V.—*On the Connection between Chemical Constitution and Physiological Action.* Part. I.—*On the Physiological Action of the Salts of the Ammonium Bases, derived from Strychnia, Brucia, Thebaia, Codeia, Morphia, and Nicotia.*

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There can be no reasonable doubt that a relation exists between the physiological action of a substance and its chemical composition and constitution, understanding by the latter term the mutual relations of the atoms in the substance. There are numerous indications of such a relation, and attempts have been made to express it formally in certain cases. Thus it has been long observed, that the salts of the same base have a common physiological action, and it has been pointed out by Mr Blake* that, with some exceptions, the salts of isomorphous bases have a similar action. A corresponding likeness in physiological action may be traced in salts having the same acid, but beyond these generalisations we are not aware that any approach has been made to the statement of a law connecting the physiological action of a substance with its chemical constitution.

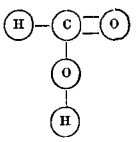
Some observers have endeavoured to connect physiological action with composition, looking for the cause of the peculiar action of substances in the presence or proportion of particular elements. It is a sufficient answer to this to point to isomeric or polymeric bodies—bodies having identically the same composition—which differ totally in action, such as acetic acid ($C_2H_4O_2$), and sugar ($C_6H_{12}O_6$); glycocoll ($C_2H_5NO_2$), and nitrite of ethyl ($C_2H_5NO_2$); or to instance kakodylic acid, which is inert, although perfectly soluble, and containing more than 54 per cent. of metallic arsenic.

Examples such as these clearly show that composition alone is quite insufficient to explain physiological action, and that constitution must also be taken into account in every attempt to connect the chemistry of substances with their action on the animal body.

The most direct way of making such an attempt would obviously be to compare physiological action and chemical constitution in a sufficiently large number of cases, and by classifying the results to deduce a law; but, unfortunately, the data which we possess are quite insufficient for this. We know, indeed, the "structure" of a considerable number of substances; that is, we know the *order*

* Proceedings of the Royal Society of London, vol. iv. Jan. 28, 1841, p. 285.

in which the atoms of these substances are related to each other, but something more than this is implied in the term *constitution*, as we have used it above. For this involves not only the "structure," or the arrangement of the equivalents in atoms and in mutually united pairs, but also what we may call the *potential* of each pair of united equivalents.* For instance, the structural formula of formic acid is



which indicates—1*st*, That the four carbon equivalents form one atom, the four oxygen equivalents two atoms, and the two hydrogen equivalents two atoms; 2*d*, that these equivalents are united in pairs, thus—*co*, *co*, *co*, *ch*, *ho*, but it does not in any way indicate (and we do not know) what is the *potential* of each of these pairs—that is, how much energy would be required to separate the equivalents from each other. We know that this potential depends upon the structure, and we can to a certain extent trace the nature of this dependence, but we cannot as yet express the potential numerically, or give a rule for finding its value from the structure, and till we can do this we do not fully know the constitution.

But even the structure of the majority of substances is not at all, or only very imperfectly known, and this is especially the case with those whose physiological action has been most fully investigated, such as the natural alkaloids.

Seeing, then, that we could not follow the direct road of induction, it occurred to us that a by-path might be found, by making use of a method resembling in its main features a mathematical *calculus of finite variations*. This method consists in performing upon a substance a chemical operation which shall introduce a known change into its constitution, and then examining and comparing the physiological action of the substance before and after the change. We may express this in mathematical language thus:—Let C represent the constitution of the original substance and Φ its physiological action. After the operation, C becomes $C + \Delta C$ and Φ, $\Phi + \Delta\Phi$. Here ΔC, Φ, and $\Phi + \Delta\Phi$ are known, and by applying the method to a sufficient number of substances, and by varying ΔC, we might hope to determine what function Φ is of C. The only reason why this method is not a strictly mathematical one is, that we cannot express our known terms ΔC, Φ, and $\Phi + \Delta\Phi$ with sufficient definiteness to make them the subjects of calculation. But although, on this account, we cannot obtain an accurate mathematical definition of f in the equation $\Phi = fC$, we may be able, in an approximate manner, to discover the nature of the relation.

In applying this method, we must select a chemical operation which satisfies

* More correctly, "the exhaustion of the potential energy" of each pair of united equivalents. See THOMSON and TAIT'S Treatise in Natural Philosophy, § 547.

the following conditions:—1*st*, That it is unambiguous; that is, that the change of structure produced by it is susceptible of only one interpretation. 2*d*, That the change of *structure* produced by the operation is, in all cases investigated, the same, and the change of *constitution* (ΔC)—that is, the change of structure and *potential*—as nearly as possible the same. 3*d*, That the operation is completely under our control, so that it cannot be either performed or reversed spontaneously, in ordinary circumstances, within the animal body. 4*th*, That the substance is equally suitable for absorption into the system before and after the change (that is, that Φ and $\Phi + \Delta\Phi$ are observed under similar conditions); and 5*th*, That a decided change of physiological action is, in some cases at least, produced (that is, that $\Delta\Phi$ is not always $= 0$).

Chemical operations may be divided into two classes—1*st*, operations of substitution; and 2*d*, operations of addition or subtraction. In the first, an atom or group of atoms is replaced by an *equivalent* atom or group of atoms, without any change taking place in the active atomicity of any atom or radical in the substance.

In the case of addition (and by subtraction we mean to express merely the inverse operation to addition), the active atomicity of one or more atoms or radicals in the compound is increased, and the bonds thus set free, or rendered active, are saturated by atoms or radicals (the sum of whose active atomicity is of course an even number), which are thus *added* to the substance. We shall apply the name *condensation* to capability of being added to in whatever way the addition takes place, and distinguish two kinds of condensation, *intra-atomic* and *inter-atomic;* in the first of which it is an atom, and in the second a compound radical, the active atomicity of which is increased. Thus, carbonic oxide, sulphide of methyl, and protochloride of tin, are examples of *intra-atomic* condensation; olefiant gas, the dibasic anhydrous acids, and allylic alcohol, of *inter-atomic* condensation; while hydrocyanic acid (if we assume for it the formula Ⓗ–Ⓝ≡Ⓒ) shows both.

Many operations of addition and also of substitution satisfy the 1st, 2d, 3d, and 4th of the five conditions mentioned above; but when we examine them in reference to the 5th condition, we find a marked difference. Operations of substitution (satisfying the 1st, 2d, 3d, and 4th conditions) do not appear greatly to change the physiological activity of a substance, except, 1st, where the activity depends on direct local action; or 2d, where the operation removes or introduces an atom or radical, the compounds of which are as a rule active. As examples of the first exception, we may take sulphuric acid (H_2SO_4) and caustic soda (HNaO), both poisonous; while sulphate of soda (Na_2SO_4) and water (H_2O) are not: as examples of the second, acetate of lead and cyanide of sodium, both poisonous, acetate of potash and chloride of sodium not. Besides the exceptions which can be reduced to the two classes just mentioned, there are several isolated

cases of change of activity produced by replacement, such as the singular inertness of ferrocyanide of potassium and of the analogous double cyanides, as compared with the activity of cyanide of potassium and its analogues.

On the other hand, operations of addition, particularly where the condensation diminished by the addition is intra-atomic, seem, in many cases, to produce very decided change both in the kind and in the degree of the physiological activity of the substance acted on. The following examples will illustrate this statement.

Some are cases of direct and some of indirect addition, and in all of them the change of structure produced is known, and there is in none of them much risk of fallacy arising from the change taking place spontaneously in the animal system. The first column contains the names and formulæ of the substances before addition, the second the atoms or groups added, and the third the names and formulæ of the substances produced.

I.	II.	III.
Carbonic oxide, CO	O	Carbonic acid, CO_2
Hydrocyanic acid, HCN	$2H_2 + HCl$	Hydrochlorate of methylamine, CNH_6Cl.
Arsenious acid, As_2O_3, $[HAsO_2]$	$(CH_3)_2$	Kakodylic acid, $AsC_2H_7O_2$ *
Strychnia, $C_{21}H_{22}N_2O_2$	$(CH_3(HO))$	Methyl-strychnia (hydrate), $C_{22}H_{26}N_2O_3$ †
Brucia, $C_{23}H_{26}N_2O_4$	$(CH_3(HO))$	Methyl-brucia (hydrate), $C_{24}H_{30}N_2O_5$ ‡

It will be observed that all the substances in the first column are highly poisonous, while those in the third column are either quite inert, or possess an action entirely different in kind from that of the bodies from which they are derived, and very much less in degree.

A consideration of the hitherto isolated facts collected in the above table leads not unnaturally to a suspicion that *condensation* (and in particular *intra-atomic condensation*) is in some way connected with physiological activity, as the first is, and the second appears to be, diminished or removed by chemical addition. This suspicion is strengthened when we observe that in a very large proportion of the cases as yet investigated saturated bodies (that is, bodies whose condensation is 0) are inert, or nearly so.

Kakodylic acid, as already mentioned, is a remarkable example of this, and the salts of tetrethyl-arsonium § seem to be equally inert. Similarly, the salts of tetramethyl-stibonium ‖ are not emetic. So that, as far as experiment goes, it would seem that the stable compounds of pentatomic arsenic and antimony have a very different and much less strongly marked action than the compounds in which these elements are contained as triads, or than those (such as arsenic acid)

* Bunsen, Annalen der Chemie and Pharmacie, vol. xlvi. p. 10 (1843).
† Stahlschmidt, Poggendorff's Annalen, vol. cviii. p. 523 (1859).
‡ Ibid. p. 541.
§ Landolt, Annalen der Chemie und Pharmacie, vol. lxxxix. p. 331 (1854).
‖ Ibid. vol. lxxxiv. p. 49 (1852).

in which, although present as pentads, they are easily reduced by subtraction to the state of triads.

In reference to this, we cannot avoid referring to a very remarkable passage in BUNSEN's admirable paper on kakodylic acid. After describing the experiments by which he proved the inert character of this acid, he says, "Gehen wir auf den Grund dieser unerwarteten Erscheinung zurück, so bietet sich dafür nur in der Annahme eine Erklärung dar, dass die Verbindungsweise des Arseniks im Kakodyl eine andere ist, als in seinen unorganischen Verbindungen. Indem es darin aufgehört hat, für sich einen Angriffspunkt der Verwandtschaft zu bilden, hat es zugleich seine Reaction auf den Organismus verloren." (Annalen, vol. xlvi. 1843, p. 11.) While it is plain that BUNSEN does not here refer to the different degree of saturation of the arsenic in arsenious and kakodylic acids, both because the whole theory of saturation is of a much later date, and because he makes no distinction between the mode of combination of the arsenic in those compounds in which kakodyl is monad and arsenic triad, and those in which kakodyl is triad and arsenic pentad, he points out in an exceedingly clear manner the striking coincidence of peculiar chemical constitution and peculiar physiological action in the case of kakodylic acid.

While, however, the cases mentioned incline us to believe that physiological activity is related to condensation, the occurrence of saturated substances, such as alcohol, corrosive sublimate, and oxalic acid, having a well marked poisonous action, and of condensed substances, such as benzoic acid and salicine, which are comparatively inert, shows that condensation is not the only condition of physiological activity. There can, at the same time, be little doubt that if the effect of condensation were discovered and eliminated, the other conditions might be much more hopefully sought for.

Under these circumstances, we turned our attention, in the first place, to the effect of chemical addition in altering the physiological action of the natural alkaloids. We were led to do so, partly by a consideration of the ease with which, by means of iodide of methyl, the nitrogen of nitrile bases can be rendered stably pentatomic, and partly by the hope, grounded on the observations of STAHLSCHMIDT in reference to the salts methyl-strychnium and methyl-brucium, that we should obtain marked changes of physiological action.

The great majority of natural alkaloids belong to the class of *nitrile bases*, that is, they contain one or more atoms of triatomic nitrogen directly united to carbon by three bonds. This nitrogen atom (or, in the case of poly-acid bases, atoms) can become pentatomic, as in the formation of salts; thus in the formation of hydrochlorate of morphia the nitrogen takes up H and Cl, thus becoming pentatomic, united by three bonds to carbon, by one to hydrogen, and by one to chlorine. But by this change it is not rendered permanently or stably

pentatomic; it easily loses the hydrogen and chlorine it has acquired, and returns to the triatomic state. The action of alkalies, or, in many cases, even of alkaline carbonates, is sufficient to effect this, and reprecipitate the alkaloid. It is obvious, therefore, that the chemical addition of an acid does not satisfy the third condition mentioned above, for it is certain that the addition can be performed in the stomach, which is acid, and very probable that it may be reversed in the blood and other alkaline fluids of the body. But if, instead of an acid, we make use of such a substance as iodide of methyl, we find that while the triatomic nitrogen takes up CH_3 and I, and becomes pentatomic (just as in the former case it took up H and Cl), it does not lose these newly-acquired atoms when the substance is treated with alkalies, but remains pentatomic even when subjected to attacks more violent than any to which it can be exposed in the animal system. This operation, the addition of iodide of methyl to nitrile bases, satisfies the first condition, for we know precisely what change of structure is produced. It satisfies the second, for the change of structure is the same in all nitrile bases; and the change of *potential*, as far as can be judged from a very rough estimate of the heat produced by the change, and from the general character of the substances produced, is not very different in different cases. It satisfies the third, as we have seen above; and as the iodides of the compound ammoniums thus formed from the alkaloids are all tolerably soluble in warm water, and can easily be transformed into other salts very readily soluble, it satisfies the fourth condition; and the observations of STAHLSCHMIDT show, and the sequel of this paper will further prove, that it satisfies the fifth.

It deserves to be noted that this operation only removes the condensation of the typical nitrogen (that is, of one atom of nitrogen for each molecule of a mono-basic acid that the alkaloid can saturate), and leaves any other condensation which may exist in the substance unaffected; so that even if physiological action should depend upon condensation, it would be unreasonable to expect $\Phi + \Delta\Phi$ to be in all cases zero, that is, that the new bodies should be quite inert.

In the present paper we communicate the results of the application of the method described to strychnia, brucia, thebaia, codeia, morphia, and nicotia. In each case we shall first describe the action of the alkaloid itself, then give the method of preparing the derived substances, and describe their physical characters, and, with some detail, their physiological action. Our investigation of the physiological action of these substances has been chiefly directed to the determination of their poisonous activity, and of the most prominent differences between the nature of their action and that of the alkaloids from which they are derived.

STRYCHNIA.

It is well known that strychnia acts on the living economy in a distinctly defined and characteristic manner, and that it is one of the most active of poisons. When administered subcutaneously, doses varying from one-twentieth to one-fiftieth of a grain rapidly produce in rabbits the most violent tetanic convulsions, and in a few minutes kill the animal. Few poisons have been more carefully studied, and it is now almost undoubtedly established that the phenomena produced by strychnia are due to a localisation of its action on the spinal cord.

Iodide of methyl-strychnium.—Strychnia ($C_{21}H_{22}N_2O_2$) is a mono-acid nitrile base, that is, it contains one atom of nitrogen united by three bonds to carbon; the structure of the radical or radicals $(C_{21}H_{22}NO_2)'''$ is unknown. How first demonstrated that strychnia is a nitrile base by subjecting it to the action of iodide of ethyl, and described, in a paper read before this Society,* the ethyl-strychnium and amyl-strychnium compounds. STAHLSCHMIDT subsequently prepared and described the compounds of methyl-strychnium.† We prepared the iodide of methyl-strychnium by STAHLSCHMIDT'S method. Strychnia, in fine powder, was treated, in a flask, with excess of pure iodide of methyl;‡ the flask was allowed to stand in the cold for some hours, then heated in the water-bath, the excess of iodide of methyl distilled off, and the iodide of methyl-strychnium dissolved in boiling water, filtered, and recrystallised.

Iodide of methyl-strychnium ($C_{21}H_{22}N_2O_2CH_3I$) crystallises in brilliant white scales, tastes distinctly bitter, though not so strongly or persistently so as strychnia, and when treated with strong sulphuric acid and peroxide of manganese, or bichromate of potash, it gives the colour reaction of strychnia, somewhat obscured by the presence of free iodine. It dissolves in 133 parts of water at 37° C., and in 385 parts of water at 9° C.

STAHLSCHMIDT has published a statement to the effect that the methyl-strychnium compounds are inert. As the sequel will show, we do not confirm this assertion; but it is proper to admit that our investigation arose principally from it.

We first examined the effects of this substance by subcutaneous administration. For this purpose, it was reduced to the form of very fine powder, suspended and dissolved in warm distilled water, and injected into a previously formed

* Transactions, vol. xxi. p. 32 (1854).

† POGGENDORFF'S Annalen, vol. cviii. p. 513 (1859).

‡ As iodide of methyl prepared directly from pyroxylic spirit is apt to become acid, it is advisable, if such impure iodide of methyl be used, to add a small quantity of an alkali (such as carbonate of potash), in order to prevent any of the strychnia being converted into a salt, and thus remaining unacted on by the iodide of methyl.

cavity in the subcutaneous cellular tissue. In this way, by a series of progressively increasing doses, it was found that as much as twelve grains could be given to a rabbit, weighing three pounds and four ounces, without any effect whatever. Fifteen grains, however, produced serious symptoms, though followed by recovery, and death was caused by the exhibition of twenty grains. Short abstracts of the majority of the experiments will be found in the table at the end of this paper; we shall, however, give some details of several experiments, in order to illustrate the mode of action.

EXPERIMENT VII.—Two very small incisions were made through the skin, one in either flank, of a rabbit, weighing three pounds and eight ounces; and by inserting an aneurism needle into these incisions, two cavities were formed in the cellular tissue. Into each of these we injected seven and a-half grains of iodide of methyl-strychnium (in all fifteen grains), suspended and dissolved in warm distilled water. No effect was caused until forty-five minutes, when the rabbit moved about uneasily, the limbs gradually yielded, and it soon lay on its chin and abdomen. When placed on the side, it remained quiet, without any efforts to recover a normal posture. Irritation did not cause any spasm nor give the slightest evidence of any increase in the reflex excitability. In one hour, when lifted by the ears, it hung in a perfectly flaccid and unresisting condition; the respirations were sixty-four per minute; and there were no voluntary movements. In one hour and thirteen minutes, a few spontaneous movements occurred in the limbs, but these, apparently, were merely feeble efforts to change its position. The external temperature appeared to be somewhat elevated, and the respirations were sixty-five per minute. In an hour and twenty-two minutes, a few twitches of the body, and especially of the abdominal muscles, occurred during the respiratory movements, which were now at the rate of sixty-six per minute; the eyelids did not contract when the conjunctiva or cornea was touched; but the animal was still conscious. In two hours, the condition was nearly the same as at last note, except that faint twitches of the eyelids could be excited by gentle irritation of their edges. In two hours and fifteen minutes, a number of very feeble spasmodic-like movements of the limbs occurred along with the twitches of the body, and these could also be excited by irritation. In two hours and thirty-five minutes, the condition of the rabbit had greatly improved. Efforts to rise were frequently made, in the intervals between which it lay perfectly quiet and flaccid, and the sensibility of the conjunctiva and cornea appeared to be normal.

The observations were now stopped until the following morning, when the rabbit was found jumping actively about, and apparently in a perfectly normal condition.

EXPERIMENT VIII.—We injected ten grains of iodide of methyl-strychnium, suspended and dissolved in warm distilled water, into each of two subcutaneous

cavities (twenty grains in all) of a rabbit, weighing three pounds and two and a-half ounces. Fifty minutes afterwards, the animal was lying flaccid, and exhibited the continuance of life only by slow and laboured respiratory movements. In one hour, tremulous movements of the body and limbs accompanied the respirations; and it was extremely difficult to excite even a feeble reflex movement by pretty strong stimulation. In one hour and ten minutes, the rabbit was dead.

The autopsy was immediately made: the heart was contracting with regularity and considerable force, at the rate of 160 beats per minute; the intestinal peristalsis seemed normal; galvanic stimulation of the exposed muscles caused energetic contractions, and continued to do so until more than thirty minutes after death; and similar stimulation of the exposed sciatic nerves caused contractions of the posterior extremities at four minutes after death, but ceased to do so in other five minutes.

These experiments are sufficient to illustrate the physiological effects that are produced when iodide of methyl-strychnium is administered to rabbits by subcutaneous injection. We have made similar experiments, with exactly analogous results, on dogs and cats, the more important details of which are mentioned in the table at the end of this paper.

The effects of internal administration were examined by passing a gum-elastic catheter down the œsophagus of a rabbit, and so injecting iodide of methyl-strychnium, suspended and dissolved in warm distilled water. It is unnecessary to give any description of these experiments, at this place, as no effect was produced by this method of exhibition, although as much as thirty grains was given at one time, and it was inconvenient, as well as unnecessary, to give larger doses. It is well known that to produce symptoms with a poison in a rabbit, a much larger quantity is required when it is administered by the stomach than when it is injected subcutaneously. The contrast between the action of iodide of methyl-strychnium and strychnia itself was, however, well shown in the rabbit to which thirty grains of the former had been given without any effect; for one-tenth of a grain of strychnia, also administered by the stomach, quickly produced violent tetanic convulsions, and, in a few minutes, killed the animal.

As iodide of methyl-strychnium is a sparingly soluble substance, it appeared proper, in conformity with our fourth condition, and in order to compare the actions of strychnia and of methyl-strychnium, that the properties of the sulphate of the latter, which is extremely soluble, should be examined.

Sulphate of methyl-strychnium ($(C_{21}H_{22}N_2O_2CH_3)_2SO_4$) was prepared by precipitating a hot aqueous solution of the iodide by a hot solution of sulphate of silver, the slight excess of the latter was precipitated by chloride of sodium, the filtrate evaporated to dryness, and the sulphate of methyl-strychnium extracted by means of alcohol. It crystallises in delicate white needles, is very soluble in cold

water, tastes like the iodide, and gives the usual strychnia-reaction with oxidising agents.

As had been anticipated, it is much more active than the iodide. One grain, dissolved in water, and injected under the skin of a small rabbit, caused its death in eighteen minutes. Half-a-grain, however, produced no effect. When eight-tenths of a grain was similarly administered, the following symptoms were produced, but death did not result.

EXPERIMENT XXIII.—Eight-tenths of a grain of sulphate of methyl-strychnium, dissolved in a few minims of distilled water, was injected into the subcutaneous tissue over the abdomen of a rabbit, weighing three pounds and three and a-half ounces. It caused no immediate uneasiness, and the animal was unaffected for about twenty-five minutes, after which, however, it became restless. In twenty-eight minutes, movements of the limbs were made with obvious difficulty, and the rabbit occasionally stumbled. In twenty-nine minutes, the limbs could no longer support the body, and a position was assumed in which the rabbit lay on the abdomen with the chin resting on the table. It was now perfectly flaccid, and remained on the side when so placed. There was no evidence of exaggeration in the reflex motor function; indeed, an extremely violent stimulus was required to produce even a faint reflex movement. In thirty-two minutes, slight quiverings occurred, and the respirations were laboured, and at the rate of sixty-eight per minute. This condition continued until one hour after the administration, and during all this time consciousness seemed unaffected, and sensibility was not lost, as was shown by stimulation of the conjunctiva or cornea causing movements of the eyelids. Repeated efforts were, however, now made to recover a normal posture, and the frequency of the respirations increased. In one hour and eleven minutes, the head was raised from the table; and in eleven minutes afterwards, the rabbit succeeded in rising on its feet and maintained itself thus, though at first somewhat unsteadily. In one hour and twenty-two minutes, all the symptoms had disappeared. The rabbit was perfectly well on the following morning.

The sequence of symptoms to a fatal termination, and the *post mortem* appearances, are well shown in the experiment where one grain was exhibited (Experiment XXV.).

EXPERIMENT XXV.—We dissolved one grain of sulphate of methyl-strychnium in fifteen minims of distilled water, and injected this solution into the subcutaneous tissue of a rabbit, weighing two pounds and fourteen ounces. In eleven minutes, the first symptom, unsteadiness, appeared. In twelve minutes, the rabbit was lying on the abdomen and chest, with the lower jaw resting on the table. There were no voluntary movements; strong irritation caused feeble reflex movements only, and the respirations were shallow and laboured, and at the rate of sixty per minute. In sixteen minutes, quivering movements of the chest and abdominal muscles occurred, from which it was nearly impossible to distinguish the

respiratory movements; and the sensibility of the eyeball was greatly impaired. In seventeen minutes, there were no movements, except occasional faint twitches of the muscles of the body, while irritation of the skin or of the eyeball did not cause any reflex movements. The rabbit was quite dead in eighteen minutes.

Four minutes after death, the heart was contracting in proper rhythm and with regularity, at the rate of 164 beats per minute, and the intestinal peristalsis was well marked; the heart had however ceased to contract in other twenty-four minutes, but the intestinal peristalsis continued for some time after this. Six minutes after death, the gluteal muscles were exposed, and exposure caused them to twitch. The sciatic nerves were at the same time stimulated with galvanism and mechanical irritation, but no contractions were produced. *Rigor mortis* commenced about two hours and forty minutes after death.

When sulphate of methyl-strychnium is administered to rabbits by the stomach, twenty-five grains appears to be about the minimum fatal dose. The symptoms and mode of death are the same as those that result from subcutaneous injection.

These experiments clearly prove that the methyl derivatives of strychnia possess a very different action from strychnia itself. In none of our experiments, not even in the fatal cases, were the symptoms those of strychnia-poisoning; no starts nor spasms occurred, nor did stimulation give evidence of the slightest increase of reflex excitability. In fact, a condition exactly the reverse of that produced by strychnia was produced by these compounds. In place of violent spasmodic contractions and muscular rigidity, the appearances were those of paralysis, with a perfectly flaccid condition of the muscles. The limbs of the animal first yielded, its head gradually sank until it rested on the table, by-and-by, it lay in a perfectly relaxed condition, and when death occurred, it was due to stoppage of the respiratory movements. In the autopsis, further evidence was obtained to distinguish the effects of the methyl-strychnium compounds from those of strychnia. The heart was found acting with nearly its normal rapidity; the spinal motor nerves were either paralysed or nearly so; and, in place of the almost immediate occurrence of *rigor mortis* that follows the action of strychnia, the muscles continued flaccid, contractile, and alkaline for many hours.

These symptoms are sufficient to suggest a close resemblance between the action of the methyl derivatives of strychnia and that of curare (*wourali*), a well known and elaborately studied poison. In a recent publication, Professor SCHROFF, of Vienna, has indicated a resemblance of this kind between the nitrate of methyl-strychnium and curare.* Both substances undoubtedly produce a condition of

* Wochenblatt der Zeitschrift der k. k. Gesellschaft der Aertze in Wien; vi. Band, 1866, pp. 157–162.

general paralysis; but the special characteristic of curare-poisoning is, that this paralysis is the result of an impairment or destruction of the function of the peripheral terminations (end-organs) of the motor nerves. It is impossible to demonstrate such an action without undertaking experiments of a special character. We, accordingly, extended our research for the purpose of examining this question.

EXPERIMENT XXVIII.—The sciatic artery and vein were tied at the knee of a frog, and one-tenth of a grain of sulphate of methyl-strychnium, dissolved in distilled water, was injected under the skin of the back. Eight minutes afterwards, the frog was lying in a perfectly flaccid state, and, in ten minutes, irritation of any portion of the skin produced energetic movements of the tied limb, *below the points of ligature*, but nowhere else. The sciatic nerve of the untied limb was now exposed, and on stimulating it with a weak, interrupted galvanic current, movements occurred in the tied limb only; not the slightest effect occurred in any part to which the poison had access. At the same time, the muscles were everywhere active, and freely contracted when directly stimulated. The sciatic nerve was then exposed in the tied limb, *above the points of ligature*, and on stimulating it, energetic movements occurred below the knee of that limb, and there only. The heart was, at this time, acting at the rate of fifty per minute.

This experiment was repeated with one grain of iodide of methyl-strychnium, and the same general results were obtained. The evidence that was thus acquired in favour of an action on the peripheral terminations of the motor nerves was strengthened by a modification of this method of experiment.

EXPERIMENT XXIX—The right gastrocnemius muscle of a frog was carefully dissected from its connections, excepting that its origin and insertion, and the nerve-fibres entering it, were untouched, and that all its blood-vessels were ligatured. One-tenth of a grain of sulphate of methyl-strychnium, dissolved in five minims of distilled water, was then injected under the skin of the back. Twenty minutes afterwards, the animal being in a perfectly relaxed and motionless condition, the two sciatic nerves were exposed. Galvanism of the left produced no movement in the left limb, while galvanism of the right produced energetic movements of the right limb, which were seen to be due solely to contractions of the right gastrocnemius muscle, the other muscle remaining motionless. At the same time, direct stimulation by galvanism caused contractions as freely in the poisoned muscles as in the non-poisoned right gastrocnemius.

In an experiment, in which iodide of methyl-strychnium was substituted for sulphate, the effects were the same. We have, therefore, demonstrated that the methyl-strychnium derivatives produce paralysis and death by destroying the function of the motor nerve end-organs, and that their mode of action is, therefore, identical with that of curare. This conclusion is an extremely curious and

interesting one. It is difficult to imagine a more decided modification in the action of any substance than has been produced by the addition of iodide or sulphate of methyl to strychnia. The striking characteristic of strychnia-action is the great and uncontrollable activity of the muscular system; that of curare, of iodide, and sulphate of methyl-strychnium, and, as we shall presently see, of several other similarly modified poisons, is the flaccid and motionless condition caused by the impossibility of exciting muscular action through the nervous system. So opposite are their effects that physiologists look upon curare as a powerful counteragent to strychnia, while physicians have employed it with success in the treatment of strychnia-poisoning and of tetanus. It is remarkable that by so simple a chemical process so thorough a change should be produced in physiological action.

The experiments we have already described have also shown that this change in chemical constitution has greatly reduced the poisonous activity of strychnia. This effect is still more clearly exhibited in the following table:—

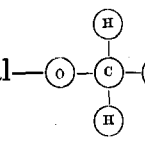
No.*	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.
VII.	Iodide of methyl-strychnium.	Rabbit, 3 lbs. 8 oz.	Subcutaneously.	15 grs. (containing 10·5 grs. of strychnia).	Paralysis in 50 minutes, continuing for more than 2 hours, and followed by recovery.
XIII.	Strychnia (suspended in distilled water).	Do. (same rabbit as in Expt. VII.)	Subcutaneously.	0·05 gr.	Tetanus in 15 minutes; death in 30 minutes.
XVII.	Iodide of methyl-strychnium.	Do., 3 lbs. 13 oz.	By stomach.	30 grs. (containing 21·1 grs. of strychnia).	No effect.
XIX.	Strychnia (as hydrochlorate).	Do., (same rabbit as in Ex. XVII.)	By stomach.	0·1 gr.	Tetanus in 22 minutes; death in 31 minutes.
XXIII.	Sulphate of methyl-strychnium.	Do., 3 lbs. 3½ oz.	Subcutaneously.	0·8 gr. (containing 0.67 gr. of strychnia).	Paralysis in 29 minutes, continuing for 53 minutes, and followed by recovery.
XXXIII.	Sulphate of methyl-strychnium.	Do., 3 lbs. 5¾ oz.	By stomach.	20 grs. (containing 16·8 grs. of strychnia).	No effect.

We have made experiments with nitrate of methyl-strychnium and hydrochlorate of ethyl-strychnium, and have found that their action is identical with that of the iodide or sulphate of methyl-strychnium.

* The numbers in this, and in the other short tables that are appended to the description of the physiological action of the derivatives of each alkaloid, have reference, in common with the numbers in the text, to the arrangement in the complete table at the end of the paper.

BRUCIA.

Brucia is a poisonous alkaloid derived from some plants belonging to the genus *Strychnos*. It possesses a physiological action exactly similar in character to that of strychnia, but less in degree.

Iodide of methyl-brucium ($C_{23}H_{26}N_2O_4CH_3I + 8H_2O$).—Brucia ($C_{23}H_{26}N_2O_4 + 4H_2O$) is, like strychnia, a mono-acid nitrile base: here also the structure of the group $(C_{23}H_{26}NO_4)'''$ is unknown, but the action of nitric acid on brucia renders it probable that it contains the radical  . The ethyl-brucium compounds were discovered and described by GUNNING,* and the methyl-brucium compounds by STAHLSCHMIDT.† We prepared the iodide of methyl-brucium by adding excess of iodide of methyl to a saturated solution of brucia in rectified spirit, allowing the mixture to stand for some hours, evaporating, and recrystallising from hot water.

It forms thin white scales, and dissolves in 79 parts of water at 37°C, and in 225 parts of water at 9°C. Its taste resembles that of the corresponding strychnia compound.

When administered by subcutaneous injection, iodide of methyl-brucium was reduced to the form of a very fine powder, and suspended and dissolved in warm distilled water. In a series of experiments, it was found that as much as twelve grains could be thus given to a rabbit without any effect, that fifteen grains produced marked symptoms, and that eighteen grains was about the minimum fatal dose. Its method of action is well shown in the following experiment.

EXPERIMENT XL.—We injected seven and a-half grains of iodide of methyl-brucium, suspended and dissolved in warm distilled water, into each of two cavities (fifteen grains in all) previously formed in the subcutaneous cellular tissue over the abdomen of a rabbit, weighing four pounds. This did not produce the slightest effect until two hours and forty-three minutes after the administration, when the rabbit's movements became sluggish. Shortly after, a difficulty was observed in standing, and this posture soon become impossible on account of the increasing feebleness of the limbs. In three hours and three minutes, the rabbit subsided on the abdomen and chest, with the lower jaw resting on the table. The condition was one of perfect quietness, there being no twitches; and, though frequently tested, the reflex excitability appeared normal.

* Journal für praktische Chemie, vol. lxvii. p. 46.

† POGGENDORFF's Annalen, vol. cviii. p. 535 (1859).

It remained on the side when so placed, but unsuccessful resistance was made to this change of position. In three hours and thirty-eight minutes, the flaccid state was even more marked, the position was changed without any resistance on the part of the rabbit, severe pinching only occasionally excited a reflex movement, but the respiratory movements were at the rate of sixty-eight per minute. These symptoms continued for other twenty minutes, when some voluntary movements were made, and soon after, the flaccid condition had nearly disappeared. On the following morning, the animal appeared to be perfectly well.

In the experiment we next give, a fatal dose was administered.

EXPERIMENT XLI.—We injected, in all, eighteen grains of iodide of methyl-brucium, suspended and dissolved in warm distilled water, into two subcutaneous cavities formed over the abdomen of a rabbit, weighing three pounds and twelve ounces. No result was observed until twenty-seven minutes, when uneasiness was manifested by restless movements, and slight quivers were seen in the muscles of the neck. In thirty minutes, there was great difficulty in supporting the head, which shook tremulously, and frequently fell on the table, where it eventually remained at thirty-two minutes. The body was still supported on the limbs, though by no means steadily. In thirty-seven minutes, it lay on the table and remained on the side, unresisting and flaccid. The respirations were, at this time, at the rate of forty-eight per minute, and were occasionally interrupted by faint quivering movements, but these had no spasmodic character. In forty-five minutes, the respirations were thirty-six per minute, and the heart's contractions 160 per minute. In one hour, the respirations were twenty-five per minute; and irritation of the conjunctiva did not now cause any movements of the eyelids. In one hour and seven minutes, the respiratory movements were irregular and shallow, only about sixteen occurring in the minute, while the heart was contracting at the rate of 120 per minute. The limbs were perfectly flaccid and motionless. The respiratory movements gradually became less apparent, a series of feeble quivers occurred in the muscles of the face, and death immediately afterwards occurred, one hour and thirteen minutes after the administration.

In the autopsy, the cardiac action was found to be regular and rhythmical, though only at the rate of seventy-four per minute. In three minutes after death, galvanism of the sciatic, phrenic, and other nerves, did not produce any muscular contraction; while it was found by direct galvanism that the muscles retained their contractibility for many minutes afterwards. *Rigor mortis* did not occur until more than one hour after death.

For the purpose of contrasting these symptoms with those that are caused by brucia itself, we shall describe, very briefly, an experiment in which the rabbit, that recovered after the administration of fifteen grains of iodide of methyl-brucium, was rapidly killed by a somewhat large dose of brucia.

EXPERIMENT XLIII.—One-fifth of a grain of brucia was dissolved in ten minims of very dilute hydrochloric acid, and injected, with WOOD'S syringe, into the subcutaneous tissue of the rabbit that had, some days previously, been subjected to an experiment with fifteen grains of iodide of methyl-brucium. In seven minutes, a constrained position was assumed by the rabbit, and the slightest touch caused a sudden spasmodic contraction of the four limbs by which the body was swiftly elevated. In eight minutes, the rabbit sprang to a considerable height, and fell in a well-marked tetanic convulsion, which lasted about fifteen seconds. After this, a series of violent tetanic convulsions, of a distinctly opisthotonic character, followed each other in rapid succession; and at the termination of one of these, eighteen minutes and thirty seconds after the injection of the poison, the rabbit died. There was distinct *rigor mortis* thirty minutes after death.

For internal administration, the iodide of methyl-brucium was also reduced to a very fine powder, and suspended and dissolved in warm distilled water. It was then introduced into the stomach, by means of a gum-elastic catheter. In this way, we performed several experiments, but never succeeded in producing any effect, although as large a dose as thirty grains was at one time administered. It is well known that there is considerable difficulty in affecting a rabbit by a poison introduced into the stomach. That this difficulty was not due, in the present instance, to any recognised cause peculiar to the stomach of the rabbit, was shown by an experiment in which we produced tetanic symptoms and death by introducing two grains of brucia into the stomach of the rabbit that had previously received thirty grains of iodide of methyl-brucium without any effect whatever.

Sulphate of methyl-brucium ($(C_{23}H_{26}N_2O_4CH_3)_2SO_4$, dried at 100°C) was prepared by precipitating a hot solution of the iodide by means of sulphate of silver. It forms a white crystalline mass, readily soluble in water, and, as well as the iodide, gives the ordinary brucia reaction with nitric acid. It is freely soluble in cold water.

We examined the effects of this substance by subcutaneous injection and by introduction into the stomach. For the former purpose, it was dissolved in a few minims of distilled water, and injected under the skin with a WOOD'S syringe. In a rabbit, one grain could be thus given without any effect, two grains caused marked effects, which were not, however, fatal; while two grains and a-half soon killed the animal. The symptoms were the same as those of the iodide, and, therefore, very different from the exaggerated reflex action, convulsions, and tetanus, which are caused by brucia itself. They are illustrated in the following experiments.

EXPERIMENT LIII.—We injected two grains of sulphate of methyl-brucium, dissolved in fifteen minims of distilled water, under the skin of a rabbit, weighing two

pounds and thirteen ounces and three-quarters. In ten minutes, the animal had obviously some difficulty in moving about, and it could not stand steadily. The limbs soon after yielded, and it lay down on the abdomen, chest, and lower jaw; while occasional quivering movements occurred in the muscles of the body. In thirty-four minutes, it lay unresisting and quiet on the side, and the respirations were at the rate of seventy-four per minute. In forty minutes, the respirations were at the rate of fifty-four per minute. It lay in a perfectly relaxed and quiet condition, and when the skin was severely irritated, only extremely feeble reflex movements followed. In one hour and two minutes, the respirations were at the rate of forty-eight per minute; and though irritation of the cornea or conjunctiva did not cause any movement of the eyelids, reflex movements could be excited by severe pinching of the skin. This condition of helpless prostration continued for about thirty minutes, during which some faint twitches of the body and jerking movements of the limbs occasionally occurred. Soon after this, however, a marked improvement was observed: the respirations became fuller and more frequent; irritation of the eyeball was followed by contractions of the eyelids; and, at last, well-directed efforts were made to recover a normal position, and these ultimately proved successful at about two hours after the poison had been injected. The rabbit recovered perfectly.

Experiment LIV.—Two and a-half-grains of sulphate of methyl-brucium was dissolved in fifteen minims of distilled water, and administered by subcutaneous injection to a rabbit, weighing three pounds and fourteen ounces and a-half. In twenty-two minutes, the animal was lying on the abdomen and chest, but the head was still supported by the muscles of the neck; there was distinct congestion of the ears and conjunctiva. In thirty-five minutes, the head had fallen on the table, and the rabbit was perfectly flaccid, and apparently unable to make any voluntary movements. The respirations were at the rate of eighty-two per minute. In fifty-three minutes, the number of the respirations had diminished to twenty-four per minute, while their character was extremely feeble and shallow. In one hour and two minutes, the respiratory movements occurred at long intervals, and were accompanied with a faint tremor of the body and limbs; and it was ascertained that the cardiac contractions were occurring regularly, at the rate of 160 beats per minute. In one hour and ten minutes, the respirations altogether ceased, and death occurred. During the progress of the symptoms, the reflex excitability was frequently tested, with the result that not the slightest increase was ever observed.

The autopsy was immediately made: the heart was found contracting at the rate of 120 per minute; the vermicular action of the intestines was well marked; the conductivity of the sciatic nerves was lost three minutes after death; and idio-muscular irritability persisted for more than twenty minutes afterwards. *Rigor mortis* had not commenced forty minutes after death.

For administration by the stomach, we dissolved this substance in warm distilled water, and introduced the solution through a gum-elastic catheter. We found that as much as twenty grains could be thus given without any effect, and it was not considered advisable to increase this dose. Its magnitude is apparent when we recollect that it contains about seventeen grains of brucia; and we have already seen that when two grains of this alkaloid is introduced into the stomach of a rabbit, the most violent tetanic convulsions are quickly produced, and death soon follows.

The short account we have given of a few of our experiments with iodide and sulphate of methyl-brucium is sufficient to show that these substances have an action that is very different from that of brucia itself. Brucia is a violent convulsant poison, and it causes death by either exhaustion or asphyxia; its methyl derivatives never produce convulsions, nor do they even increase the reflex activity; and although they cause death by asphyxia, this asphyxia, in place of being the result of prolonged and continuous muscular action, due to abnormal nerve activity, is the result of muscular paralysis, due to partial or complete absence of normal nerve activity. We have demonstrated the latter effect by the following experiments, which further show that the influence of the methyl derivatives of brucia is exercised on the terminations of the motor nerves.

EXPERIMENT LVI.—The left iliac artery of a frog, weighing 608 grains, was tied, after exposing it by removing a portion of the sacrum, and one-fifth of a grain of sulphate of methyl-brucium, dissolved in ten minims of distilled water, was then injected into the abdomen. In four minutes, every portion of the frog except the left leg was paralysed. In five minutes and thirty seconds, weak interrupted galvanism, applied to any portion of the skin, caused violent movements of the left leg, and of it alone, every other part of the body remaining motionless. The heart, as ascertained by its impulse, was contracting thirty times per minute. In seven minutes, the right sciatic nerve was exposed—the incisions necessary for which excited energetic reflex movements of the left limb—and on galvanising it, strong contractions of the left limb occurred, but no movement occurred in the right limb. The muscles were everywhere in a normal state, and freely responded to direct galvanic stimulation; and the heart still contracted at the rate of thirty beats per minute.

In a similar experiment, with half a grain of iodide of methyl-brucium, the same effects were observed. It is, therefore, apparent that these substances do not directly influence the action of the heart, of the muscles, of the spinal cord, or of the sensory (afferent) nerves, but that the paralysis, which they so prominently cause, is the result of an action on the motor nerves. In the above experiment, the whole course of the sciatic nerve, from the pelvis to the extremity of the left posterior limb, was protected from the influence of the poison. The experiment does not, therefore, show if the methyl-brucium compounds have

an elective action for any special portion of the nerve. In the next experiment, a much more limited portion of the nerve was protected from the poisonous action.

EXPERIMENT LVII.—In a frog, weighing 542 grains, the right gastrocnemius muscle was exposed; the muscle was separated from all its connections, excepting its origin and insertion and the nerve-fibres that entered it. One-sixth of a grain of sulphate of methyl-brucium, dissolved in ten minims of distilled water, was then injected into the abdomen. In twenty minutes, a condition of complete paralysis was present everywhere except in the right leg. The two sciatic nerves were exposed, and on galvanising the left nerve, feeble movements occurred in the right leg, and there only. When the right nerve was galvanised, movements occurred in the right leg, which were observed to be solely due to contractions in the right gastrocnemius muscle.

In this experiment, the terminations of the sciatic nerve in the right gastrocnemius muscle were alone protected from the direct influence of sulphate of methyl-brucium. This substance had access to all the other terminations of the right sciatic nerve, to the trunk of this nerve, and to all the other nerves of the body. No manifestation of vitality was obtained anywhere, except in the right limb, and it was restricted to contractions of one muscle of that limb. As these contractions could be produced by a stimulus originated in and conducted along the nerve trunk, it is obvious that the vitality of this portion of the nerve was not lost. And as the stimulus produced no effect on the terminations of the nerves to which sulphate of methyl-brucium had access, while it produced an effect on those that were protected from its direct influence, it is evident that this poison acts on the peripheral terminations of the motor nerves.

The physiological action of brucia is, therefore, completely changed by the addition of iodide or sulphate of methyl. It is also apparent that its activity as a poison is greatly lessened; and the following table, which contains a succinct statement of some of the previously-mentioned facts, will clearly illustrate this:—

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.
XL.	Iodide of methyl-brucium.	Rabbit, 4 lbs.	Subcutaneously.	15 grs. (containing 8·7 grs. of dry brucia).	Paralysis in 3 hours and 3 minutes, continuing for more than 28 minutes, and followed by recovery.
XLIII.	Brucia (crystallised).	Do. (same rabbit as in Experiment XL.)	Subcutaneously.	0·2 gr. (containing 0·17 gr. of dry brucia).	Tetanus in 8 minutes; death in 18 minutes 30 seconds.
XLVI.	Iodide of methyl-brucium.	Do., 4 lbs. 2 oz.	By stomach.	30 grs. (containing 17·4 grs. of dry brucia).	No effect.
LI.	Brucia (crystallised).	Do. (same rabbit as in Experiment XLVI.)	By stomach.	2 grs. (containing 1·7 gr. of dry brucia).	Tetanus in 44 minutes; death after 3 hours.
LIII.	Sulphate of methyl-brucium, dried.	Do., 2 lbs. 13¾ oz.	Subcutaneously.	2 grs. (containing 1·7 gr. of dry brucia).	Paralysis in 20 minutes, continuing for about 1 hour and 40 minutes, and followed by recovery.
LVIII.	Sulphate of methyl-brucium, dried.	Do., 4 lbs. 2 oz.	By stomach.	20 grs. (containing 17·2 grs. of dry brucia).	No effect.

THEBAIA.

One of the active principles of opium possesses an action in all respects the same in character as that of strychnia or brucia. We principally owe our knowledge of the method in which thebaia acts to the admirable researches of CLAUDE BERNARD. This distinguished physiologist has further demonstrated that thebaia does not possess any soporific property, that it is the most active toxic principle in opium, and that it ranks first among the alkaloids of this drug that have a convulsant action.* From our experience of its properties, we should assign to it a lower rank than brucia as a toxic and convulsant substance.

Iodide of methyl-thebaium.—The close analogy in physiological action that exists between thebaia ($C_{19}H_{21}NO_3$) on the one hand, and strychnia and brucia on the other, led us to subject this alkaloid to the action of iodide of methyl. The method adopted was the same as that described for the preparation of iodide of methyl-brucium, and the reaction takes place as readily. The product crystallises from alcohol in hard, shining, transparent crystals, which, when air-dried, have the composition ($C_{19}H_{21}NO_3CH_3I$). They dissolve in 16·5 parts of water at 37°C., and in 63·5 parts of water at 9°C.† When a hot, saturated, aqueous solution is allowed to cool, it gelatinises, and the jelly, when left to itself, in some hours, and, when stirred, in a few minutes, is converted into a mass of minute silky needles, which when dried in the air, have the same composition as the crystals obtained from the alcoholic solution.

* Comptes Rendus, vol. lix. 1864, p. 413.

† The methyl derivatives of thebaia have not been described. We shall take some other opportunity of giving details of their chemical relations.

It is much more soluble in water than the iodides of methyl-strychnium and methyl-brucium, and, on this account, we commenced its administration in relatively small quantities. We found that doses of one, five, and six grains, nearly completely dissolved in very dilute spirit, and administered to rabbits by subcutaneous injection, produced absolutely no effect. When, however, the dose was increased to ten grains, partial and then complete paralysis was caused, and death quickly occurred; while serious symptoms were caused by eight grains, but they did not terminate fatally. We shall give some details of these two experiments.

EXPERIMENT LXII.—We dissolved eight grains of iodide of methyl-thebaium in very dilute alcohol, and injected the solution, with WOOD'S syringe, into the subcutaneous cellular tissue of a rabbit, weighing two pounds and twelve ounces. Symptoms of uneasiness occurred in thirty minutes, and were soon followed by quivering movements of the head and ears, and, to a slight extent, of the rest of the body. It was soon apparent that the neck muscles were scarcely able to support the head, for it frequently fell on the table,but the rabbit did not permit it to remain there until forty-five minutes after the administration. At this time, the respirations were at the rate of seventy-eight per minute, and, although the head was resting on the table, the body of the animal was supported, in a comparatively normal posture, on the limbs. There were occasional tremulous movements of the body, but no exaggeration of the reflex function could be discovered. The rabbit remained in this state for about thirty minutes; but soon after this, the tremulous movements disappeared, the head was raised and supported normally, and a perfectly natural posture was assumed. Every symptom had disappeared within two hours after the administration.

EXPERIMENT LXIII.—Ten grains of iodide of methyl-thebaium, reduced to a very fine powder, was partially dissolved and partially suspended in very dilute alcohol, and injected under the skin of a rabbit, weighing two pounds and eleven ounces. There was no obvious effect until ten minutes, when it was observed that the animal moved with difficulty. Tremulous movements then occurred, the limbs occasionally yielded, and the head frequently fell. In twelve minutes, the rabbit lay on the abdomen and chest, with the lower jaw resting on the table; and the tremulous movements only occurred at intervals. It could now be lifted without any struggles. In nineteen minutes, the condition was one of complete flaccidity, the only movements were an occasional gasping respiration, but common sensibility was still retained. It continued thus, on the very verge of death, for about four minutes, when a few quivering contractions occurred in the muscles of the face and neck, and the respirations altogether ceased. During the course of the symptoms, there was never the slightest trace of any exaggeration in the reflex activity, nor of spasmodic or convulsive movements.

The autopsy was immediately made. The heart was found contracting, in normal rhythm, at the rate of eighty-five per minute, and its spontaneous contractions did not cease until eight minutes; and the intestinal peristalsis was active. The sciatic nerves were exposed four minutes after death, and stimulated with weak and strong currents of interrupted galvanism, but no muscular contractions were thereby caused. The muscles themselves readily contracted when the poles were applied directly to their surface, and continued to do so for more than fifteen minutes after death. There was no appearance of *rigor mortis* one hour and five minutes after death, and the muscles were, at this time, alkaline in reaction.

We administered to the rabbit, which had survived the administration of eight grains of iodide of methyl-thebaium (Experiment LXII.), a fatal dose of the thebaia from some of which the methyl compound had been prepared. The striking contrast in the symptoms that were produced will be seen from the following account of the Experiment.

EXPERIMENT LXVI.—We injected one-fifth of a grain of thebaia, dissolved in very dilute hydrochloric acid, into the subcutaneous cellular tissue of the rabbit, which had been subjected to an experiment, some days previously, with eight grains of iodide of methyl-thebaium. The injection did not appear to cause much annoyance, as the animal jumped about naturally for forty minutes after it. Soon after, however, its movements became more constrained and cautious, and occasional twitches occurred in the muscles of the back. These gradually became more marked and powerful, and in forty-eight minutes, they assumed the character of spasmodic starts. In forty-nine minutes, a touch, even when very gentle, of any portion of the skin excited a violent spasmodic jump, and in fifty-two minutes, a spontaneous violent opisthotonic convulsion took place, and continued for forty-five seconds. The rabbit now lay on its side; every respiratory movement provoked a short fit of tetanus, while, occasionally, a violent and prolonged fit occurred. This condition lasted for two minutes, when, at the termination of one of the more violent of these fits, death occurred,—fifty-four minutes after the administration of the poison.

It was found, in the autopsy, that the sciatic nerves retained their motor conductivity for at least fifteen minutes after death. A certain degree of muscular rigidity was observed at twenty-eight minutes, and *rigor mortis* was perfectly established at forty minutes, when all the muscles were acid in reaction, although the temperature of the abdominal cavity was as high as 95° F.

The internal administration of iodide of methyl-thebaium was effected in the same way as we have described for the corresponding strychnia and brucia compounds. It was found that, with this substance also, so large a dose as thirty grains could be introduced into the stomach of a rabbit without any effect. Well-marked symptoms were produced in the same animal by three, and, on another

occasion, by three and a-half grains of thebaia similarly administered, but it recovered after both doses. Four grains was, however, a fatal dose, as will be seen from the following Experiment.

EXPERIMENT LXXIV.—Four grains of thebaia, almost completely dissolved in very dilute hydrochloric acid, was introduced, by a gum-elastic catheter, into the stomach of the rabbit that had received thirty grains of iodide of methyl-thebaium (Experiment LXXI.) In six minutes, a violent tetanic convulsion occurred; after this, the rabbit remained on the side, and convulsion succeeded convulsion until its death, nineteen minutes after the administration of thebaia. *Rigor mortis*, with an acid reaction of the muscles, was completely established at thirty-seven minutes after death.

Sulphate of methyl-thebaium ($(C_{19}H_{21}NO_3CH_3)_2SO_4$, dried at 100° C.), was prepared by precipitating an aqueous solution of the iodide by means of sulphate of silver. It forms a white, indistinctly crystalline mass. It dissolves readily in water, and gives, with sulphuric acid, the reaction of thebaia.

We found it to be a less active substance than the corresponding derivative of either strychnia or brucia, as doses of four and of four-and-a-half grains were not fatal, though they produced symptoms, when injected into the subcutaneous cellular tissue of rabbits. Five grains appears to be about the smallest quantity that can produce death when administered to rabbits in this manner. The experiments in which four and a-half and five grains were given are sufficient to illustrate the general physiological effects of this substance.

EXPERIMENT LXXVII.—We dissolved four and a-half grains of sulphate of methyl-thebaium in fifteen minims of distilled water, and injected this solution into the subcutaneous tissue at the flank of a rabbit, weighing three pounds and eleven ounces and a-half. In seventeen minutes, the rabbit had some difficulty in jumping about, for it occasionally stumbled, and rested for a few seconds on the chest. In twenty-one minutes, it was lying on the abdomen, with the lower jaw resting on the table; and, occasionally, a series of shivering tremors took place in the muscles of the back. In thirty minutes, it remained on the side, when so placed, and was perfectly flaccid. The respirations were at the rate of sixty per minute. In forty-one minutes, the respirations had diminished in frequency to forty per minute, and during inspiration the abdominal muscles contracted in a tremulous manner. In fifty-five minutes, the respirations had increased in number to seventy-one per minute, and in one hour and thirty minutes, they appeared to have regained their normal rapidity; but it was impossible to ascertain this definitely, on account of frequent interruptions by tremulous movements of the abdominal muscles. The rabbit was still lying on the side in a perfectly flaccid state. In one hour and thirty-two minutes, however, it suddenly raised the head, rose, and assumed a normal posture; but the trembling continued. This trembling, very faint and not at

all spasmodic, was the last symptom to disappear, which it did about two hours and thirty minutes after the injection of the poison. We frequently tested the condition of the reflex activity, and did not find it increased at any period during the experiment.

EXPERIMENT LXXVIII.—Five grains of sulphate of methyl-thebaium was dissolved in thirty minims of distilled water, and injected under the skin of a rabbit, weighing four pounds and half an ounce. Its effects began to be seen in thirteen minutes, when, after a few restless movements, the rabbit subsided on the abdomen and chest. Complete flaccidity soon after occurred; and the respirations became shallow and gasping, and they diminished in frequency until, at twenty-five minutes after the injection, they were only at the rate of twenty-three per minute. Occasional, very weak, tremulous movements occurred at this time. In thirty-five minutes, severe pinching of the skin caused only a feeble reflex movement, while the contraction of the eyelids, after irritation of the eyeball, was almost imperceptible. The rabbit appeared still to retain consciousness. In fifty minutes, no movement followed severe pinching of the skin, or irritation of the eyeball, and the respirations were gasping and infrequent. In fifty minutes, a few twitches occurred in the muscles of the face, and either immediately before or during these the rabbit expired.

In the autopsy, which was immediately performed, the heart was seen contracting at the rate of seventy-eight per minute, and the intestinal peristalsis seemed normal. Four and a-half minutes after death, neither a weak nor a powerful galvanic current could excite any muscular contraction when applied to the trunk of a sciatic nerve; but idio-muscular irritability was not lost for many minutes after this. At two hours and thirty minutes after death, the rabbit was still perfectly flaccid, and there was not the slightest appearance of muscular rigidity.

We have not observed any symptoms follow the internal administration of this substance, as no effect was produced when we introduced twenty grains, dissolved in warm water, into the stomach of a rabbit. It has been shown by Experiment LXXIV. that four grains of thebaia is a fatal dose when thus exhibited.

The experiments we have narrated contain the most satisfactory proof that the chemical addition of iodide and sulphate of methyl has produced a complete change in the physiological action of thebaia. The nature of the change appears to be identical with that we have described as occurring under similar circumstances in strychnia and brucia. Thebaia acts in the same way as these alkaloids; for it causes increase of the reflex activity, convulsions, and tetanus by an action on the spinal cord. The action of iodide and sulphate of methyl-thebaium is strikingly different; for they diminish reflex excitability, and produce a condition of paralysis in which death occurs by asphyxia. This paralysis, as we have seen, is dependent on an effect on the spinal nerve system.

We will now describe an experiment in which we endeavoured to determine what portion of this system is affected.

EXPERIMENT LXXIX.—The sciatic artery and the two principal veins were tied in the right thigh of a frog, weighing 420 grains, and one-fifth of a grain of sulphate of methyl-thebaium, dissolved in seven minims of distilled water, was injected into the abdominal cavity. In six minutes, the animal was flaccid and motionless, and in other four minutes the respiratory movements of the chest and abdomen had ceased, while those of the throat continued, and did so for several minutes longer. In sixteen minutes, galvanic stimulation by an interrupted current, applied to any portion of the skin, caused movements of the right leg *below the points of ligature*, but nowhere else. In twenty-one minutes, the left sciatic nerve was exposed, and on galvanising it, energetic movements occurred in the right leg, while the left leg and every other part of the body remained motionless. The heart was now contracting at the rate of thirty-six beats in the minute. The muscles that had been laid bare in the left leg, by the dissection necessary for the exposure of the left sciatic nerve, were stimulated by the direct application of an interrupted galvanic current, and they contracted powerfully. This condition continued during other two days; on the second day, even a feeble stimulus applied to the left sciatic nerve was followed by well-marked contractions of the right leg, below the points of ligature; while it caused no movements in those parts of the frog that had been directly acted upon by the poison, although the muscles everywhere contracted when directly stimulated.

We learn from this experiment that sulphate of methyl-thebaium produces paralysis by destroying the conductivity of the motor nerves, and not by interfering with the function of the spinal cord, or of the sensory (afferent) nerves. The next experiment was made with the view to determine what portion of the motor nerve is paralysed by this substance.

EXPERIMENT LXXX.—The left gastrocnemius muscle was exposed in the leg of a frog, weighing 604 grains. The blood-vessels that entered it were ligatured or twisted, and it was carefully separated from all its connections, excepting that its origin and insertion were untouched, and that the nerve fibres that entered it were not divided. Immediately after this somewhat tedious preparation, one-fifth of a grain of sulphate of methyl-thebaium, dissolved in ten minims of distilled water, was injected in the abdomen. Omitting the details of the effects that ensued, it is sufficient to mention that, at thirty minutes after this injection, the sciatic nerve was exposed in each thigh and galvanised, with the result that in the case of the right nerve movements followed in the left leg alone, and in the case of the left nerve movements followed in the left leg, and there only. It was seen that these movements in the left leg were entirely caused by contractions of the left gastrocnemius muscle, that is, of the muscle which had been protected from the direct influence of the poison.

We obtained the same results on repeating these experiments with half-grain doses of iodide of methyl-thebaium.

These experiments demonstrate clearly that the methyl derivatives of thebaia produce their principal physiological effects by impairing and destroying the function of the peripheral termination of the motor nerves—an action that is very different from that of thebaia itself. They also differ from thebaia in being considerably less potent as poisons. Several of these characters are summarised in the appended table.

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition	Dose.	Effect.
LXII.	Iodide of methyl-thebaium.	Rabbit, 2 lbs. 12 oz.	Subcutaneously.	8 grs. (containing 5·5 grs. of thebaia).	Paralysis in 45 minutes, continuing for about 30 minutes, and followed by recovery.
LXVI.	Thebaia.	Do. (same rabbit as in Experiment LXII.)	Subcutaneously.	0·2 gr.	Tetanus in 52 minutes, and death in 54 minutes.
LXXI.	Iodide of methyl-thebaium.	Do., 4 lbs. 6 oz.	By stomach.	30 grs. (containing 20·6 grs. of thebaia).	No effect.
LXXIV.	Thebaia.	Do. (same rabbit as in Exp. LXXI.)	By stomach.	4 grs.	Tetanus in 6 minutes, and death in 19 minutes.
LXXVII.	Sulphate of methyl-thebaium.	Do., 3 lbs. 11½ oz.	Subcutaneously.	4·5 grs. (containing 3·7 grs. of thebaia).	Paralysis in 21 minutes, continuing for 2 hours and 9 minutes, and followed by recovery.
LXXXI.	Sulphate of methyl-thebaium.	Do., 4 lbs. 4 oz.	By stomach.	20 grs. (containing 16·6 grs. of thebaia).	No effect.

CODEIA ($C_{18}H_{21}NO_3 + H_2O$).

We have examined the effect of the addition of iodide and sulphate of methyl to codeia—an opium alkaloid, which, according to CLAUDE BERNARD, is the second in toxic activity, and possesses distinct convulsant but feeble soporific properties.*

Iodide of methyl-codeium.—How† obtained by the action of iodide of ethyl on codeia, iodide of ethyl-codeium, and from it a number of ethyl-codeium compounds, and proved that codeia is a nitrile base. As was to be expected, iodide of methyl acts even more readily on codeia.‡ It is only necessary to heat codeia with a little alcohol and an excess of iodide of methyl to 100° C. for an hour, in a sealed tube, to complete the reaction. The excess of iodide of methyl is distilled off, the alcohol evaporated, and the product crystallised from hot water. It

* Comptes Rendus, vol. lix. (1864) p. 413.

† Chemical Society's Quarterly Journal, vol. vi. (1853) p. 134.

‡ We shall give details of the chemical relations of the methyl derivatives of codeia on some other occasion.

forms large transparent prisms, soluble in 14·5 parts of water at 37°C., and in 49 parts of water at 9°C. Its solution is not precipitated by caustic potash, and in all respects, except in the appearance of its crystals, agrees with iodide of ethyl-codeium.

As iodide of methyl-codeium is tolerably soluble in warm water, we could administer it by subcutaneous injection in the form of solution. It was found, in rabbits, that a dose of five grains was quite inert, that one of fifteen grains caused prolonged and serious symptoms which were recovered from, and that one of twenty grains produced death in a short time. The following details include the principal symptoms that appeared when fifteen and twenty grains were thus administered.

EXPERIMENT LXXXIV.—Fifteen grains of iodide of methyl-codeium was dissolved in some warm distilled water, to which a few drops of rectified spirit had been added, and the solution was injected into the subcutaneous cellular tissue of a rabbit, weighing two pounds and fourteen ounces. The rabbit remained sitting quietly until twenty-two minutes afterwards, but in a few seconds more it had some difficulty in retaining a sitting posture, and, on standing, the fore-limbs occasionally yielded, until, at twenty-five minutes, it subsided on the abdomen, chest, and lower jaw. In thirty minutes, it remained on the side without struggling; and now, after considerable intervals, faint twitches occurred in the body and limbs, which, however, had no convulsive character. In thirty-seven minutes, irritation of the cornea or conjunctiva did not cause any movement in the eyelids, but the respirations, though weak, shallow, and somewhat jerking, were at the rate of sixty-seven in the minute. In forty-five minutes, the frequency of the respirations had diminished to sixty in the minute, and there were now no twitches. The rabbit continued to lie in this flaccid state for about two hours longer; at the end of which time, twitches reappeared, at first extremely faint, but, by-and-by, of considerable strength, and involving the muscles of the abdomen, chest, neck, and limbs. In four hours and twenty minutes, the rabbit was again in a perfectly quiet state, the twitches had disappeared, and the common sensibility was in a normally active condition. Frequent attempts were made, soon after, to recover a natural position, and success was at length attained, four hours and twenty-five minutes after the injection of the poison. There were no further symptoms.

EXPERIMENT LXXXV.—We injected twenty grains of iodide of methyl-codeium, dissolved as in the preceding experiment, into the subcutaneous cellular tissue of a rabbit, weighing two pounds and twelve ounces and a-half. The animal began to tremble in thirteen minutes, and the head, after being unsteadily supported for a short time, fell on the table. In fifteen minutes, the rabbit remained on the side; the respirations were weak and irregular, and slight starts occurred occasionally. Severe irritation of the skin was now required to cause

even an extremely feeble reflex movement. In twenty-four minutes, no movement followed irritation of either the skin or eyeball, and the respirations were mere gasping jerks. In thirty-two minutes, a series of feeble twitches occurred in the face-muscles, and then the respirations entirely ceased.

We immediately exposed the sciatic nerves, and examined their condition: when they were stimulated with galvanism, slight movements followed in the hind limbs at one minute after death; but no movement could be excited at one minute and thirty seconds. The heart was found to be contracting in regular rhythm, at the rate of eighty-two in the minute. Forty-five minutes after death, the body was perfectly flaccid, and there was not the slightest appearance of muscular rigidity.

We may best display the marked differences between these physiological effects and those that are caused by codeia, by describing an experiment in which the rabbit that survived the administration of fifteen grains of iodide of methyl-codeium, was quickly killed by the subcutaneous injection of one grain of codeia.

EXPERIMENT LXXXIX.—We dissolved one grain of codeia in some warm distilled water, to which a few drops of rectified spirit had been added, and injected the solution into the subcutaneous tissue of the rabbit, which was some days previously the subject of Experiment LXXXIV. In fifteen minutes, faint twitches occurred in some of the muscles of the back; and, soon after, a slight touch excited a violent start. Spontaneous spasmodic starts now followed each other, until one hour and eleven minutes, when a violent tetanic convulsion of an opisthotonic character occurred. For some time before this, it was observed that the hind limbs trailed slightly when movements were attempted, indicating, apparently, a slight degree of motor paralysis. The first tetanic convulsion was followed by trismus, which lasted for a few seconds, and by a succession of slight spasms; and soon after its occurrence, unsuccessful efforts were made to recover a normal position. In one hour and thirty minutes, a second violent tetanic convulsion took place, and this presented the character of emprosthotonos rather than of opisthotonos. Such convulsions now recurred after intervals of a few minutes, and at the termination of one of them, one hour and forty-five minutes after the administration of the poison, the rabbit died. In fifteen minutes after death, strong *rigor mortis* was present.

We introduced iodide of methyl-codeium into the stomach of rabbits on two occasions. In one of these, fifteen grains were thus administered, and in the other, thirty grains; but no effect was produced by either dose. Codeia itself, however, is by no means a violent poison when given to rabbits in this manner. We made a considerable number of experiments, but did not succeed in causing death even with fifteen grains. In the following experiment we employed ten grains.

EXPERIMENT XCIV.—By means of a gum-elastic catheter, we injected ten grains of codeia, dissolved in warm distilled water to which a few drops of

dilute hydrochloric acid had been added, into the stomach of a rabbit, weighing three pounds and thirteen ounces. In twenty-four minutes, some symptoms of sleepiness were observed, which chiefly manifested themselves by nodding movements of the head. In thirty-nine minutes, the reflex excitability seemed increased, as a slight touch caused a sudden, somewhat spasmodic start. In one hour, the sleepy condition had so far increased, that the head rested on the table, and the eyelids were semi-closed. In one hour and twenty minutes, the rabbit could be placed in almost any position, provided physical rest were allowed; and it would remain sleeping in these attitudes until roused by sounds or by pretty violent irritations. It continued in this condition for more than two hours; but in three hours, the sleepiness was less marked, and on the following morning the rabbit was in a perfectly natural state.

Sulphate of methyl-codeium was prepared from the iodide, by precipitating it by means of sulphate of silver. It forms a white crystalline mass, readily soluble in cold water.

It is a rather more active poison than the iodide, for we found that ten grains, exhibited subcutaneously, was sufficient to kill a rabbit. We observed only slight symptoms with eight grains.

EXPERIMENT XCVI.—Eight grains of sulphate of methyl-codeium was dissolved in twenty minims of distilled water, and injected under the skin of a rabbit, weighing four pounds. No distinct effect was observed until thirty minutes, when some uneasiness was shown by restless movements of the limbs, and, soon after, a little trembling occurred. Weakness of the limbs was then exhibited by occasional stumbles, and, in thirty-three minutes, the rabbit fell, and remained resting on the abdomen, with the lower jaw on the table. There were no starts nor spasms, and even the trembling had now ceased; while severe irritation of the skin caused merely slight reflex movements. After remaining in this state for twenty minutes, the symptoms gradually improved, and the rabbit appeared to be quite well two hours after it had received the poison.

EXPERIMENT XCVII.—Ten grains of the sulphate of methyl-codeium was dissolved in distilled water, and injected under the skin of a rabbit, weighing four pounds and four ounces. In twenty-three minutes, the head and portions of the body shook in a quivering manner; and, gradually, the head sank until it rested on the table. In twenty-five minutes, the legs gave way, and the animal fell; faint twitches occurred over the body, but otherwise the condition was one of complete flaccidity. In thirty-five minutes, it remained on the side, without any resistance. In thirty-eight minutes, the respirations were laboured, and at the rate of thirty-six per minute; and in other four minutes, they had fallen to twenty per minute. In forty-one minutes, these movements were extremely shallow and irregular; and in forty-two minutes, they altogether ceased. In the course of this experiment, no convulsive symptoms occurred, and no hypnotism was observed.

In the autopsy, the heart was seen acting, one minute after death, at the rate of 160 beats per minute, and the intestinal peristalsis was found to be normal. The motor conductivity of the sciatic nerves was retained at three minutes after death, but it had disappeared in other four minutes; while the idio-muscular irritability was not lost until more than sixty minutes after death.

For internal administration, we followed the plan already described. No symptom whatever was observed when the large dose of twenty grains was introduced into the stomach of a rabbit. We did not, accordingly, consider it advisable to continue this method of administration any further.

As we have already stated, and as the experiments we have narrated clearly show, the principal effects that are caused by codeia are convulsions and hypnotism. In our experiments with rabbits, the latter effect was manifested only when large doses were introduced into the stomach. It was not seen when this alkaloid was administered by subcutaneous injection, probably because sleep was then prevented by the spasmodic starts and convulsions that were so prominently caused. We learn from our experiments that the iodide and sulphate of methyl-codeium have a very different action from codeia. We have never observed any hypnotic effect follow their administration, and, in place of convulsions, we have seen that they produce paralysis. This, indeed, is the only marked symptom that follows their administration, and it is apparent that it does not depend on an effect on the muscles, nor on the cerebral lobes. We endeavoured to determine the exact cause of this paralysis by experiments with localised poisoning on frogs.

Experiment XCVIII.—Having tied the right sciatic artery and vein of a frog, weighing 722 grains, one grain of sulphate of methyl-codeium, dissolved in distilled water, was injected into the abdominal cavity. In fifteen minutes, voluntary movements had disappeared, and the frog was lying on the abdomen, in a flaccid state. In thirty minutes, pinching of the skin with a pair of forceps excited movements in all the limbs, but these were most energetic in the right posterior extremity. In one hour and thirty minutes, similar stimulation excited no movement except in the right posterior extremity (where the vessels had been tied). The application of an interrupted galvanic current to the exposed trunk of the left sciatic nerve was now followed by active movements of the right leg, but of no other part; while, at the same time, the muscles in the poisoned regions freely responded to galvanic stimulation directly applied to them. In two hours and forty minutes, the condition was the same, and, judging from the cardiac impulse, the heart was contracting at the rate of thirty-five per minute.

We need not again enter into the reasons for concluding from such an experiment that the paralysis caused by sulphate of methyl-codeium is due to an action on the motor nerves. As has been already done with the corresponding substances treated of in the previous portion of this paper, we, in the next place, determined what portion of the motor nerve—trunk or periphery—is acted on.

EXPERIMENT XCIX.—In a frog, weighing 694 grains, the left gastrocnemius muscle was prepared in the manner described in Experiments XXIX., LVII., and LXXX., and one grain of sulphate of methyl-codeium, dissolved in distilled water, was injected into the abdomen by means of a WOOD'S syringe. In one hour after this, a condition of flaccidity being present, the trunks of the two sciatic nerves were exposed, and stimulated with an interrupted galvanic current. When the right nerve was thus treated, some contractions followed in the left leg, and nowhere else; and when the left nerve was thus treated, vigorous contractions followed in the left leg; and it was observed that the movements of the left leg were caused by contractions restricted to its gastrocnemius muscle, that is, the muscle to which the poison had no direct access. At this time, the muscles in all parts of the body contracted freely when the poles of the battery were applied to their surfaces, and continued to do so for many hours longer.

We repeated these last experiments with iodide of methyl-codeium, and obtained the same general results.

We have, therefore, demonstrated that iodide and sulphate of methyl-codeium produce paralysis, by destroying the function of the peripheral terminations (end-organs) of the motor nerves—a mode of action that distinguishes them, as physiological agents, in a most striking manner from codeia. It will also be seen from the following table, that the poisonous (toxic) activity of the codeia in these methyl-compounds is considerably diminished.

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.
LXXXIV.	Iodide of methyl-codeium.	Rabbit, 2lbs. 14oz.	Subcutaneously.	15 grs. (containing 10·2 grs. of dry codeia).	Paralysis in 25 minutes, continuing for about 3 hours, and followed by recovery.
LXXXIX.	Codeia (crystallised).	Do. (same rabbit as in Ex. LXXXIV.)	Subcutaneously.	1 gr. (containing 0·94 gr. of dry codeia).	Spontaneous twitches in 15 minutes, tetanus in 1 hour and 11 minutes, and death in 1 hour and 45 minutes.
XCI.	Iodide of methyl-codeium.	Do., 2 lbs. 13 oz.	By stomach.	30 grs. (containing 20·3 grs. of dry codeia).	No effect.
XCIV.	Codeia (crystallised).	Do. (same rabbit as in Ex. XCI.)	By stomach.	10 grs. (containing 9·4 grs. of dry codeia).	Sleepiness in 24 minutes, increase of reflex excitability in 39 minutes, and followed by recovery in more than 3 hours.
XCVI.	Sulphate of methyl-codeium.	Do., 4 lbs.	Subcutaneously.	8 grs. (containing 6·6 grs. of dry codeia).	Paralysis in 33 minutes, continuing for more than 20 minutes, and followed by recovery.
C.	Sulphate of methyl-codeium.	Do., 4 lbs. 13 oz.	By stomach.	20 grs. (containing 16·5 grs. of dry codeia).	No effect.

MORPHIA.

The most recent and trustworthy investigations show that, among the opium alkaloids, morphia ($C_{17}H_{19}NO_3 + H_2O$) is next in activity as a soporific to narceia, that it possesses a less convulsant action than codeia, and that its fatal dose is one of the largest of those of the active principles of opium.*

Iodide of methyl-morphium ($C_{17}H_{19}NO_3CH_3I$).—How subjected morphia to the action of iodide of ethyl and of iodide of methyl, prepared and described a number of the ethyl-morphium and methyl-morphium compounds, and proved that morphia is a nitrile base.† We prepared the iodide of methyl-morphium by How's method, viz., by treating morphia with alcohol and an excess of iodide of methyl in a sealed tube, at 100° C., for an hour, distilling off the excess of iodide of methyl, and recrystallising from hot water.

It forms long, transparent, prismatic needles; and dissolves in 34 parts of water at 37° C., and in 88·5 parts of water at 9° C.

As it is well known that comparatively large doses of morphia are required to produce any symptom in such animals as rabbits, we at once commenced the administration of iodide of methyl-morphium in very large doses. We were unable to produce any effect whatever when so large a dose as twenty grains was injected under the skin of a small rabbit; and, as this could only be administered as a fine powder, suspended in warm distilled water, it was extremely inconvenient to give any larger quantity in a form necessarily so bulky. Eight grains of morphia was afterwards exhibited, in the same way, to this rabbit, and it caused the usual symptoms and death. It may be interesting and satisfactory to give some details of these two experiments.

Experiment CI.—Twenty grains of iodide of methyl-morphium was reduced to a fine powder, mixed with two drachms of warm distilled water, and injected into two previously formed subcutaneous cavities at the flanks of a rabbit, weighing two pounds and fourteen ounces. The rabbit was carefully observed for four hours, but no symptom occurred during this time. It was perfectly well on the following morning.

Experiment CV.—Eight grains of morphia, suspended in warm distilled water, was introduced into the subcutaneous cellular tissue of the rabbit that had been employed, two days previously, in Experiment CI. In one hour and four minutes, an inclination to sleep was observed, the eyelids closed, and the head sank on the table, but a slight sound immediately roused the rabbit. In two hours, the soporific effect was more marked; and the animal remained in almost any position in which it could be placed, provided the change was made gradually and gently;

* Claude Bernard, Comptes Rendus, vol. lix. 1864, p. 413.
† Chemical Society's Quarterly Journal, vol. vi. (1853) p. 126.

and, however unnatural the position might seem to be, if it were consistent with rest, sleep immediately occurred. In three hours, there was some difficulty in rousing it, and when this was done, it remained awake for a few seconds only. In six hours, the respirations had fallen to the slow rate of twenty-six in the minute. This condition lasted, altogether, for about forty-eight hours, when spasms made their appearance, which, by-and-by, assumed all the characters of epileptiform convulsions. These epileptic fits frequently recurred, and could be excited, at any time, by pinching the skin. They consisted of tonic spasms of the limbs and of the abdominal muscles, followed by twisting of the head to the right, grinding movements of the lower jaw, and violent opisthotonos. The rabbit was found dead on the morning of the third day after the administration.

The two subcutaneous cavities into which the morphia had been introduced were laid open, and a small quantity of unabsorbed morphia was found in both. The cavities into which iodide of methyl-morphium had been introduced were also laid open, but none of this substance was found.

We were unsuccessful in producing any symptoms by the internal administration of iodide of methyl-morphium. Thirty grains was found to be perfectly inert when exhibited by the stomach, while the same rabbit was decidedly narcotised with five grains of morphia similarly exhibited. It is interesting, for the purpose of comparison, to give a short account of these two Experiments.

EXPERIMENT CVI.—We suspended thirty grains of finely-powdered iodide of methyl-morphium in distilled water, and injected the mixture into the stomach of a rabbit, weighing three pounds and twelve ounces. It was observed for more than two hours, but no symptoms could be detected.

EXPERIMENT CVII.—We suspended five grains of finely-powdered morphia in distilled water, and injected the mixture into the stomach of the rabbit that was used, two days previously, in Experiment CVI. In one hour and six minutes, the rabbit was observed to be sleepy, and it soon after laid its head on the table. This sleepy condition became gradually more marked: in one hour and twenty-five minutes, the rabbit could be placed in almost any position, and slept thus; while about the same time, a condition resembling that of catalepsy was present, for when we placed the rabbit on the back and raised the fore legs perpendicularly upwards, it remained in this extraordinary attitude for several minutes. In two hours and forty-one minutes, it was observed that the pupils, which were small, did not contract on the approach of a bright light, nor did this stimulus excite any movement of the body; but the common sensibility was not lost. The condition of cataleptic-like hypnotism lasted, altogether, about three hours and twenty minutes. Soon after this, some voluntary movements were made, and the rabbit gradually recovered to a perfectly normal state.

Any conclusion drawn from experiments on such animals as rabbits, with a substance whose predominating action is a soporific one, are always liable to

objection. For this reason, we were induced to try the effect of iodide of methyl-morphium on man. One of us,* who is perfectly susceptible to the action of morphia, took on one occasion, half a grain of iodide of methyl-morphium, in the form of powder; but this produced no effect. On another occasion, one grain was taken, also as a powder; but not the slightest soporific or other action was caused. The latter dose contained about three-fourths of a grain of morphia, and this is certainly much above the usual narcotic dose of this substance.

It is important to mention, that although we have failed in causing any symptoms in warm-blooded animals with this substance, we have found that it acts with considerable energy on frogs. The nature of this action will be explained in the description of the effects of sulphate of methyl-morphium.

Sulphate of methyl-morphium ($(C_{17}H_{19}NO_3CH_3)_2SO_4$), was prepared by precipitating a solution of the iodide by means of sulphate of silver. It forms a white crystalline mass, very soluble in water. It gives the ordinary blue colour-reaction of morphia with persalts of iron.

This salt of methyl-morphium is much more active than the iodide. By subcutaneous injection, doses of two, three, four, five and eight grains caused marked symptoms; while a dose of ten grains was sufficient to kill a large rabbit. The effects of eight and of ten grains are described in the two following Experiments.

EXPERIMENT CXII.—Eight grains of sulphate of methyl-morphium, dissolved in distilled water, was injected under the skin, over the two flanks of a rabbit, weighing three pounds and one ounce. In twelve minutes, it appeared to be rather sleepy, and disinclined to move. In fourteen minutes, the head fell on the table, and the animal remained in this position, without any movements, except those that were necessary for respiration. In twenty-five minutes, the hypnotism was extremely well-marked; it was possible to place the animal in any position, and if this were compatible with stability, sound sleep occurred. A considerable stimulus was now required before the rabbit could be roused from sleep. In two hours and twenty minutes, this condition still continued, but the observations were now discontinued. On the following morning, the rabbit appeared to be perfectly well. No convulsive symptoms nor exaggeration of reflex activity was observed in this Experiment.

EXPERIMENT CXIII.—We dissolved ten grains of sulphate of methyl-morphium in 200 minims of distilled water, and injected the solution under the skin of a rabbit, weighing three pounds and eight ounces. In seven minutes, difficulty in moving about was observed; and, in rapid succession, some stumbles occurred, the limbs yielded, and the animal lay in a state of flaccidity, on the abdomen, chest, and lower jaw. It could now be placed without any resistance in almost

* DR FRASER.

any position. In twenty-four minutes, the respirations were very feeble and shallow, and at the rate of twenty-four in the minute; the rabbit was perfectly quiet and flaccid; and severe pinching of the skin excited only feeble reflex movements. There was not the slightest appearance of muscular rigidity, nor of starts, spasms, or even quivering movements. In forty-seven minutes, the respirations were extremely weak and jerky, and at the rate of ten per minute, while the sensibility of the conjunctiva and cornea had greatly diminished. In fifty-six minutes, the respirations occurred only eight times in the minute, and no movement of the eyelids could be excited by irritating the conjunctiva or cornea. Exophthalmos was now markedly present. Death occurred in one hour and two minutes after the administration of the poison.

In the autopsy, the heart was found to be distended, and acting irregularly and slowly. There was no appearance of *rigor* two hours after death.

When administered by the stomach, twenty grains of sulphate of methyl-morphium produced no effect on a rabbit.

Our experiments with morphia confirmed the observations made by others, which show that this alkaloid has two prominent actions on rabbits—a convulsant and a hypnotic one. We shall now consider how far each of these is modified by the addition of sulphate of methyl to morphia. The addition of iodide of methyl appears, no doubt, to have produced a very important change, but as this is rather in the direction of diminishing, or, as our experiments indicate, altogether destroying, the physiological activity of morphia, the iodide of methyl-morphium may, in the mean time, be removed from consideration.

It has been proved, in a most satisfactory manner, that sulphate of methyl-morphium possesses no convulsant action; for neither in the experiments we have described in detail, nor in any of the others we performed with this substance, was there any trace of spasmodic action or of exaggeration of the reflex function. It, however, undoubtedly causes hypnotic symptoms. In small non-fatal doses, hypnotism was chiefly manifested, and this rendered it somewhat difficult to judge whether paralysis were present or not. In large non-fatal doses, and in fatal doses, on the other hand, paralysis appeared to be the chief effect, though hypnotism was also present. It would, therefore, seem that sulphate of methyl-morphium agrees with morphia in possessing a hypnotic action, but differs from it in producing paralysis, and in being free from all convulsant action. It is obvious that an objection might be urged against the latter part of this statement; for both the absence of convulsions and the production of paralysis might be merely the effects of hypnotism. Though we were ourselves convinced, from our experiments on rabbits, that such is not the case, we made some experiments on frogs to determine this more clearly.

EXPERIMENTS CXV. and CXX.—The blood-vessels were tied in one limb near the knee of two frogs, selected because of their resemblance to each other in weight

and in activity. One grain of sulphate of methyl-morphium, in solution, was injected into the abdominal cavity of one of these frogs (*a*), and three-fourths of a grain of morphia, dissolved in very dilute sulphuric acid, into the abdominal cavity of the other (*b*).

(*a*). *Frog with Sulphate of Methyl-morphium.*

In eight minutes, the limbs yielded, and the frog subsided on the abdomen and chest.

In twenty minutes, it was perfectly flaccid, and the respirations had entirely ceased. Pinching of any portion of the skin excited energetic movements of the leg whose vessels were tied, and feeble movements in various other parts.

In thirty minutes, the two sciatic nerves were exposed; galvanism applied to their trunks caused contractions of the *tied limb, below the ligatures*, and nowhere else. The heart was now acting at the rate of forty-two in the minute, and the idio-muscular irritability was normal everywhere.

In twenty-four hours, the frog was still perfectly flaccid, the heart was contracting at the rate of thirty per minute, and the muscles of the poisoned and non-poisoned regions contracted when directly galvanised. Galvanism of the sciatic nerve of the poisoned leg, however, produced no movement; but galvanism of the sciatic nerve of the non-poisoned leg, even when applied to a part where the poison had access, still caused vigorous movements below the ligatures.

(*b*). *Frog with Sulphate of Morphia.*

In sixteen minutes, some slight sprawling occurred, before which the frog was jumping about vigorously.

In fifty minutes, pinching of the skin occasioned a series of clonic spasms, in which both posterior extremities were forcibly and slowly extended and then withdrawn, somewhat regularly, during three or four minutes, about four times in the minute. The movements then ceased, but they could be again excited.

In one hour, there was marked increase of the reflex excitability, a slight touch causing a spasmodic start.

In one hour and thirty-eight minutes, a slight touch of the skin excited a short tetanic convulsion.

In two hours, the same condition existed, and a tetanic convulsion could be at any time excited by a slight touch. During these convulsions, the muscles in the non-poisoned limb were contracted as forcibly as those in the poisoned regions.

In twenty-four hours, the frog was found dead, with all its muscles rigid.

These experiments prove distinctly that sulphate of methyl-morphium does not possess, in any degree, the convulsant action of morphia, but that it causes paralysis in place of convulsions. They also prove that this paralysis is due to an effect on the motor nerves. We have further determined, by the same method of experiment as has been already frequently described, that the peripheral terminations are the parts of the motor nerves which are primarily affected.

Iodide of methyl-morphium produces the same effects on frogs as sulphate, only a larger dose is required.

The poisonous activity of sulphate of methyl-morphium does not appear to be very different from that of a salt of morphia; for we have seen that for rabbits ten grains is about the minimum fatal dose of the former by subcutaneous injection, and this contains about eight grains of morphia, which is little above the fatal dose when subcutaneously exhibited. We have placed these and several other results, in a form convenient for comparison, in the following table.

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.
CI.	Iodide of methyl-morphium.	Rabbit, 2 lbs. 14 oz.	Subcutaneously.	20 grs. (containing 13·3 grs. of dry morphia).	No effect.
CV.	Morphia.	Do. (same rabbit as in Experiment CI.)	Subcutaneously.	8 grs. (containing 7·5 grs. of dry morphia).	Sleep in 1 hour and 4 minutes, epileptic convulsions in about 48 hours, and death some hours afterwards.
CVI.	Iodide of methyl-morphium.	Do., 3 lbs. 12 oz.	By stomach.	30 grs. (containing 20 grs. of dry morphia).	No effect.
CVII.	Morphia.	Do. (same rabbit as in Experiment CVI.)	By stomach.	5 grs. (containing 4·7 grs. of dry morphia).	Sleep in 1 hour and 6 minutes, and catalepsy in 1 hour and 25 minutes; these symptoms lasted for nearly 3 hours and 30 minutes, and were followed by recovery.
CXII.	Sulphate of methyl-morphium.	Do., 3 lbs. 1 oz.	Subcutaneously.	8 grs. (containing 6·6 grs. of dry morphia).	Sleep and partial paralysis in 14 minutes, continuing for more than 2 hours and 16 minutes, and followed by recovery.
CXIII.	Sulphate of methy-morphium.	Do., 3 lbs. 8 oz.	Subcutaneously.	10 grs. (containing 8·2 grs. of dry morphia).	Paralysis in 8 minutes, and doubtful sleepiness in 10 minutes; the paralysis became gradually more complete, and terminated in death, at 1 hour and 2 minutes after the administration of the poison.
CXXI.	Sulphate of methyl-morphium.	Do., 4 lbs. 3½ oz.	By stomach.	20 grs. (containing 16·4 grs. of dry morphia).	No effect.

NICOTIA.

The last substance in which we have now to describe the modifications produced by chemical addition is nicotia. This is a liquid alkaloid of great poisonous energy, derived from tobacco. It is a di-acid nitrile base, and has the formula $(C_{10}H_{14}N_2)$.

Iodide of methyl-nicotium.—Von Planta and Kekulé* investigated the action of iodide of ethyl on nicotia, and described a number of the ethyl-nicotium salts. The compounds of methyl-nicotium were investigated and described by Stahlschmidt.† When excess of iodide of methyl is added to nicotia, a considerable amount of heat is developed, and it is advisable to immerse the flask in which the mixture is made in cold water, in order to moderate the action; by this means the product (iodide of methyl-nicotium $(C_{10}H_{14}N_2(CH_3I)_2)$ is obtained nearly colourless, and crystallises almost as soon as it is cold. The crystalline

* Annalen der Chemie und Pharmacie, vol. lxxxvii. p. 1 (1853).
† Ibid. vol. xc. p. 222 (1854).

powder is washed with a little cold alcohol, and crystallised from hot rectified spirit. Thus obtained, it forms tolerably large prismatic crystals, perfectly transparent and colourless, and free from the peculiar odour of nicotia. It is extremely soluble in water, so that for our purpose it was scarcely necessary to prepare the sulphate. More for the sake of symmetry, however, than because we expected to find any difference in action, we did so.

A dose of five grains of iodide of methyl-nicotium, exhibited by subcutaneous injection, produced no effect on a rabbit. Ten grains caused trembling and slight impairment of motility; and the same symptoms occurred, in a somewhat exaggerated form, after the administration of fifteen grains: but recovery took place after both doses. The subcutaneous injection of twenty grains was followed, after several hours, by death. In the following account of the experiments in which fifteen and twenty grains were exhibited, it will be seen that no convulsive movements occurred during the progress of the symptoms.

EXPERIMENT CXXVII.—We injected fifteen grains of iodide of methyl-nicotium, dissolved in ninety minims of distilled water, into the subcutaneous cellular tissue of a rabbit, weighing three pounds. In eleven minutes, some trembling occurred, which, however, did not continue long; but it recurred in twenty-three minutes. In thirty minutes, it was observed that the head was supported with great difficulty, and shortly after it fell on the table, and the rabbit assumed a crouching attitude. There was no trembling so long as it was not disturbed; but whenever this was done, and when attempts were spontaneously made to assume some different position, the trembling recommenced. It continued in this condition for about an hour; soon afterwards the head was raised, and the trembling ceased. The rabbit was jumping about in a perfectly normal state two hours and three minutes after the administration.

EXPERIMENT CXXVIII.—We injected twenty grains of iodide of methyl-nicotium, dissolved in ninety minims of distilled water, into the subcutaneous cellular tissue of a rabbit, weighing about three pounds. In eight minutes, some trembling of the fore-legs was observed, which, however, soon ceased, and the rabbit sat down and remained quiet. In twenty minutes, the head fell upon the table, the neck muscle being apparently unable to support it; and in twenty-eight minutes, the paralysis had so far extended to the body that the rabbit, being unable to maintain even a crouching attitude, fell on the side. In one hour, it was in the flaccid condition of the last note, but the respiratory movements were few and feeble. In two hours and ten minutes, the respirations consisted of occasional gasps merely, and death appeared imminent. The observationswere unfortunately now (4 P.M.) interrupted until the following morning, when (10·15 A.M.) the rabbit was dead, and in *rigor mortis*.

In accordance with the plan followed in this investigation, we shall now

describe the effects that are produced by nicotia itself,—and in order to obtain as exactly comparable data as possible, a portion of the nicotia used in the preparation of the iodide of methyl-nicotium employed in Experiments CXXVII. and CXXVIII. was administered to the rabbit which recovered from fifteen grains of the latter substance.

EXPERIMENT CXXXII.—One half-minim of nicotia (about 0·5 grain) was dissolved in fifteen minims of very dilute sulphuric acid, and the solution was injected into the subcutaneous cellular tissue of the rabbit employed, a week previously, in Experiment CXXVII. Symptoms were rapidly produced. In two minutes, spasmodic contractions occurred in the four limbs, which became extended, and raised the body in a convulsive manner. In three minutes, violent tremors occurred, and the whole body was convulsively agitated. In a few seconds afterwards, the limbs altogether yielded; the rabbit lay on the abdomen; and strong twitches occurred in the muscles of the neck, by which the head was jerked upwards, and in the limbs, by which the body was partially raised. This condition continued until ten minutes, when the spasmodic twitches ceased, and the rabbit fell on the side. It was now perfectly flaccid, with only twenty-five laboured respirations in the minute. In fourteen minutes, the respiratory movements were so feeble as to be scarcely visible; and, in fifteen minutes, they altogether ceased.

In the autopsy, the heart was found contracting, five minutes after death, at the rate of 160 per minute, but its contractions were feeble. The vermicular movements of the intestines appeared to be normal. The trunk of a sciatic nerve was irritated, ten minutes after death, and energetic movements followed in the limb to which the nerve was distributed.

Having found, in the case of iodide of methyl-nicotium, that so large doses of an extremely soluble substance were necessary to affect a rabbit by subcutaneous injection, we did not consider it advisable to determine how much was required to produce symptoms when it is exhibited by the stomach. For it may be almost positively asserted that, in the latter case, a much larger dose would be necessary; and while the administration of this would be inconvenient, because of its bulkiness, and of the difficulty of obtaining a large quantity in a perfectly pure form, the data obtained by subcutaneous injection are sufficient to prove the principal change that the addition of iodide of methyl produces in the physiological action of nicotia—namely, a great diminution in its poisonous activity.

Sulphate of methyl-nicotium ($C_{10}H_{14}N_2(CH_3)_2SO_4$) was prepared by precipitating a solution of the iodide by means of sulphate of silver. It forms a white, crystalline mass, extremely soluble in water.

On account of the readiness with which iodide of methyl-nicotium dissolves in water, it was not to be expected that any change in poisonous activity would be caused by its conversion into a sulphate; and the following experiment con-

firms this surmise, by showing that the activity of the sulphate is apparently no greater than that of the iodide.

EXPERIMENT CXXXIII.—Ten grains of sulphate of methyl-nicotium, dissolved in ninety minims of distilled water, was injected into the subcutaneous cellular tissue of a rabbit, weighing four pounds and three ounces. In ten minutes, some trembling occurred, accompanied with partial paralysis of the fore-legs. In twenty minutes, the head fell on the table, and, at intervals, series of tremors shook the whole body. It continued in this condition, the body being still supported by the legs, until fifty minutes, when ineffectual attempts were made to raise the head. These attempts were frequently repeated, and were finally successful at one hour and ten minutes; but the trembling, though now very slight, did not altogether cease until one hour and twenty minutes. After this, the rabbit seemed perfectly well.

In the absence of any very trustworthy or complete investigation into the mode in which nicotia acts, we cannot ascertain exactly how far its physiological properties are modified by chemical addition. It would appear, however, that the convulsive movements which are described as always occurring during nicotia poisoning, and which were well marked in Experiment CXXXII., are not among the symptoms produced by either iodide or sulphate of methyl-nicotium. The action of these substances is characterised by paralysis, accompanied with tremors, but unattended with spasms or convulsions. We performed the following experiments on frogs, in order to determine if this change were due not only to the disappearance of convulsive action, but also to the appearance of a paralysing action on motor nerves, similar to that so prominently possessed by the methyl derivatives of the other alkaloids examined in this paper.

EXPERIMENT CXXX.—The blood-vessels were tied in the left thigh of a frog, weighing 430 grains, and one grain of iodide of methyl-nicotium, dissolved in fifteen minims of distilled water, was then injected into the abdomen. In ten minutes, the anterior extremities had become so weak that they could not altogether support the thorax, but still the frog jumped about with considerable activity. In twenty-five minutes, the movements were sluggish, and the jumps were by no means so active as formerly, while some trailing of the posterior extremities was observed. The heart was acting at the rate of forty-two in the minute. In thirty-five minutes, irritation of any portion of the skin was followed by contractions of all the limbs, but these appeared to be rather more energetic in the left posterior (non-poisoned) limb than in the others. In forty minutes, the respirations were feeble, but the frog was sufficiently powerful to turn itself when placed on the back. In fifty-five minutes, severe pinching caused only slight reflex movements, of nearly equal strength, in both posterior extremities. In fifty-seven minutes, it was unable to turn when placed on the back, and the heart's contractions were at the rate of thirty-seven per minute. In one hour and

thirty-nine minutes, irritation of any portion of the skin was followed by feeble, but nearly equal, movements of the four limbs. The observations were now interrupted. On the following morning the frog was jumping about normally.

EXPERIMENT CXXXI.—The blood-vessels were tied at the right knee of a frog, weighing 630 grains, and three grains of iodide of methyl-nicotium, dissolved in twenty minims of distilled water, was injected into the abdomen. In twenty-six minutes, the frog was lying, flaccid, on the abdomen and chest; and when the skin was irritated, reflex movements of equal strength were caused in the four limbs. In one hour and sixteen minutes, the flaccid state had become more marked, and, now, a somewhat stronger irritation was requisite in order to cause reflex movements, while these appeared to be of greatest strength in the right posterior (non-poisoned) limb. In two hours and forty-six minutes, the condition was exactly the same as last noted. The observations were now interrupted; and on the following morning the frog was found dead, and in *rigor*.

We obtained similar results with the sulphate.

It would, therefore, appear that though the convulsant effects of nicotia are not produced by its methyl derivatives, these derivatives do not possess any paralysing action on motor nerves. The change that is produced in the physiological action of nicotia is not the same as that which we have described in strychnia, brucia, thebaia, codeia, and morphia. We are inclined to believe, on account of this difference, that the convulsions of nicotia are not due to the same cause as in the other alkaloids we have examined.

A great diminution in physiological activity has, however, been produced by this chemical addition, and this will be at once recognised by referring to the following table:—

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.
CXXVII.	Iodide of methyl-nicotium.	Rabbit, 3 lbs.	Subcutaneously.	15 grs. (containing 5·4 grs. of nicotia).	Trembling in 11 minutes, and partial paralysis in 30 minutes; these continued for about 49 and 50 minutes respectively, and a perfect recovery afterwards occurred.
CXXXII.	Nicotia (as sulphate).	Do. (same rabbit as in Experiment CXXVII.)	Subcutaneously.	0·5 min. (0.5 gr. nearly).	Convulsions in 3 minutes, and partial paralysis in less than 4 minutes; followed by death, 15 minutes after administration.
CXXXIII.	Sulphate of methyl-nicotium.	Do., 4 lbs. 3 oz.	Subcutaneously.	10 grs. (containing 5·6 grs. of nicotia).	Trembling in 10 minutes, slight paralysis in 20 minutes; perfect recovery in 1 hour and 20 minutes after administration.

Some experiments were made to determine, for our satisfaction, the physiological effects of iodide of methyl. The only bearing of these on the present investigation is, that no evidence was obtained in support of the extremely improbable hypothesis, that some of the changes produced in the action of the substances we have described might have been due to addition of the physiological action of the methyl compounds.

We have thus shown that chemical addition produces some important modifications in the action of those poisons which have been treated of in this communication. The action of strychnia, brucia, thebaia, codeia, morphia, and nicotia is evidently greatly diminished in degree, and, at the same time, strikingly changed in character.

The former effect is shown with all these alkaloids, especially when their action is compared with that of the iodides of their methyl derivatives. As all these iodides are much less soluble than the salts of the alkaloids themselves, it might be supposed that the diminution in activity could be explained by this difference in solubility. Some support is given to this supposition, by examining the relations between various of the substances included in this investigation. Thus, it has been demonstrated, on the one hand, that, for rabbits, the fatal dose of iodide of methyl-strychnium administered subcutaneously, is about twenty grains, and that of iodide of methyl-thebaium is about ten grains; while the former is soluble in 133 parts of distilled water, at a temperature of 37° C., and the latter in 16·5 parts at the same temperature. On the other hand, the fatal dose for rabbits, of sulphate of methyl-strychnium, is about four-fifths of a grain, and that of sulphate of methyl-thebaium is about five grains; while both substances are freely soluble, and with nearly equal readiness, in cold water. In these examples, the greater activity of strychnia over thebaia is manifested when a soluble salt of the methyl derivative of strychnia is employed; but when an extremely insoluble salt—the iodide—is employed, its activity is nearly the same as that of a corresponding preparation of thebaia; although the latter alkaloid is itself considerably less energetic than strychnia. It is, therefore, apparent that poisonous activity may be modified by the degree of solubility,—a well-recognised principle in toxicological physiology. But while the diminished activity of the iodides of many of these methyl derivatives may be greatly due to the difficulty of dissolving them, this explanation is inapplicable to iodide of methyl-nicotium,—an extremely soluble substance,—and it is insufficient to account for the differences of activity between the majority of the sulphates of the methyl derivatives and the salts of the alkaloids themselves. Our investigation has not furnished us with any explanation of the change in these sulphates. There are several possible explanations, but we shall not specially allude to them, as their discussion can only be properly undertaken after experimental examination of a laborious and difficult nature, and but indi-

rectly connected with our present subject. When, however, we compare the activity of the sulphates of the majority of the ammonium bases considered in this paper with that of the corresponding iodides, we observe striking differences, which cannot be explained by differences of solubility alone, but which, we believe, must be also due to the remarkable stability possessed by these iodides. Strychnia is a much less soluble substance than iodide of methyl-strychnium, and yet a rabbit that survived the administration of fifteen grains of iodide of methyl-strychium, was killed in a few minutes by the administration of one-twentieth of a grain of strychnia. Before absorption, the strychnia may have been converted into a more soluble form, and this change may have facilitated its absorption, and permitted it to be carried by the blood-stream to the tissues it affects; but the great *stability* of the iodide of methyl-strychnium prevents its conversion into a more soluble form, and so impedes greatly the absorption. Just as in the more familiar case of the salts of lead, the sulphate is inert while the carbonate is poisonous, although they are both insoluble; and this difference of physiological action is undoubtedly due to the fact, that the carbonate, on account of its instability, is readily converted in the stomach into a soluble salt, while no such change takes place in the case of the sulphate. Stability may also influence the physiological activity of these iodides, even after their absorption, by preventing those chemical actions on the tissues by which many of the effects of poisons are probably caused.

The change in the *character* of the physiological action is remarkably illustrated by strychnia, brucia, and thebaia, whose purely spinal-stimulant action is converted into a paralysing action on the periphery (end-organs) of motor nerves; it is apparent in codeia and morphia, whose convulsant action is also converted into a paralysing action on motor nerve end-organs, and whose hypnotic action is apparently altogether destroyed in the case of codeia, and certainly greatly diminished in that of morphia; and it is obviously, though less so than with the others, in the case of nicotia, whose convulsant action is diminished if not altogether removed. We may conclude from these facts, that when a nitrile base possesses a strychnia-like action, the salts of the corresponding ammonium bases have an action identical with that of curare.

It is well known that curare and strychnia are derived from plants belonging to the same *genus*, and it is, therefore, interesting to observe such a relationship. It may not, however, be altogether superfluous to add, that strychnia, brucia, and the other spinal-stimulant alkaloids examined in this paper, have not been converted by chemical addition into curarina,—the active principle of curare. The action of the methyl derivatives of these bases is of precisely the same character as that of curare, and they possess the same peculiarity of slow absorption by the mucous membrane of the digestive system, but the degrees of their activity are very different. If we confine our

attention to the salts of the methyl derivatives of strychnia, brucia, and thebaia, where the action is uncomplicated, we observe that they form a series in which the fatal dose varies for each, while this dose in the case of the most active of the three is considerably above that of curare, and greatly above that of curarina. Besides, curarina has a characteristic colour reaction that belongs to none of these bodies; and the latter further prove this dissimilarity by each of them possessing special colour reactions by which they may be distinguished from each other.

It is not only of great interest, but probably of some practical value, that five new compounds should be found having the physiological action of curare. The great difficulty of obtaining this substance has hitherto proved a serious barrier to its therapeutical employment. Although none of the compounds that we have shown to act as curare does are so energetic as that substance, three of them—sulphate of methyl-strychnium, sulphate of methyl-brucium, and sulphate of methyl-thebaium—are sufficiently so to fulfil all possible therapuetical requirements, and even to rank as powerful poisons. Moreover, they may be readily obtained in a state of perfect purity, and, therefore, of constant strength; and, in this respect, they possess a great advantage over curare.

The six alkaloids we have examined may be divided into two classes, according to the readiness with which they combine with iodide of methyl. The one class includes strychnia, brucia, thebaia, and nicotia; and the other, codeia and morphia; and the combination is much more easy with the former than with the latter class. Without attaching any general significance to the occurrence, it may not be altogether unworthy of being pointed out that in our experience, therefore, the more active poisons are the more readily acted upon by iodide of methyl.

It is curious, though not unexpected, that the ordinary colour reactions of the alkaloids are retained by their methyl derivatives. This may possibly prove of some importance to the medical jurist; and as these compounds are not precipitated by alkalies, nor by the carbonates of the alkalies, some difficulty may be met with in discovering their presence in cases of poisoning.

TABULAR SUMMARY OF EXPERIMENTS.

No 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-strychnium.	Rabbit, 3 lbs.	Subcutaneously.	5 grs.	None.			
II.	Do.	Do., 3 lbs. 14 oz.	Do.	6 grs.	None.			
* III.	Do.	Do., 3 lbs. 12 oz.	Do.	8 grs.	None.			
IV.	Do.	Do., 3 lbs. 4 oz.	Do.	8 grs.	None.			
V.	Do.	Do., 3 lbs. 4 oz.	Do.	10 grs.	None.	...	...	Same rabbit, on three consecutive days.
VI.	Do.	Do., 3 lbs. 4 oz.	Do.	12 grs.	None.			
VII.	Do.	Do., 3 lbs. 8 oz.	Do.	15 grs.	Paralysis followed by recovery.	45 minutes.	More than 2 hours.	
VIII.	Do.	Do., 3 lbs. 2½ oz.	Do.	20 grs.	Death, preceded by paralysis.	20 minutes.	50 minutes.	
IX.	Do.	Cat (full grown).	Do.	1 gr.	None.			
X.	Do.	Do. „	Do.	5 grs.	None.			
XI.	Do.	Frog, 541 grs.	Do.	1 gr.	Paralysis.	11 minutes.	Not observed.	
* XII.	Do.	Do., 410 grs.	Do.	0·5 gr.	Paralysis.	12 minutes.	Not observed.	
XIII.	Strychnia (suspended in distilled water).	Rabbit, 3 lbs. 8 oz.	Do.	0·05 gr.	Death, preceded by spasms and numerous tetanic convulsions.	8 minutes.	22 minutes.	Same rabbit as survived 15 grs. of iodide of methyl-strychnium (Experiment VII.)
XIV.	Iodide of methy-strychnium.	Rabbit, 2 lbs. 10 oz.	By stomach.	12 grs.	None.	...	...	Same rabbit. Experiment XIV. was made 48 hours after Experiment XV.
XV.	Do.	Do., 2 lbs. 10 oz.	Do.	15 grs.	None.			
XVI.	Do.	Do., 3 lbs. 2 oz.	Do.	20 grs.	None.			
XVII.	Do.	Do., 3 lbs. 13 oz.	Do.	30 grs.	None.			
XVIII.	Strychnia (as hydrochlorate).	Do.. 3 lbs. 2 oz.	Do.	0·075 gr.	Death, preceded by numerous spasms and tenanic convulsions.	Exaggeration of reflux function in 24 minutes.	37 minutes.	Same rabbit as survived 20 grs. of iodide of methyl - strychnium (Experiment XVI.)

* Several of the experiments included in this Table were performed after the reading of the paper. They are distinguished by an asterisk; and it will be observed that the details of a few of them have been incorporated in the text.

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of symptoms.	Notes.
XIX.	Strychnia (as hydrochlorate).	Rabbit, 3 lbs. 13 oz.	By stomach.	0·1 gr.	Death, preceded by numerous spasms and tetanic convulsions.	17 minutes.	24 minutes.	Same rabbit as survived 30 grs. of iodide of methyl - strychnium (Experiment XVII.)
XX.	Sulphate of methyl-strychnium.	Do., 2 lbs. 5 oz.	Subcutaneously.	0·1 gr.	None.			
XXI.	Do.	Do., 3 lbs. 3½ oz.	Do.	0·2 gr.	None.			
XXII.	Do.	Do., 2 lbs. 5 oz.	Do.	0·5 gr.	None.			
XXIII.	Do.	Do., 3 lbs. 3½ oz.	Do.	0·8 gr.	Paralysis, followed by recovery.	28 minutes.	54 minutes.	
XXIV.	Do.	Do., 3 lbs. 1 oz.	Do.	0·8 gr.	Death, preceded by paralysis.	Paralysis in 9 minutes.	21 minutes.	Some doubt of the absolute purity of the sulphate used in this Experiment.
XXV.	Do.	Do., 2 lbs. 14 oz.	Do.	1 gr.	Do. do.	11 minutes.	7 minutes.	
XXVI.	Do.	Do., 3 lbs. 10 oz.	Do.	5 grs.	Do. do.	13 minutes.	4 minutes.	
XXVII.	Do.	Dog, 40 lbs. (?).	Do.	12 grs.	Do. do.	Partial paralysis in 4 minutes.	15 minutes.	
XXVIII.	Do.	Frog, 820 grs.	Do.	0·1 gr.	Paralysis.	4 minutes.	Not observed.	
* XXIX.	Do.	Do., 615 grs.	Do.	0·1 gr.	Paralysis.	3 minutes.	Not observed.	
* XXX.	Do.	Rabbit, 3 lbs. 3 oz.	By stomach	2 grs.	None.	...	...	Same rabbit. Experiments XXX. and XXXI. were performed after an interval of 48 hours, and Experiments XXXI. and XXXII. after one of 24 hours.
* XXXI.	Do.	Do., 3 lbs. 3 oz.	Do.	5 grs.	None.			
*XXXII.	Do.	Do., 3 lbs. 3 oz.	Do.	10 grs.	None.			
XXXIII.	Do.	Do., 3 lbs. 5¾ oz.	Do.	20 grs.	None.			
*XXXIV.	Do.	Do., 3 lbs. 3 oz.	Do.	25 grs.	Death, preceded by tremors and paralysis.	55 minutes.	More than 2 hours.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of symptoms.	Notes.
XXXV.	Nitrate of methyl-strychnium.	Rabbit, 4 lbs. 1 oz.	Subcutaneously.	10 grs.	Death, preceded by tremors and paralysis.	6 minutes.	4½ minutes.	
XXXVI.	Hydrochlorate of ethyl-strychnium.	Frog, 240 grs.	Placed on skin.	0·5 gr. (?).	Paralysis, followed by recovery.	2 minutes and 30 sec.	More than 4 hours.	
XXXVII.	Do.	Do., 400 grs.	Subcutaneously.	0·5 gr.	Death, preceded by paralysis.	2 minutes.	About 15 ho.	
XXXVIII.	Iodide of methyl-brucium.	Rabbit, 3 lbs. 11 oz.	Do.	8 grs.	None.			
XXXIX.	Do.	Do., 3 lbs. 11 oz.	Do.	12 grs.	None.			
XL.	Do.	Do., 4 lbs.	Do.	15 grs.	Paralysis, followed by recovery.	2 hours and 43 minutes.	More than 1 hour and 15 minutes.	
XLI.	Do.	Do., 3 lbs. 12 oz.	Do.	18 grs.	Death, preceded by paralysis.	27 minutes.	46 minutes.	
XLII.	Brucia (as hydrochlorate).	Do., 4 lbs.	Do.	0·1 gr.	None.			
XLIII.	Do.	Do., 4 lbs.	Do.	0·2 gr.	Death, preceded by numerous spasms and tetanic convulsions.	7 minutes.	11 minutes and 30 sec.	Same rabbit as survived 15 grs. of iodide of methyl-brucium (Experiments XL.)
XLIV.	Iodide of methyl-brucium.	Frog, 380 grs.	Do.	0·5 gr.	Death, preceded by paralysis.	16 minutes.	Not observed.	
XLV.	Do.	Rabbit, 3 lbs.	By stomach.	20 grs.	None.			
XLVI.	Do.	Do., 4 lbs. 2 oz.	Do.	30 grs.	None.			
* XLVII.	Brucia (as hydrochlorate.	Do., 3 lbs.	Do.	0·2 gr.	None.			
* XLVIII.	Do.	Do., 2 lbs. 1 oz.	Do.	0·3 gr.	None.			
* XLIX.	Do.	Do., 3 lbs. 11 oz.	Do.	0·5 gr.	None.			
* L.	Do.	Do., 2 lbs. 13 oz.	Do.	1 gr.	None.			
LI.	Do.	Do., lbs. 2 oz.	Do.	2 grs.	Death, proceded by spasms and tetanic convulsions.	40 minutes.	More than 2 hours and 10 minutes.	Same rabbit as survived 30 grs. of iodide of methyl-brucium (Experiment XLVI.)

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of symptoms.	Notes.
LII.	Sulphate of methyl-brucium.	Rabbit, 2 lbs. 4 oz.	Subcutaneously.	1 gr.	None.			
LIII.	Do.	Do., 2 lbs. 13¾ oz.	Do.	2 grs.	Paralysis, followed by recovery.	10 minutes.	About 1 hour and 50 min.	
LIV.	Do.	Do., 3 lbs. 14½ oz.	Do.	2·5 grs.	Death, preceded by paralysis.	20 minutes.	50 minutes.	
* LV.	Do.	Do., 3 lbs. 5 oz.	Do.	3 grs.	Do. do.	12 minutes.	16 min. and 15 seconds.	
LVI.	Sulphate of methyl-brucium.	Frog., 608 grs.	Injected into abdomen.	0·2 gr.	Do. do.	3 to 4 minutes.	Not observed.	
* LVII.	Do.	Do., 542 grs.	Do.	0·16 gr.	Do. do.	6 minutes.	Not observed.	
LVIII.	Do.	Rabbit, 4 lbs. 2 oz.	By stomach.	20 grs.	None.			
LIX.	Iodide of methyl-thebaium.	Do., 2 lbs. 12 oz.	Subcutaneously.	1 gr.	None.	...	...	Same rabbit; intervals of at least 24 hours elapsed between each experiment.
LX.	Do.	Do., 2 lbs. 12 oz.	Do.	5 grs.	None.	...	...	
LXI.	Do.	Do., 2 lbs. 12 oz.	Do.	6 grs.	None.	...	...	
LXII.	Do.	Do., 2 lbs. 12 oz.	Do.	8 grs.	Paralysis, followed by recovery.	30 minutes.	1 hour and 30 minutes.	
LXIII.	Do.	Do., 2 lbs. 11 oz.	Do.	10 grs.	Death, preceded by paralysis.	10 minutes.	13 minutes and 30 sec.	
* LXIV.	Do.	Do., 2 lbs. 15 oz.	Do.	12 grs.	Do. do.	Less than 11 minutes.	10 minutes nearly.	
LXV.	Thebaia (as hydrochlorate).	Do., 2 lbs. 12 oz.	Do.	0·1 gr.	Slight exaggeration of the reflex function.	About 50 minutes.	About 1 hour.	Same rabbit as survived 8 grs. of iodide of methyl-thebaium (Experiment LXII.)
LXVI.	Do.	Do., 2 lbs. 12 oz.	Do.	0·2 gr.	Death, preceded by spasms and tetanic convulsions.	40 minutes.	14 minutes.	
LXVII.	Do.	Do., 2 lbs. 14 oz.	Do.	0·2 gr.	Do. do.	33 minutes.	1 hour, 12 minutes and 44 seconds.	
LXVIII.	Iodide of methyl-thebaium.	Frog, 460 grs.	Do.	0·5 gr.	Death, preceded by paralysis.	12 minutes.	Not observed.	
* LXIX.	Do.	Do., 540 grs.	Do.	0·5 gr.	Do. do.	16 minutes.	Not observed.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of Symptoms.	Notes.
* LXX.	Iodide of methyl-thebaium.	Rabbit, 3 lbs.	By stomach.	10 grs.	None.			
LXXI.	Do.	Do., 4 lbs. 6 oz.	Do.	30 grs.	None.			
LXXII.	Thebaia (as hydrochlorate).	Do., 4 lbs. 6 oz.	Do.	3 grs.	Spasms, followed by recovery.	16 minutes.	More than 1 hour.	Same rabbit as survived 30 grs. of iodide of methyl-thebaium (Experiment LXXI.) The experiments were made at intervals of at least 48 hours.
LXXIII.	Do.	Do., 4 lbs. 6 oz.	Do.	3·5 grs.	Spasmodic convulsions, followed by recovery.	14 minutes.	More than 2 hours.	
LXXIV.	Do.	Do., 4 lbs. 6 oz.	Do.	4 grs.	Death, preceded by numerous tetanic convulsions.	4 minutes.	15 minutes.	
LXXV.	Sulphate of methyl-thebaium.	Do., 2 lbs. 14 oz.	Subcutaneously.	2 grs.	None.			
LXXVI.	Do.	Do., 3 lbs. 15 oz.	Do.	4 grs.	Slight increase of reflex activity, followed by recovery.	22 minutes.	15 minutes.	Faintly coloured preparation.
* LXXVII.	Do.	Do., 3 lbs. 11½ oz.	Do.	4·5 grs.	Paralysis, followed by recovery.	15 minutes.	About 2 hours and 15 min.	Pure preparation.
LXXVIII.	Do.	Do., 4 lbs. 0½ oz.	Do.	5 grs.	Death, preceded by paralysis.	13 minutes.	37 minutes.	
* LXXIX.	Do.	Frog, 420 grs.	Injected into abdomen.	0·2 gr.	Do. do.	5 minutes.	Not observed.	
* LXXX.	Do.	Do., 604 grs.	Do.	0·2 gr.	Do. do.	7 minutes.	Not observed.	
* LXXXI.	Do.	Rabbit, 4 lbs. 4 oz.	By stomach.	20 grs.	None.			
LXXXII.	Iodide of methyl-codeium.	Do., 3 lbs. 1 oz.	Subcutaneously.	5 grs.	None.			
LXXXIII.	Do.	Do., 3 lbs.	Do.	10 grs.	Paralysis, followed by recovery.	27 minutes.	More than 2 hours.	
LXXXIV.	Do.	Do., 2 lbs. 14 oz.	Do.	15 grs.	Do. do.	22 min. and 20 seconds.	4 hours and 3 minutes.	
* LXXXV.	Do.	Do., 2 lbs. 12½ oz.	Do.	20 grs.	Death, preceded by paralysis.	13 minutes.	19 minutes.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiments.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of Symptoms.	Notes.
LXXXVI.	Iodide of methyl-codeium.	Frog, 701 grs.	Subcutaneously.	2 grs.	Death, preceded by paralysis.	21 minutes.	Not observed.	
*LXXXVII.	Do.	Do., 610 grs.	Do.	2·5 grs.	Do. do.	11 minutes.	Not observed.	
LXXXVIII.	Codeia.	Rabbit, 3 lbs.	Do.	0·5 gr.	Abnormal frequency of respiration, increase of reflex activity, and slight hypnotism, followed by recovery.	14 min. and 30 seconds.	About 4 hours.	
LXXXIX.	Do.	Do., 2 lbs. 14 oz.	Do.	1 gr.	Death, preceded by spontaneous twitches, and numerous tetanic convulsions.	15 minutes.	1 hour and 30 minutes.	Same rabbit as survived 15 grs. of iodide of methyl-codium (Experiment LXXXIV.)
XC.	Iodide of methyl-codeium.	Do., 3 lbs. 12 oz.	By stomach.	15 grs.	None.			
XCI.	Do.	Do., 2 lbs. 13 oz.	Do.	30 grs.	None.			
XCII.	Codeia (as hydrochlorate).	Do., 2 lbs. 5 oz.	Do.	5 grs.	None.			
* XCIII.	Do.	Do., 2 lbs. 5 oz.	Do.	7 grs.	Hypnotism, and increase of reflex cavity, followed by recovery.	43 minutes.	More than 2 hours and 30 seconds.	
* XCIV.	Do.	Do., 3 lbs. 13 oz.	Do.	10 grs.	Do. do.	24 minutes.	More than 2 hours and 36 minutes.	Same rabbit as received into the stomach, without any effect, 30 grs. of iodide of methyl-codeium (Experiment XCI.)
XCV.	Sulphate of methyl-codeium.	Do., 3 lbs. 2 oz.	Subcutaneously.	4 grs.	None.			
* XCVI.	Do.	Do., 4 lbs.	Do.	8 grs.	Paralysis, followed by recovery.	30 minutes.	About 1 hour and 20 min.	No hypnotism was observed in either of these experiments.
XCVII.	Do.	Do., 4 lbs. 4 oz.	Do.	10 grs.	Death, preceded by paralysis.	23 minutes.	19 minutes.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiments.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of Symptoms.	Notes.
XCVIII.	Sulphate of methyl-codeium.	Frog, 722 grs.	Injected into abdomen.	1 gr.	Death preceded by paralysis.	14 minutes.	Not observed.	
* XCIX.	Do.	Do., 694 grs.	Do.	1 gr.	Do. do.	11 minutes.	Not observed.	
C.	Do.	Rabbit, 4 lbs. 13 oz.	By stomach.	20 grs.	None.			
CI.	Iodide of methyl-morphium.	Do., 2 lbs. 14 oz.	Subcutaneously.	20 grs.	None.			
CII.	Do.	Do., 2 lbs.	Do.	20 grs.	None.			
* CIII.	Do.	Frog, 501 grs.	Do.	1 gr.	Paralysis, followed by recovery.	1 hour and 25 minutes.	More than 24 hours.	
* CIV.	Do.	Do., 410 grs.	Do.	2 grs.	Death, preceded by paralysis.	50 minutes.	Not observed.	
CV.	Morphia.	Rabbit, 2 lbs. 14 oz.	Do.	8 grs.	Death, preceded by hypnotism and epileptic convulsions.	1 hour and 4 minutes.	More than 48 hours.	Same rabbit as survived 20 grs. of iodide of methyl-morphium (Experiment CI.)
CVI.	Iodide of methyl-morphium.	Do., 3 lbs. 12 oz.	By stomach.	30 grs.	None.			
CVII.	Morphia.	Do., 3 lbs. 12 oz.	Do.	5 grs.	Hyptonism and catalepsy, followed by recovery.	1 hour and 6 minutes.	About 3 hours and 30 min.	Same rabbit as received 30 grs. of iodide of methyl-morphium (Experiment CVI.)
CVIII.	Sulphate of methyl-morphium.	Do., 3 lbs.	Subcutaneously.	2 grs.	Hypnotism (and paralysis?), followed by recovery.	54 minutes.	More than 3 hours.	
* CIX.	Do.	Do., 3 lbs. 5 oz.	Do.	3 grs.	Do. do.	15 minutes.	More than 2 hours.	
* CX.	Do.	Do., 3 lbs. 1oz.	Do.	4 grs.	Do. do.	18 minutes.	More than 3 hours.	
* CXI.	Do.	Do., 3 lbs. 8 oz.	Do.	5 grs.	Do. do.	15 minutes.	More than 3 hours.	
CXII.	Do.	Do., 3 lbs. 1 oz.	Do.	8 grs.	Hypnotism and paralysis, followed by recovery.	12 minutes.	More than 2 hours.	

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiments.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of Symptoms.	Notes.
CXIII.	Sulphate of methyl-morphium.	Rabbit, 3 lbs. 8 oz.	Subcutaneously.	10 grs.	Death, preceded by paralysis.	7 minutes.	55 minutes.	
* CXIV.	Do.	Do., 2 lbs. 13 oz.	Do.	15 grs.	Do. do.	5 minutes.	7 minutes.	
CXV.	Do.	Frog, 480 grs.	Injected into abdominal cavity.	1 gr.	Do. do.	8 minutes.	Not observed.	
* CXVI.	Do.	Do., 444 grs.	Do.	1 gr.	Do. do.	4 minutes.	Not observed.	
CXVII.	Morphia (as sulphate).	Rabbit, 3 lbs. 8½ oz.	Subcutaneously.	2 grs.	Hypnotism, followed by recovery.	20 minutes.	More than 3 and less than 24 hours.	
CXVIII.	Do.	Do., 3 lbs. 2 oz.	Do.	4 grs.	Do. do.	7 minutes.	More than 48 and less than 72 hours.	
CXIX.	Do.	Do., 3 lbs. 7 oz.	Do.	5 grs.	Do. do.	7 minutes.	Not observed.	
CXX.	Do.	Frog, 510 grs.	Injected into abdominal cavity.	0·75 gr.	Death, preceded by increase of the reflex function, spasms, tetanic convulsions, and partial paralysis.	16 minutes.	More than 1 hour and 44 min. and less than 24 hours.	
CXXI.	Sulphate of methyl-morphium.	Rabbit, 4 lbs. 3½ oz.	By stomach.	20 grs.	None.			
CXXII.	Nitrate of methyl-morphium.	Do., 3 lbs. 2 oz.	Subcutaneously.	20 grs.	Death, preceded by tremors and paralysis.	3 minutes and 30 seconds.	10 minutes.	
CXXIII.	Iodide of methyl-nicotium.	Do., 3 lbs. 7 oz.	Do.	5 grs.	None.			
* CXXIV.	Do.	Do., 2 lbs. 3 oz.	Do.	5 grs.	None.			
CXXV.	Do.	Do., 3 lbs. 4 oz.	Do.	10 grs.	Tremors and partial paralysis, followed by recovery.	10 minutes.	1 hour and 18 minutes.	Not an absolutely pure preparation; the colour being yellowish brown.
CXXVI.	Do.	Do. 2 lbs. 10 oz.	Do.	10 grs.	Slight tremors, followed by recovery.	13 minutes.	About 20 min.	Pure, nearly colourless and odourless preparation.

TABULAR SUMMARY OF EXPERIMENTS—*continued.*

No. of Experiment.	Substance employed.	Animal and its weight.	Method of exhibition.	Dose.	Effect.	Interval between administration and commencement of symptoms.	Duration of symptoms.	Notes.
CXXVII.	Iodide of methyl-nicotium.	Rabbit, 3 lbs.	Subcutaneously.	15 grs.	Tremors and partial paralysis, followed by recovery.	11 minutes.	49 minutes.	
CXXVIII.	Do.	Do., 3 lbs.	Do.	20 grs.	Death, preceded by tremors and paralysis.	8 minutes.	About 2 hours.	
* CXXIX.	Do.	Do., 3 lbs. 2 oz.	Do.	25 grs.	Do. do.	6 minutes.	1 hour and 38 minutes.	
CXXX.	Do.	Frog, 430 grs.	Injected into abdominal cavity.	1 gr.	Partial paralysis, followed by recovery.	15 minutes.	More than 1 and 30 min. and less than 15 hours.	
* CXXXI.	Do.	Do., 630 grs.	Do.	3 grs.	Death, preceded by paralysis.	10 minutes.	More than 2 and 26 min. and less than 20 hours.	
CXXXII.	Nicotia (as sulphate).	Rabbit, 3 lbs.	Subcutaneously.	6·5 minim (=about 0·5 gr.).	Death, preceded by tremors, violent convulsions, and partial paralysis.	2 minutes.	13 minutes.	Same rabbit as survived 15 grs. of iodide of methyl-nicotium (Experiment CXXVII.)
CXXXIII.	Sulphate of methyl-nicotium.	Do., 4 lbs. 3 oz.	Do.	10 grs.	Slight tremors, and partial paralysis, followed by recovery.	10 minutes.	1 hour and 10 minutes.	
CXXXIV.	Do.	Frog, 683 grs.	Injected into abdominal cavity.	3 grs.	Death, preceded by paralysis.	32 minutes.	More than 2 and less than 48 hours.	