ON THE CONNECTION BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION; WITH SPECIAL REFERENCE TO THE PHYSIOLOGICAL ACTION OF THE SALTS OF THE AMMONIUM BASES DERIVED FROM STRYCHNIA, BRUCIA, THEBAIA, CODEIA, MORPHIA, AND NICOTIA.

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IT is obvious that there must exist a relation between the chemical constitution and the physiological action of a substance, but as yet scarcely any attempts have been made to discover what this relation is. All that is known is, that as a general rule (with some striking exceptions) the compounds of certain elements, such as mercury or arsenic, and of certain radicals, such as cyanogen, possess (when soluble in water, or the fluids of the body) a physiological action which appears to be of the same kind for the whole series of compounds of each element or radical.

Although we cannot obtain a rational explanation of the connection between the chemical and physiological characters of a substance until we know more of the *modus operandi* of poisons, it might be supposed that a careful examination and comparison of known facts would lead to the discovery of some empirical law or laws by means of which we could deduce the action from the chemical constitution. Unfortunately, however, we know next to nothing of the constitution of the majority of those substances (such as the natural alkaloids) the physiological action of which has been most carefully investigated. It appears, therefore, to us that there is more hope of arriving at some definite conclusion by studying the changes produced in the action of physiologically active substances by performing upon them certain well-defined chemical operations which in-

troduce known changes into their constitution, but do not break up the molecule. To use a mathematical analogy, if we represent the constitution by C and the physiological action by Φ, Φ is some unknown function of C, say fC; to discover this we produce a known change on the constitution by which it becomes $C+\Delta C$, and examine the corresponding change of physiological action which has become $\Phi+\Delta\Phi$. We thus obtain the relation between ΔC and $\Delta\Phi$ or $\Delta f.C$, and by sufficiently varying C and ΔC, we may hope to get at all events an approximate solution of the problem. Operations which introduce a known change into the constitution without breaking up the molecule are of two kinds, (1) replacements (or more properly displacements), and (2) additions. As this paper is not addressed exclusively to chemists, we think it right to give here such an explanation of these terms as may make what follows generally intelligible.

When one or more constituents of a chemical substance are exchanged for one or more new constituents, the process is called replacement; thus when zinc acts on sulphate of copper producing metallic copper and sulphate of zinc, the copper is said to be replaced by the zinc[1]; and when carbonate of soda acts on sulphate of lead producing carbonate of lead and sulphate of soda, sodium is said to be replaced by lead in the carbonate, and lead by sodium in the sulphate[2]. Similarly, when pentachloride of phosphorus acts on water producing oxychloride of phosphorus and hydrochloric acid, the chlorine is said to replace oxygen, and *vice versâ*[3]. The molecule thus produced may be very different from the original one, but the new constituents occupy the place and perform the functions of the old, though often in a very different way.

When new constituents enter a molecule without displacing any thing already there, the process is called addition; thus hydrochloric acid (HCl) is added to ammonia (NH_3) producing chloride of ammonium (NH_4Cl). In the same way iodide of methyl (CH_3I) is added to ammonia (NH_3) producing

[1] $CuSO_4 + Zn = ZnSO_4 + Cu$.
[2] $Na_2CO_3 + PbSO_4 = PbCO_3 + Na_2SO_4$.
[3] $PCl_5 + H_2O = POCl_3 + 2HCl$.

hydriodate of methylamine ($NH_3(CH_3)I$). To take another example, chlorine (Cl_2) is added to olefiant gas (C_2H_4) producing Dutch liquid ($C_2H_4Cl_2$). Here the new constituents do not represent anything which was in the original molecule; the place they now occupy was, in a certain sense, vacant, and the new substance belongs to a different order of compounds from the old. The examples given above illustrate two different (or at least apparently different) ways in which a substance may be susceptible of addition, (1) by the increase of the external chemical activity of an atom (in the examples, N, which before the addition is united to three equivalents and after it to five), and (2) by the increase of the external chemical activity of a group of atoms (in the example C_2, which before the addition is united to four equivalents and after it to six). In the latter case the substance to which addition can be made is said to be 'condensed.' We shall, however, apply the term 'condensation' to susceptibility of addition in either way, and distinguish the two cases as *intra-atomic* and *extra-atomic* condensation. The degree of condensation is measured by the extent to which the process of addition can be carried; thus carbonic oxide, ammonia, olefiant gas, allylic alcohol, &c. are of the same degree of condensation, each being capable of taking up *two* additional equivalents. Hydrocyanic acid, acetylene, diallyl, &c. are twice as condensed as the former group, being capable of taking up *four* additional equivalents.

In commencing our investigation of the change produced by chemical operations on the physiological action of substances, we had thus two distinct kinds of chemical operation to choose between. We have selected as the first subject of study the effect of chemical addition; our reasons for doing so will be best explained by a short statement of what was already known in this department. As a general rule replacement does not appear to produce any marked change in physiological activity. The exceptions to this are of three kinds, (1) where the replacement changes the physical character of the substance, so as to render it more or less easily absorbed into the system, thus acetate of lead is poisonous, sulphate of lead is inert; (2) where the activity depends on direct local action, thus sulphuric acid

(H_2SO_4) and caustic soda (NaHO) are both poisonous, while sulphate of soda (Na_2SO_4) and water (H_2O) are not; (3) where the replacement removes or introduces the atom or radical upon the presence of which the activity depends, thus acetate of lead is poisonous, acetate of soda not. Besides these exceptions there are several isolated cases of change of activity produced by replacement, such as the very different action of the two classes of metallic cyanides.

In order to discover the physiological effect of addition we must compare the action of the substance before and after the addition is performed upon it; and that this may be done fairly, three conditions must be fulfilled; (1) that the two substances should be equally capable of absorption into the system; (2) that the process of addition can neither be performed nor reversed in the system; and (3) that neither substance has such a powerful local action as would prevent our observing its general or remote effect. These conditions exclude from our consideration a very large number of cases. Thus we cannot compare the action of the ferrous or arsenious compounds with that of the ferric or arsenic, on account of the readiness with which the former are oxidized, and the latter reduced; we cannot compare the action of corrosive sublimate with that of calomel, because the one is so much more readily absorbed than the other; we cannot compare the action of anhydrous sulphurous (SO_2) with that of anhydrous sulphuric acid (SO_3) on account of the violent local action of the latter; and, to content ourselves with another example, we cannot compare the action of an alkaloid with that of its salts, because the alkaloid is converted into a salt in the stomach, and the salt is probably converted into the alkaloid in the blood and other alkaline fluids of the body. After making all the deductions required in order that the three conditions stated above may be satisfied, there remains, however, a very large number of cases in which the action of a substance before and after addition may be fairly compared. We subjoin a list of some of the more important of these, in which the physiological action has been studied by previous observers. 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 bodies produced.

I.	II.	III.
Carbonic oxide CO	O	Carbonic acid CO_2
Hydrocyanic acid HCN	H_4	Methylamine CNH_5
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 stated to be inert, or nearly so, their action, when they have any, differing entirely from that of the bodies from which they are derived.

Such a connected view of these hitherto isolated facts not unnaturally leads to a suspicion that *condensation* (which is diminished by addition) is in some way connected with physiological activity, which seems also 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[1], as already mentioned, is a remarkable example of this, and the salts of tetrethyl-arsonium[2] seem to be equally inert. Similarly, the salts of tetramethyl-stibonium[3] are not emetic. So that, as far as experiment goes, it would appear that the stable compounds of pentatomic arsenic and antimony have a very different and much less intense action than the compounds containing these elements as triads. The occurrence, however, of saturated substances, such as alcohol, oxalic acid, and corrosive sublimate, 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; but

[1] Bunsen, *Annalen der Chemie und Pharmacie*, XLVI. 10.
[2] Landolt, *Ann. d. Ch. und Ph.* LXXXIX. 331.
[3] Landolt, *Ann. d. Ch. und Ph.* LXXXIV. 49.

there can be little doubt that if the effect of condensation were discovered and eliminated, the other conditions might be much more hopefully sought for.

For these reasons we have turned our attention to the effect of chemical addition in modifying the action of poisons, and have selected, as the first subject of investigation, the addition of iodide of methyl to the natural alkaloids belonging to the class of nitrile bases[1].

As this addition removes only the *intra-atomic* condensation of the typical nitrogen, and leaves any other condensation untouched, and as the radical or radicals united to the nitrogen are in the case of all the natural alkaloids highly condensed, we should not expect, even supposing that condensation and poisonous action go together, to find the action entirely removed by this addition. The results of experiment, as will be seen from the subsequent part of this paper, confirm this expectation.

As the iodides of the complex ammoniums thus produced are, in most cases, sparingly soluble in water, we have also examined the action of the corresponding sulphates, which are very soluble.

The vegetable alkaloids to which we have applied this method are strychnia, brucia, thebaia, codeia, morphia, and nicotia.

STRYCHNIA.

Iodide of methyl-strychnium. Stahlschmidt, the chemist who discovered the methyl-strychnium compounds, has published a statement to the effect that they are inert[2]. As the sequel will show, we do not altogether confirm this assertion, but it is proper to acknowledge that our investigation arose entirely from it.

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 and energetic of toxic agents. Doses varying from the one-twentieth to the one-thirtieth of a grain

[1] We have also examined the action of some of the iodides prepared by the addition of iodide of ethyl, and have found, as might have been expected, that it is the same as that of the corresponding methyl compounds.

[2] Poggendorff's *Annalen*, CVIII. 523.

rapidly produce in rabbits the most violent 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 localization of its action on the spinal cord.

In our first experiments with iodide of methyl-strychnium, we administered, subcutaneously, a number of doses, varying in amount from one to five grains, to rabbits and dogs, but were disappointed by finding that, although our iodide of methyl-strychnium was much less active than strychnia itself, it still produced spasms and convulsions, and, sometimes, even tetanus. It was not until we had adopted certain precautions, which at first appeared unnecessary, in the process of preparation, that a body of almost absolute purity, and, therefore, nearly completely free from any trace of unchanged strychnia, was obtained. It is obvious that the greatest possible care is necessary to prevent fallacy in the case of such powerful poisons as we were examining; for a very minute quantity of the unchanged poison—that is of the poison which had escaped the chemical addition—would quickly prove its presence by special symptoms, and so either mask or seriously modify any action that might be caused by the changed substance. In the case of iodide of methyl-strychnium, the presence of 0·5 per cent. of strychnia in a dose of five grains would produce marked symptoms of strychnia-poisoning.

Having succeeded in obtaining a pure preparation, its effects on rabbits were first examined by subcutaneous injection. It was administered as a fine powder suspended in warm distilled water, in which menstruum it is but sparingly soluble, though more so than in water at the ordinary temperature. 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, without any effect whatever. Fifteen grains, however, produced serious symptoms, though followed by recovery, and death was caused by the exhibition of twenty grains. 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 activity. In fact, a condition exactly the reverse of that produced by strychnia was caused by iodide of methyl-strychnium. In place of violent spasmodic convulsions and muscular rigidity, the appearances were those of paralysis, with a perfectly flaccid condition of all 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 autopsies further evidence was obtained to distinguish the effects of iodide of methyl-strychnium 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 early or almost immediate occurrence of *rigor mortis* that follows the action of strychnia, the muscles continued flaccid, contractile, and alkaline for many hours.

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 in warm distilled water. No effect was produced by this method of exhibition, although as much as thirty grains was given at one time. This rabbit was killed, some days afterwards, by introducing, in the same way, one-tenth of a grain of strychnia into the stomach. As thirty grains of iodide of methyl-strychnium contain about twenty-one grains of strychnia, this experiment proves that the addition of iodide of methyl diminishes the poisonous activity of strychnia at least two hundred and ten times.

As iodide of methyl-strychnium is a sparingly soluble substance, it appeared proper, 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.—As had been anticipated, the sulphate of methyl-strychnium is a much more active substance 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 to a rabbit, weighing three pounds and a quarter, symptoms of a most serious character were produced, but death did not result. Some days afterwards, one-twentieth of a grain of strychnia, dissolved in very dilute sulphuric acid, was administered to this rabbit by subcutaneous injection; and it produced symptoms of strychnia action, followed by death fifteen minutes after the injection. Eight-tenths of a grain of sulphate of methyl-strychnium contain about six-tenths of a grain of strychnia; the effect of the addition had been, therefore, to reduce the poisonous activity of strychnia at least twelve times.

When this substance is administered to rabbits by the stomach, twenty grains appears to be about the minimum fatal dose.

The symptoms that are produced by sulphate of methyl-strychnium are the same as those that are caused by the corresponding iodide. The very short account we have given of the symptoms and *post mortem* phenomena that occur after the administration of iodide of methyl-strychnium, is sufficient to suggest a close resemblance between its action 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[1]. Both substances undoubtedly produce a condition of 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.

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 per-

[1] *Wochenblatt der Zeitschrift der k. k. Gesellschaft der Aertze in Wien;* VI. Band, 1866, pp. 157—162.

fectly 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 50 per minute.

This experiment was repeated with one grain of iodide of methyl-strychnium, and the same results were obtained. We have, therefore, demonstrated that sulphate and iodide of methyl-strychnium 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 added-to 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 process of chemical addition so thorough a change should be produced in physiological action. It has also been shewn that this addition has greatly reduced the poisonous activity of strychnia.

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.—In a series of experiments it was found that ten grains of iodide of methyl-brucium, suspended in warm distilled water, could be administered subcutaneously to a rabbit without any effect. Eighteen grains rapidly produced death, with exactly the same phenomena as are observed with the corresponding strychnia compound, and, therefore, without the slightest trace of those symptoms of exaggerated reflex action, convulsions, and tetanus, that are caused by brucia itself. Fifteen grains were injected under the skin of a rabbit, and produced a condition of general paralysis, from which a complete recovery had taken place in forty-five minutes after the administration. Some days afterwards, this rabbit was rapidly killed by the subcutaneous injection of one-fifth of a grain of brucia. Fifteen grains of iodide of methyl-brucium contain about thirteen grains of brucia; the addition of iodide of methyl, therefore, diminishes the poisonous activity of brucia at least sixty times. The fatal dose of brucia is about twice as large as that of strychnia; but that of iodide of methyl-brucium is about the same as that of iodide of methyl-strychnium. The latter is, however, less soluble in water than the former, and the similarity in the poisonous activity is probably due to this difference in solubility.

Some experiments were made in which this substance was administered by the stomach, and it was found that thirty grains—containing about twenty-five grains of brucia—could be thus given to a rabbit without any effect.

Sulphate of methyl-brucium.—One grain of sulphate of methyl-brucium produced no effect when injected under the skin of a rabbit. Two grains, exhibited in the same way, caused complete loss of motility, and other symptoms in no way distinguishable from those produced by the corresponding preparation of strychnia. The fatal dose of this substance for

an average-sized rabbit was found to be two grains and a half. Two grains of this sulphate contains about 1·7 grain of brucia; and as one-fifth of a grain is a large fatal dose of the latter, the addition of sulphate of methyl renders brucia at least nine times less poisonous.

It was found that twenty grains of sulphate of methyl-brucium could be introduced into the stomach of a rabbit, without the slightest symptom being produced. This dose contains about seventeen grains of brucia, and its magnitude is apparent when we recollect that about a quarter of a grain of uncombined brucia thus administered will rapidly kill a rabbit.

The addition of iodide or sulphate of methyl modifies not only the fatal dose, but also the physiological action of this alkaloid. By the same methods of investigation as were adopted with the corresponding compounds of strychnia, we have demonstrated that iodide and sulphate of methyl-brucium destroy the function of the peripheral terminations of the motor nerves—the addition having produced the same remarkable change in the action of brucia as in that of strychnia.

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 mode 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[1]. 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 is more soluble in hot water and in dilute spirit 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,

[1] *Comptes Rendus*, 1864, p. 413.

produced absolutely no effect. When, however, the dose was increased to ten grains, partial and then complete paralysis was caused, and death occurred eleven minutes after the administration. The effects were, in all respects, the same as those observed with the methyl derivatives of strychnia and brucia; there was, therefore, a complete absence of any convulsive symptoms and of exaggeration of reflex activity, and the *post mortem* phenomena were those that follow curare-poisoning. In another experiment, eight grains was injected under the skin of a rabbit weighing two pounds and three quarters: this produced general paralysis and complete muscular flaccidity, but it was ultimately recovered from. For the purpose of testing the poisonous activity of the thebaia itself, one-fifth of a grain was injected under the skin of the same rabbit: convulsive starts and spasms, great exaggeration of reflex activity, and violent attacks of tetanus were quickly produced, and soon terminated in death. *Post mortem* rigidity, with an acid reaction of the muscles, occurred in less than forty minutes afterwards, and while the temperature of the body was as high as 95° F. About 5·5 grains of the alkaloid thebaia are contained in eight grains of iodide of methyl-thebaium; the poisonous activity of thebaia is, therefore, reduced at least thirty times by the addition of iodide of methyl.

Without describing the experiments in which this substance was exhibited by internal administration, nor those in which the sulphate was employed, it is sufficient to observe that we have obtained the most satisfactory proof of a complete change having been produced in the physiological action of thebaia by chemical addition. This change is the same as that which occurs with strychniá and with brucia.

Codeia.

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

Iodide of methyl-codeium.—Five grains of iodide of methyl-codeium can be readily dissolved in a sufficiently small quantity

of warm water to allow of its injection into the subcutaneous tissue of a rabbit; but no effect was produced by this dose. Serious and prolonged symptoms were caused by the administration, in the same way, of fifteen grains; but even this large quantity did not induce a fatal termination. The rabbit to which this had been given was quickly affected with convulsions and opisthotonos after the subcutaneous administration of one grain of codeia; and this proved a fatal dose.

As much as thirty grains of iodide of methyl-codeium may be given to rabbits, by the stomach, without producing any apparent effect.

Sulphate of methyl-codeium seems to have precisely the same action as iodide, but the fatal dose of the sulphate is somewhat less than that of the iodide.

Neither iodide nor sulphate of methyl-codeium possess the slightest convulsant action. Experiments with frogs have shewn us that reflex exaggeration is never produced, but that, with comparatively large doses and after some time, paralysis of the motor nerve end-organs occurs. Codeia has but a feeble soporific action, and it is, therefore, difficult to determine if this is affected by chemical addition. We are at present inclined to believe that it is not.

Morphia.

The only other opium alkaloid in which the effects of chemical addition were examined is morphia. The most recent and trustworthy investigations shew that this substance 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[1].

Iodide of methyl-morphium.—As iodide of methyl-morphium is nearly insoluble in cold and but sparingly soluble in warm water, it was administered in the form of a fine powder suspended in water. We were unable to produce any effect whatever, even when so large a dose as twenty grains was injected under the skin of a small rabbit, and from the bulky character of the powder a larger quantity could not be conveniently

[1] Claude Bernard. *Op. cit.*

administered. Eight grains of morphia was afterwards exhibited, in the same way, to this rabbit. In about an hour, a tendency 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; and, however unnatural the position might seem to be, if it were consistent with rest, sleep immediately occurred. This condition lasted for about forty-eight hours, when spasms made their appearance, and, by and by, assumed all the characters of epileptiform convulsions. The rabbit was found dead on the morning of the third day after the administration. On one occasion twenty grains of iodide of methyl-morphium was introduced into the stomach of a rabbit, but even this large quantity was insufficient to produce any effect.

As we have completely failed in causing any symptom, in warm-blooded animals, with this preparation, we have no data by which to determine how far the poisonous activity of the morphia that it contains has been reduced.

Any conclusions drawn from experiments made 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[1], 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.

Sulphate of methyl-morphium is, in common with the other sulphates we are occupied with in this paper, an extremely soluble compound. Ten grains, administered in solution by subcutaneous injection, produced paralysis, well-marked narcosis, and death, in a rabbit. Eight grains was not a fatal dose, but it

[1] Dr Fraser.

caused complete paralysis with long-continued narcosis. Neither in these, nor in any of the many other experiments we performed with this substance, was there any trace of spasmodic action or of exaggeration of the reflex function. The predominating symptoms were those of paralysis, but it was somewhat difficult to judge how much of this was due to the co-existing narcotism.

To determine this, the blood-vessels were tied in one limb near the knee of each 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, and three-fourths of a grain of morphia, dissolved in very dilute sulphuric acid, into the abdominal cavity of the other. The frog with sulphate of morphia was affected, in about an hour, with clonic spasms and exaggeration of reflex activity; in two hours, with several distinct attacks of tetanus; and it was found dead and in *rigor* on the following morning. The frog with sulphate of methyl-morphium was flaccid and paralysed in twenty minutes; and, in thirty minutes, galvanic stimulation of any portion of the skin was followed by energetic movements of the *tied limb*, but of no other part. The further phenomena proved that the peripheral terminations of the motor nerves were paralysed.

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

When administered by the stomach the same quantity of sulphate as of iodide of methyl-morphium—twenty grains—has been found insufficient to affect a rabbit. It has, however, been ascertained that soporific effects may be produced in man by sulphate of methyl-morphium.

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 energy, derived from tobacco.

Iodide of methyl-nicotium is a crystalline body readily soluble in cold water. A dose of five grains, 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; no convulsive movements having occurred during the progress of the symptoms. An experiment was made with a very small dose of the nicotia with some of which this iodide of methyl-nicotium had been prepared, and it was found to have the usual energetic properties of the alkaloid. As about eight grains of nicotia are contained in fifteen grains of iodide of methyl-nicotium, and as one-tenth of a grain of nicotia is a fatal dose for a rabbit, while fifteen grains of iodide of methyl-nicotium is less than a fatal dose; it follows, that the addition of iodide of methyl renders nicotia at least eighty times less powerful as a poison.

On account of the readiness with which iodide of methyl-nicotium dissolves in water, it was not to be expected that any change of poisonous activity would be caused by its conversion into a sulphate; and our experiments have shewn us that the fatal dose of sulphate of methyl-nicotium is nearly the same as that of iodide of methyl-nicotium.

In the absence of any very trustworthy 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 always occur during nicotia-poisoning, are not among the symptoms produced by either iodide or sulphate of methyl-nicotium. We have also found that this modification is not due to an action of the changed substance on the motor nerves; for it has been ascertained that paralysis of neither the trunks nor end-organs of these nerves exists after the action of iodide or sulphate of methyl-nicotium.

Some experiments were made to determine 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 shewn 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, completely changed in character. The latter effect is strikingly and remarkably illustrated by the complete change that is produced in the action of strychnia, brucia, and thebaia; it is apparent in codeia and morphia; and it is least obvious in the case of nicotia. 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 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 actions of the methyl derivatives of these bases are 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 their 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 shewn to act as curare does, are so energetic as that substance, three of them—sulphate of methyl-strychnium, of methyl-brucium, and of methyl-thebaium—are sufficiently so to rank as powerful poisons, and to fulfil all possible therapeutical requirements. 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. For all purposes of physiological study and demonstration, they may also be substituted, with advantage, for this poison.

There is another result of this investigation, from which, without being considered over-sanguine, we may anticipate an important practical advantage. The action of morphia is not a simple one. In addition to its chief action as a soporific, it exerts a stimulant effect on the spinal cord. The latter sometimes manifests itself in human adults, it frequently does so when large doses of morphia are administered to children, and it invariably appears in the lower animals as a symptom of nearly equal prominence with narcosis. The soluble salts of methyl-morphium have been shewn to possess a narcotic but no spinal stimulant action. It is therefore hoped that, in certain cases, they will prove advantageous substitutes for the salts of morphia; but the data we have as yet obtained on this question are insufficient to warrant any positive statement.

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.

This investigation has done little more than merely introduce us into a vast field of inquiry, but it has justified us in expecting that important fruits may be obtained by further and careful cultivation.