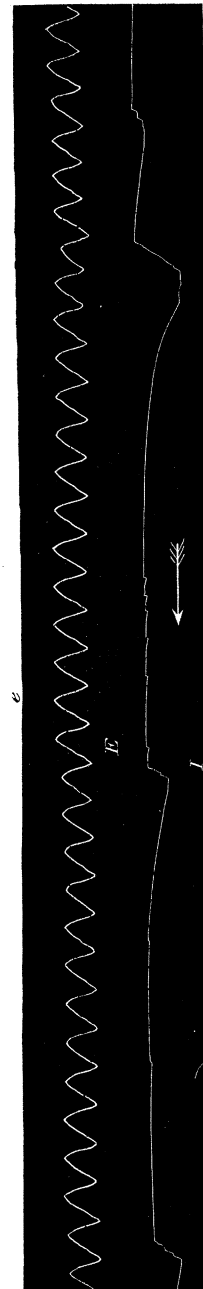


Fig. 25. Quick Drum. Pulse and respiration. 180<sup>m</sup>

*Iodobenzene.*

In the experiment which we shall quote, iodobenzene was injected into a loop of intestine which was carefully returned to the peritoneal cavity after the operation, the small abdominal incision being closed.

A slight increase of respiration was soon followed by a fall in the rate per minute.

The heart was greatly accelerated, the increase in number of pulsations amounting to over sixty per minute. The blood-pressure which had remained fairly constant for two hours, rose considerably at the commencement of the third hour. After ligation of the vagi the pulse became even more rapid and the pressure higher. There was not, however, a very marked slowing of respiration. Death as usual was due to cardiac failure.

In the experiment quoted, death of the animal occurred suddenly after dilute ether vapour had been re-administered for a short time; the respiration outlasted the cardiac contraction. This result, or, short of it, a great and sudden fall in the blood-pressure, we have seen produced on several occasions by ether, when administered after large doses of the drugs contained in our series, even when the previous administration had been altogether unattended by any unusual effect of this character.

CAT, 8 lbs. Cannulæ in Carotid and Trachea. Vagi prepared on loose threads.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes				
0	(Fig. 26) . . . . .	132	110	25
22	Injected 5 minims monoiodobenzene into a loop of intestines. Rise of 4 millims. at time of injection, and more permanent elevation of 2 millims.			
32	. . . . .	204	108	26
70	Injected 15 minims as before			
90	(Fig. 27)			
105	Injected 20 minims as before . . . . .	180	110	20
160	30 " " " . . . . .			
185	(Fig. 28) . . . . .	204	124	25
140	Injected 30 minims as before			
210	Respiration feeble. . . . .	..	140	
212	Tied left vagus. Rise of 24 millims., then fall, first gradual then rapid, to 48. After which gradual recovery occurred. Ligatured right vagus . . . . .	240	150	20
225	(Fig. 29)			
230	Administered ether. Blood-pressure fell to within 24 millims. of abscissa, and in spite of artificial respiration being carried on in addition to spontaneous respiration, the heart did not recover itself			

Tracings of the pulse by Fick's Kymograph. Action of Monoiodobenzene.

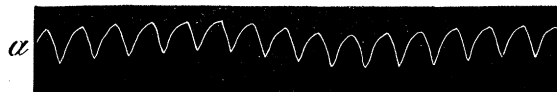


Fig. 26. Time 0. Pulse before injection of monoiodobenzene.



Fig. 27. 68<sup>m</sup> after first injection and after 20 *minims* in all of monoiodobenzene have been injected.



Fig. 28. 163<sup>m</sup> after first injection and after 70 *minims* in all have been injected.



Fig. 29. 203<sup>m</sup> after the first injection. Both vagi have been divided.

#### *Methylbenzene (Toluene).*

When injected subcutaneously this substance causes a rise of blood-pressure, succeeded by a fall. The pulse is greatly accelerated. In the first instance the respiration is somewhat accelerated.

Intravenous injection accelerates the respiration at the same time that it reduces the blood-pressure and lessens the pulse-rate, the beats becoming irregular and fused without a complete diastole intervening. This depression of the blood-pressure is to some extent central, as there is a great rise after vagotomy, and the pulse becomes very rapid. The respiration was not so greatly slowed by this operation as is usually the case.

In the experiment we shall quote, death appeared to be due to pulmonary oedema.

## CAT, 7½ lbs.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes 0		118	122	26
12	Injected 12 minims methylbenzene subcutaneously			
25	Fluctuations appear in the blood-pressure tracing which are not of respiratory origin . . . . .	164	134	
30	Ether abolishes these. . . . .	..	..	28
45	Injected 20 minims subcutaneously			
60		..	120	
55	Waves now reappear. . . . .	156	112	
78	Injected 2 minims in 2 c.c. salt solution into femoral vein. Waves become more marked; they are abolished by ether, which lowers blood-pressure			
85	Injected 5 minims in 10 c.c. salt solution. At once a rise of 7 millims., succeeded by waves fluctuating from 94 to 108. (Fig. 30)			
92	These waves are abolished by ether			
100	Injected 8 minims as before . . . . .	..	110	
103	Irregularity in pulse beats, which tend to form pairs without complete diastole intervening			
113	Irregularity of pulse disappeared. Well sustained double summit; second somewhat lower than the first . . . . .	119	99	40
115	Injected 8 minims as before . . . . .	..	98	
117	Pulse irregular, with abortive systole preceding strong contraction of ventricle. Cut vagi, pulse and pressure rise. (Fig. 31)			
120		144	114	21
128	Injected 10 minims rapidly . . . . .	168	44	18
132		136	72	8
135		..	58	
138	About 20 c.c. of bloody serous fluid has come from cannula in last ten minutes. Animal died of suffocation			

*Post-mortem.*—Both sides of heart (contain blood) in diastole. Right enormously distended. Lungs very œdematous throughout; rosy red.

*Dimethylbenzene (Para).*

When injected into a loop of the intestine which was then returned to the peritoneal cavity, dimethylbenzene somewhat lowered the blood-pressure and slowed both respiration and pulse in the first instance, subsequently the respiration became more rapid, the pulse nearly as rapid as it had previously been.

Small doses, 2 minims (largely diluted) injected into vein caused a transitory rise of pressure. Larger doses of 4 to 8 minims, also largely diluted, caused at once a fall succeeded by a slow return of the pressure to the former level.

Failure of respiration tended to occur. After vagotomy in the experiment recorded, the pulse became much accelerated, the pressure rose, and the respirations fell from



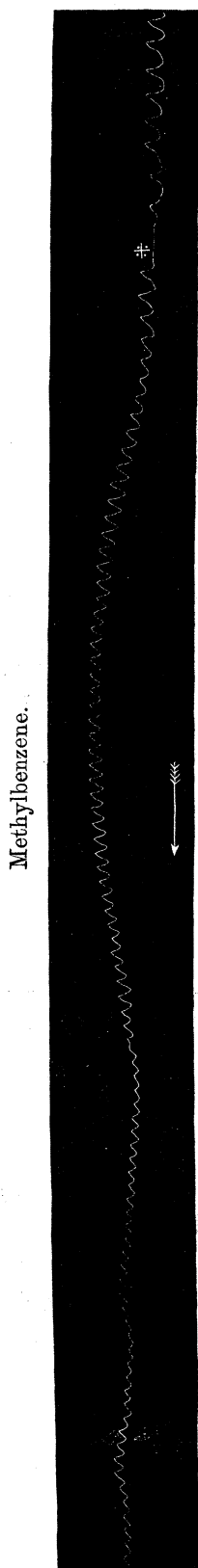


Fig. 30. 117<sup>m</sup>. Division of vagi whilst inhibition from the drug was present. The tracing reads from right to left in the direction of the arrow, and 29 millims correspond to 5<sup>s</sup>.

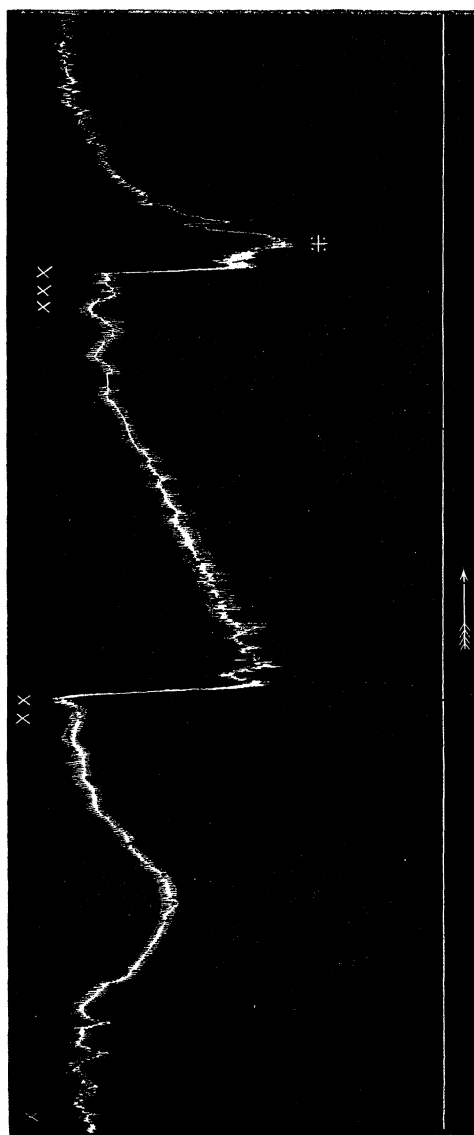


Fig. 31. 85<sup>m</sup> to 120<sup>m</sup>. Showing the result of intravenous injection of 5 minims slowly,<sup>x</sup> then of 8 minims of methylbenzene,<sup>xx</sup> and, lastly, of 8 minims immediately followed by<sup>xxx</sup> section of the vagi (see Tracing 30 on quick cylinder).

16 to 10 per minute. The succeeding injection of 10 minims completely paralysed respiration. The heart continued to beat so long as artificial respiration was kept up, and then failed.

*Post-mortem.*—In case quoted, showed great pulmonary œdema.

Action of Dimethylbenzene on Circulation and Respiration.

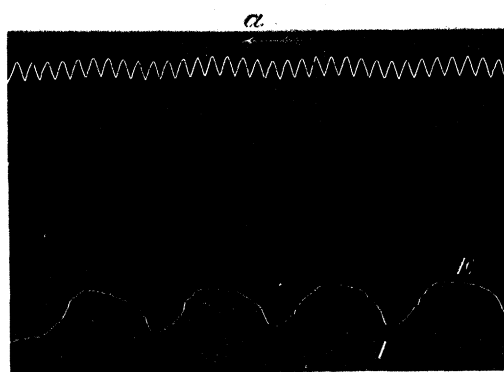


Fig. 32. Quick drum. Time 0. Normal pulse and respiration.

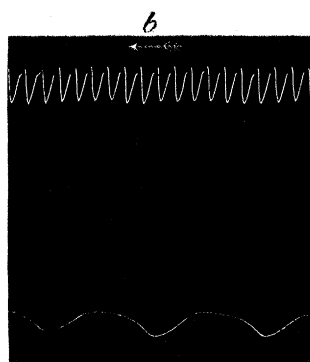


Fig. 33. Pulse and respiration 62<sup>m</sup>.

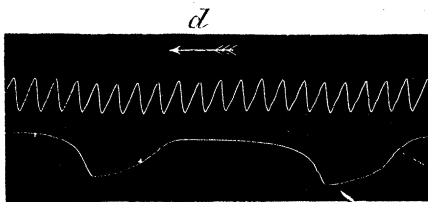


Fig. 34. 98<sup>m</sup>. Vagi not yet divided.

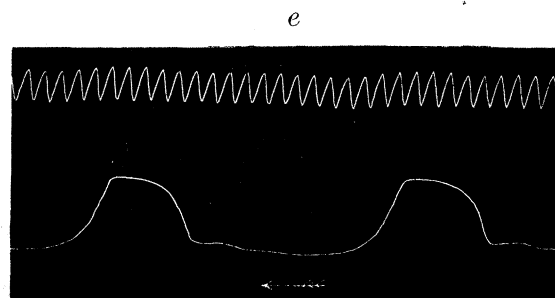


Fig. 35. Time 99<sup>m</sup>. The vagi have been divided. Speed of quick drum 31 millims. equal to 5<sup>s</sup>.

## Action of Dimethylbenzene on Circulation and Respiration.

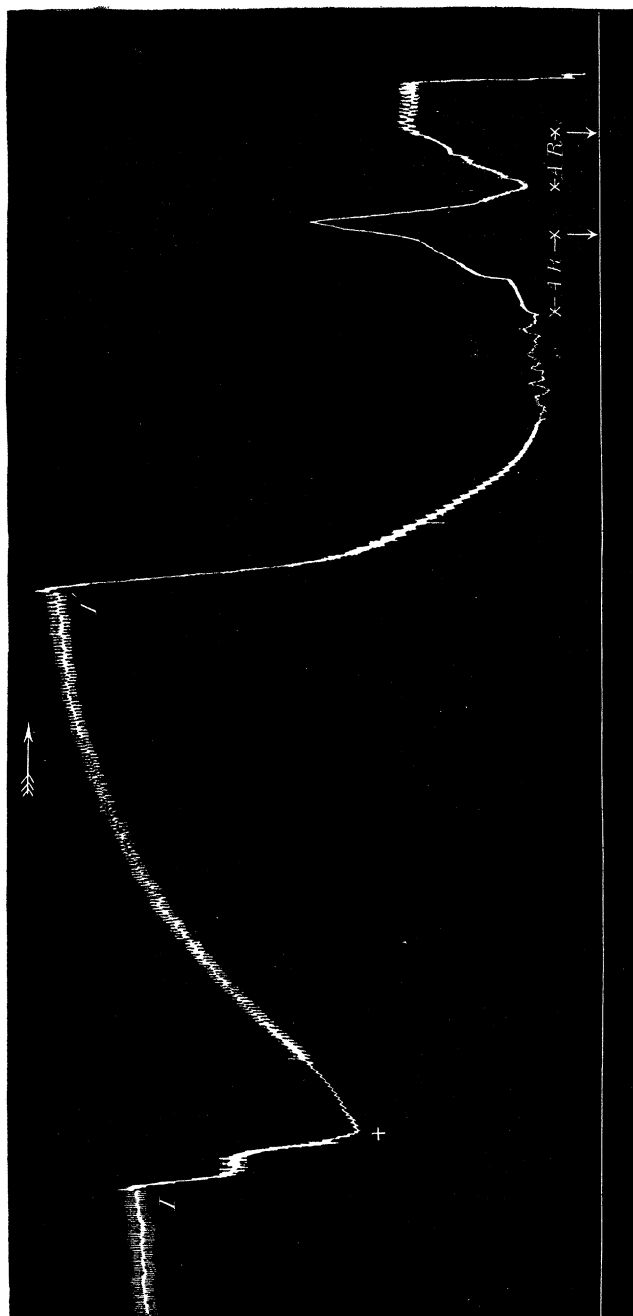


Fig. 36. Slow cylinder. Blood-pressure tracing of two successive injections of 8 minims dimethylbenzene (1 and 1'). Vagi divided at +. Death occurs on suspension of artificial respiration AR.

CAT of 7 lbs. Dimethylbenzene. Animal in Warm Box to maintain Temperature.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes.				
0	(Fig. 32) . . . . .	192	144	25
16	Injected 6 minims dimethylbenzene into intestine			
30	Respiratory waves well marked in manometer . . . . .	168	140	20
50		..	136	
62	Very distinct wave in descent has developed itself, though it was already discernible at 30 <sup>m</sup> to a lesser extent. (33) . . . . .	168	131	27
65	Ether causes fall of pressure of 33 millims.			
67		..	128	
69	Injected 2 minims suspended in 2 c.c. salt solution into femoral vein			
70	Rise of pressure of 8 millims. succeeded by fall to such level			
76	Rise to . . . . .	..	130	
77	Injected 4 minims in 2 c.c. salt solution . . . . .	..	104	
87	Systole sharp, and shows a second summit in descent of curve . . . . .	158	120	23
95		..	121	
96	Injected 8 minims suspended in 4 c.c. salt solution			
98	Blood-pressure falls very rapidly (34). Both vagi divided (35) . . . . .	140	64	21
100	Prolonged pause in inspiration. Pressure rises rapidly . . . . .	170	..	10
115		..	143	
116	Injected 8 minims in 4 c.c. salt solution. At once a fall (36)			
118	All attempts at respiration over . . . . .	..	13	
123	Artificial respiration raises blood-pressure; when discontinued, death results. Pulse good till artificial respiration discontinued	..	50	

*Post-mortem.*—Some very dark blood in right ventricle. A little in the left ventricle. No clots here nor in the pulmonary artery. Lungs congested; contain much œdematous bloody fluid.

#### *Trimethylbenzene (1 : 2 : 3).*

Injected under the skin trimethylbenzene causes at first a slight fall in blood-pressure, a decrease in the number of cardiac contractions, and an acceleration in the respiration. The pulse then tends to quicken as a set-off to the reduced pressure, and the respiration becomes slower.

Injections of small doses of the drug (largely diluted with salt solution) into the femoral vein cause a slight decline in blood-pressure, an acceleration of both respiration and pulse, but this acceleration is only temporary. The fall of blood-pressure becomes more marked as the amount of the drug in the circulation increases.

Section of both vagi, as in experiment quoted, rapidly raises the blood-pressure above its original level, an acceleration of the pulse being well marked. The respira-

tion is reduced to half its previous frequency, the long pause in inspiration characteristic of vagotomy being well marked. After further injections the respiration became much embarrassed, a bloody cedematous fluid running freely from the tracheal cannula.

After the last injection spontaneous respiration ceased and artificial respiration failed to raise pressure, death ensuing.

## CAT 8 lbs. Trimethylbenzene.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes				
0	(Fig. 37) . . . . .	204	142	36
8	Ether causes fall of blood-pressure			
9	Injected 3 minims trimethylbenzene subcutaneously			
15	. . . . .	180	142	33
30	Injected 30 minims			
35	Distinct second summit after active systole of heart . . . . .	168	134	48
53	(Fig. 38) . . . . .	192	134	31
72	Injected 2 minims in 2 c.c. salt solution into femoral vein			
80	Injected 6 minims in 6 c.c. salt solution			
82	. . . . .	162	112	42
90	Injected 10 minims in 5 c.c. salt solution	..	126	
92	. . . . .	108	56	33
	Divided both vagi . . . . .	168	..	25
100	Indications of second rise in pulse very faint. Long inspiratory pause . . . . .	180	158	13
122	. . . . .	..	139	
123	Injected 10 minims trimethylbenzene in 5 c.c. salt solution into vein. Fall of 18 millims. blood-pressure. Respiration becomes very laboured. Fluctuations of pressure. Redtinged cedematous fluid begins to run into tracheal cannula, and secretion of this is soon so rapid that animal threatened with suffocation			
	(Fig. 39, slow drum, shows course of pressure to end of experiment)			
135	. . . . .	..	111	
140	(Fig. 40) . . . . .	204	110	12
145	Injected 20 minims trimethylbenzene . . . . .	..	88-100	
148	Artificial respiration fails to raise pressure. Death . . . . .	..	12	

*Post-mortem.*—Right heart in diastole. Left in systole. Lungs are congested and cedematous. There is a soft clot in pulmonary artery. Kidneys are fatty, congested.



Action of Trimethylbenzene.

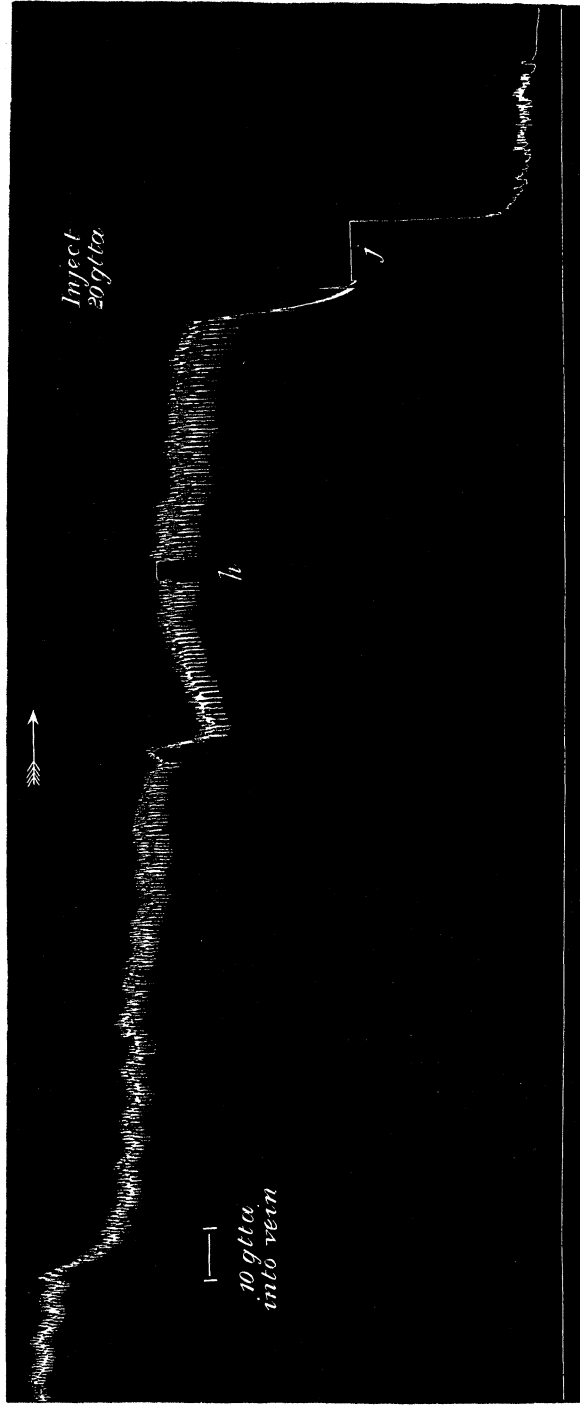


Fig. 39. Last half hour of experiment. Vagi divided. One injection (intravenous) of 10 minims trimethylbenzene and one of 20 minims rapidly fatal.

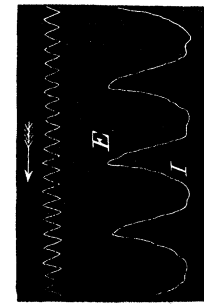


Fig. 37. Time 0<sup>m</sup>. Normal pulse and respiration.

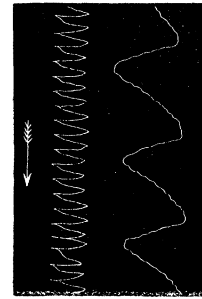


Fig. 38. 55<sup>m</sup>. After injection of 28 minims of trimethylbenzene in all.

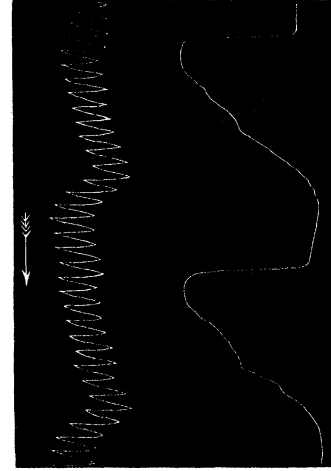


Fig. 40. 140<sup>m</sup>. Vagi have been divided. Extreme dyspnoea.

Time of quick drum, 31 millims. = 5<sup>s</sup>.

*Ethylbenzene.*

When injected into a loop of the intestine, which was subsequently returned to the abdominal cavity, ethylbenzene caused some increase in blood-pressure and also acceleration in the speed of the pulse. A prolonged inhalation of ether reduced this high pressure to or below the normal.

Small doses, 2 to 3 minims, injected into a vein raised the blood-pressure, but larger ones, 5 minims, greatly reduced it, whilst the respiration became much accelerated. The dyspnoea produced by each intravenous injection soon subsided.

*Section of the vagi* only caused a feeble and gradual rise in blood-pressure and produced a very faint acceleration of the pulse. The speed of respiration was reduced to one-half. The respiration and heart both tended to fail, occasional pauses in the former occurring. A few respiratory efforts were made after the heart had stopped.

CAT of 8 lbs., anæsthetised by Ether. Cannulas in Right Carotid, Trachea, and Femoral Vein. Vagi prepared. A Small Loop of Ilium Ligatured and Returned to Abdominal Cavity. Usual arrangement of apparatus.

- 0<sup>m</sup>. Original blood-pressure 138 millims. Respirations 14. Pulse 168; there is a considerable pause in inspiration, breathing appeared to be for time altered, owing probably to irritation of vagi. (Fig. 41.)
- 10<sup>m</sup>. Injected 10 minims ethylbenzene into loop of intestine.
- 12<sup>m</sup>. Blood-pressure has risen to 140, but rise rapidly reduced by administration of ether.
- 17<sup>m</sup>. Blood-pressure 120 to 149 (great variation owing to respiratory waves). Respirations 18 (assuming a more normal form). Pulse 192.
- 39<sup>m</sup>. Blood-pressure 137.  
Injected 10 minims ethylbenzene into ligatured loop of intestine.
- 35<sup>m</sup>. Fig. 42.
- 42<sup>m</sup>. Blood-pressure rose rapidly to 144 millims. Fell slightly and again—
- 50<sup>m</sup>. Rose steadily to 143.
- 55<sup>m</sup>. Ether reduced the pressure rapidly to 117.
- 62<sup>m</sup>. Blood-pressure 133. Respirations 13. Pulse 162.
- 80<sup>m</sup>. Injected into femoral vein 3 minims of ethylbenzene, shaken up with 2 c.c. salt solution
- 82<sup>m</sup>. Blood-pressure rose rapidly from 117 to 127, and then fell to 119 gradually; the respiratory waves being very extensive. (Fig. 46 slow drum.)
- 87<sup>m</sup>. Slowly injected 5 minims ethylbenzene, suspended in 4 c.c. salt solution. (c.)
- 89<sup>m</sup>. Blood-pressure fell rapidly to 62, but soon began to recover itself. Respirations 40. Pulse 144.
- 91<sup>m</sup>. Ligature left vagus. Respirations 29. Pulse 144. (Fig. 43.)
- 94<sup>m</sup>. Blood-pressure 107.
- 100<sup>m</sup>. Blood-pressure steady 109 millims. (c.)  
Injected 5 minims ethylbenzene in 5 c.c. salt solution.
- 102<sup>m</sup>. Blood-pressure fell to 46.  
Respirations 28. Pulse 150. The right (remaining) vagus was now tied. 5<sup>s</sup> after ligature :—  
Respirations 18. Pulse 150.
- 115<sup>m</sup>. Blood-pressure only rose very slowly and partially, so that at 115<sup>m</sup> it only reached 81 millims.

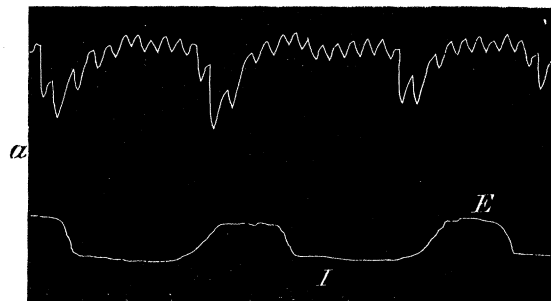


Fig. 41. Before injection of ethylbenzene. There is probably irritation of the superior laryngeal nerve provoked by preparation of the vagi.

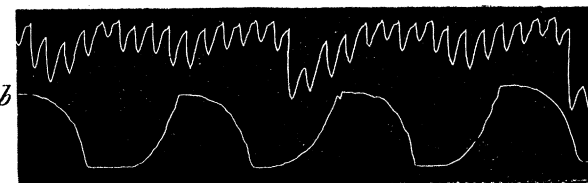


Fig. 42. 35<sup>m</sup>. After injection of 10 minims ethylbenzene into a loop of intestine.

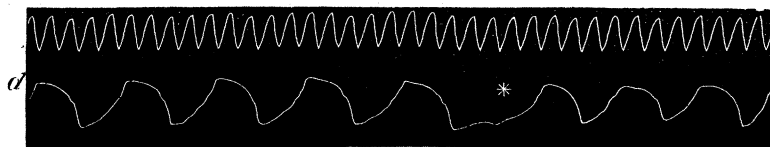


Fig. 43. 91<sup>m</sup>. \*Ligature of left vagus. Blood-pressure is low from the preceding injection of 5 minims of ethylbenzene.

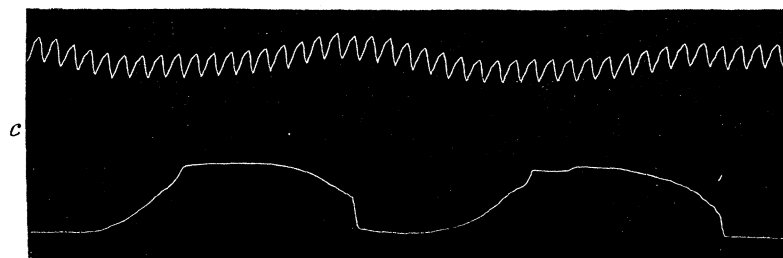


Fig. 44. 115<sup>m</sup>. After ligature of the second vagus.

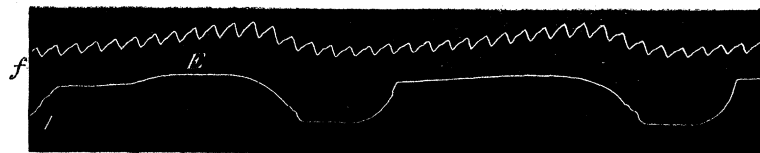


Fig. 45. 139<sup>m</sup>. 10<sup>m</sup> before death. Blood-pressure 42 millims.

Speed of drum 31 millims. = 5<sup>s</sup>.

Action of Ethylbenzene on the Circulation.

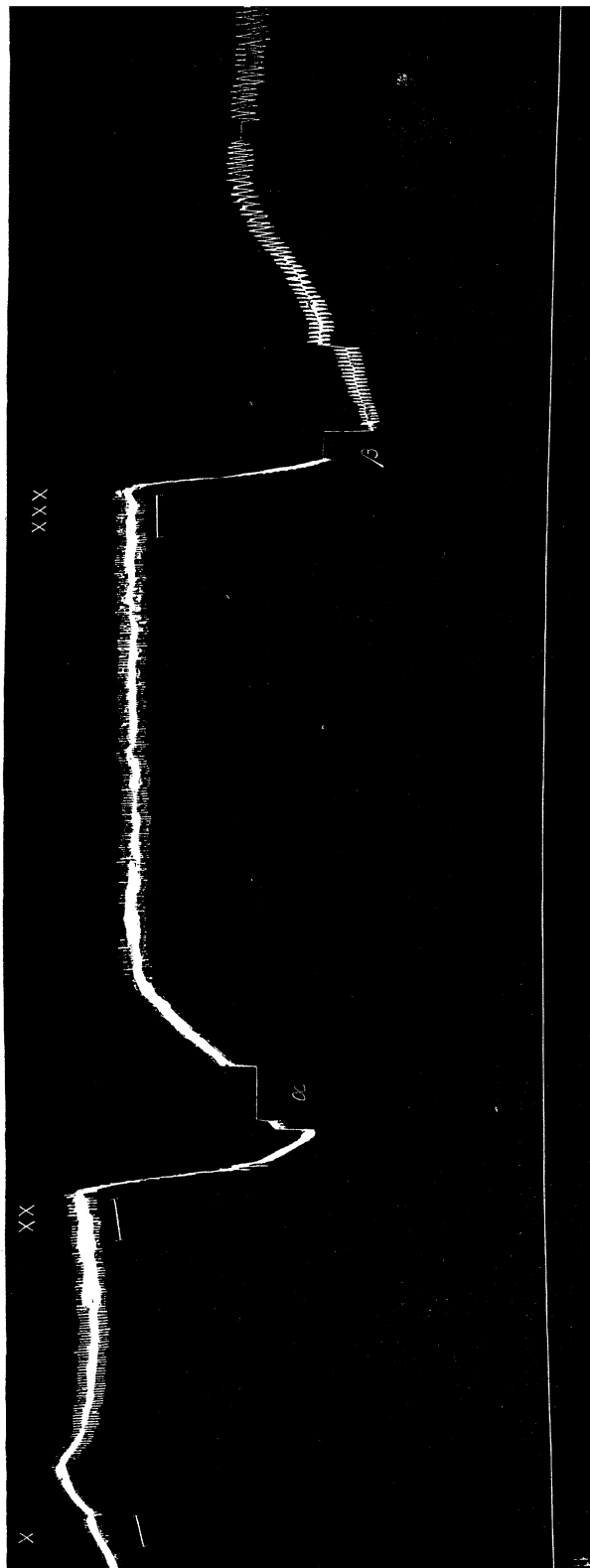


Fig. 46. Slow drum. Tracing from 80<sup>m</sup> to 115<sup>m</sup>. Shows three injections of ethylbenzene. The first injection (intravenous) is of 3 minims, the next <sup>xxx</sup> of 5 minims (one, the left vagus ligatured,  $\alpha$ ), the last <sup>xxx</sup> of 5 minims (the right vagus ligatured,  $\beta$ ).

and thereafter declined. Respirations 7. Pulse 150. The respiratory curves became very well marked and persisted from this time to end of experiment. (Fig. 44.)

122<sup>m</sup>. Blood-pressure 74 millims.

Injected 5 minims ethylbenzene in 5 c.c. salt solution.

128<sup>m</sup>. The succeeding fall has not been so extensive as formerly, it has now reached 52 millims.

130<sup>m</sup>. Respiration ceased for 2<sup>m</sup>, its curves in the blood-pressure of course disappearing.

132<sup>m</sup>. Respiration recommenced.

134<sup>m</sup>. Respiratory curves reinstated.

Blood-pressure 40 millims. Respirations 7. Pulse 150. There is a much longer pause in expiration than before at 115<sup>m</sup>. The fluctuation of blood-pressure holds a somewhat different relationship to the respiration, the maximum corresponding closely with active expiration, whereas before (115<sup>m</sup>) there was a much more distinct rise before the inspiratory pause had terminated.

139<sup>m</sup>. (Fig. 45.)

140<sup>m</sup>. Injected 5 minims ethylbenzene quickly. Fall of pressure very slight, respiration slowed.

145<sup>m</sup>. Blood-pressure 34 millims.

148<sup>m</sup>. 5 minims ethylbenzene injected rapidly caused death in a few minutes.

Respiration outlasted the heart's action.

#### *Dioxybenzene. (Resorcin.) (1 : 3.)*

As in the case of experiments made upon lower animals, we confined our attention to resorcin when studying the action of metadioxybenzene upon Carnivora (Cats).

BRIEGER ('Arch. f. Anat. u. Phys.,' 1879, Sup.-Bd.) has shown that resorcin is not only weaker in its action upon Frogs than its isomers, pyrocatechin and hydrochinon, but that this difference obtains with regard to Rodents. He found that .5 gm. of pyrocatechin was fatal to a Rabbit in 30 minutes, which had survived a dose of 1 gm. of resorcin administered some days previously.

We have carefully examined the action of the drug administered subcutaneously and by injection into the peritoneal cavity.

*Injection into the Peritoneal Cavity.*—For this purpose a 5 per cent. solution was made by aid of warm salt solution.

Small doses, .75 c.c., and 2 c.c., had but little effect upon blood-pressure. A slight fall of pressure amounting to from 4 to 10 millims. was produced, but from this recovery took place to a considerable extent, though on repeated injection a permanent reduction remained. In 3 hours' time, after 7.75 c.c. had been injected in all (.38 gm., resorcin), the blood-pressure had fallen from 126 to 110, or through 16 millims. only. The pulse was reduced from 156 to 144, but the respiration was not materially altered; faint twitchings of the thoracic muscles were produced.

Section of the vagi caused a marked rise in pressure, accelerations of the pulse and the usual type of slowed respiration. The effects of such small doses were therefore very slight.

*Subcutaneous Administration.*—Doses of 1 centigram. produced no appreciable effect. After 1.0 gm. had been injected, distinct jerking of the extremities was



noticed in 15 minutes, but this jerking was abolished by deepening the anæsthesia. This first injection, after causing a slight acceleration of respiration, produced a steady fall of 5 per minute, and reduced the pulse by 34 per minute. The blood-pressure fell 14 millims. The jerking which takes place in the muscles of the trunk is itself a factor in producing dyspnœa, as it makes the emptying of the lungs irregular and hinders their expansion. So much is this the case that the rhythm may vary 8 or 10 per minute, according to the depth of anæsthesia. When the animal is deeply narcotised, the respiration becomes slow, though often irregular, with a prolonged pause in inspiration, jerking being abolished. An acceleration in respiration was observed every time that the anæsthetic was relaxed, whilst the returning muscular contractions greatly interfered with the act. The jerking occurred when the animal was entirely unconscious from the action of the ether, and even when the narcotic action which the drug itself causes had been slightly reduced; but under the deeper action of resorcin a condition of narcosis occurred, in which jerking was only very feeble.

There is little doubt, we think, that ether greatly prolongs life in poisoning with resorcin, by reason of the power it possesses of relieving and steadying respiration. In the experiment we are about to quote, we administered to a Cat of 6 lbs. no less than 3 grms. of resorcin in the course of 3 hours, and at the expiration of 5 hours, when the experiment terminated, the blood-pressure was still 74 millims.

DIOXYBENZENE on Blood-pressure of Cat. Cannula in Trachea. Cannula in Right Carotid Artery. MAREY'S Tambour on Chest. Ordinary Connection with Mercurial and FICK'S Manometers.

- 0<sup>h</sup> 0<sup>m</sup>. Experiment commenced.
- 30<sup>m</sup>. Blood-pressure varies from 120 to 128 millims., and is rather easily reduced by ether. The pulse averages 184 and the respiration 42 per minute. (Fig. 47.)
- 35<sup>m</sup>. *Injected 1 grm. of resorcin dissolved in 20 c.c. salt solution subcutaneously.*
- 48<sup>m</sup>. Jerking of muscles of limbs and trunk has commenced. Blood-pressure 116 millims. Pulse 180. Respiration, 54.
- A small clot formed in the cannula immediately after taking the tracing.
- 60<sup>m</sup>. Blood-pressure 113. Pulse 172 (fig. 48). Respiration about 60, but, owing to jerking, estimation is difficult. Urine passed, but has no abnormal odour. Jerking easily subdued by ether, and respiration reduced to 40. (Fig. 49)
- 67<sup>m</sup>. Blood-pressure 110. Pulse 156. Respiration 36.
- 82<sup>m</sup>. Pulse 156; appears to be unaltered by ether, whilst jerking abolished and respiration slowed by it.
- 110<sup>m</sup>. Blood-pressure 102. Pulse 150. Respiration 37.
- 113<sup>m</sup>. *Injected 1 grm. of resorcin in two places as above.*
- 128<sup>m</sup>. Jerking very powerful, but disappears when deeply anæsthetised. Blood-pressure 96.
- 150<sup>m</sup>. Blood-pressure (94) is very steady, except for gradual tendency to fall.
- 160<sup>m</sup>. Pulse 146 per minute.
- 175<sup>m</sup>. *Injected 1 grm. of resorcin in two places as above.*

- 183<sup>m</sup>. Blood-pressure 95 millims. Pulse 140. Respiration 40, irregular.
- 195<sup>m</sup>. Blood-pressure 90. Pulse 108 (fig. 50). Respiration 30; pause in inspiration.  
At this time the temperature in the rectum was reduced to 29°·5 C., though the laboratory was warm and the animal had been kept carefully covered by cloths.
- 210<sup>m</sup>. Though ether has been suspended for 20 minutes, the animal is completely narcotised; muscular jerking has greatly diminished. No clotting has occurred for nearly three hours. The respiration is superficial. Pulse 108. Pressure 84 millims.  
Powerful sensory stimulation of sciatic nerve causes a rise of blood-pressure of 4 millims., but on second application had no effect.
- 245<sup>m</sup>. Blood-pressure 76. Pulse 108. The respiration is feeble, and is still marked by the twitchings of thoracic muscles.
- 270<sup>m</sup>. Pressure 74. Pulse 96. Respiration very irregular. (Fig. 51.)
- 275<sup>m</sup>. Both vagi divided.
- 278<sup>m</sup>. Pressure 66. Pulse 90. Respiration 14, extremely feeble and failing.
- 285<sup>m</sup>. The experiment was now terminated.

*Trioxybenzene.* (1 : 2 : 3, *Pyrogallol.*)

As this is a soluble salt, no mechanical difficulty was found in its administration. A 10 per cent. freshly-prepared solution was employed, and the desired dose of this was largely diluted with salt solution, for the purpose of subcutaneous or intravenous injection.

Subcutaneous injections of ·065 gm. were not succeeded by any great change in pulse or blood-pressure beyond a slight slowing of the former and fall of the latter. The respiration, however, was distinctly slowed.

Intravenous injections of amounts varying from ·033 to ·065 slowly made into the femoral vein, were rapidly succeeded by a marked rise of 6 to 13 millims. of pressure; this rise, after persisting for 2 to 5 minutes, was followed by a fall to the previous level. The cumulative action of the drug was shown by a gradual, but steady, fall of pressure after a total dose of ·12 gm. had been injected.

Larger doses of ·4 and ·6 gm., well diluted and slowly injected, caused also a rapid rise of pressure; but this rise quickly reached its maximum, and the pressure fell much below the previous level. During this fall respiration was very slow, a long pause in expiration being succeeded by a rapid and incomplete inspiratory movement. The heart beat only at the rate of 19 per minute for some time after the large injection; the systole was sharp, and succeeded by what appeared to be a second feeble contraction passing into a prolonged diastole. As the immediate effect of the drug passed off, this second cardiac effort developed still further, so as to give a bigeminal character to the pulse, and gradually the previous rhythm was restored. After 1·252 gm. in all had been injected, in the experiment quoted, the blood-pressure gradually fell, the respiration declined and ceased simultaneously with cardiac action.

Action of Dioxybenzene. 1 : 3. Resorcin.

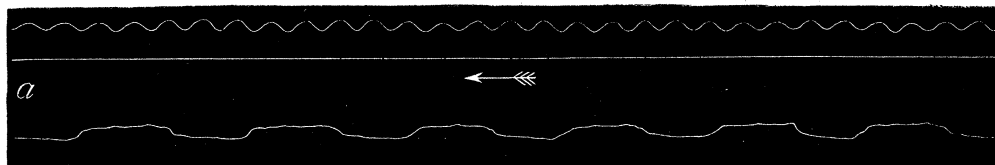
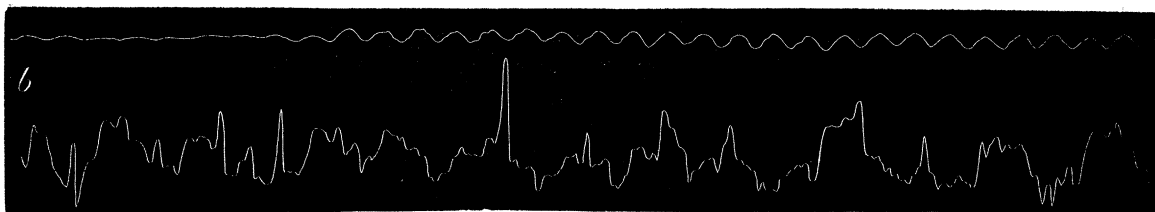
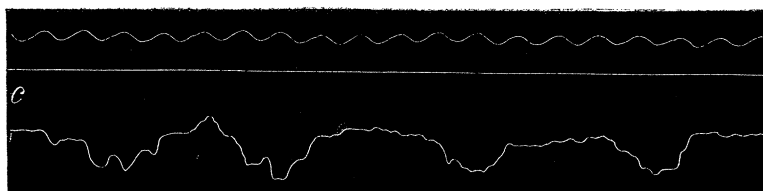
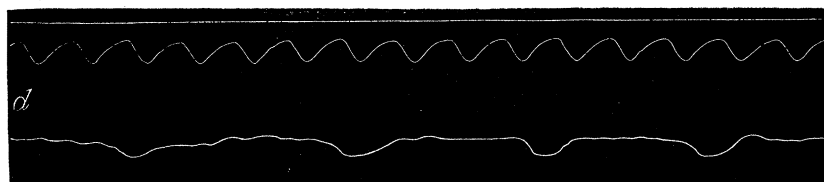
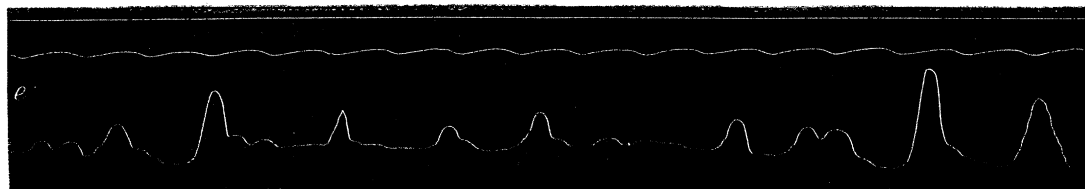


Fig. 47. Before injection of Resorcin.

Fig. 48. Time 60<sup>m</sup>. 1 gram. of Resorcin injected 25<sup>m</sup> previously.Fig. 49. Time 62<sup>m</sup>. Deep anaesthesia.Fig. 50. Time 195<sup>m</sup>. Three grms. of Resorcin have been injected.Fig. 51. Time 270<sup>m</sup>.Speed of drum, 64 millims. = 5<sup>s</sup>.

CAT of 7 lbs. Ether was used as an Anæsthetic. Animal placed in Warm Box. Cannulas were placed in the Right Carotid, Femoral Vein, and Trachea. Immediately after placing the animal in position the Heart suddenly failed, though but little Ether had been given, and Pressure fell from 134 to 22. Artificial Respiration restored Animal.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes				
0	(Fig. 52)	180	124-130	32
17	Injected 10 minims of a 10 per cent. solution of trioxybenzene			
35		..	121	
50		..	102	
62	Much tremor of hind legs	158	94	24
73	Blood-pressure risen under ether. Respiratory blood-pressure waves become very large	181	102	15
76	Injected 2 minims diluted with 2 c.c. salt solution. Rise of 5 millims. in the pressure			
80	Injected 5 minims, 10 per cent. solution			
82	Blood-pressure risen 6 millims., falls rapidly to former level			
90	Clot far down in right carotid artery. Insert cannula into left carotid. (15 <sup>m</sup> lost)			
105	Injected 10 minims of a 10 per cent. solution as before (fig. 53)	156	93-106	24
110	Both vagi divided. No rise of blood-pressure (fig. 52)	156	..	23
112		..	84	
115	Injected 10 minims of a 10 per cent. solution as before (fig. 54)	..	96	
118		150	64	19
122		157	76	17
124	Injected .1 gm. in 3 c.c. salt solution. Rise of 16 millims. succeeded by fall	156	..	19
130	Injected .4 gm. in large solution (fig. 54, <i>d</i> <sup>x</sup> )	165	76-82	23
135	Pressure begins to rise again	..	51	
142	Injected .6 gm. trioxybenzene (fig. 54, <i>d</i> <sup>xx</sup> )	19-73	79-22	3-6
146		168	36	11
150	(Fig. 55)	..		
158		..	23	
179	Heart stopped. For some time before death there was no indication for ether			

*Post-mortem.*—Lungs pale. Heart in diastole; on cutting much dark blood escaped and ventricle commenced active vermicular movement. Intestines pale, peristalsis active. Kidneys congested.

Action of Trihydroxybenzene. 1 : 3. Pyrogallol. Experiment on a Cat.

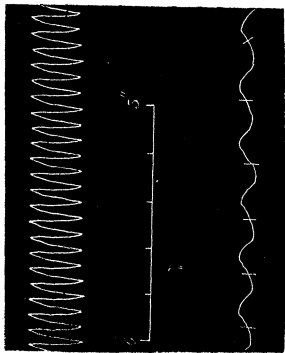


Fig. 52. Quick drum. Normal pulse and respiration.

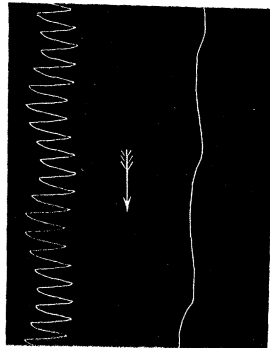


Fig. 53. Quick drum. After injection of pyrogallol.

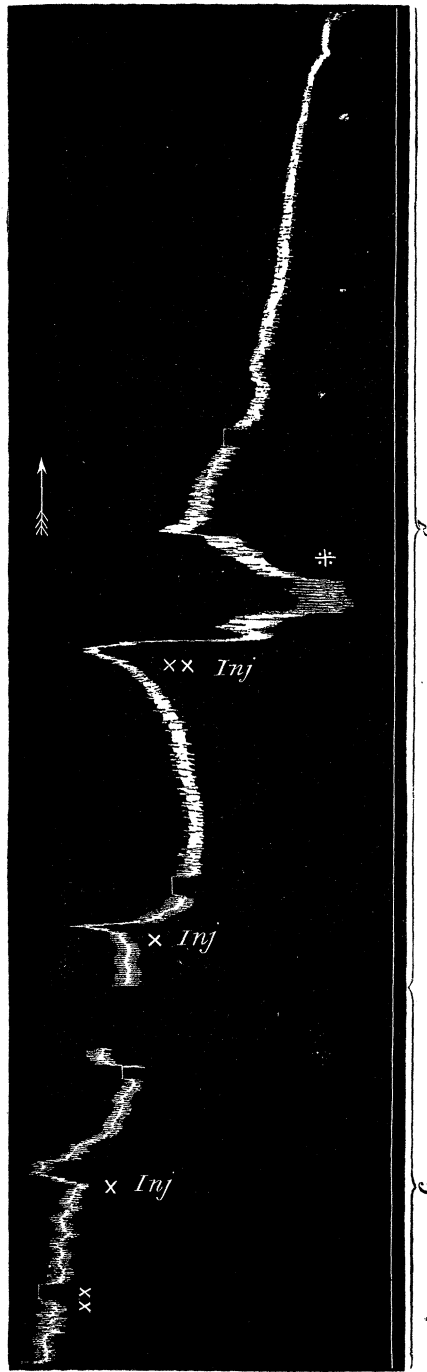


Fig. 54. (c) Slow drum. Injection of .05 gm. of pyrogallol (both vagi cut).  
 (d) Slow drum. Shows the effect of injection of .4 gm. and of .6 gm. pyrogallol.  
 For \* see fig. 55.

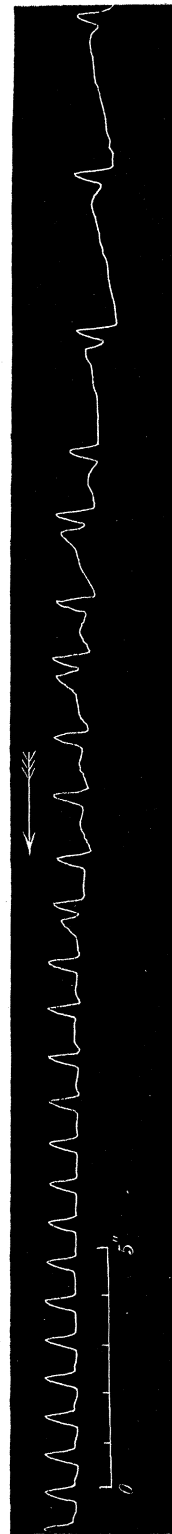


Fig. 55. Quick drum. Tracing taken at \*, showing great slowing and irregularity of the heart succeeded by recovery.



*Amidobenzene (Anilin).*

Many experiments were made with this drug, the mode of administration being varied.

Intravenous injection produced a slight rise of pressure, when  $\frac{1}{2}$  minim of anilin largely diluted was employed; when the dose was increased to 2 minims a much more distinct rise was observed.

Large doses of 1 c.c. caused a marked fall of blood-pressure. When introduced subcutaneously, or into the stomach, no rise of blood-pressure was observable, though the fall was slow in developing. In one case of subcutaneous administration of 1.25 c.c. in one dose to a Cat of  $5\frac{1}{2}$  lbs although death resulted in 2 hours 10 minutes, the fall of pressure during the first 40 minutes was quite insignificant.

After absorption has taken place to some extent marked tremors develop, and even jerking of the trunk and limbs, which disappear when the narcosis is rendered very deep. The vagi remain active till the last.

Respiration is greatly slowed and a long pause occurs in inspiration. Section of vagi at this stage has an additional effect in slowing the breathing.

The heart is at first somewhat slowed, but is quickened before death. A systole is succeeded by a diastole which is often cut short midway by a second systole; such a rhythm, consisting of a bigeminal systole alternating with a single beat, was in one instance persisted in for a considerable time.

The production of TRAUBE'S curves was observed several times as a result of the administration of anilin; these curves were reduced in extent, but became more frequent on exposing the intestines to the air.

After death the irritability of the muscular tissue was found to be greatly impaired.

## BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION. 625

CAT of 6 lbs. Subcutaneous injection.

Time.	Remarks.	Pulse for 1 minute.	Blood- pressure.	Respiration.
minutes				
0	(Fig. 56) . . . . .	216	145	25
20	Injected 10 drops amidobenzene . . . . .			
28		216	145	18
45	Injected 10 drops amidobenzene . . . . .			
56	Character of pulse changed, a distinct second wave in descent appearing (fig. 57) . . . . .	204	137	22
82	Ether causes fall of 38 millims. . . . .			
85	Same character of pulse as at 56 <sup>m</sup> , though showing higher tension. No more amidobenzene has been injected . . . . .	214	130	30
90	(Fig. 58) . . . . .			
100	Steady fall of blood-pressure (fig. 59) . . . . .			
112	Inject 20 drops as before . . . . .			
116		212	100	28
145	Periodic rise of blood-pressure, corresponding with powerful inspiratory movement with long pause in inspiration. Pulse shows peculiar variation in second notch of descent (fig. 60) . . . . .			
	Slow drum . . . . .	..	60	
155	Both vagi now divided. Temporary rise of pressure. Curves persist (fig. 60) . . . . .			
170	Rise of pressure consonant with deep inspiration already mentioned. Sinking of pressure occurs as soon as inspiration relaxes. The other inspiratory jerk appears to be abortive. . . . .	200	..	13
180	After long inspiration has relaxed, there are few rapid inspiratory movements, and these become more seldom till the next deep inspiration . . . . .	..	40	
190	Curves persist. Pressure declining very slowly . . . . .			
200	Stimulating sciatic raises blood-pressure very slightly, 4 millims. (fig. 61). Stimulating vagi lowers blood-pressure slightly (9 millims.) . . . . .	..	34	
215	Opened abdominal cavity and exposed intestines thoroughly, mesenteric vessels are found to be contracted (fig. 62). Exposure destroys the marked waves which have so far existed, though respiratory waves appear, the pressure does not rise as before . . . . .	196	30	
227	. . . . .	174	22	
250	A further attempt at respiration still observed . . . . .	..	0	

*Post-mortem.*—Intestines very empty of blood, no peristalsis. Hardly any local contraction or stimulation. Both sides of heart dilated with dark blood. Lungs very pale and putty-like in appearance. Muscle gave only very feeble tetanus to direct and indirect stimulation.



Fig. 56. Pulse before injection.



Fig. 57. 5.5m. After total subcutaneous injection of 20 minims.



Fig. 58. 90m. Total injection still 20 minims.



Fig. 59. 100m. After total subcutaneous injection of 40 minims.

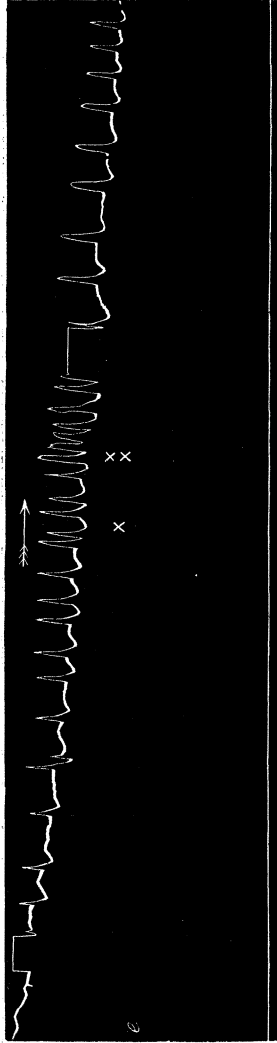


Fig. 60. 145m to 170m. Showing vaso-motor fluctuations of blood-pressure before and after section of the vagi. xx

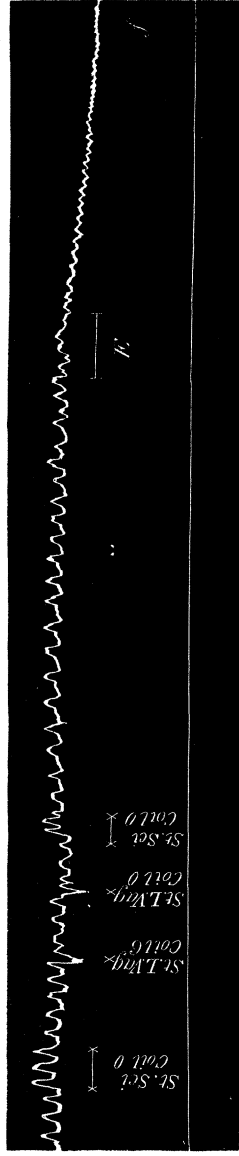


Fig. 61. 195m to 225m. Stimulation of sciatic and vagi. Exposure (*E*) of intestines with resulting change in wave.

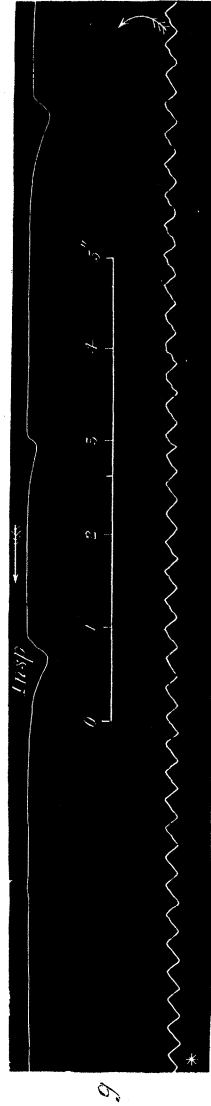


Fig. 62. 218m. Shows respiration and its effect on blood-pressure.

*Nitrobenzene.*

Small doses (one to two minims of nitrobenzene) cause a slight fluctuation in blood-pressure usually in the direction of a fall ; larger doses, 4 to 10 minims, cause a marked fall of blood-pressure. This fall, from which the recovery is only very gradual, is associated with great slowing of the pulse. When the vagi are divided during such a condition, a marked rise in the frequency of the pulse with elevation of the blood-pressure takes place, but a repetition of the injection may even then cause a distinct fall of pressure and slowing of heart.

The respiration was not found to be markedly affected in rate, the experiment quoted shows limit of variation of 8 per minute up to the time of division of the vagi ; a marked acceleration occurred before death, however, even after vagotomy, and the respiration distinctly outlasted cardiac systole.

The form of the pulse was modified throughout by the action of nitrobenzene, the systole became slower and more gradual with a sustained maximum, whilst the diastolic relaxation was distinctly prolonged ; this pulse can be scarcely considered indicative of a peripheral relaxation of the vessels, though, presumed a certain amount of pulmonary obstruction, which the post-mortem appearances seem to justify, the venous congestion may have served to mask the change in the arterioles.

Administration of 62 drops in the course of 3 hours of nitrobenzene was fatal to the animal in question.

This benzene compound is certainly one of the most active we have examined with reference to its action upon the heart.

## CAT of 7 lbs. Usual arrangement of apparatus.

Time.	Remarks.	Pulse for 1 minute.	Blood-pressure.	Respiration.
minutes				
0	Blood-pressure lowered from commencement by inhalation of ether (fig. 63) . . . . .	152	110-120	40
10	Inject 1 minim nitrobenzene into femoral vein in 2 c.c. salt solution			
11	. . . . .	..	Slight rise followed by little fall	
30	Injected 2 drops . . . . .	..	Fall of 3 millims.	
54	Injected 4 minims in 3 <sup>m</sup> (in 5 c.c. salt solution). An occasional very extensive excursion above or below the abscissa is seen . . . . .	..	Gradual fall of 6 millims.	
67	Injected 10 minims in 5 <sup>m</sup> as before. Total fall resulting amounts to 42 mm.; a tendency to recovery occurs before completion of injection. Excursions very extensive. Systole long maintained. (Fig. 64, slow drum) . . . . .	96	104-62	36
70	(Fig. 65)			
80	. . . . .	..	97	
100	Decided tendency of pressure to fall. Systole long maintained	132	80	44
108	Rapid injection of 10 minims. Long respiratory pause in inspiration. Maximum of pulse pressure long continued, one or more waves in descent . . . . .	107	Fall of 28	36
112	(Fig. 66)			
113	Divided both vagi, rapid rise of blood-pressure commenced . . . . .	132	52	26
118	. . . . .	144		
122	(Fig. 67). Slow drum and quick drum (fig. 68)	..	103	
123	Inject 15 minims (in large drops not well shaken up)			
126	Excursions of mercury extensive. Recovery very gradual . . . . .	..	65	
135	Strong stimulation of vagus . . . . .	..	Fall of 31	
138	Injection of 20 minims nitrobenzene not in emulsion			
143	Death . . . . .	..	Rapid fall of 52 millims.	44-60 very irregular
	Just before death (fig. 69) . . . . .	104	17	44-60 very irregular
	Respiration outlasted pulse.			

*Post-mortem.*—Right heart dilated, full of dark blood, smelling strongly of nitrobenzene. Left heart in systole. Lungs contain much frothy fluid; seem œdematous. No paralysis of nerves or muscles. Peristalsis of intestine. Vessels of mesentery dilated.



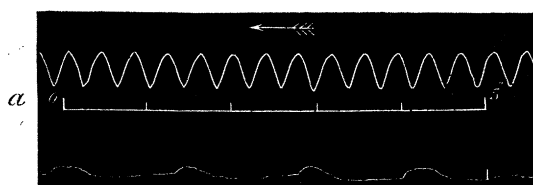


Fig. 63. Quick drum. Pulse and respiration before injection of nitrobenzene.

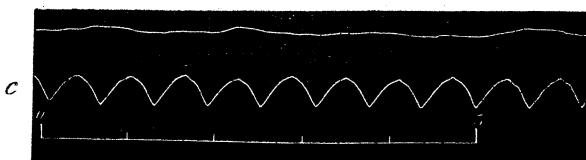


Fig. 65. At 70<sup>m</sup>, immediately after the intravenous injection of 10 minims of nitrobenzene (17 minims in all previously injected).

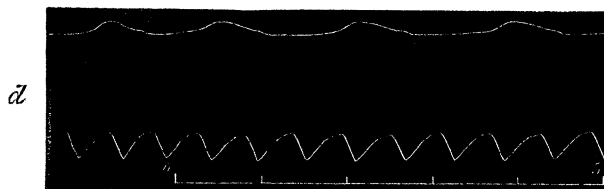


Fig. 66. At 112<sup>m</sup> (27 minims in all previously injected).

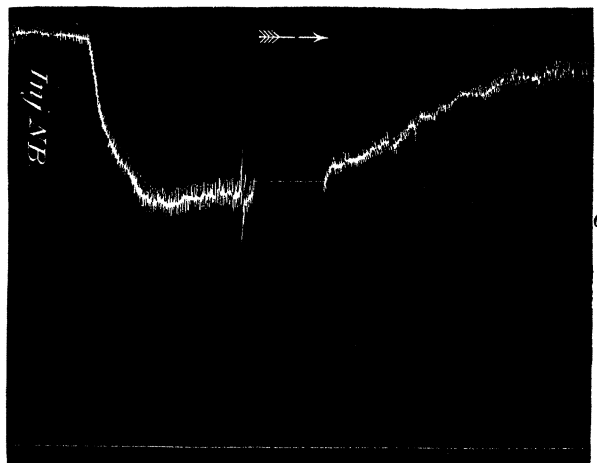


Fig. 64. Slow drum. Blood-pressure 65<sup>m</sup> to 80<sup>m</sup>. Injection of 10 minims nitrobenzene.

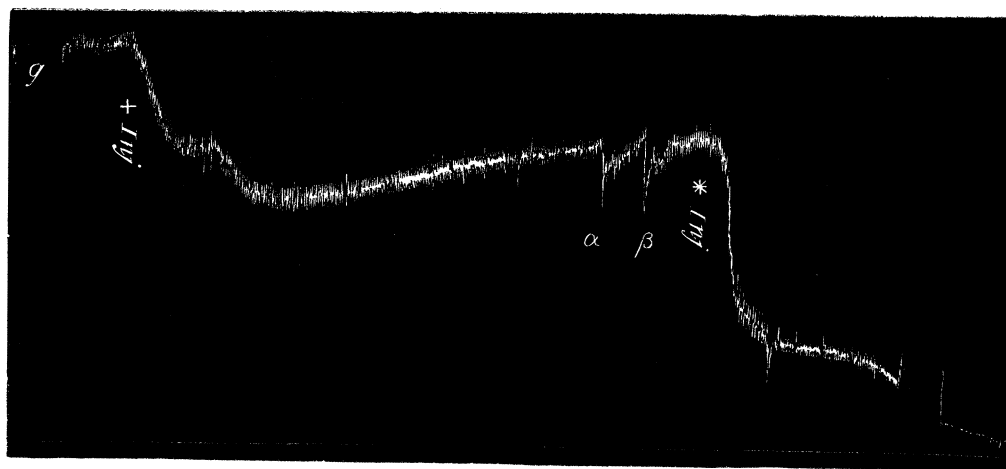


Fig. 67. Slow drum. Blood-pressure 122<sup>m</sup> to 140<sup>m</sup>. Vagi already cut. Final injections of nitrobenzene 10 gtta. (+) and 20 gtta. (\*). *a.* Stimulation of vagus, coil 4 centims. *β.* Stimulation, coil 0.

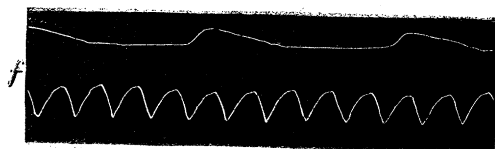


Fig. 68. At 122<sup>m</sup>. After section of both vagi.

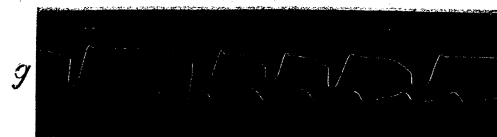


Fig. 69. At 143<sup>m</sup>. Just before cessation of heart.

Speed of quick drum 55 millims. = 5<sup>s</sup>.

„ slow „ 19.4 millims. = 5<sup>m</sup>.

## COMPARATIVE ACTION OF BENZENE AND ITS COMPOUNDS ON RESPIRATION, BLOOD-PRESSURE, AND PULSE.

*Respiration.**Benzene and the Halogen Compounds.*

An alteration of respiration was an early effect of the drugs. This acceleration has been observed to vary in degree with the different bodies.

*Intravenous* injection of aromatic benzene caused a slight acceleration, but ultimately a great slowing of respiration, whilst subcutaneous injection caused from the first a steady decline. Monochlorobenzene produced a very decided acceleration of respiration by whichever way administered, followed by slowing, and in all the experiments made, respiratory arrest was not the immediate cause of death. Monobromobenzene caused also marked respiratory acceleration in the first instance and then depression, but the respiratory movements outlasted cardiac systole.

Monoiodobenzene was not so active in causing acceleration, nor was the retardation of respiration by any means so marked as with the other halogen compounds.

In all cases the greatest acceleration occurs after intravenous administration.

*The Compound Benzenes possessing Alcoholic Radicles.*

*Methylbenzene*, whether by intravenous or hypodermic administration, accelerates the respiration in the first instance and then slows it. Pulmonary œdema was induced probably from capillary embolism caused by the compound in the lungs.

*Dimethylbenzene* acts powerfully also on respiration. A short period of slowing followed intestinal absorption of the drug, then an acceleration, and ultimately, however administered, the respiration became greatly slowed. Pulmonary œdema tended to occur after intravenous injection, but artificial respiration was capable of prolonging life, the heart beating moderately well after all natural attempts at respiration ceased.

*Trimethylbenzene*, by intravenous and hypodermic injection, produced an acceleration of respiration, then a slowing which was still further increased after vagotomy. Death occurred here also from pulmonary œdema and arrest of respiration.

*Ethylbenzene* likewise accelerated respiration, and this to a considerable extent when intravenous injection was made, though recovery towards the normal tended to occur soon afterwards. The heart, however, failed before respiration.

*Hydroxyl Compounds.*

*Dioxybenzene (Resorcin)*.—Hypodermic administration slightly slowed the respiration; dyspnoea was produced, apparently as a result chiefly of jerking of the thoracic muscles, which the drug induces, as it is to a great extent removed by deepening the

anæsthesia. A marked slowing of the respiration was ultimately caused by resorcin. The respiration tended to cease somewhat before the heart.

*Pyrogallol.* 1 : 2 : 3.—Appeared from the first to slow respiration, this retardation being specially marked after intravenous injection. A tendency to an expiratory pause was observed.

*Respiration* ceased simultaneously with the heart.

*Amidobenzene* caused some acceleration of respiration with changes in its character, succeeded by a decided slowing. The respiration was greatly reduced by double vagotomy.

Feeble respiration occurred during fall of pressure, and thoracic movement slightly outlasted cardiac contraction.

*Nitrobenzene* did not greatly affect respiratory rhythm, though ultimately some slowing with long pauses in inspiration supervened. Double vagotomy caused a marked slowing, but on further injection the respiration again became rapid and outlasted the pulse. Some œdema of the lung was found after death.

#### *Pulse and Blood-pressure.*

*Aromatic benzene* produced in the first instance but a slight effect in the direction of raising the blood-pressure and slowing the pulse, with a tendency to irregularity and incomplete systole. Section of the vagi was followed by a rise of blood-pressure with cardiac acceleration. Death was due to cardiac arrest.

#### *The Halogen Compounds.*

*Monochlorobenzene* showed considerable activity in the earlier part of its action, in raising the blood-pressure and accelerating the pulse. Cardiac arrest was the cause of death.

*Monobromobenzene* in small doses subcutaneously, and in small doses slowly injected into veins, caused an elevation of the blood-pressure with some acceleration of the pulse. Both these effects were weaker than after monochlorobenzene. Rapid injection of even a small quantity occasioned a marked fall in the pressure. Death was due to cardiac arrest.

*Monoiodobenzene* caused marked cardiac acceleration of the pulse after intestinal administration, the pressure also rising. An increase of pressure and pulse rate was produced by vagal section. Death was due to cardiac failure.

*Methylbenzene.*—A marked acceleration of the pulse with a rise of pressure resulted from the earlier action of this drug. Large doses reduced both and rendered the pulse irregular. The pulse was accelerated by vagotomy. Cause of death, pulmonary œdema.

*Dimethylbenzene.*—Whilst intestinal injection of this drug reduced the pressure to a slight degree, intravenous injection of the emulsified body in very small doses

produced a very slight rise of pressure, whilst doses of 4 minims and upwards, even freely diluted, caused a marked fall. Larger injections reduced blood-pressure, but the heart outlasted respiration.

*Trimethylbenzene*.—Small doses, both by hypodermic administration and intravenous injection, slightly reduced the pressure, whilst an acceleration of the pulse was observable. The pulse by the former method was slowed, by the latter somewhat accelerated. Section of vagi raised pressure and accelerated the pulse, after the period of depression had been produced. This appears to be the most active of the methyl compounds.

*Ethylbenzene*.—In small doses, both by intestinal and intravenous administration, this drug caused an elevation of blood-pressure and acceleration of the pulse. Large doses produced a rapid fall of pressure with slow recovery. This effect was to some degree central, as division of the vagi caused some rise and acceleration.

*Dioxybenzol (Resorcin)*.—Caused some fall of pressure and slowing of pulse, but neither effect well marked except with very large doses. A great slowing of the pulse ultimately ensued.

*Pyrogallol*.—Small doses to some extent reduced pulse and blood-pressure. Injections were succeeded by a rise, which suddenly gave place to a considerable fall from which recovery was comparatively slow. The pulse became very slow, of irregular rhythm and peculiar form.

*Amidobenzene (Anilin)*.—From the subcutaneous cellular tissue and the stomach this compound produced a slowly developing fall of pressure, the heart being slowed. Intravenous injection, however, caused a rise of pressure if the dose was only a small one, 1–2 minims. After a single large dose, or repeated small doses, a great fall in pressure took place.

*Nitrobenzene*.—Small doses caused a fluctuation in the blood-pressure usually in the direction of a fall. Large doses greatly reduced the pressure and slowed the pulse. Section of the vagi during the effect caused a rise and acceleration, but further injection caused a fall and slowing. Death was from cardiac failure.