XX.—*On the Connection between Chemical Constitution and Physiological Action.* Part II.—*On the Physiological Action of the Ammonium Bases derived from Atropia and Conia.* By Dr A. Crum Brown and Dr Thomas R. Fraser.

(Read 18th January 1869.)

Atropia.

Atropia is a nitrile base, obtained from *Atropa Belladonna*. All we know of its constitution is, that by the action of strong acids and bases it is decomposed, in accordance with the equation—

$$\underset{\text{Atropia.}}{C_{17}H_{23}NO_3} + \underset{\text{Water.}}{H_2O} = \underset{\text{Tropic Acid.}}{C_9H_{10}O_3} + \underset{\text{Tropia.}}{C_8H_{15}NO}\,*$$

So that atropia may be considered as tropia, in which one atom of hydrogen has been replaced by tropyl, the radical of tropic acid.

Atropia has a somewhat complicated physiological action, for it directly influences the functions of the cerebro-spinal and sympathetic nervous systems. The principal effects produced by it on the former system are paralysis of the sensory and motor nerves, and excitation of the spinal cord. By its action on the sympathetic nerves, it influences the contraction of the unstriped muscles; but as the mechanism of this action is by no means exactly defined, we shall merely allude to it in our comparison of the actions of the methyl and ethyl derivatives, with those of the alkaloid itself. In addition to these general actions, atropia influences, in a special manner, the functions of the vagi nerves and of the iris, suspending the cardiac inhibitory power of the former, and producing contraction of the latter.

To cause death in the lower animals, it is necessary that atropia be administered in comparatively large doses, even when it is exhibited by subcutaneous injection. Thus, the minimum fatal dose of sulphate of atropia for a dog, weighing eight or nine pounds, is about fifteen grains; for a full-grown rabbit, more than fifteen grains; and for a frog, a dose equivalent to the $\frac{1}{1000}$th or the $\frac{1}{900}$th of its weight.

Iodide of methyl-atropium.—Iodide of methyl acts very readily on atropia; a good deal of heat is produced; and after the reaction is over, the iodide of

* Kraut, "Annalen du Ch. u. Ph." band cxxviii. 1863, p. 280; band cxxxiii. 1865, p. 87; band cxlviii. 1868, p. 236. Lossen, *ibid.* band cxxxi. 1864, p. 43; band cxxxviii. 1866, p. 230.

methyl-atropium remains as a white mass. From this, the excess of iodide of methyl is removed by a current of air, and the dry salt dissolved in water, filtered, and evaporated at a temperature not exceeding 40° C. The concentrated solution thus obtained, on cooling deposits the salt in prismatic crystals, apparently belonging to the monoclinic system; sometimes, part of the salt separates as a heavy oil, which soon crystallises. These crystals have the composition $C_{17}H_{23}NO_3CH_3I$. They are tolerably stable, bearing a temperature of 100° C. without much alteration. When they are powdered, or when their solution is warmed, a pleasant fruity smell is observed.*

Pursuing the plan adopted in our former communication, we shall, in the first place, describe the effects of this substance when it is exhibited by subcutaneous injection. As it is tolerably soluble in warm water, we were enabled to administer sufficiently large doses in the form of solution. In the previous part of this research, we found that the chemical addition of iodide, or sulphate of methyl, or of ethyl, greatly diminishes the lethal† activity of strychnia, brucia, thebaia, codeia, morphia, and nicotia. We have now to announce that a similar operation performed on atropia, in place of diminishing, considerably increases the lethal activity of this alkaloid. In our experiments with iodide of methyl-atropium, we were somewhat surprised to find that a dog was rapidly killed by the subcutaneous injection of ten grains, and that a rabbit survived for but a short period after the administration of three. We shall first describe the experiment referred to on a dog, as it illustrates not only the difference between the lethal activity of iodide of methyl-atropium and that of atropia, but also some of the more prominent differences between the symptoms produced by these two substances.

Experiment I.—A solution of ten grains of iodide of methyl-atropium, in about one hundred minims of warm distilled water, was injected under the skin of a healthy English terrier, weighing eight pounds and six ounces. In a few minutes, there was some difficulty in performing voluntary movements, and in ten minutes this was more marked. Soon after, the anterior extremities became gradually more and more weak, until they could no longer support the body, and the dog subsided on the chest, with the muzzle resting on the floor. In thirteen minutes, it fell over on the side in a state of flaccid helplessness; the respirations became somewhat laboured and shallow, and their frequency diminished until, at twenty-three minutes, only an infrequent gasp occurred. There were now some faint twitches in the *panniculus carnosus* muscle and in the musles of the limbs; and irritation of the skin still excited feeble reflex move-

* We shall give details of the chemical relations of the methyl derivatives of atropia on some other occasion.

† We have employed the phrase "lethal activity" as a substitute for the French "l'activité toxique," or death-producing action.

ments. With the exception of these rare gasps, and of a continuance of the cardiac contractions, at the rate of 100 beats in the minute, the animal appeared to be quite dead at twenty-seven minutes after the injection; for even the sensibility of the skin, conjunctiva, and cornea was at this time suspended. The respiratory gasps, however, continued at the rate of five or six in the minute, until thirty-two minutes after the administration of the poison, when death occurred.

In autopsy, it was found, five minutes after death, that the heart was beating at the rate of 96 per minute. The conductivity of the motor nerves and the contractility of the muscles were retained for several minutes afterwards.

The dog, which was the subject of this experiment, had received, some weeks previously, ten grains of sulphate of atropia; and it will be seen from the following account of the experiment, that this dose produced in it some of the more prominent effects of atropia-poisoning.

EXPERIMENT XXII.—Ten grains of sulphate of atropia was dissolved in fifty minims of distilled water, and injected under the skin of the dog that was used, some weeks afterwards, in Experiment I. Omitting many details of the earlier symptoms that were observed, it is sufficient for our present purpose to mention, that in five minutes, there was evident impairment of vision; that in seven minutes, some efforts were made to vomit; that in twelve minutes, urine was voided; that in thirteen minutes, partial paralysis was decidedly present; and that in thirty-eight minutes, frequent spasmodic starts and marked exaggeration of the reflex excitability coexisted with considerable lose of voluntary motor power. After this time, certain effects were observed that contrast in a remarkable manner with those observed in the previous experiment. Gradually the paralysis became more marked until the dog was unable to support itself on its limbs; and the spasmodic action acquired a greater prominence, so that, in a short time, it produced violent tetanic convulsions of an opisthotonic character. The first of these convulsions occurred at fifty-two minutes, and it was succeeded by a series, following each other at intervals of eight or nine minutes, until four hours and ten minutes after the administration, when the observations were interrupted. At nine hours, the dog was still affected with considerable paralysis, but no tetanic convulsions now occurred, though spasmodic starts and exaggeration of the reflex excitability had not yet disappeared. On the following morning, the dog was running about, and it ultimately recovered perfectly.

These two experiments appear to show that the chemical addition of iodide of methyl to atropia increases the lethal activity, and removes the convulsant action of this alkaloid. These changes have been carefully examined in many experiments on rabbits and frogs. In rabbits, we have ascertained that a dose of two and a-half grains produces marked paralytic symptoms, which do not terminate in death; while three grains is a sufficient dose to kill a large animal.

The special symptoms that were observed with these doses will be best described by a short narration of each experiment.

EXPERIMENT VII.—Two grains and a-half of iodide of methyl-atropium was dissolved in fifty-five minims of slightly warm distilled water, and one-half of the solution was injected under the skin at each flank of a rabbit, weighing three pounds and thirteen ounces and a half. Before the administration, the pupils measured $\frac{15}{50}$ths × $\frac{14}{50}$ths of an inch, and at six minutes after it, the size of the pupils had increased to $\frac{17}{50}$ths × $\frac{15}{50}$ths of an inch. This was the first symptom observed. At sixteen minutes, there was evident difficulty in retaining a normal posture, and soon after the fore-legs yielded, and the rabbit lay on the chest, with the lower jaw resting on the table. At twenty-four minutes, some uneasy movements were executed, during which the body was pushed forward, in the position last described, by the use of the posterior extremities alone. There was now a succession of very slight fibrillary twitches of the muscles of the head, body, and limbs. At fifty minutes, the rabbit lay altogether on the abdomen and chest, with the lower jaw still resting on the table, and it was obvious that the posterior extremities had become powerless like the anterior. The respirations were now shallow and abdominal, at the rate of 68 per minute; the pupils were dilated to $\frac{19}{50}$ths × $\frac{17}{50}$ths; the common sensibility appeared to be suspended; and paralysis had so far advanced that the rabbit lay flaccid on the abdomen and chest, with the head resting on the side. This condition continued for about fifteen minutes, when the head was again raised from the side, and, for short periods, even supported normally by the neck muscles. The symptoms then slowly disappeared until a normal condition was reassumed.

EXPERIMENT VIII.—In this experiment, the rabbit weighed three pounds and ten ounces, and it received, by injection under the skin of the two flanks, three grains of iodide of methyl-atropium dissolved in sixty minims of slightly warm distilled water. Dilatation of the pupils appeared in five minutes, and this symptom was soon succeeded by trembling and unsteady movements. In fifteen minutes, the head sunk until it rested on the chin; and in twenty minutes, the paralysis had become so severe that the limbs were unable to support the body. In twenty-eight minutes, the respiratory movements had diminished in number to thirty-four in the minute, while they had become laboured and abdominal in character. The rabbit was now lying on the side in a completely flaccid state. In fifty-four minutes, the respirations were so weak and shallow that it was somewhat difficult to determine the rate of their occurrence. In fifty-six minutes, merely an occasional gasp occurred, and this was frequently accompanied by weak, successive tremors. In fifty-eight minutes, all movement ceased, and death took place.

In the autopsy, it was found that, at three minutes after death, the conductivity of the motor nerves and the contractility of the muscles were retained; and that, at six minutes after death, the heart was motionless and distended.

These experiments are sufficient to illustrate the physiological effects that are produced in rabbits by the subcutaneous administration of iodide of methyl-atropium. They likewise show—and the result is confirmed by other experiments briefly described in the table at the end of this paper—that iodide of methyl-atropium is a much more active poison for rabbits than any salt of atropia. We have already mentioned that the minimum fatal dose, by subcutaneous administration, of even so soluble a salt as the sulphate of atropia, is greater than fifteen grains; whereas it is proved by Experiment VIII. that three grains of iodide of methyl-atropium, administered subcutaneously, is a fatal dose for a rabbit.

We have not succeeded in obtaining any data by which to compare the relative activity of these substances when given to rabbits by the stomach. We have given in this manner as large a dose of both as thirty grains, but have observed no obvious symptom with either substance, except dilatation of the pupils.

Though iodide of methyl-atropium is tolerably soluble in water, it is less so than sulphate of atropia. In Part I. of this investigation we have mentioned as a condition which it is advisable to fulfil, "that the substance is equally suitable for absorption into the system before and after the change."* In conformity with this condition, we have examined, with considerable care and detail, the poisonous activity and physiological action of the sulphate of methyl-atropium, a much more soluble salt than the iodide, and, therefore, a more suitable substance for comparison with sulphate of atropia.

Sulphate of methyl-atropium $((C_{17}H_{23}NO_3CH_3)_2SO_4)$.—This salt was prepared from the iodide by the method formerly described for the preparation of the sulphates of methyl-strychnium, methyl-brucium, &c. It is a white, crystalline substance, very deliquescent, and very soluble in cold water.

Apparently on account of its greater solubility, it is a rather more active salt than the iodide; and both in rabbits and frogs its lethal activity was, accordingly, found to be much greater than that of sulphate of atropia.

We administered it to rabbits by injecting it under the skin, and also by introducing it into the stomach. The symptoms produced by the former method of administration are in character exactly the same as those produced by the iodide, as will be seen from the following detailed account of several of our experiments.

EXPERIMENT XXXII.—We dissolved two grains of sulphate of methyl-atropium in twenty-five minims of distilled water, and injected the solution under the skin at the right flank of a rabbit, weighing three pounds and seven ounces and a-half. In seven minutes, the animal moved about in an uneasy manner,

* Transactions of the Roy. Soc. of Edinburgh, vol. xxv. part 1, 1867–68, p. 153.

and, soon, some weakness of the limbs was observed. This weakness increased until the limbs were no longer able to support the body; and, in fourteen minutes, the rabbit subsided on the abdomen and chest, with the lower jaw resting on the table. There were now some slight twitches in several of the muscles of the chest and thighs, and the respiratory movements were weak, though they occurred at the rate of sixty-two in the minute. During other seven minutes, voluntary movements could not be performed; but at the end of this period, some unsteady trembling movements occurred. In twenty-four minutes, the rabbit succeeded in raising the head, though only for a few seconds. It continued at short intervals to raise the head, until increasing strength at length enabled it to support the head normally by the neck muscles. In thirty minutes, the partial paralysis had so far disappeared, that the rabbit succeeded in raising the body on the limbs, and in assuming a natural sitting posture.

Before the administration of sulphate of methyl-atropium, the pupils measured $\frac{9}{50}$ths × $\frac{7}{50}$ths of an inch, and seven minutes thereafter they had become dilated to $\frac{16}{50}$ths × $\frac{16}{50}$ths.

In the next experiment we administered a fatal dose.

EXPERIMENT XXXIV.—Two grains and a-half of sulphate of methyl-atropium, dissolved in twenty minims of distilled water, was injected under the skin at both flanks of a rabbit, weighing three pounds and half an ounce. In two minutes, there were some uneasy restless movements; in two minutes and a half, slight twitches occurred in the limbs; in three minutes, the rabbit had great difficulty in going about, and weakness of the limbs was manifested by frequent stumbles; and in four minutes, paralysis had so far advanced that the limbs were unable to support the body. In four minutes and a half, the animal lay flaccid on the side, with shallow and infrequent respirations, and now and then a feeble jerking contraction of the diaphragm accompanied inspiration. Soon, the respirations were so feeble as to be hardly recognisable, and they altogether ceased at six minutes after the injection.

In the autopsy, it was found that the sciatic nerves retained their conductivity at ten minutes after death, and that the heart's contractions were rhythmical, and at the rate of thirty in the minute, at eleven minutes.

In this experiment, also, the pupils were greatly dilated a few minutes after the administration of the poison.

The account we have given of these two experiments shows that the effects of the sulphate of methyl-atropium are exactly the same as those of the iodide, the former salt, however, being more active as a poison than the latter.

In order to obtain some data by which to compare the action on rabbits of iodide and sulphate of methyl-atropium with that of sulphate of atropia, we made many experiments in which large doses of sulphate of atropia were administered by subcutaneous injection; but we found that this method of

exhibition usually failed to produce any serious symptom, even when so large a dose as fifteen grains was given. In this experiment (Experiment XXIII.), the symptoms were merely dilatation of the pupils with impaired vision, increase in the rapidity of the cardiac and respiratory movements, diuresis and catharsis, general excitement and slight spasms, and languor. In a few minutes, many of these effects had disappeared, and the rabbit recovered perfectly.

These experiments render it apparent that the action of the methyl derivatives of atropia differs in several striking respects from that of the natural base.

We have seen from Experiments XXII. and XXIII. that large doses of atropia produce diuretic and cathartic effects in both dogs and rabbits, effects that are universally recognised among the symptoms of atropia action. These are not produced by the methyl derivatives.

We have also seen, and our observations agree with those of many previous experimenters, that when a salt of atropia is administered in a large dose to a dog, the predominant symptoms are those of paralysis coexisting with convulsions. The experiments we have now described show that convulsions are never produced by the salts of methyl-atropium, but that the predominating symptoms of their action are those of paralysis alone. It is, therefore, obvious that by the chemical addition of iodide or sulphate of methyl, some important change has been effected in the action of atropia, by which its power to produce convulsions has been removed. The determination of the exact nature of this change can be conveniently effected only by experiments on frogs, for the causation of the convulsive symptoms that appear in mammals has not yet been referred with certainty to any special organ or structure.

One of us has shown, in a paper published in this volume of the Transactions, that when a dose of a salt of atropia near the minimum fatal is given to a frog, a distinctly defined stage of paralysis is in the first place produced, which lasts for many hours, or for several days; and that this stage is succeeded by one in which violent convulsive and tetanic symptoms are present. Further, it is demonstrated in that paper that the convulsive and tetanic symptoms which characterise the second stage, are due to an action of atropia on the spinal cord; in fact, to an action that may with propriety be likened to that of strychnia. From our knowledge of these facts, we are enabled to examine if this strychnia-like action of atropia is possessed by the salts of its methyl derivative. For this purpose, we have made numerous experiments on frogs, of which the following are examples.

Experiment XXXVI.—Two minims of a solution of two-tenths of a grain of sulphate of methyl-atropium, in forty minims of distilled water, was diluted with two minims of distilled water, and the four minims of solution thus obtained, containing one-hundredth of a grain of sulphate of methyl-atropium, was injected under the skin of a frog, weighing 230 grains. In six minutes, the frog had

difficulty in jumping, and the anterior extremities were somewhat feeble, for they could not properly support the chest. In ten minutes, progression was accomplished by vigorous pushing movements of the posterior extremities, the loss of power being so decided that jumping was impossible. In twenty minutes, the frog lay on the abdomen and chest, but still the condition was not one of complete flaccidity, for the posterior extremities were flexed, and retained their proper tone, while the anterior partially supported the head and upper part of the chest. At this time, the respiratory movements were confined to the muscles of the throat, and reflex contractions of a vigorous character followed slight irritations of the skin. In thirty-five minutes, the paralysis was still more decided, for irritation now produced merely a series of interrupted and weak movements in the extremities; but, otherwise, the frog was in much the same state as that last noted. It continued thus for other twenty minutes, when the paralysis became less severe. A normal posture was assumed, and, by-and-by, vigorous voluntary movements were performed. In about two hours after the administration, the frog was in a normal condition.

It is of interest to observe that these marked symptoms were produced by a dose equivalent to only the $\frac{1}{32000}$th of the weight of the frog, while such a dose of sulphate of atropia produces no obvious effect in frogs.

EXPERIMENT XXXVII.—We injected under the skin at the right flank of a frog, weighing 407 grains, one-twentieth of a grain of sulphate of methyl-atropium, dissolved in four minims of distilled water. Very soon after, the movements were performed with some difficulty; and in five minutes, the anterior extremities were sprawling, and the frog was unable to jump. In eleven minutes, the frog was in a flaccid state on the abdomen, chest, and lower jaw; and but feeble reflex contractions could be excited. In fifteen minutes, the reflex function was suspended, and all respiratory movements had disappeared. In twenty-five minutes, a sciatic nerve was exposed and subjected to galvanic stimulation, but no muscular contractions were thereby produced, although direct galvanic stimulation of the muscles caused vigorous contractions. The cardiac impulse was at this time ascertained to be pretty strong, and the beats at the rate of thirty-two per minute. During the two following days, the frog remained in this condition. On the fourth day, however, it was found that the motor nerves had recovered their conductivity, but still the reflex function of the spinal cord was suspended. On the fifth day, the latter function was again present, and, indeed, the action of the poison had now so far disappeared that the frog had resumed a normal posture, and jumped freely when stimulated. There was no symptom whatever on the following day.

The dose given in this experiment was equivalent to the $\frac{1}{8140}$th of the weight of the frog used. To produce complete paralysis of the motor nerves for more than two days with sulphate of atropia, it is necessary to exhibit a dose of

about seven times the relative weight. The symptoms following the paralysis produced by sulphate of atropia would, however, be very different from those just described; for in place of a gradual recovery to normality, violent convulsive and tetanic symptoms would appear, and probably continue for several days, before perfect recovery took place. This experiment, therefore, shows in the most satisfactory manner that sulphate of methyl-atropium, administered in a dose rather less than the minimum fatal, does not cause any convulsant action in frogs.

In the next experiment, a dose about the minimum fatal was given.

EXPERIMENT XL.—One-tenth of a grain of sulphate of methyl-atropium was dissolved in four minims of distilled water, and injected under the skin at the right flank of a frog, which weighed 460 grains. Symptoms followed with great rapidity; for in two minutes, the frog could not jump, and the anterior extremities were extended almost powerlessly at right angles to the body, while the respirations were extremely feeble and infrequent. In five minutes, the latter had entirely ceased, and, now, only feeble twitches of the toes could be excited by rather severe irritation of the skin, the limbs being perfectly flaccid and motionless. In nine minutes, irritation caused no reflex movement whatever, and the cardiac contractions were at the rate of thirty beats in the minute. In twenty-nine minutes, it was ascertained that the motor conductivity of the sciatic nerves was suspended, while idio-muscular contractility was still retained. During the two following days, the state of the frog was the same as that last described. On the fourth day, however, it was impossible to discover any cardiac impulse. The muscles still contracted vigorously when they were directly galvanised, and they continued to do so until the seventh day, when *rigor mortis* set in.

We learn from this experiment, that a dose of sulphate of methyl-atropium equivalent to the $\frac{1}{4600}$th of the weight of a frog, is sufficient to produce a fatal result. As we have already mentioned, the minimum fatal dose of sulphate of atropia for frogs is about the $\frac{1}{900}$th or the $\frac{1}{1000}$th of the weight of the animal, but after such doses death is usually preceded by a stage of tetanus. This stage was entirely absent in the experiment with sulphate of methyl-atropium.

As, however, it might be supposed that sulphate of methyl-atropium will cause convulsive and tetanic symptoms if it be given in the same relative proportion as is required to produce these symptoms with sulphate of atropia—viz., in a dose equivalent to about the $\frac{1}{1000}$th of the frog's weight—an experiment was performed to meet this supposition.*

EXPERIMENT XLIV.—A solution, containing four-tenths of a grain of sulphate of methyl-atropium, dissolved in five minims of distilled water, was injected

* The frogs used in Experiments XXXVI., XXXVII., and XL. had been kept in the laboratory for more than two months before the performance of each experiment. The convulsive and tetanic effects of atropia appear to be more readily produced in frogs that have been thus kept, than in those recently obtained from their natural habitat.

under the skin at the right flank of a frog, weighing 461 grains. The usual paralytic symptoms very quickly supervened; and in seven minutes and thirty seconds, it was ascertained by galvanic stimulation that the motor conductivity of the sciatic nerves was suspended, while muscular contractility was retained. On the following day, this condition of the motor nerves and of the muscles continued, and the heart's contractions were found to be occurring at the rate of thirty in the minute. On the third day, the body was slightly rigid, galvanism of the nerves and muscles caused no contraction, and the heart was motionless.

Similar experiments were made with iodide of methyl-atropium, and no convulsive symptoms were produced by this salt. It was found that its poisonous activity for frogs is less than that of the corresponding sulphate, though considerably greater than that of sulphate of atropia, being equivalent to the $\frac{1}{2000}$th of the frog's weight. Short details of these experimeuts will be found in the Tabular Summary.

Having thus determined, by our experiments on dogs, rabbits, and frogs, that the salts of methyl-atropium do not possess the convulsant action of atropia, it is important that we should next ascertain by what action the paralytic symptoms of the salts of methyl-atropium are produced. Before doing this, however, it may be of advantage to show in what manner atropia itself produces paralysis.

The mechanism of the paralytic action of atropia is a complicated one, for there is good reason to suppose that it consists of actions on the sensory and motor nerves, and probably, also, on the spinal cord.* The following experiment illustrates the order in which several of these actions are produced.

EXPERIMENT XXV.—The sciatic artery and vein were ligatured at the upper part of the right thigh of a frog, weighing 215 grains; and, a few minutes afterwards, one-fourth of a grain of sulphate of atropia, dissolved in four minims of distilled water, was injected under the skin at the left flank. In eight minutes, a slight degree of paralysis was present, but the frog was able to perform somewhat imperfect jumping movements until thirty-five minutes. In forty minutes, however, it lay flaccid on the abdomen, with the head resting on the table, and, now, irritation of the skin *of any region* caused no other effect than a number of pretty vigorous movements in both posterior extremities, of rather greater energy in the non-poisoned (right) than in the poisoned. These reflex contractions could likewise be excited by gently touching the skin, in the poisoned as well as in the non-poisoned regions. The heart was now contracting at the rate of twenty-six beats in the minute. With the exception of a gradual diminution in the rate of the heart's contractions, no notable change occurred in the state of the animal until one hour and twenty minutes after the injection. At this time, gentle

* Authorities differ somewhat in their interpretation of the relations of these actions, some considering that the motor nerves are paralysed more rapidly than the sensory (BOTKIN, &c.), and others that the sensory are paralysed more rapidly than the motor (LEMATTRE, MEURIOT, &c.).

stimulation of the skin of the poisoned region caused no movement whatever, but feeble movements could still be excited in both poisoned and non-poisoned regions by strong stimulation; and the sensibility of the non-poisoned region was in much the same condition. In one hour and forty-five minutes, it was impossible to excite any reflex movement whatever. Galvanic stimulation of the right (non-poisoned) sciatic nerve was followed by vigorous movements restricted to the right leg; and, when this stimulation was applied to the left (poisoned) sciatic nerve, similar movements were produced in the left leg, and nowhere else. The heart was now contracting at the rate of twenty beats per minute. This state of suspension of the reflex function, with retention of conductivity in the motor nerves and of contractility in the muscles, continued until at least three hours after the administration of the poison, when the observations were interrupted. On the following morning, it was found that the conductivity of the poisoned sciatic nerve was suspended, while the poisoned muscles contracted when directly stimulated by an interrupted current. The conductivity of the non-poisoned sciatic nerve was still retained.

We learn from this experiment, that although a large dose of atropia quickly produces in frogs a condition of marked paralysis, the conductivity of the sensory and motor nerves and the reflex function of the spinal cord are not completely suspended until considerable intervals after the administration. Of these special paralytic actions, that on the motor nerves appears to be the last to be effected; indeed, in this experiment an interval of least an hour and fifteen minutes elapsed between the complete suspension of the reflex function and that of conductivity of these nerves.

We shall now endeavour to discover if the salts of the methyl derivative of atropia produce their paralytic symptoms by the same actions as atropia does.

Experiment XLIII.—Having ligatured the artery and veins at the upper third of the right thigh of a frog that weighed 235 grains, we injected under the skin of the left flank one-tenth of a grain of sulphate of methyl-atropium, in four minims of distilled water. Paralytic symptoms followed with great rapidity: so that in five minutes and thirty seconds, the frog was motionless, excepting that vigorous spontaneous movements frequently occurred in the right (non-poisoned) posterior extremity; and stimulation of the skin of any part, even though severe, *did not produce the faintest muscular contraction in the poisoned region, although it produced strong contractions in the non-poisoned (right) posterior extremity.* In six minutes, it was ascertained that the heart was contracting at the rate of forty beats in the minute. Frequent observations were made, and it was found that no change whatever occurred during the subsequent three hours—the conductivity of the poisoned sensory (afferent) nerves, and the reflex function of the spinal cord being retained, while the conductivity of the poisoned motor nerves was completely suspended. On the two following days, this condition

was still present, except that on the third day, the rate of the heart's contractions had diminished to thirty-six in the minute. Death, with commencing rigidity, occurred on the fourth day.

The dose given in this experiment was greatly above the minimum fatal. We shall now describe the effects of a dose that was considerably below the minimum fatal.

EXPERIMENT XXXVIII.—The blood-vessels at the upper third of the right thigh were ligatured in a frog, weighing 379 grains, and immediately afterwards a solution of one-twentieth of a grain of sulphate of methyl-atropium, in four minims of distilled water, was injected under the skin at the left flank. In three minutes, the respiration had ceased, and the frog was lying on the abdomen, perfectly flaccid and motionless in the poisoned region; but retaining the normal tone in the non-poisoned posterior extremity, where spontaneous vigorous movements frequently occurred. Irritation of the skin of any region did not cause any movement in the poisoned region, but it caused energetic contractions in the non-poisoned. In ten minutes, the left (poisoned) sciatic nerve was subjected to galvanic stimulation, with the result that *no movement was thereby caused in the left posterior extremity or in any part to which the poison had access, while energetic reflex contractions were caused in the right (non-poisoned) posterior extremity.* The poisoned muscles freely contracted when directly stimulated. It was found that the cardiac impulse was, at this time, powerful, while contractions occurred forty-four times in the minute. Repeated observation showed that the conditions of the poisoned heart, spinal cord, nerves, and muscles, and of the non-poisoned nerves and muscles, described as being present at ten minutes after the injection, continued unchanged during the succeeding three hours. On the following day, the frog had resumed a normal posture. It moved and jumped about actively, and there was now no symptom present.

We have made experiments similar to these with iodide of methyl-atropium, and the same general results were obtained.

It has thus been shown, in the most satisfactory manner, that the salts of methyl-atropium produce their paralytic effects in a very different manner from atropia. The former substances do not appear to influence the sensory nerves or the spinal cord, but they act solely on the motor nerves. We have seen that this last action is possessed by atropia also, though in a comparatively feeble degree; and the experiment we have described confirms the opinion of previous observers, that it is primarily restricted to the peripheral terminations of these nerves. The evidence contained in the experiments we have narrated with sulphate of methyl-atropium is in favour of the paralysis produced by this substance being likewise due to an action on the peripheral terminations of the motor nerves, and the following experiment clearly proves that such is the case.

EXPERIMENT XLII.—The right gastrocnemius muscle of a frog, weighing

312 grains, was exposed, the blood-vessels that entered it were carefully ligatured, and all the connections of the muscle divided, except its origin and insertion. Immediately afterwards, a solution of one-tenth of a grain of sulphate of methyl-atropium, in five minims of distilled water, was injected under the skin of the back. Paralytic effects were quickly produced. In fifteen minutes, the left sciatic nerve was exposed and stimulated by galvanism, with the result that while no contraction was produced in the left limb, energetic movements occurred in the right. The right sciatic nerve was then exposed and subjected to galvanic stimulation; energetic movements occurred in the right leg, which were ascertained to be entirely caused by contractions of the gastrocnemius muscle (non-poisoned); and no movement occurred elsewhere. On directly galvanising the poisoned muscles it was found that their contractility was still retained.

We learn from Experiments XLIII. and XXXVIII. that sulphate of methyl-atropium does not paralyse the motor nerve trunks. We further learn from Experiment XLII. that certain terminations of a motor nerve protected from the direct action of this poison are not paralysed, while other terminations exposed to its action are very quickly paralysed. It is, therefore, apparent that the paralysis of the motor nerves, which this substance so energetically produces, is due to an action that is restricted to their peripheral terminations.

The valuable and interesting researches of BOTKIN,* VON BEZOLD and BLOEBAUM,† MEURIOT,‡ and others, have shown that atropia exerts a paralysing influence on the inhibitory cardiac branches of the vagi nerves. When administered, even in very small doses, this substance so completely paralyses these nerves, that powerful galvanic stimulation of the main trunk of one of the vagi does not produce stoppage of the heart's action, or even appreciably diminish the rate of its contractions. It seemed important that we should determine if the methyl and ethyl derivatives of atropia possess this remarkable action.

EXPERIMENT XXIX.—The two vagi nerves were exposed in the neck of a rabbit, weighing three pounds and eight ounces. On subjecting each vagus separately to galvanic stimulation of a certain strength, obtained by the use of DU BOIS REYMOND'S induction apparatus, it was found that total stoppage of the heart's contractions resulted on each occasion, during the ten seconds the galvanic stimulation was applied. A solution containing half-a-grain of sulphate of methyl-atropium, in fifteen minims of distilled water, was injected under the skin of the abdomen.

* VIRCHOW'S Archiv. Bd. xxiv. 1862, p. 89.

† Untersuchungen aus dem Physiologischen Laboratorium in Würzburg, 1tes heft, 1867, p. 43.

‡ De la Méthod Physiologique en Thérapeutique et de ses Applications à l'étude de la Belladonne, 1868, p. 76.

5	minutes after the injection,		the heart was contracting 28 times in 10 seconds.
7	,,	,,	,, ,, 28 ,, ,,
7	,, and 10 seconds	,,	the right vagus was galvanised* for ten seconds, and the heart continued to contract, during the galvanism, 28 times in 10 seconds.
10	,,	,,	the heart was contracting 29 times in 10 seconds.
19	,,	,,	,, ,, 30 ,, ,,
20	,,	,,	the left vagus was galvanised for ten seconds, and the heart continued to contract, during the galvanism, 30 times in 10 seconds.
20	,, and 20 seconds	,,	the heart was contracting 30 times in 10 seconds.
26	,,	,,	,, ,, 30 ,, ,,
26	,, and 20 seconds	,,	the right vagus was galvanised for ten seconds, and the heart continued to contract, during the galvanism, 30 times in 10 seconds.

No general symptoms of the action of sulphate of methyl-atropium were developed during this period, the dose that was administered being but small.

The paralytic action on the inhibitory cardiac branches of the vagi, which this experiment clearly exhibits, would appear to be a very powerful one; for it was not counteracted, within twenty minutes, by half a grain of extract of physostigma subcutaneously administered, nor, within thirty minutes, by a second dose of three-fourths of a grain of extract of physostigma, administered twenty minutes after the first.

In other similar experiments on rabbits, we succeeded in completely paralysing the vagi nerves with one-tenth and with one-twentieth of a grain of iodide of methyl-atropium, and with one-tenth of a grain of iodide of ethyl-atropium.

We have seen, from Experiments VII., VIII., XXXII., and XXXIV., that iodide and sulphate of methyl-atropium, when acting through the blood, produce marked dilatation of the pupils. A number of experiments were made to determine whether the topical application of these salts to the conjunctiva similarly affects the pupil, and, thus, further exhibits a similarity in action to atropia and its salts.

The largest dose we applied was the $\frac{1}{500}$th of a grain.

Experiment CXI.—This dose, dissolved in one minim of distilled water, was applied to the left eyeball of a rabbit, and it caused extreme dilatation of the left pupil ($\frac{20}{50}$ths × $\frac{19}{50}$ths of an inch) in less than five minutes, which lasted for more than three days. The left pupil was of normal size on the sixth day.

In order to test the delicacy of this reaction, we made the following experiments:—

Experiment CXII.—One minim of a solution of one grain of sulphate of methyl-atropium, in 1000 minims of distilled water ($= \frac{1}{1000}$th of a grain of sulphate of methyl-atropium), was placed on the *right* eyeball of a rabbit.

* Throughout the experiment the strength of the galvanic current was the same as that which produced stoppage of the heart's contractions before the administration of sulphate of methyl-atropium.

Before the application, the *right* pupil measured	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths,	and the left,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths of an inch.			
8 minutes after the application,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,	
13 ,,	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
17 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{8}{0}$ths,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
55 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{8}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
2 hours	,,	,,	$\frac{1}{5}\frac{9}{0}$ths × $\frac{1}{5}\frac{8}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
On the 2d day	,,	,,	$\frac{1}{5}\frac{9}{0}$ths × $\frac{1}{5}\frac{8}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
,, 3d ,,	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{4}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,
,, 4th ,,	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
,, 5th ,,	,,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{5}{0}$ths,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,

EXPERIMENT CXIII.—One minim of a solution of one grain of sulphate of methyl-atropium, in 5000 minims of distilled water ($=\frac{1}{5000}$th of a grain of sulphate of methyl-atropium), was paced on the *left* eyeball of a rabbit.

Before the application, the *left* pupil measured	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths,	and the right,	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths of an inch.			
13 minutes after the application,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths,	,,	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths	,,	
15 ,,	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths	,,
17 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{8}{0}$ths,	,,	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths	,,
20 ,,	,,	,,	$\frac{1}{5}\frac{9}{0}$ths × $\frac{1}{5}\frac{9}{0}$ths,	,,	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths	,,
2 hours	,,	,,	$\frac{1}{5}\frac{9}{0}$ths × $\frac{1}{5}\frac{9}{0}$ths,	,,	$\frac{1}{5}\frac{3}{0}$ths × $\frac{1}{5}\frac{2}{0}$ths	,,
22 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{4}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,

EXPERIMENT CXIV.—One minim of a solution of one grain of sulphate of methyl-atropium, in 20,000 minims of distilled water ($=\frac{1}{20000}$th of a grain of sulphate of methyl-atropium), was placed on the *right* eyeball of a rabbit.

Before the application, the *right* pupil measured	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths,	and the left,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths of an inch.			
35 minutes after the application,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,	
45 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
1 hour 10 minutes	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{8}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
25 hours	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,

EXPERIMENT CXV.—One minim of a solution of one grain of sulphate of methyl-atropium, in 50,000 minims of distilled water ($=\frac{1}{50000}$th of a grain of sulphate of methyl-atropium), was placed on the *right* eyeball of a young rabbit.

Before the application, the *right* pupil measured	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths,	and the left,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths of an inch.			
42 minutes after the application,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{5}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,	
1 hour 5 minutes	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,
1 ,, 10 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,
2 hours	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,
22 ,,	,,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{3}{0}$ths	,,

EXPERIMENT CXVI.—One minim of a solution of one grain of sulphate of methyl-atropium in 100,000 minims of distilled water ($=\frac{1}{100000}$th of a grain of sulphate of methyl-atropium) was placed on the *right* eyeball of a rabbit.

Before the application, the *right* pupil measured	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths,	and the left,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths of an inch.			
39 minutes after the application,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{5}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,	
1 hour	,,	,,	$\frac{1}{5}\frac{7}{0}$ths × $\frac{1}{5}\frac{6}{0}$ths,	,,	$\frac{1}{5}\frac{6}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
1 ,, 30 minutes	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths + $\frac{1}{5}\frac{4}{0}$ths	,,
2 hours 10 ,,	,,	,,	$\frac{1}{5}\frac{8}{0}$ths × $\frac{1}{5}\frac{7}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,
22 ,,	,,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths,	,,	$\frac{1}{5}\frac{5}{0}$ths × $\frac{1}{5}\frac{4}{0}$ths	,,

It seemed to us unnecessary to proceed further in our examination of the delicacy of this action on the iris. The researches of DE RUYTER have placed at our disposal a number of experiments with sulphate of atropia, similarly applied in extremely dilute solutions. From these researches we learn that a drop of a solution containing the $\frac{1}{128600}$th of a grain of sulphate of atropia is capable of producing dilatation of the pupil in a dog, which lasts for eighteen hours.* Comparing this result with that obtained in our experiment with the $\frac{1}{100000}$th of a grain of sulphate of methyl-atropium, we are justified in considering that the addition of sulphate of methyl to atropia does not diminish the mydriatic action of this alkaloid to any marked extent.

Iodide of ethyl-atropium ($C_{17}H_{23}NO_3CH_3I$).—Our investigation also includes an examination of the physiological action of this ethyl derivative of atropia. The results of this examination prove that this substance acts in precisely the same manner as the previously described methyl derivatives.

Iodide of ethyl acts readily on atropia, but not so energetically as iodide of methyl. In preparing the iodide of ethyl-atropium, atropia was treated with a considerable excess of iodide of ethyl, in a sealed tube, at 100° C., for an hour. The remainder of the process is the same as in the case of the methyl derivative, which in general appearance and character it closely resembles.

We found that two grains of this substance, administered by subcutaneous injection, is a poisonous dose for a full-grown rabbit.

EXPERIMENT XLVIII.—In a rabbit, weighing three pounds and seven ounces, it was found that the right pupil, under exposure to a full light, had a diameter of $\frac{13}{50}$ths × $\frac{12}{50}$ths of an inch, and that the respirations were irregular and at the rate of twenty-four in ten seconds.

A solution containing two grains of iodide of ethyl-atropium, in one hundred and twenty minims of slightly warmed distilled water, was then injected under the skin at the back of the rabbit. In two minutes, the pupils measured $\frac{15}{50}$ths × $\frac{14}{50}$ths. In three minutes, the respirations occurred regularly at the rate of twenty per ten seconds; but there was no other symptom present. In six minutes, some faint quivers occurred, and a slight degree of paralysis was present. The latter gradually increased in severity until, in sixteen minutes, the rabbit was unable to move about, and lay on the abdomen with the head resting on the table in an utterly flaccid state. The respirations were now shallow and somewhat jerking in character, and they occurred at the rate of fourteen per ten seconds. In twenty-two minutes, the respirations were extremely feeble, and at the rate of only nine per ten seconds, After this, they quickly diminished in number, until they altogether ceased in twenty-four minutes after the injection. At the time of the occurrence of death, the pupils measured $\frac{15}{50}$ths × $\frac{14}{50}$ths of an inch.

* Quoted by MEURIOT, *op. cit.* p. 118, from Nederlandsch Lancet, 1853.

In the autopsy, it was found that the sciatic nerves retained their afferent (motor) and efferent (sensor) conductivity for at least fifteen minutes after death, and that the heart had ceased to contract previous to twenty minutes after this event.

These general effects very closely resemble those that have been described in the experiments with the iodide of methyl-atropium. We shall see from the following experiment that the effects on frogs of this ethyl derivative are likewise the same in character with those of the methyl derivatives.

EXPERIMENT LII.—We injected under the skin of the left flank of a frog, weighing 290 grains, three-twentieths of a grain of iodide of ethyl-atropium, dissolved in eight minims of distilled water. In six minutes, the frog was perfectly motionless and flaccid; and so complete was the paralysis, that even severe irritation of the skin did not cause any reflex movement. The heart was now contracting in regular rhythm, at the rate of thirty-nine beats in the minute. In seven minutes, the right sciatic nerve was exposed, and it was found, by galvanic stimulation, that its motor conductivity was completely suspended. The muscles, at this time, contracted vigorously when the electrodes were applied to their surface. This condition of the motor nerves and of the muscles was retained for other two days; but on the second day the cardiac impulse was weak, and the beats occurred at the diminished rate of twenty in the minute, while, on the third day, no cardiac impulse could be observed. On the fourth day, the muscles had become rigid.

These symptoms are in all essential characters the same as those we have described, with fatal doses of iodide of methyl-atropium. We have besides, given a dose considerably below the minimum fatal, and have observed a temporary stage of complete paralysis of the motor nerves, which was recovered from without the occurrence of the slightest spasmodic or convulsive symptoms. This ethyl derivative of atropia, therefore, resembles the methyl derivatives, in that it does not possess the well-marked convulsant action of atropia.

We have seen from the last experiment that the paralysis is accompanied by total suspension of the conductivity of the motor nerves. It is important that we should now discover whether the sensory nerves and spinal cord are also implicated in the production of this paralysis. This may readily be determined by experiments in which certain limited regions are protected from the direct action of the poison—as has been done in experiments with the methyl derivatives of atropia.

EXPERIMENT LI.—Having ligatured the blood-vessels in the lower third of the right thigh of a frog, weighing 301 grains, we injected three-twentieths of a grain of iodide of ethyl-atropium, dissolved in ten minims of distilled water, under the skin of the left flank. Paralysis very quickly supervened; and in two minutes, stimulation of the skin anywhere was followed by vigorous movements of the

right (non-poisoned) leg, but no movement occurred in any part of the poisoned region. It was likewise observed that frequent spontaneous movements of an energetic character occurred in the right (non-poisoned) leg. In twelve minutes, the symptoms were as last described, and the heart's contractions occurred thirty-eight times in the minute. In thirteen minutes, the left sciatic nerve was exposed, and on being stimulated by galvanism, *it was found that the conductivity of its motor fibres was suspended, while that of its sensory fibres continued;* no movement occurring in the left (poisoned) posterior extremity, although the muscles of that limb yet retained their contractility unimpaired, while vigorous reflex movements occurred in the right (non-poisoned) posterior extremity.

The occurrence of these reflex movements shows that the reflex function of the spinal cord is not destroyed by the direct action of this poison. It is obvious, from the details we have just given, that the sensory nerve fibres and the striped muscles are likewise unaffected; while the motor nerve fibres are powerfully affected. The paralytic effects of iodide of ethyl-atropium, like those of iodide and sulphate of methyl-atropium, are, therefore, caused entirely by an action on the motor nerves. The last experiment further shows that the trunks of the motor nerves are unaffected, while their peripheral portions are paralysed. It will be seen from the next experiment that the ultimate terminations of these nerves in the muscles are the portions of the periphery that are affected.

EXPERIMENT L.—In a frog, weighing 450 grains, the left gastrocnemius muscle was carefully dissected from all its connections, excepting its origin and insertion and the nerve fibres that entered it; and its blood-vessels were ligatured and divided. Two-tenths of a grain of iodide of ethyl-atropium, dissolved in ten minims of distilled water, was then injected under the skin at the right flank. In ten minutes, the frog was completely flaccid and motionless; and, when the skin anywhere was irritated, no movement occurred in the poisoned region, while well marked movements occurred in the left leg and foot. In twelve minutes, the right sciatic nerve was subjected to galvanic stimulation, with the result that while no movement occurred in the right leg, vigorous contractions occurred in the left. The left sciatic nerve was then similarly stimulated, and vigorous movements followed in the left leg, but nowhere else. *It was seen that these movements were due solely to contractions of the left gastrocnemius muscle, which was protected from the direct action of the poison.*

The results we have obtained from these experiments are of an extremely interesting character. They clearly prove that the ammonium bases derived from atropia possess an action which is very different from that of atropia itself. The latter substance produces paralysis chiefly by affecting the motor centres and the sensory nerves; it produces convulsions by stimulating the spinal cord; and it produces diuresis and catharsis by influencing the urinary apparatus and the intestinal functions. The salts of the ammonium basis possess none of these

actions. They, however, retain the dilating action of atropia on the pupil, and the paralysing action on the cardiac inhibitory branches of the vagi, and on the spinal motor nerves.

This last action, though resembling that of atropia in *character*, differs greatly from it in *degree*. While in atropia, this action has only a secondary prominence, and, in the presence of other and more potent paralysing actions, only a subsidiary influence in causing paralysis and death; in the methyl and ethyl derivatives, it assumes the prominence of the sole paralysis-producing action, and the primary cause of the poisonous activity of these substances.

As it is shown by our experiments that the poisonous activity of the methyl and ethyl derivatives is much greater than that of the salts of atropia, it is apparent that the paralysing action of the former on the motor nerve terminations must be very much greater than that of the latter.

In the following Table, we summarise the chief details of a few of our experiments, so as clearly to exhibit the difference of poisonous activity.

No. of Experiment.	Substance Employed.	Animal and its Weight.	Dose, by subcutaneous administration.	Relation of Dose to Weight of Animal.	Effect.
I.	Iodide of methyl-atropium.	Dog, 8 lbs. 6 oz.	10 grs. (containing 6·6 grs. of atropia).	$\frac{1}{3\,8\,6\,3}$d.	Decided paralysis in 10 minutes, accompanied with very faint twitchings; and death in 32 minutes.
XXII.	Sulphate of atropia.	Dog (same dog as in Expt. I.)	10 grs. (containing 8·48 grs. of atropia).	$\frac{1}{3\,6\,3}$d.	Diuresis in 12 minutes; partial paralysis in 13 minutes; spasms in 38 minutes; decided paralysis in 48 minutes; tetanic convulsions in 52 minutes, and until 3 hours and 18 minutes; and followed by recovery.
VIII.	Iodide of methyl-atropium.	Rabbit, 3 lbs. 10 oz.	3 grs. (containing 2 grs. of atropia).	$\frac{1}{9\,4\,5\,8}$th.	Decided paralysis in 15 minutes; and death in 58 minutes.
XXIII.	Sulphate of atropia.	Do., 2 lbs. 5 oz.	15 grs. (containing 13·12 grs. of atropia).	$\frac{1}{1\,5\,4\,0}$th.	Diuresis, catharsis, and langour; followed by recovery in more than 3 hours and less than 9.
XXXIV.	Sulphate of methyl-atropium.	Do., 3 lbs. 0½ oz.	2·5 grs. (containing 2·05 grs. of atropia).	$\frac{1}{1\,5\,6\,5}$th	Slight paralysis and feeble twitches in 3 minutes; decided paralysis in 4 minutes; and death in 6 minutes.
XL.	Do.	Frog, 460 grs.	0·1 gr. (containing 0·08 gr. of atropia).	$\frac{1}{5\,7\,5\,0}$th.	Decided paralysis in 2 minutes; complete paralysis in 9 minutes; and death on the 7th day.
XXIV.	Sulphate of atropia.	Do., 490 grs.	0·5 gr. (containing 0·42 gr. of atropia).	$\frac{1}{9\,8\,0}$th.	Incomplete paralysis 1st and 2d days; complete paralysis 3d day; tetanus 3d to 5th days; and recovery 7th day.
XLVIII.	Iodide of ethyl-atropium.	Rabbit, 3 lbs. 7 oz.	2 grs. (containing 1·27 gr. of atropia).	$\frac{1}{2\,7\,5\,6}$th.	Slight paralysis and tremors in 6 minutes; decided paralysis in 16 minutes; and death in 24 minutes.

Conia.

This substance is obtained from *Conium maculatum* (hemlock), and has been shown by Von Planta and Kekulé* to be a variable mixture of two bases, to which they give the names of "Conia" and "Methyl-conia." These bases resemble one another very closely in physical properties. Their composition is represented by the formulæ $C_8H_{15}N$ and $C_9H_{17}N$. The chemists above named investigated very completely the action of iodide of ethyl on conia, and proved that "conia" (or, as it is called in the present paper, *normal conia*) is an imide base, and that "methyl-conia" is a nitrile base.

The substances examined in the present paper are:—

1*st*, *Conia*—samples of which were obtained from Messrs Duncan & Flockhart, Macfarlan & Co., and Morson. We are also indebted to Dr Christison for the opportunity of examining the action of a specimen of conia, which he prepared in 1835.

2*d*, *Methyl-conia*—prepared from hydriodate of methyl-conia, produced by the union of iodide of methyl and *normal conia*. Our experiments were made with the hydrochlorate of this substance.

3*d*, *Iodide of dimethyl-conium*—obtained by the union of iodide of methyl and methyl-conia contained in conia, as obtained from the plant.

Conia.—The careful and elaborate investigations of Christison,† Schroff,‡ Von Praag,§ Kölliker,‖ and Guttmann,¶ have rendered important service to our knowledge of the effects and mode of action of conia. From the results obtained by these authors, it is now certainly established that this alkaloid is a poison of great activity, and that it produces marked paralytic and less obvious spasmodic symptoms. The former symptoms have been shown to depend principally on an action on the peripheral terminations of the motor nerves; but the causation of the latter is as yet unknown. It has also been ascertained, chiefly by the investigations of Kölliker and Guttmann, that conia does not directly influence the functions of the sensory nerves, striped muscles, or heart.

In a general manner, our experiments confirm the above results; but they also prove that considerable differences occur both in the nature of the action and in the lethal activity of various samples of conia. In these respects, we observed the most marked differences between the conia prepared by Dr Christison and

* Annalen der Chemie und Pharmacie, bd. lxxxix. 1854, p. 129.

† Transactions Roy. Soc. of Edinburgh, vol. xiii. 1837, pp. 398–415.

‡ Wochenblatt der Gesellschaft der Aerzte zu Wien, 1856; and Lehrbuch der Pharmacologie, 1869, p. 531.

§ Journ. f. Pharm, i. 44.

‖ Virchow's Archiv. bd. x. 1856, p. 238.

¶ Berliner Klinische Wochenschrift, 1866, pp. 45, 55, 71, 81.

that obtained from Mr MORSON; and as these, therefore, represent the extremes among our samples, we shall describe in detail their action only.

Our experiments were made with the hydrochlorate, which we obtained as a nearly colourless, imperfectly crystalline, and deliquescent substance. The difference of activity between the hydrochlorate of Dr CHRISTISON'S conia and that of Mr MORSON was so great, that while two-tenths of a grain of the former speedily caused death in a full-grown rabbit, this dose of the latter did not produce any distinct effect, one grain being the smallest fatal dose for a rabbit. The symptoms that are produced in mammals by the different samples are very similar in character. The more prominent of these are stiffness of the limbs, causing difficulty in moving about; spasmodic starts; distinct increase of reflex excitability; gradually increasing paralysis, with diminution, and, afterwards, disappearance of the increased reflex excitability; and, finally, death by asphyxia. The exact causation of the paralytic symptoms differs, however, in a remarkable manner in different samples of conia; and the nature of this difference will be shown in the detailed descriptions that follow.

We shall consider, in the first place, the action of *hydrochlorate of Dr CHRISTISON'S conia*. The following experiment illustrates the symptoms in mammals.

EXPERIMENT LIV.—Two-tenths of a grain of hydrochlorate of Dr CHRISTISON'S conia, dissolved in four minims of distilled water, was administered by subcutaneous injection to a rabbit, weighing three pounds and six ounces and-a-half. In two minutes and thirty seconds, the limbs became somewhat stiff and abnormally extended, so that the body was raised and an awkward posture assumed. In three minutes, a slight touch of any part of the skin caused a sudden spasmodic start; and soon after a series of starts in rapid succession occurred spontaneously, during which the limbs were still stiffly extended. In eight minutes, these starts ceased, and the limbs assumed a nearly normal position; but the rabbit had now considerable difficulty in moving about, the limbs being slightly paralysed. In sixteen minutes, the rabbit lay down and rested in a crouching attitude, on the abdomen and chest. Soon after the neck muscles were unable properly to support the head, which frequently subsided on the table; but there was now no distinct evidence of exaggeration of reflex activity. In twenty-five minutes, the paralysis was so decided, that even a sitting posture could not be maintained, and the rabbit lay on the side. The respirations were infrequent and laboured, while common sensibility seemed to be unimpaired, and the heart was ascertained to be contracting with nearly normal force and rapidity. In twenty-eight minutes, some convulsive movements occurred in the body and limbs, and now the respirations were so weak as to be scarcely observable. The convulsive movements continued for other two minutes, but at the end of this period they consisted of extremely feeble spasmodic starts. In thirty-one minutes, the sensibility of the conjunctiva and cornea had dis-

appeared, the respirations had become mere infrequent gasps, but the heart was contracting at the rate of 120 beats in the minute. Death occurred thirty-two minutes after the administration. The pupils were frequently observed; they retained the same diameter during the experiment as they had immediately before it, but on the occurrence of death they contracted considerably.

After death, galvanic stimulation of the left sciatic nerve caused active movements in the left leg, and also well-marked reflex movements in the right. The exposed heart was contracting, six minutes after death, in proper rhythm, and at the rate of 100 beats in the minute.

In our experiments with frogs, we found that a dose equivalent to the $\frac{1}{4400}$th of the weight of the animal was sufficient to cause death. In the two experiments with Dr CHRISTISON'S conia, which we shall now describe, somewhat larger doses than that above mentioned were administered, the complete physiological action being but slowly developed with small doses.

EXPERIMENT LXI.—One-tenth of a grain of hydrochlorate of Dr CHRISTISON'S conia was dissolved in four minims of distilled water, and injected under the skin at the right flank of a frog, weighing 300 grains. The frog jumped about actively until five minutes after the administration, when it appeared to experience some difficulty in moving about, and it was observed that this difficulty was chiefly due to tonic spasm of the anterior extremities. This spasm, though by no means powerful, was sufficient to retain the extremities in a constrained perpendicular position, and in extreme extension, during the five minutes that succeeded its first appearance. In ten minutes, the frog was unable to jump, and it lay on the abdomen and chest; while the respirations had now ceased. In twenty-five minutes, it was perfectly flaccid, and the head rested on the table, but the heart's impulse was still well marked, and the rate of its contractions was forty per minute. At frequent intervals, the two posterior extremities were somewhat suddenly pushed out to extreme extension, and after remaining in this position, for one or two seconds, again partially flexed. In fifty minutes, these extension movements of the posterior extremities ceased, and irritation of the skin now caused merely faint twitches of the toes. In one hour and thirty minutes, it was impossible to excite any reflex movement whatever; and on applying galvanic stimulation to the trunk of a sciatic nerve, it was found that the motor conductivity was completely suspended. The heart was at this time contracting thirty-seven times in the minute, and the contractility of the striped muscles was unimpaired. On the following day, the frog was still in a flaccid and motionless state. The heart was contracting twenty-two times in the minute, and the nerves and muscles were in the condition last described. On the morning of the third day, rigor mortis was established.

In the next experiment, one limb was protected from the direct influence of the poison.

EXPERIMENT LXV.—Having ligatured the sciatic artery and the two principal veins at the middle of the right thigh in a frog weighing 195 grains, we injected six-tenths of a grain of hydrochlorate of Dr CHRISTISON'S conia, dissolved in four minims of distilled water, under the skin of the left flank. In two minutes, stiffness occurred in the anterior extremities. They gradually became curved inwards until the fore-paws were pressed against each other, and they were retained in this position by tonic spasm, the frog having apparently no voluntary control over them. Jumping movements could not now be accomplished, but the frog pushed itself about by vigorous contractions of the posterior extremities. In five minutes, there was marked weakness on the left posterior extremity, the right remaining unaffected. In eight minutes, the stiff incurvation of the anterior extremities had disappeared; and, now, the animal was flaccid everywhere, except in the right posterior extremity. In nine minutes, irritation of the poisoned skin was followed by barely perceptible twitches in the toes of the left posterior extremity, and extremely vigorous movements of the whole right posterior extremity. Occasionally, the right posterior extremity was extended stiffly, and retained thus for one or two seconds, the movements presenting a somewhat spasmodic appearance. In thirty minutes, the reflex contractions that followed irritation of the skin were confined to the right posterior extremity; and the heart was now contracting at the rate of twenty-four beats in the minute. In thirty-four minutes, the left sciatic nerve was exposed, the necessary dissection causing vigorous movements in the right leg, and on stimulating the nerve by an interrupted galvanic current, it was found that its motor conductivity was completely suspended, while its sensory (efferent) conductivity was retained; no movements occurring in the left posterior extremity, while energetic contractions occurred in the right (non-poisoned) posterior extremity. The contractility of the poisoned muscles was still unimpaired. Irritation of the skin in the poisoned region excited reflex movements of the right (non-poisoned) posterior extremity until two hours and fifteen minutes after complete paralysis had occurred in the poisoned motor nerves; but ten minutes after this, reflex movements could not be excited. The frog did not recover from the poisoning.

A considerable interval occurred, therefore, between the complete suspension of conductivity in the motor nerves and the loss of the reflex function of the spinal cord; and, accordingly, it is evident that the condition of paralysis and flaccidity caused by Dr CHRISTISON'S conia is mainly dependent on its action on the motor nerves. The experiment further shows that this paralysing action is restricted, in the first place, at least, to the peripheral terminations of the motor nerves.

In the last two experiments, we have shown that certain slight spasmodic symptoms are produced in frogs by conia. It is probable that these represent the more violent convulsions that occur in mammals, and to which we have drawn

attention in the description of an experiment on a rabbit (Experiment LIV.). Both in frogs and in mammals those spasmodic symptoms appear at an early stage in the poisoning.

Although our main object, in describing the action of *hydrochlorate of Mr Morson's conia*, is to point out certain peculiarities in the mode in which it produces paralysis, it may be advisable that we should also give some evidence in support of the assertion that its lethal activity is much less than that of the hydrochlorate of Dr Christison's conia. We shall thus be able to show clearly that both the nature of the action and the lethal activity of various specimens of conia may differ considerably, while the symptoms produced by them are very similar in character.

In the following experiment, a dose below the minimum fatal was given.

Experiment LXVII.—We dissolved seven-tenths of a grain of hydrochlorate of Mr Morson's conia in fifteen minims of distilled water, and injected the solution under the skin at the back of a rabbit, weighing three pounds and three ounces and-a-quarter. The animal remained quiet until six minutes, when it moved about in an excited manner, and during these movements it was observed that the four limbs were abnormally and stiffly extended. This stiff extension of the limbs gradually became more marked, until it seriously impeded the movements of the rabbit. In fourteen minutes, a slight touch of the skin excited a sudden spasmodic start of the whole body. In twenty-five minutes, the stiffness of the limbs had greatly diminished, and now it was obvious that a slight degree of paralysis was present. From this time, these symptoms gradually but slowly disappeared; and the rabbit was jumping about actively one hour after the injection.

In the next experiment, the dose was a fatal one.

Experiment LXVIII.—One grain of hydrochlorate of Mr Morson's conia, dissolved in twenty minims of distilled water, was injected under the skin at the right side of a rabbit, weighing four pounds and one ounce. The symptoms were very similar to those observed with two-tenths of a grain of hydrochlorate of Dr Christison's conia. Stiffness of the limbs and tremors occurred in six minutes; evidence of exaggeration of the reflex activity was obtained in eight minutes; decided paralysis was present in thirteen minutes; and, after the occurrence of a number of attacks of convulsive tremors, a condition of flaccid motionlessness, interrupted by infrequent respiratory gasps, supervened, which terminated in death, thirty-three minutes after the administration.

The general character of the symptoms produced by Mr Morson's conia in frogs was likewise found to be the same as that produced by Dr Christison's conia; and, in proof of this, we shall briefly describe an experiment with a fatal dose of the former.

Experiment LXXVI.—We injected three-tenths of a grain of hydrochlorate of

Mr MORSON's conia, dissolved in four minims of distilled water, under the skin at the right flank of a frog, weighing 140 grains. The effects were very speedily produced; for in less than two minutes, the frog was quite unable to jump, and a decided degree of general paralysis was present. In four minutes, some stiffness was present in the anterior extremities and the fingers, causing the latter to be continuously and stiffly elevated until eight minutes after the poisoning. At nine minutes, the frog was in a flaccid state, but, still, somewhat vigorous movements were spontaneously made in the posterior extremities. These consisted at first of extension and flexion movements of a normal character; soon, however, they became spasmodic, the extension being prolonged; and, at fourteen minutes, they assumed an almost tetanic character, extreme extension being maintained on each occasion for nearly two seconds. In twenty-five minutes, the spontaneous movements of the posterior extremities were extremely feeble, and in thirty minutes, they altogether ceased. In thirty-five minutes, the frog was perfectly flaccid and motionless, and irritation, even of a severe character, failed to excite any reflex movement whatever. The heart was now contracting in normal rhythm, at the rate of twenty-four beats in the minute.

On the following morning, the frog was dead and in rigor. In this experiment, the dose (equivalent to the $\frac{1}{467}$th of the frog's weight) was considerably above the minimum fatal. Our experiments have shown that in frogs, as in mammals, this sample of conia is much less active than that of Dr CHRISTISON, for the smallest dose which we have found to produce death is equivalent to the $\frac{1}{850}$th of the weight of the frog used.

The last experiment shows that after a fatal dose of Mr MORSON's conia the predominant symptoms are those of paralysis. We shall now describe some experiments performed for the purpose of determining by what action or actions this paralysis is produced.

EXPERIMENT LXXI.—We ligatured the blood-vessels in the right thigh of a frog, weighing 112 grains, and, immediately afterwards, injected one-tenth of a grain of hydrochlorate of Mr MORSON's conia, dissolved in five minims of distilled water, under the skin of the left flank. Complete general paralysis was quickly produced in the poisoned regions. In twenty-seven minutes after the injection, irritation of the skin caused active and apparently tetanic reflex movements of the right posterior extremity, but it failed to cause any movement in the parts to which the poison had access. In one hour, the left sciatic nerve was exposed, and subjected to galvanic stimulation; with the result, that no movement whatever was thereby excited in the left posterior extremity, or in any poisoned part, while pretty active reflex movements were excited in the right posterior extremity. This condition continued until one hour and twenty minutes after the injection, but at this time the reflex movements that were excited in the right posterior extremity were extremely feeble. In one hour and thirty-five minutes,

it was impossible to excite any reflex movement, although strong irritations were applied to the skin of both the poisoned and non-poisoned regions, and to the left sciatic nerve. At this time, the contractility of the muscles was unimpaired, the conductivity of the right (non-poisoned) sciatic nerve was retained, and the contractions of the heart were at the rate of twenty in the minute.

It is obvious that, in this experiment, the motor nerves were completely paralysed before the reflex function of the spinal cord was suspended.

EXPERIMENT LXXVIII.—After ligaturing the blood-vessels in the right thigh of a frog, weighing 110 grains, we injected a solution containing three-tenths of a grain of hydrochlorate of Mr MORSON'S conia, under the skin at the left flank. In forty-nine minutes, no reflex movements could be produced by irritation of the skin, whether of the poisoned or non-poisoned regions. The left sciatic nerve was now exposed; and, on galvanising its trunk, it was found that feeble twitches occurred in the toes of the left (poisoned) posterior extremity, while no reflex movements occurred in the right (non-poisoned) posterior extremity, or in any part. It was ascertained, at the same time, that the muscles everywhere contracted freely when directly stimulated, that the right sciatic nerve retained its functional activity, and that the heart's beats were occurring at the rate of eighteen in the minute. The condition of retained, though impaired, conductivity of the poisoned motor nerves, of retained conductivity of the non-poisoned (right) sciatic nerve, of apparently unimpaired contractility of the muscles, coexisting with complete suspension of the reflex function of the spinal cord, continued until one hour and ten minutes after the administration of the poison. At one hour and fourteen minutes, however, the left (poisoned) sciatic nerve was found to be completely paralysed.

We learn from this experiment that Mr MORSON'S conia may so energetically affect the spinal cord, as to suspend its reflex function, before the motor nerves are completely paralysed. The motor nerves, certainly, were affected at an early stage, and, even before the suspension of the reflex function of the spinal cord, their conductivity was so far impaired, that merely very feeble twitches could be excited by galvanising them. The general paralysis that was present in the poisoned region was, no doubt, to a considerable extent due to their impaired activity. Still, the action of this substance on the reflex function of the spinal cord was, at least, as important a cause of paralysis as the action on the motor nerves. In Experiment LXXI., likewise, both actions co-operated in the production of the paralysis, but the motor nerves were paralysed in it before the reflex function of the spinal cord was completely suspended.

These two experiments represent two varieties of action, which we have observed in our experiments with Mr MORSON'S conia. In both, the motor nerves and the spinal cord were markedly affected; but in the one, complete loss of function occurred in the motor nerves before it occurred in the spinal cord, and

in the other, complete loss of function occurred in the spinal cord before it occurred in the motor nerves.

The following Table contains a short account of these experiments:—

No. of Experiment.	Weight of Frog.	Relation of Weight of Frog to Dose.	Dose.	Effect.
LXXI.	112 grs.	$\frac{1}{1120}$th.	0·1 gr.	Complete paralysis of *motor nerves* in 1 hour. " " *reflex function of spinal cord* in 1 ho. 35 min.
LXXII.	200 grs.	$\frac{1}{1000}$th.	0·2 gr.	Complete paralysis of *motor nerves* in 40 minutes. " " *reflex function of spinal cord* in 1 ho. 10 min.
LXXIII.	256 grs.	$\frac{1}{853}$d.	0·3 gr.	Complete paralysis of *motor nerves* in 1 hour 25 minutes. " " *reflex function of spinal cord* in 1 ho. 25 min.
LXXIV.	290 grs.	$\frac{1}{805}$th.	0·36 gr.	Complete paralysis of *motor nerves* in 18 minutes. " " *reflex function of spinal cord* in from 2 to 18 hours.
LXXV.	110 grs.	$\frac{1}{550}$th.	0·2 gr.	Complete paralysis of *reflex function of spinal cord* in 47 minutes. " " *motor nerves* in from 1 ho. 20 min. to 22 ho.
LXXVI.	140 grs.	$\frac{1}{466}$th.	0·3 gr.	Complete paralysis of *reflex function of spinal cord* in 35 minutes. " " *motor nerves* in from 1 ho. 20 min. to 21 ho.
LXXVII.	110 grs.	$\frac{1}{366}$th.	0·3 gr.	Complete paralysis of *motor nerves* in 30 minutes. " " *reflex function of spinal cord* in 1 ho. 30 min.
LXXVIII.	110 grs.	$\frac{1}{366}$th.	0·3 gr.	Complete paralysis of *reflex function of spinal cord* in 49 minutes. " " *motor nerves* in 1 hour 14 minutes.
LXXIX.	115 grs.	$\frac{1}{287}$th.	0·4 gr.	Complete paralysis of *reflex function of spinal cord* in 28 minutes. " " *motor nerves* in 35 minutes.

In the experiments in this Table, in which doses between the $\frac{1}{1120}$th and the $\frac{1}{805}$th of the frog's weight were given, the complete paralysis of the motor nerves occurred *before* the complete paralysis of the reflex function of the spinal cord; and in the experiments in which doses between the $\frac{1}{550}$th and the $\frac{1}{287}$th were given (excepting Experiment LXXVII.), the complete paralysis of the motor nerves occurred *after* that of the reflex function of the spinal cord. As we have already said, these two actions are, however, of nearly equal energy; for, at the time when the one has been completed, the other is usually nearly so. Experiment LXXVII., in which a dose equivalent to the $\frac{1}{366}$th was administered, conspicuously illustrates this nearly simultaneous progress, by its occurrence as an exception to the order in which the two actions are usually completed after such a dose.

We have accordingly shown that Mr MORSON'S conia differs from that of Dr CHRISTISON, both in lethal activity and in mode of action. We shall endeavour to explain these differences in a subsequent portion of this paper; the explanation of the varieties in the mechanism of the paralysing action of Mr MORSON'S conia being dependent on results obtained by our experiments with methyl-conia.

Hydrochlorate of methyl-conia ($C_8H_{14}(CH_3)NHCl$).—Iodide of methyl acts readily upon conia, producing a syrupy or crystalline substance, which is a mixture

of hydriodate of methyl-conia and iodide of dimethyl-conium—the former produced from the normal conia, and the latter from the methyl-conia. If the conia be free from water, this action is very rapid, and as heat is developed it is necessary that the vessel should be kept cool; if the conia contain water, the chemical change is very slowly effected. Caustic potash is added to the mixture, and it decomposes the hydriodate of methyl-conia, setting the base free as an oil, while it leaves the iodide of dimethyl-conium unacted upon. The methyl-conia was converted, after separation, into a hydrochlorate, which is extremely deliquescent, and has a brownish, semicrystalline appearance.

We found that this substance possesses a poisonous (lethal) activity, considerably greater than that of Mr MORSON's conia, but nearly equal to that of Dr CHRISTISON's conia; for two-tenths of a grain, exhibited by subcutaneous injection, speedily caused death in a rabbit, and a dose, equivalent to the $\frac{1}{4560}$th of the weight of the animal, is about the minimum fatal dose for a frog. The general character of the symptoms is likewise similar to that of Dr CHRISTISON's conia, and, therefore, to that also of Mr MORSON's; but the causation of these symptoms rather resembles that of the latter than of the former conia. Paralysis is the main symptom; and a careful examination, by experiments on frogs, of the mechanism by which this symptom is produced, showed that it is a result of actions on the motor nerves and spinal cord, and that with large doses the former action is completed before the latter, while with small doses the latter action is completed before the former.

We shall, in the first place, describe the symptoms that appeared in a rabbit, after the administration of a fatal dose.

EXPERIMENT LXXXI.—Two-tenths of a grain of hydrochlorate of methyl-conia was dissolved in twenty-five minims of distilled water, and injected under the skin at the right flank of a healthy rabbit, weighing two pounds and ten ounces and-a-half. The rabbit moved about in a normal manner until four minutes after the injection, when the movements became constrained, and it was observed that this was owing to stiff extension of the four limbs. A slight touch of the animal caused a series of rapid tremors, during which, as well as at other times, the body was elevated on the stiffly extended limbs. This somewhat remarkable condition continued without change until ten minutes, when the stiffness of the posterior extremities disappeared; but, in place of assuming a normally flexed position, these extremities became flaccidly abducted; and, when the animal moved about, they trailed behind it in a somewhat powerless manner. In eighteen minutes, the symptoms of exaggerated reflex activity, and the spasmodic extension of the anterior extremities had disappeared; and, now, there was so great a degree of general paralysis present, that the rabbit was unable to move about, and it lay quietly on the abdomen and chest. In nineteen minutes, the neck muscles could no longer continuously support the head, which, soon after, rested on the table. In twenty

minutes, the respiratory movements were laboured, and they occurred only twenty-four times in the minute. The rabbit now lay on the side, quite flaccid and powerless; and, at times, a series of slight tremors occurred. The respirations gradually became weaker and less frequent, the common sensibility disappeared, and death occurred, twenty-two minutes after the administration.

Three minutes after death, the exposed heart was contracting in normal rhythm, at the rate of seventy-four beats in the minute; and it was ascertained that the conductivity of the afferent and efferent nerve fibres of the sciatic nerves, the reflex function of the spinal cord, and the contractility of the striped muscles were still retained.

This description is sufficient to show that in rabbits hydrochlorate of methyl-conia produces very similar effects to hydrochlorate of conia. That this similarity also occurs in frogs will be seen from the following experiment.

EXPERIMENT LXXXVI.—A solution containing six-hundredths of a grain of hydrochlorate of methyl-conia, in five minims of distilled water, was injected under the skin at the right flank of a frog, weighing 185 grains. In ten minutes, a slight degree of stiffness, with rigid elevation of the fingers, was present in the anterior extremities, but the frog still jumped about actively. Gradually the movements became less energetic; some sprawling occurred; and, soon, the frog lay on the abdomen and chest, quite unable to jump or move about. In twenty minutes, the power of voluntary movement was completely lost, and irritation of the skin caused but feeble reflex twitches in both posterior extremities. The frog remained in this state until forty-seven minutes after the administration; but in fifty minutes, the most severe stimulation of the skin was unable to excite any reflex movement whatever. The right sciatic nerve was now exposed and galvanised; twitches were thereby excited in the right toes, but these were unaccompanied by any movement in the left posterior extremity or elsewhere. At this time the cardiac impulse was of fair strength, and the contractions of the heart were occurring at the rate of forty in the minute.

On the morning of the following day, the frog was dead and in rigor.

These symptoms agree closely in their general character with those described after corresponding doses of hydrochlorate of Dr CHRISTISON's conia (Experiment LXI.), and of Mr MORSON's conia (Experiment LXXVI.); but the slight spasmodic symptoms that appeared in the anterior extremities were not invariably observed in our other experiments with this substance. Paralysis is shown to be the predominant symptom, and the causation of this paralysis, after the small fatal dose exhibited in this experiment, appears to be due to an abolition of the reflex function of the spinal cord, rather than to a suspension of the conductivity of motor nerves. The action of hydrochlorate of methyl-conia, therefore, apparently resembles that of hydrochlorate of MORSON's conia; and we shall see from the following experiments that the special variations pointed out as occurring with

different doses of conia obtained from that chemist, occur also with different doses of hydrochlorate of methyl-conia.

EXPERIMENT LXXXVIII.—Immediately after ligaturing the blood-vessels at the upper part of the right thigh in a frog, weighing 140 grains, we injected a solution, containing one-tenth of a grain of hydrochlorate of methyl-conia, under the skin at the left flank. In thirteen minutes, the frog was flaccid, and no voluntary movements occurred in the poisoned region; but vigorous movements, consisting of extreme and somewhat spasmodic extensions, occurred at frequent intervals in the right (non-poisoned) posterior extremity. Irritation of the skin in the poisoned region now caused merely feeble twitches in the left (poisoned) posterior extremity, and energetic movements in the right posterior. In fifty minutes, however, no reflex movement could be excited anywhere by irritation of the skin. The left sciatic nerve was exposed and subjected to galvanic stimulation, with the result that, while well-marked movements occurred in the left posterior extremity, no movement occurred in the right (non-poisoned). It was at the same time ascertained that the motor conductivity of the right sciatic nerve was not appreciably impaired, even in that part of the trunk exposed to the direct action of the poison; that the poisoned muscles retained their contractility; and that the heart was contracting, in normal rhythm, at the rate of twenty beats per minute. Several observations were made during the succeeding fifty minutes, but no change had occurred during this time, with the exception of a slight diminution in the rate of the heart's contractions.

On the following morning, the frog was dead.

EXPERIMENT XCI.—The blood-vessels were tied at the lowest third of the right thigh of a frog, weighing 200 grains, and two-tenths of a grain of hydrochlorate of methyl-conia, dissolved in four minims of distilled water, was then injected under the skin at the left flank. The first symptom that was observed occurred in three minutes, and consisted of a stiff extension of the anterior extremities, causing unnatural elevation of the thorax. After a few seconds, this symptom was modified to the extent that the anterior extremities became rigidly incurved, with the fore-paws in contact with each other. Vigorous jumping movements were still attempted, but as the anterior extremities took no part in these, they were very imperfect, and frequently resulted in the frog falling on one side. In ten minutes, this spasmodic condition of the anterior extremities disappeared, and now the frog lay flaccid on the lower jaw, chest, and abdomen. The power of voluntary movement seemed to be suspended in the poisoned region, but it was retained in the non-poisoned (right posterior extremity), where vigorous and somewhat spasmodic movements of extreme extension frequently occurred. In thirty-three minutes, irritation of the skin caused energetic reflex movements in the right posterior extremity, but no movement in any part of the poisoned region. In thirty-four minutes, the left sciatic nerve was exposed, and

it was found that its motor conductivity was completely suspended—galvanism of its trunk causing no contractions in the left posterior extremity; while its sensory conductivity was retained—galvanism causing energetic reflex movements in the right (non-poisoned) posterior extremity. The heart was now contracting twenty-four times in the minute; and the contractility of the striped muscles was apparently unimpaired. It was possible to excite reflex movements in the right posterior extremity by stimulating the skin of the poisoned region, until one hour and forty minutes after the administration. Very soon after this time, the activity of the reflex function was completely suspended. Irritation of the skin in the poisoned and non-poisoned regions, as well as galvanic stimulation of the poisoned (left) sciatic nerve, caused no movement, notwithstanding that the non-poisoned (right) sciatic nerve and muscles, and even the trunk of the right sciatic nerve above the position of the ligatures, retained their functional activity.

These two experiments are selected from nine which were made on frogs with different relative doses, and in which distinct evidence was obtained of the primary cause of the paralysis. The conductivity of the motor nerves was suspended before the reflex function was abolished in experiments in which doses were administered, equivalent to the $\frac{1}{350}$th, the $\frac{1}{875}$th, the $\frac{1}{960}$th, the $\frac{1}{1000}$th, and the $\frac{1}{1100}$th of the weight of the frog employed; while the activity of the reflex function was abolished before the motor nerves were paralysed in experiments in which doses were administered, equivalent to the $\frac{1}{1335}$th, the $\frac{1}{1400}$th, the $\frac{1}{1950}$th, and the $\frac{1}{3083}$d of the weight of the frog.

The details we have narrated of Experiments LXXXVIII. and XCI. demonstrate that paralysis of the motor nerves is due to an action on their peripheral terminations; as well when this paralysis precedes the abolition of the reflex function, as when it occurs subsequently thereto. It would appear that the abolition of the reflex function depends, at least in part, on an action on the spinal cord; for these experiments show that, after its occurrence, irritation of the skin of a region protected from the direct action of the poison, or galvanic stimulation of the trunk of a mixed nerve likewise protected from the direct action of the poison, does not cause any reflex movement, notwithstanding that the motor nerves and muscles everywhere retain their functional activity.

We have accordingly shown that conia and methyl-conia produce very similar symptoms; the more prominent of which are spasms and paralysis.

Our analysis of the mode in which the paralysis is produced, has resulted in proving its dependence on an action on the motor nerves and on the spinal cord. The rate at which each of these actions is produced by the substances examined (estimating this by the time of completion) varies in a remarkable, and, at first sight, perplexing manner. In the case of the conia prepared by Dr CHRISTISON, the former of these actions is the more powerful; while in that prepared by Mr MORSON, and in methyl-conia, the two are nearly equally prominent. In a series

of experiments on frogs with varying doses, it was found that Dr CHRISTISON'S conia invariably produced complete paralysis of the motor nerves before that of the reflex function of the spinal cord; that Mr MORSON'S conia usually produced complete paralysis of the motor nerves before that of the reflex function of the spinal cord in those experiments of the series where the dose was small, and complete paralysis of the reflex function of the spinal cord before that of the motor nerves where the dose was large; and that methyl-conia produced complete paralysis of the reflex function of the spinal cord before that of the motor nerves in those experiments where the dose was small, and complete paralysis of the motor nerves before that of the reflex function of the spinal cord where the dose was large.

As already mentioned, our chemical examination of the two specimens of conia proved that that of Dr CHRISTISON contains a much smaller proportion of methyl-conia than that of Mr MORSON. Our physiological examination has confirmed this result; for the action of the latter specimen of conia more closely resembles that of methyl-conia than the former. In other words, the conia containing the smallest proportion of methyl-conia acts most purely as a paralyser of motor nerves. It seems a legitimate deduction from this, that conia altogether free from methyl-conia (*i.e.*, *normal* conia) will be free also from all spinal action, and will, accordingly, produce paralysis solely by influencing the motor nerves.*

Our experiments have shown that the lethal activity of Dr CHRISTISON'S conia is considerably greater than that of Mr MORSON'S. The comparatively feeble potency of the latter cannot be explained by its containing a large proportion of methyl-conia, for the activity of this substance is about the same as that of Dr CHRISTISON'S conia; it may be due to the presence of ammonia.

Iodide of dimethyl-conium.—When a moderately dilute solution of caustic potash is added to the mixture of iodide of dimethyl-conium and hydriodate of methyl-conia, the latter salt, as stated above, is decomposed, while the former remains in solution, and may be purified by crystallisation from strong aqueous, caustic potash. It is tolerably soluble in hot solutions of caustic potash, but on cooling the solution, it separates in the form of colourless silky needles. It is readily soluble in water, and its composition may be represented by the formula, $C_8H_{14}(CH_3)NCH_3I$.

In various experiments, we have administered to rabbits, by subcutaneous injection, doses of half-a-grain, two grains, two grains and-a-half, three, four, and five grains. No obvious effects were produced by half-a-grain, or by two grains; slight temporary paralysis was produced by two grains and-a-half, and death by three, four, and five grains respectively. It is, therefore, obvious that the

* We have not as yet succeeded in obtaining a pure specimen of *normal conia;* and the quantities of ordinary conia at our disposal have not been sufficient to enable us to attempt a separation of normal conia from methyl-conia.

lethal activity of iodide of dimethyl-conium is greatly less than that of either conia or methyl-conia. That the character of the symptoms it produces is also different, will be seen from the following experiment.

EXPERIMENT XCVIII.—Having dissolved three grains of iodide of dimethyl-conium in forty minims of distilled water, we injected the solution under the skin of a rabbit, weighing four pounds. The animal remained sitting quietly for more than half an hour, during which time no symptom was observed. In thirty-two minutes, however, it became restless, and faint tremors occurred. Soon, it had difficulty in moving about; and after some endeavours to maintain a sitting posture, it lay down on the abdomen and chest. In forty-one minutes, the head rested on the table; and at this time the respirations were shallow, and at the increased rate of 144 in the minute. The rabbit remained quietly in this position until one hour and four minutes, when it succeeded, after some efforts, in rising on its limbs, but, being unable to support itself thus, it again lay down on the abdomen and chest, with the head resting on the table. The respirations were now eighty-four in the minute. In one hour and eleven minutes, slight tremors again occurred, and then the rabbit became perfectly flaccid, and the respirations infrequent and laboured. In one hour and twelve minutes, the respirations were mere gasps, occurring at the rate of about twelve in the minute; and soon after they became so shallow as to be hardly visible. In one hour and fifteen minutes, a few twitches occurred in the muscles of the face, and in a few seconds the rabbit was dead.

In the autopsy, the motor nerves and muscles were found active, twelve minutes after death; but at this time the exposed heart was found to be contracting irregularly and feebly.

In this experiment, we frequently tested the reflex excitability, but never observed the slightest evidence of its being increased.

We shall now briefly describe the experiment in which we administered five grains.

EXPERIMENT C.—A solution, containing five grains of iodide of dimethyl-conium, in fifty minims of distilled water, was injected under the skin of a rabbit, which weighed three pounds and six ounces and-a-half. As in the previous experiment, the first effects observed were a number of restless, uneasy movements, which occurred in eleven minutes. Soon afterwards, paralytic symptoms appeared; and in twenty minutes, these had so far advanced that the rabbit lay flaccid on the abdomen, chest, and lower jaw, while irritation of the skin was followed by extremely feeble movements of the head, or one or other of the extremities. In twenty-four minutes, the head fell over on the side, and rested thus on the table; and the respirations were infrequent, shallow, and laboured. After this, the respirations became greatly more infrequent and laboured, until they altogether ceased, thirty-one minutes after the injection of the poison.

In this experiment, likewise, we failed in discovering the slightest evidence of exaggeration in the reflex excitability, or any spasmodic symptom.

These descriptions are sufficient to show that iodide of dimethyl-conium acts simply as a paralysing agent, and that it does not produce any spasmodic effects in rabbits.

The general symptoms that appear in frogs after the administration of a fatal dose are illustrated in the following experiment.

EXPERIMENT CVII.—Having dissolved one-tenth of a grain of iodide of dimethyl-conium in four minims of distilled water, we injected the solution under the skin at the right flank of a frog, weighing 150 grains. In two minutes and thirty seconds, a slight degree of paralysis was observed in the anterior extremities, which were scarcely able to support the chest; and the jumping movements were now less active than before. Quickly, the paralysis became more decided; until at six minutes, the frog was lying on the abdomen and the lower jaw. The respiratory movements of the chest had now ceased, while those of the throat continued for several minutes longer. In nine minutes, irritation of the skin produced merely feeble movements in the posterior extremities; and in thirty minutes, it was impossible to excite any reflex movement whatever, even by severe irritation of the skin. The right sciatic nerve was now exposed in the thigh, and stimulated by an interrupted galvanic current, but no muscular contractions were thereby produced, although the muscles contracted actively when the electrodes were directly applied to their surfaces. At this time, the heart's impulse was of fair strength, and the beats occurred twenty-two times in the minute.

On the following day, the frog was found to be in the condition last noted; but on the third day, the contractility of the muscles had disappeared, and the heart's contractions had ceased.

In many other experiments on frogs, the same general phenomena were observed. The spasmodic symptoms to which we have drawn attention in our description of the effects of conia and of methyl-conia were entirely absent in our experiments with iodide of dimethyl-conium; and, accordingly, the symptoms we observed were those of paralysis only. We made several experiments to determine what structures are influenced in the production of this paralysis.

EXPERIMENT CVIII.—Immediately after ligaturing the blood-vessels at the upper part of the right thigh of a frog, weighing 192 grains, we injected three-twentieths of a grain of iodide of dimethyl-conium, dissolved in four minims of distilled water, under the skin of the left flank. In one minute thereafter, the movements of the frog had become somewhat feeble, the poisoned extremities being obviously weakened. In two minutes and thirty seconds, the frog lay on the abdomen and lower jaw, apparently unable to execute any voluntary movements with any part of the body except the right (non-poisoned) posterior

extremity, and there were no respiratory movements whatever. In nine minutes, stimulation of the skin in any region was followed by energetic reflex movements in the right posterior extremity, but no movements occurred in the poisoned region. In fourteen minutes, the left sciatic nerve was stimulated by an interrupted galvanic current, and, although active reflex movements of the right (non-poisoned) posterior extremity were thereby excited, no movement occurred in the left (poisoned) posterior extremity, or in any other part of the poisoned region. The heart's impulse was, at this time, found to be of fair strength, and occurring forty-two times in the minute; and the muscles contracted vigorously on direct stimulation. In three hours, the condition of the frog was the same as last noted, excepting that the rate of the heart's contractions had diminished to thirty-eight in the minute. The observations were now interrupted until the following morning, when the frog was found dead and in rigor.

In many other similar experiments with different doses of this substance, the symptoms and mode of action were exactly the same as in the last experiment. They show that the paralysis produced by dimethyl-conium is dependent on an action on the motor nerves, primarily restricted to the peripheral terminations. Even after the administration of a fatal dose, we have never observed any action on the spinal cord, beyond its necessary implication in the progress towards death. On the other hand, in experiments where doses below the minimum fatal, and therefore considerably smaller than in Experiments CVII. and CVIII., were given, the condition of complete paralysis of the peripheral terminations of the motor nerves existed along with retained functional activity of the spinal cord and sensory nerves, for periods protracted over many hours. Thus, in an experiment where the dose was equivalent to the $\frac{1}{2300}$th of the frog's weight (Experiment CIII.), the poisoned motor nerves remained completely paralysed for more than twenty-six hours, while, during this time, the poisoned sensory nerves and the spinal cord retained their functional activity.

We conclude from our experiments, that in physiological action iodide of dimethyl-conium differs from conia and methyl-conia in being entirely free from spasmodic and spinal-paralysing actions.

It is shown in the following Table of minimum fatal doses, that iodide of dimethyl-conium is much less active than either conia or methyl-conia:—

No. of Experiment.	Substance Employed.	Animal and its Weight.	Dose, by subcutaneous injection.	Relation of Dose to Weight of Animal.	Effect.
LIII.	Hydrochlorate of Dr CHRISTISON's conia.	Rabbit, 3 lbs. 14¼ oz.	0·1 gr.	$\frac{1}{272\frac{1}{2}70}$th.	Slight degree of stiffness in the limbs, followed by recovery.
LIV.	Do.	Do., 3 lbs. 6½ oz.	0·2 gr.	$\frac{1}{115\frac{1}{2}80}$th.	Death, in 32 minutes.
LXVI.	Hydrochlorate of Mr MORSON's conia.	Do., 2 lbs. 12 oz.	0·2 gr.	$\frac{1}{86\frac{1}{2}50}$th.	None.
LXVIII.	Do.	Do., 4 lbs. 1 oz.	1 gr.	$\frac{1}{32\frac{1}{2}75}$th.	Death, in 33 minutes.
LXXX.	Hydrochlorate of methyl-conia.	Do., 3 lbs. 14¼ oz.	0·1 gr.	$\frac{1}{272\frac{1}{2}70}$th.	None.
LXXXI.	Do.	Do., 2 lbs. 10½ oz.	0·2 gr.	$\frac{1}{82\frac{1}{2}60}$th.	Death, in 22 minutes.
XCVII.	Iodide of dimethyl-conium.	Do., 3 lbs. 6½ oz.	2·5 grs.	$\frac{1}{85\frac{1}{2}4}$th.	Slight paralysis, followed by recovery.
XCVIII.	Do.	Do., 4 lbs.	3 grs.	$\frac{1}{88\frac{1}{2}3}$d.	Death, in 1 hour and 15 minutes.

[This investigation into the physiological action of atropia and its methyl and ethyl derivatives, and of conia and its methyl derivatives, was commenced in July 1867; but, after performing a number of experiments, we considered it advisable to postpone the further examination of these substances until we had finished that portion of our researches which is published in Vol. XXV. Part 1 of the "Transactions." Although an abstract was read before the Society on the 18th of January 1869, this paper was not delivered to the Secretary for publication until the month of October.]

The subjoined Tabular Summary contains the leading facts of all the Experiments included in the present part of this investigation.

TABULAR SUMMARY OF EXPERIMENTS.

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
I.	Iodide of methyl-atropium.	Dog, 8 lbs. 6 oz.	Subcutaneously.	10 grs.	Death, preceded by paralysis, &c.*	6 minutes.	26 minutes.	Same dog as survived 10 grs. of sulphate of atropia (Experiment XXII.)
II.	Do.	Rabbit, 2 lbs. 5 oz.	Do.	0·05 gr.	Paralysis of the vagi nerves, followed by recovery.			
III.	Do.	Do., 2 lbs. 7 oz.	Do.	0·1 gr.	Do. do.			
IV.	Do.	Do., 3 lbs. 9 oz.	By injection into a facial vein.	0·5 gr.	Paralysis, followed by recovery.			
V.	Do.	Do., 3 lbs. 10 oz.	Subcutaneously.	2 grs.	Slight tremors and paralysis, followed by recovery.	8 minutes.	1 hour and 20 minutes.	
VI.	Do.	Do., 3 lbs. 9 oz.	By injection into a facial vein.	2 grs.	Paralysis and slight tremors, followed by recovery.	2 minutes.	About 29 min.	Same rabbit as in Experiment IV.
VII.	Do.	Do., 3 lbs. 13½ oz.	Subcutaneously.	2·5 grs.	Paralysis and fibrillary twitches, followed by recovery.	16 minutes.	More than 1 hour and 50 minutes.	
VIII.	Do.	Do., 3 lbs. 10 oz.	Do.	3 grs.	Death, preceded by paralysis.	6 minutes.	52 minutes.	Same rabbit as in Experiment V.
IX.	Do.	Do., 4 lbs. 13 oz.	Do.	4 grs.	Death, preceded by paralysis and slight tremors.	10 minutes.	44 minutes.	
X.	Do.	Do., 4 lbs. 2 oz.	Do.	8 grs.	Death, preceded by paralysis and fibrillary twitches.	3 minutes.	6 minutes.	
XI.	Do.	Frog, 392 grs.	Do.	0·005 gr.	Incomplete general paralysis, followed by recovery.	3 minutes.	About 1 hour and 20 min.	
XII.	Do.	Do., 465 grs.	Do.	0·01 gr.	Complete paralysis of motor nerves, followed by recovery.	1 minute.	More than 3 hours.	
XIII.	Do.	Do., 455 grs.	Do.	0·025 gr.	Complete paralysis of motor nerves, followed by recovery.	Less than 4 minutes.	More than 6 hours and less than 18.	
XIV.	Do.	Do., 482 grs.	Do.	0·05 gr.	Complete paralysis of motor nerves, followed by recovery.	1 minute.	More than 26 hours and less than 40.	

* Dilatation of the pupils was observed in all the experiments on mammals with atropia and its methyl and ethyl derivatives.

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
XV.	Iodide of methyl-atropium.	Frog, 422 grs.	Subcutaneously.	0·1 gr.	Complete paralysis of poisoned motor nerves, followed by recovery.	Less than 2 minutes.	More than 72 hours and less than 94.	Vessels of the right posterior extremity were ligatured.
XVI.	Do.	Do., 204 grs.	Do.	0·1 gr.	Death, preceded by complete paralysis of motor nerves.	Less than 2 minutes.	About 6 days.	Interval of regained motility before death.
XVII.	Do.	Do., 300 grs.	Do.	0·15 gr.	Death, preceded by complete paralysis of the poisoned motor nerves.	Less than 3 minutes.	About 3 days.	Do., vessels of the left posterior extremity were ligatured.
XVIII.	Do.	Do., 300 grs.	Do.	0·2 gr.	Death, preceded by complete paralysis of the poisoned motor nerves.	Not noted.	Not noted.	Vessels of the right gastrocnemius muscle were ligatured.
XIX.	Do.	Do., 260 grs.	Do.	0·3 gr.	Death, preceded by complete paralysis of motor nerves.	About 2 min.	About 6 days.	
XX.	Do.	Do., 398 grs.	Do.	0·5 gr.	Death, preceded by complete paralysis of motor nerves.	Not noted.	About 2 days.	
XXI.	Do.	Do., 228 grs.	Do.	0·3 gr.	Death, preceded by complete paralysis of motor nerves.	Not noted.	About 2 days.	
XXII.	Sulphate of atropia.	Dog, 8 lbs. 6 oz.	Do.	10 grs.	Paralysis, spasms, and frequent tetanic convulsions, followed by recovery.	About 7 min.	More than 9 hours and less than 24.	Same dog as in Experiment I.
XXIII.	Do.	Rabbit, 2 lbs. 5 oz.	Do.	15 grs.	Diuresis, catharsis, and languor, followed by recovery.	About 15 min.	More than 3 hours and less than 9.	
XXIV.	Do.	Frog, 490 grs.	Do.	0·5 gr.	Paralysis and tetanic convulsions, followed by recovery.	Less than 15 minutes.	About 6 days.	
XXV.	Do.	Do., 215 grs.	Do.	0·25 gr.	Death, preceded by paralysis.	8 minutes.	Not noted.	Vessels of one posterior extremity were tied.
XXVI.	Iodide of methyl-atropium.	Rabbit, 4 lbs.	By stomach.	20 grs.	None (except on pupils).			
XXVII.	Do.	Do., 3 lbs. 12 oz.	Do.	30 grs.	None (except on pupils).			
XXVIII.	Sulphate of atropia.	Do. 3 lbs. 9½ oz.	Do.	30 grs.	None (except on pupils).			

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
XXIX.	Sulphate of methyl-atropium.	Rabbit, 3 lbs. 8 oz.	Subcutaneously.	0·5 gr.	Paralysis of the vagi nerves, &c., followed by recovery.	Less than 7 minutes.	Not noted.	
XXX.	Do.	Do., 3 lbs. 3 oz.	By injection into a facial vein.	0·5 gr.	Death.	Almost instantaneous.	Less than 5 minutes.	
XXXI.	Do.	Do. 4 lbs.	Subcutaneously.	1·5 gr.	Very slight paralytic symptoms, followed by recovery.	About 40 minutes.	Less than 15 minutes.	
XXXII.	Do.	Do., 3 lbs. 7½ oz.	Do.	2 grs.	Paralysis and slight tremors, followed by recovery.	About 7 minutes.	More than 23 minutes.	
XXXIII.	Do.	Do., 2 lbs. 7 oz.	Do.	2 grs.	Death, preceded by slight tremors and paralysis.	Not noted.	About 40 minutes.	Same rabbit as in Experiment III. The 2d experiment was performed immediately after the 1st.
XXXIV.	Do.	Do., 3 lbs. ½ oz.	Do.	2·5 grs.	Death, preceded by slight tremors and paralysis.	2 minutes.	4 minutes.	
XXXV.	Do.	Do., 3 lbs. 8 oz.	Do.	3 grs.	Death, preceded by slight tremors and paralysis.	Less than 3 minutes.	5 minutes.	
XXXVI.	Do.	Frog, 230 grs.	Do.	0·01 gr.	Incomplete paralysis, followed by recovery.	About 6 minutes.	About 2 hours.	
XXXVII.	Do.	Do., 407 grs.	Do.	0·05 gr.	Partial general paralysis, and complete paralysis of the motor nerves, followed by recovery.	About 4 minutes.	4 days.	
XXXVIII.	Do.	Do., 379 grs.	Do.	0·05 gr.	Incomplete general paralysis, complete paralysis of the poisoned motor nerves, followed by recovery.	1 minute.	More than 3 hours and less than 20.	Vessels of the right posterior extremity were ligatured.
XXXIX.	Do.	Do., 270 grs.	Do.	0·05 gr.	Incomplete general paralysis, complete paralysis of the motor nerves, followed by recovery.	About 3 minutes.	More than 3 hours and less than 23.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
XL.	Sulphate of methyl-atropium.	Frog, 460 grs.	Subcutaneously.	0·1 gr.	Death, preceded by incomplete general paralysis and complete paralysis of the motor nerves.	Less than 2 minutes.	About 6 days.	
XLI.	Do.	Do., 320 grs.	Do.	0·1 gr.	Death, preceded by incomplete general paralysis and complete paralysis of the poisoned motor nerves.	Less than 2 minutes.	About 5 days	Vessels of the right posterior extremity were ligatured.
XLII.	Do.	Do., 312 grs.	Do.	0·1 gr.	Death, preceded by incomplete general paralysis, followed by complete paralysis of the poisoned motor nerves.	Not noted.	Not noted.	Vessels of the right gastrocnemius muscle were ligatured.
XLIII.	Do.	Do., 235 grs.	Do.	0·1 gr.	Death, preceded by incomplete general paralysis, followed by complete paralysis of the poisoned motor nerves.	Less than 2 minutes.	About 3 days.	Vessels of the right posterior extremity were ligatured.
XLIV.	Do.	Do., 461 grs.	Do.	0·4 gr.	Death, preceded by incomplete general paralysis, followed by complete paralysis of the motor nerves.	About 1 minute.	About 2 days.	
XLV.	Do.	Rabbit, 3 lbs. 2 oz.	By stomach.	20 grs.	None (except on pupils).			
XLVI.	Iodide of ethyl-atropium.	Do., 2 lbs. 4 oz.	Subcutaneously.	0·1 gr.	Paralysis of the inhibitory cardiac branches of the vagi nerves, followed by recovery.	Less than 8 minutes.	Not noted.	
XLVII.	Do.	Do., 3 lbs. 8½ oz.	Do.	2 grs.	Death, preceded by slight tremors and paralysis.	About 8 minutes.	21 minutes.	
XLVIII.	Do.	Do., 3 lbs. 7 oz.	Do.	2 grs.	Death, preceded by slight tremors and paralysis.	6 minutes.	18 minutes.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
XLIX.	Iodide of ethyl-*atropium*.	Frog, 321 grs.	Subcutaneously.	0·05 gr.	Complete paralysis of the motor nerves, followed by recovery.	Not noted.	Less than 20 hours.	
L.	Do.	Do., 450 grs.	Do.	0·2 gr.	Death, preceded by complete paralysis of the poisoned motor nerves.	Not noted.	Not noted.	Vessels of the left gastrocnemius muscle were ligatured.
LI.	Do.	Do., 301 grs.	Do.	0·15 gr.	Death, preceded by incomplete general paralysis, followed by complete paralysis of the poisoned motor nerves.	Less than 2 minutes.	More than 30 hours and less than 44.	Vessels of the right posterior extremity were ligatured.
LII.	Do.	Do., 290 grs.	Do.	0·15 gr.	Death, preceded by incomplete general paralysis, followed by complete paralysis of the motor nerves.	2 minutes.	About 3 days.	
LIII.	Hydrochlorate of Dr CHRISTISON's conia.	Rabbit, 3 lbs. 14¼ oz.	Do.	0·1 gr.	Faint degree of stiffness in the animal's movements, followed by recovery.	10 minutes.	20 minutes.	
LIV.	Do.	Do., 3 lbs. 6½ oz.	Do.	0·2 gr.	Death, preceded by stiffness, exaggeration of reflex function, spasms, and paralysis.	2 minutes and 30 seconds.	29 minutes and 30 seconds.	
LV.	Do.	Do., 3 lbs. 6½ oz.	Do.	0·25 gr.	Death, preceded by exaggeration of the reflex function, spasms, and paralysis.	Less than 6 minutes.	15 minutes.	
LVI.	Do.	Do., 3 lbs. 3 oz.	Do.	0·5 gr.	Death, preceded by stiffness in the four limbs, exaggeration of the reflex function, spasms, and paralysis.	1 minute.	9 minutes.	
LVII.	Do.	Do., 3 lbs. 3½ oz.	Do.	1 gr.	Death, preceded by paralysis and spasms.	Less than 30 seconds.	4 minutes.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
LVIII.	Hydrochlorate of Dr CHRISTISON'S conia.	Frog, 220 grs.	Subcutaneously.	0·05 gr.	Death, preceded by paralysis.	Not noted.	Several days.	
LIX.	Do.	Do., 364 grs.	Do.	0·1 gr.	Death, preceded by stiffness of the fingers, paralysis, and spasmodic movements of the posterior extremities.	About 7 minutes.	Several days.	
LX.	Do.	Do., 180 grs.	Do.	0·05 gr.	Stiffness of the anterior extremities, and general paralysis, followed by recovery.	5 minutes.	3 days.	
LXI.	Do.	Do., 300 grs.	Do.	0·1 gr.	Death, preceded by tonic spasm in the anterior extremities, incomplete general paralysis, spasmodic movements of the posterior extremities, and complete paralysis of the motor nerves.	5 minutes.	Less than 2 days.	
LXII.	Do.	Do., 220 grs.	Do.	0·1 gr.	Death, preceded by incomplete general paralysis, followed by complete paralysis of the poisoned motor nerves.	5 minutes.	Less than 3 days.	Vessels of the right posterior extremity were ligatured.
LXIII.	Do.	Do., 202 grs.	Do.	0·1 gr.	Death, preceded by tonic spasm of the anterior extremities and paralysis.	2 minutes.	More than 3 hours and less than 20.	
LXIV.	Do.	Do., 170 grs.	Do.	0·2 gr.	Death, preceded by tonic spasm of the anterior extremities, incomplete general paralysis, spasmodic movements of the posterior extremities, and complete paralysis of the poisoned motor nerves.	Less than 4 minutes.	More than 2 hours and less than 19.	Vessels of the right posterior extremity were ligatured.

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
LXV.	Hydrochlorate of Dr CHRISTISON's conia.	Frog, 195 grs.	Subcutaneously.	0·6 gr.	Death, preceded by tonic spasm of the anterior extremities, incomplete general paralysis, and complete paralysis of the poisoned motor nerves.	2 minutes.	More than 3 hours and less than 20.	Vessels of the right posterior extremity were ligatured.
LXVI.	Hydrochlorate of Mr MORSON's conia.	Rabbit, 2 lbs. 12 oz.	Do.	0·2 gr.	None.			
LXVII.	Do.	Do., 3 lbs. 3¼ oz.	Do.	0·7 gr.	Spasms, exaggeration of the reflex activity, and partial paralysis, followed by recovery.	6 minutes.	About 40 minutes.	
LXVIII.	Do.	Do., 4 lbs. 1 oz.	Do.	1 gr.	Death, preceded by tremors, spasms, exaggeration of the reflex activity, and paralysis.	6 minutes.	27 minutes.	
LXIX.	Do.	Frog, 380 grs.	Do.	0·05 gr.	Slight paralysis, followed by recovery.	7 minutes.	About 3 hours.	
LXX.	Do.	Do., 218 grs.	Do.	0·05 gr.	Incomplete paralysis, followed by recovery.	6 minutes.	Several hours.	
LXXI.	Do.	Do., 112 grs.	Do.	0·1 gr.	Slight tonic spasm of anterior extremities, complete paralysis of the motor nerves and of the reflex function of the spinal cord.	3 minutes.	More than 24 hours.	Vessels of the right posterior extremity were ligatured.
LXXII.	Do.	Do., 200 grs.	Do.	0·2 gr.	Complete paralysis of the motor nerves and of the reflex function of the spinal cord.	4 minutes at least.	Not noted.	
LXXIII.	Do.	Do., 256 grs.	Do.	0·3 gr.	Death, preceded by tonic spasm and complete paralysis.	4 minutes.	More than 30 hours and less than 44.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symtoms.	Notes.
LXXIV.	Hydrochlorate of Mr Monson's conia.	Frog, 290 grs.	Subcutaneously.	0·36 gr.	Death, preceded by complete paralysis.	2 minutes.	More than 24 hours and less than 42.	Vessels of the right posterior extremity were ligatured.
LXXV.	Do.	Do., 110 grs.	Do.	0·2 gr.	Death, preceded by complete paralysis, &c.	2 minutes.	About 2 days.	Do.
LXXVI.	Do.	Do., 140 grs.	Do.	0·3 gr.	Death, preceded by tonic spasm and complete paralysis.	Less than 2 minutes.	More than 2 hours and less than 21.	
LXXVII.	Do.	Do., 110 grs.	Do.	0·3 gr.	Death, preceded by complete paralysis, &c.	About 1 minute.	Not noted.	Do.
LXXVIII.	Do.	Do., 110 grs.	Do.	0·3 gr.	Death, preceded by complete paralysis, &c.	2 minutes.	Not noted.	Do.
LXXIX.	Do.	Do., 115 grs.	Do.	0·4 gr.	Death, preceded by tonic spasm and complete paralysis.	2 minutes.	More than 4 hours and less than 20.	
LXXX.	Hydrochlorate of methyl-conia.	Rabbit, 3 lbs. 14¼ oz.	Do.	0·1 gr.	None.			
LXXXI.	Do.	Do., 2 lbs. 10½ oz.	Do.	0·2 gr.	Death, preceded by stiffness of the limbs, exaggeration of the reflex activity, paralysis and tremors.	4 minutes.	18 minutes.	
LXXXII.	Do.	Do., 3 lbs. 9 oz.	Do.	0·5 gr.	Death, preceded by spasms and paralysis.	5 minutes.	13 minutes.	
LXXXIII.	Do.	Do., 4 lbs. 1 oz.	Do.	1 gr.	Death, preceded by stiffness of the limbs, exaggeration of the reflex activity, paralysis, and spasms.	1 minute 30 seconds.	7 minutes.	
LXXXIV.	Do.	Frog, 249 grs.	Do.	0·05 gr.	Tonic spasm, incomplete and then complete paralysis, followed by recovery.	18 minutes.	More than 30 hours and less than 42.	
LXXXV.	Do.	Do., 228 grs.	Do.	0·05 gr.	Death, preceded by paralysis.	7 minutes.	About 2 days.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
LXXXVI.	Hydrochlorate of methyl-conia.	Frog, 185 grs.	Subcutaneously.	0·06 gr.	Death, preceded by tonic spasm and paralysis.	Less than 10 minutes.	More than 3 hours and less than 20.	
LXXXVII.	Do.	Do., 195 grs.	Do.	0·1 gr.	Death, preceded by paralysis.	Less than 7 minutes.	More than 4 hours and less than 23.	
LXXXVIII.	Do.	Do., 140 grs.	Do.	0·1 gr.	Death, preceded by clonic spasms (?) in the non-poisoned region, and by paralysis in the poisoned region.	Less than 7 minutes.	More than 2 hours and less than 22.	Vessels of the right posterior extremity were ligatured.
LXXXIX.	Do.	Do., 187 grs.	Do.	0·14 gr.	Death, preceded by paralysis in the poisoned region.	Less than 9 minutes.	More than 5 hours and less than 20.	Do.
XC.	Do.	Do., 165 grs.	Do.	0·15 gr.	Death, preceded by clonic spasms in the non-poisoned region, and by paralysis in the poisoned region.	5 minutes.	More than 2 hours and less than 24.	Do.
XCI.	Do.	Do., 200 grs.	Do.	0·2 gr.	Death, preceded by tonic and clonic (?) spasms, and by paralysis in the poisoned region.	3 minutes.	More than 3 hours and less than 19.	Do.
XCII.	Do.	Do., 192 grs.	Do.	0·2 gr.	Death, preceded by paralysis in the poisoned region.	2 minutes 30 seconds.	More than 2 hours and less than 22.	Do.
XCIII.	Do.	Do., 175 grs.	Do.	0·2 gr.	Death, preceded by clonic spasms in the non-poisoned region, and by paralysis in the poisoned region.	Less than 10 minutes.	More than 4 hours and less than 18.	Do.
XCIV.	Do.	Do., 210 grs.	Do.	0·6 gr.	Death, preceded by clonic spasms in the non-poisoned region, and by paralysis in the poisoned region.	3 minutes.	More than 3 hours and less than 16.	Do.

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
XCV.	Iodide of dimethyl-conium.	Rabbit, 3 lbs. 8 oz.	Subcutaneously.	0·5 gr.	None.			
XCVI.	Do.	Do., 4 lbs. 1½ oz.	Do.	2 grs.	None.			
XCVII.	Do.	Do., 3 lbs. 6½ oz.	Do.	2·5 grs.	Slight paralysis, followed by recovery.	29 minutes.	Less than 23 minutes.	
XCVIII.	Do.	Do., 4 lbs.	Do.	3 grs.	Death, preceded by general paralysis.	32 minutes.	43 minutes.	
XCIX.	Do.	Do., 4 lbs. 1½ oz.	Do.	4 grs.	Death, preceded by general paralysis.	11 minutes.	26 minutes.	
C.	Do.	Do.. 3 lbs. 6½ oz.	Do.	5 grs.	Death, preceded by general paralysis.	11 minutes.	20 minutes.	Same rabbit as in Experiment XCVII.; an interval of 24 hours elapsed between each experiment.
CI.	Do.	Frog, 235 grs.	Do.	0·05 gr.	Complete paralysis of the motor nerves, &c., followed by recovery.	3 minutes.	More than 24 hours and less than 41.	
CII.	Do.	Do., 210 grs.	Do.	0·05 gr.	Complete paralysis of the poisoned motor nerves, followed by recovery.	2 minutes.	More than 30 hours and less than 41.	Vessels of left posterior extremity were ligatured.
CIII.	Do.	Do., 230 grs.	Do.	0·1 gr.	Complete paralysis of the poisoned motor nerves, followed by recovery.	About 2 minutes.	More than 49 hours and less than 66.	Vessels of right posterior extremity were ligatured.
CIV.	Do.	Do., 225 grs.	Do.	0·1 gr.	Complete paralysis of the motor nerves, followed by recovery.	2 minutes.	About 5 days.	
CV.	Do.	Do., 190 grs.	Do.	0·1 gr.	Complete paralysis of the motor nerves, followed by recovery.	1 minute 30 seconds.	More than 26 hours and less than 40.	
CVI.	Do.	Do., 155 grs.	Do.	0·1 gr.	Death, preceded by complete paralysis.	3 minutes.	Several days.	
CVII.	Do.	Do., 150 grs.	Do.	0·1 gr.	Death, preceded by complete paralysis.	2 minutes 30 seconds.	More than 30 hours and less than 41.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

Number of Experiment.	Substance Employed.	Animal and its Weight.	Method of Exhibition.	Dose.	Effect.	Interval between administration and commencement of Symptoms.	Duration of Symptoms.	Notes.
CVIII.	Iodide of dimethyl-conium.	Frog, 192 grs.	Subcutaneously.	0·15 gr.	Death, preceded by complete paralysis.	1 minute.	More than 3 hours and less than 19.	Vessels of right posterior extremity were ligatured.
CIX.	Do.	Do., 127 grs.	Do.	0·1 gr.	Death, preceded by complete paralysis.	2 minutes.	More than 5 hours and less than 20.	Do.
CX.	Do.	Do., 140 grs.	Do.	0·2 gr.	Death, preceded by complete paralysis.	3 minutes.	Not noted.	

*** CXI.–CXVI. include the experiments illustrative of the topical action of sulphate of methyl-atropium on the iris.