A CONTRIBUTION TO THE PHARMACOLOGY OF CURARE AND ITS ALKALOIDS.[1]

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IN this paper I propose to show specially, among other points, that the pure alkaloid curarine, in addition to its paralysing action on motor nerve ends, produces tetanus; and that also all specimens of curare have a tetanising action on the cord.

The *curare* or *wourali arrow poison* of South America has for a long time occupied quite a special position in the physiological and pharmacological laboratory as an aid in experimental research. Yet, although a very large number of papers, dealing at length with its actions, have been published in the physiological literature of the last thirty-five years and earlier, there are still some important points on which there is complete difference of opinion; and, on the other hand, some important points are held to be firmly established, although, as will be seen, unsupported by evidence which is free from fallacy.

Especially after Claude Bernard's observations were made on curare in 1844, it was universally agreed by many investigators that the poison interrupted in some way the conductivity of a part of the endings of the motor nerves distributed to striped muscles.

Almost all those early writers further concluded that curare did not paralyse the endings of sensory nerves. Several of them, however, came to the opposite conclusion, and in this they are strongly supported by several recent authors.

[1] This paper is an abstract of part of a thesis presented to the Medical Faculty of the University of Edinburgh in April 1889 for graduation as Doctor of Medicine, to which was awarded a gold medal and the Christison (Gunning) Prize.

The main part of the work was done in the Pharmacological Laboratory of the University of Leipzig in 1887–88 while holding an Edinburgh University scholarship. The experiments with crude curare, the bark of *Strychnos toxifera*, and some of those with methyl-strychnium salts were carried out in the Pharmacological Laboratory of the University of Edinburgh in 1888–89.

Some investigators and authors who state that the sensory nerves are depressed or paralysed by curare.	Date.
Schiff (10),	...
Bœhlendorff (11),	1865
Lange (12),	1874
Romanes (14),	1876
Steiner (13),	1877
Binz (15),	1884
Lauder Brunton (16),	1887

Some investigators and authors who state that the sensory nerves are not affected by curare.	Date.
Bernard (1),	1857
Kölliker (2),	1856
Vulpian (3),	1854–9
Martin-Magron and Buisson (4),	1859
Pelikan (5),	1857
Haber (6),	1859
Von Bezold (7),	1860
Kühne (8),	1860
Bidder (9),	1865

On the important question of the action on the spinal cord of a poison, whose chief active principle is derived from the strychnos family of plants, less, but equally emphatic, difference of opinion is to be found.

The great majority of writers are agreed that curare has no "stimulant" or tetanising action on the spinal cord. But, while several consider that the poison has no action, the general opinion is that the experimental evidence is very distinctly in favour of a paralysing action. On the other hand, some of the early writers are equally clear that curare has a "stimulant" or strychnine-like action.

Some investigators and authors who state that the spinal cord is either unaffected or is paralysed by curare.	Date.
Bernard (1),	1857
Kölliker (2),	1856
Haber (6),	1859
Bidder (9),	1865
Foster (17),	1873
Rutherford (18),	1880
Brunton (16), &c.	1887

Some investigators and authors who state that the spinal cord is "stimulated" or acted upon in a strychnine-like manner by curare.	Date.
Wundt and Schelske (19),	1859
Martin-Magron and Buisson (4),	1859
Von Bezold (7),	1860
Vulpian (3),	1882

Confining attention, meanwhile, to the action on the sensory nerves and spinal cord, it may at once be suspected that there are some serious difficulties or fallacies in the investigation, otherwise, the experimental evidence detailed by distinguished physiologists on either side would not be so contradictory, and so many authors would not, time after time, arrive at different conclusions.

A serious objection to the employment of only crude curare in any kind of precise work is the circumstance that the poison is not an individual chemical body, but a more or less impure

compound vegetable extract of variable strength, composition, and origin. There is no security, therefore, that curarine is the only alkaloid present. Indeed, this objection has been emphasised quite recently by Boehm (20), who has shown that, in some varieties of curare, the alkaloid curarine is associated with another alkaloid, which he has named curine. Without a pure curarine there could be no decision free from an element of uncertainty; but it may at once be stated that the different views of the action of the poison on sensory nerves and the spinal cord are not to be explained by chemical differences in the curares, but by the fallacies caused by the actions of the poison itself.

A pure specimen of curarine, recently prepared and very kindly supplied to me by Professor Boehm, was first employed. As a preliminary to the investigation, the poisonous activity and general action of the alkaloid were determined.

In the frog, the minimum dose by subcutaneous injection which could be relied upon to produce complete paralysis of the motor nerve endings was about 0·00000028 gramme of curarine per gramme of body weight of male specimens of *Rana esculenta*. In about 30 minutes all general voluntary movements had ceased. Before 60 minutes all trace of reflex movement had disappeared, except in the throat muscles of respiration, which were not completely paralysed until about 2 hours after the administration of the poison. Recovery took place in the inverse order, and was usually complete in summer by 24 hours, and in winter by 2 to 3 days. A seventh part of the minimum paralysing dose caused distinct signs of motor weakness; and, after a third of the dose, the frog could not turn over when placed on its back, and did not fully regain motor power for 5 to 10 hours in summer, and for 10 to 24 hours in winter. The administration of this last dose daily for 20 days in summer and every alternate day during 40 days in winter produced only a similar motor weakness, which was least marked after the first dose or two.

On increasing the dose to eight times the minimum paralysing dose, the reflexes did not return until the 5th day, and the frog could not turn over for 2 or 3 days later. After sixteen times the minimum dose, the reflexes returned (respiratory muscles first) in 9 to 10 days, and the frog could turn over on the 14th to 16th day. In one case, where thirty-two times the minimum paralysing dose was given, the reflexes did not return until the 18th day, and the frog could not turn over until the 25th day. Generally, however, a dose thirty times greater than the minimum paralysing proved fatal, the heart ceasing to beat by the 2nd or 3rd day, and little or no urine being secreted. These observations were made at a temperature of 15° C.,

and precautions were taken to keep the skin of the paralysed frogs moist and freely exposed to air. During very warm weather, however, the smaller paralysing doses not unfrequently proved fatal, the cutaneous respiration being insufficient to support life.

Recovery from the motor paralysis was never accompanied or followed by any increased reflex excitability.

When fatal doses of curarine were administered by subcutaneous injection to rabbits, cats and dogs, the animals died in from 5 to 15 minutes from motor paralysis. When a dose slightly less than the minimum fatal of 0·00035 gramme of curarine per kilo [Boehm (20)] was administered daily by subcutaneous injection to a rabbit for 16 days, no prominent symptoms, except a varying degree of motor collapse, were observed. On many occasions the paralysis was complete except for the movement of the diaphragm. Usually by 45 minutes the motor weakness was recovered from, and the rabbit began to move about and to eat, and its health seemed in no way disturbed by the daily paralysis.

No increased reflex excitability accompanied or followed recovery, and in all respects the alkaloid produced the usual symptoms of curare poisoning in warm-blooded animals.

In order to ascertain in a curarised frog the condition of the sensory nerves, and of the central nervous system, it is usual to stop the circulation in some part of the body to protect its motor nerves from the paralysing action. Now, this end is not quite safely attained by the ligature of blood-vessels only, for, unless the dose is small, or the experiment of very short duration, the poison is apt to, and does, diffuse from the adjacent uninterrupted tissues and lymph spaces.[1]

In the experiments to be described, the mode of preparing the frog employed by Bernard (1) (p. 345) was, with some modification, adopted. All the tissues at the pelvis being tied on each side to the iliac bones, the lumbar nerves being excluded, and very carefully protected from pressure.

In an intact frog the operation and tying of the tissues causes of itself great depression and irregularity of the reflexes, as tested by dilute acids. When the influence of the higher centres is removed by previous section of the cord, the operation then causes a relatively slight depression, and little or no irregularity, during an ordinary experiment of several hours duration. It is evidently not, therefore, the stoppage of the

[1] In experiments on medusæ, partially divided (Romanes (14), p. 301), diffusion seems readily to occur from one half to the other. Failure of motor power must confuse any conclusions on sensibility.

circulation in the lower extremities of the frog which may produce apparent want of power or sensibility, but the presence of the brain. It seens important to state this, because, on the one hand, the stoppage of the circulation in the legs has been erroneously held to be a sufficient cause for the reflex depression which is observed after the administration of curare; and, on the other hand, some fallacious conclusions have been come to on the action of curare on the reflex centres and sensory nerves by experimenting with intact frogs, and disregarding the possible influence of the higher centres on the reflexes.

The ordinary symptoms of curare poisoning in protected frogs seem to point strongly in the direction of general nervous paralysis. It is not always easy to contrast the experiments described by different authors, as the percentage of curarine in the various curares is unknown. No common definite system of dosage in multiples of a minimum paralysing dose of any solution of unknown strength has been adopted.

After the administration, to an intact frog, of a small dose of curarine or curare, of say twice the minimum paralysing dose (0·00002 gramme curarine in a frog weighing about 36 grammes), motor weakness of the unprotected parts appears in a short time, and by 15 minutes the last reflex twitches of the throat muscles have ceased. The symptoms are the same as with curare. The protected lower extremities continue meanwhile to maintain their normal position of flexion, and generally exhibit active reflex movements when either the poisoned or the unpoisoned skin is stimulated. It is noticeable that, although the protected parts are capable of active motion, true voluntary movements are rarely seen after the first few minutes (Kölliker (2), p. 58; Vulpian (3), p. 256; Foster (17), p. 397). After nearly half an hour the reflexes have become distinctly more and more difficult to obtain (Kölliker (2), p. 39), a circumstance hardly sufficiently recognised by Vulpian and others.

Martin-Magron and Buisson (4) (p. 526), Vulpian (3) (p. 288), and many later writers have all observed that, as the reflexes, in this early stage of the poisoning, gradually fail they become irregular; and stimulation of the poisoned skin often ceases to produce an effect, while yet stimulation of the skin of the protected part causes some reflex movement.

Martin-Magron and Buisson (4) (p. 527), however, in addition state that sometimes stimulation of the poisoned skin may not only act quite well, but may do so when a stimulation of the unpoisoned skin fails. I have repeatedly observed this last fact in frogs where the higher centres were intact. Often only the first of a series of stimulations acts, and it acts whether applied to the poisoned or unpoisoned

skin. If the poisoned skin is first stimulated, and then the unpoisoned, the impression is that the sensory nerves are paralysed. Indeed, complete irregularity of response to the stimulation of any part is, over a series of experiments, almost as marked a feature as depression, for the details of the results of the systematic stimulation of the poisoned and unpoisoned skin in one experiment are often quite contradicted by the next. The condition, except at the very beginning of an experiment, is certainly not so simple as would appear from Bernard's statement (1) (p. 353): "Toute excitation portée sur cette partie paralysée eveillera dans la partie preservée des mouvements réflexes énergiques."

From the fact that the stimulation of the unpoisoned skin usually gives the best reflexes has in part arisen the view that curare paralyses the sensory nerves, although really it is only natural that, as the protected part alone can move, and the reflexes are depressed, stimulation of its own coverings should produce a greater effect than stimulation of a distant part.

On tracing the symptoms of the poisoning further we find, with this dose, that frequently after 45 to 60 minutes ($\frac{1}{2}$ to $1\frac{1}{2}$ hour; Kölliker (2), p. 55) practically no reflex movement can be obtained on stimulating either the poisoned or the unpoisoned skin, while yet stimulation of the lumbar nerves causes vigorous movements in the protected extremities.

This fact has been generally held to indicate satisfactorily a direct reflex paralysis of the cord by the poison.

After many general, and some ninety-seven special experiments directed to the conditions of the spinal cord and sensory nerves after the administration of curarine, the following results and conclusions have been arrived at.

I. *Experiments with Small Doses of Curarine of about two to five times the Minimum Paralysing.*

A. If, in an *intact* protected frog, the same dose of curarine be administered as in B, and about 45 to 60 minutes after poisoning, when the reflexes are very irregular and depressed, or have disappeared to stimulation of either the poisoned or the unpoisoned skin, *the spinal cord be successfully divided below the medulla*, the condition of reflex depression and irregularity and apparent sensory or spinal paralysis quickly changes, and active movements of the protected parts regularly follow every stimulation of either the poisoned or the unpoisoned skin.

Example.—*Exp.* No. 57. *Oct.* 1887. *Temp.* 15° C. Preparation of lower extremities as usual. Injection of 0·00003 gramme curarine—equal to twice the minimum paralysing dose—in 0·3 c.c. water.

Minutes after poisoning.

7 Spontaneous jerk of legs. No further spontaneous movements throughout thiperiment.

15 Complete motor paralysis of all parts except the lower extremities.

18 Reflexes to dilute sulphuric acid—·3 per cent.

Left foot withdrawn in 20 sec.
Right „ „ 1 „ ?

28 Left foot not withdrawn in 70 „
Right „ „ 70 „

38 Left „ „ 70 „
Right „ „ 70 „

Meanwhile the reflexes to pinching either the poisoned or unpoisoned skin continue good and fairly regular.

45 Reflexes to pinching becoming rather difficult to obtain; pinching the protected feet gives the best reflex.

50 Reflexes further impaired and very irregular. Sometimes pinching the poisoned skin acts when the unpoisoned skin fails, and sometimes both act, or twenty successive stimulations to all parts cause no movement. When systematically applied at intervals, the *first* stimulation, as a rule, causes a reflex, irrespective of the skin being poisoned or not, while second or third stimulations applied at the same time fail. There is much irregularity, however.

60 Strong acetic acid applied twice to the poisoned or unpoisoned skin without any distinct reflex movement following. Pinching usually entirely fails to act. The lower extremities remain flexed.

65 The spinal cord now carefully exposed above the level of the brachial nerves. During the cutting of the tissues and bones not the least sign of life occurred in this experiment, as if the sensory nerves or nerve centres were paralysed. Complete section of the cord, with very sharp, small, thin-bladed knife to prevent dragging or bruising. Very slight hæmorrhage.

The lower extremities vigorously extended on making the incision.

68 Complete change in the reflexes. Every pinch of either the poisoned or unpoisoned skin immediately causes a reflex movement; and the reflexes to the dilute acid have reappeared.

Right foot withdrawn in 22 sec.
Left „ „ 11 „

76 Right „ „ 10 „
Left „ „ 7 „

95 The same results, but the movements becoming very feeble.

In similar experiments with vigorous frogs, where the spinal cord was divided successfully during this stage of reflex depression, results of a like kind were always obtained. When the poisoned anterior extremities were allowed from time to time to dip into the dilute acid, after section of the spinal cord, reflex movements regularly followed in the unpoisoned posterior extremities, although, previous to the division, no form of stimulation produced any effect. In one case, notwithstanding the mutilation and the depression caused by the successive severe operations, the spinal cord retained its vitality for 7 hours after section, and stimulation of either the poisoned or the unpoisoned skin caused reflex movements.

These experiments occasionally failed, chiefly from (1) imperfect ligature of the vessels and tissues at the lower part of the abdomen; (2) pressure of the ligatures, or compressed tissues, or displaced organs (kidneys), against the trunks of the lumbar nerves; (3) rapid paralysis of the cord after section, even when every care taken in the operation. This seemed especially to occur in warm weather.

The following sets of experiments seemed to remove all chance of error.

B. If the *spinal cord in the frog be successfully divided below the medulla on the day previous to the experiment,* and the same relative dose of curarine be administered as in A, the early irregularity and depression or disappearance of the reflexes, which is usually such a marked feature of curare poisoning in experiments on the *intact protected animal, does not occur at all,* nor can any apparent difference between the sensibility of the poisoned and of the unpoisoned skin be observed.

Example.—*Exp.* No. 44. *Sept.* 1887. *Temp.* 17° C.

The spinal cord divided on the day previous to the experiment, and the lower extremities protected in the usual manner one hour before poisoning.

Minutes before poisoning.	Reflexes to ·3 per cent. Sulphuric Acid.	
21	Both feet withdrawn in 2–4	Beats of Metronome (exact equivalent in seconds omitted to be obtained).
18	,, ,, 2–4	
12	,, ,, 2–4	
6	,, ,, 2–4	
0	,, ,, 2–4	

Administration of same relative dose of curarine as in the experiments on intact frogs.

Minutes after poisoning.	Reflexes to ·3 per cent. Sulphuric Acid.
2	Both feet withdrawn in 2–4 beats.
8	,, ,, 2–4 ,,
14	,, ,, 2–4 ,,
23	,, ,, 2–4 ,,
33	,, ,, 2–4 ,,
43	,, ,, 2–4 ,,
53	,, ,, 3–4 ,,
63	,, ,, 3–4 ,,
95	,, ,, 3–4 ,,
2 hours	,, ,, 4 ,,

During the whole period, pinching either the *poisoned or the unpoisoned* skin *instantly* caused a reflex movement in the protected lower extremities.

These results were repeatedly confirmed, and made it evident that some other explanation must be given of the symptoms produced by small doses in *intact frogs* than an early direct depressing action on the cord or sensory nerves. The fact that the sensory nerves are not paralysed receives confirmation from other experiments, C.

C. If the spinal cord in a frog be successfully divided below the medulla, and *an enormous dose of curarine be injected into one extremity,* which is so isolated from the body that all transfusion of fluids is prevented, but nervous connection is retained, yet, *delicate stimulation of the skin of this paralysed and greatly over-poisoned part causes, during many hours, an active reflex movement in the rest of the body.*

Example.—*Exp.* No. 70. *Decem.* 1887. *Temp.* 15° C.

Spinal cord divided just above the brachial nerves on 10th December, and on the 13th December the lower extremities prepared in the usual manner, an extra ligature at the pelvis preventing diffusion between the isolated extremities. Subcutaneous injection of 0·0015 gramme curarine dissolved in ·25 c.c. water into the right leg. *A dose sufficient to completely paralyse ninety frogs* of the same weight as the one experimented upon was thus introduced into a part of one extremity.

Time after poisoning.	
½ hour.	Complete motor paralysis of the whole right lower extremity.
1 hour.	Faint stimulation of *any part of the skin of the paralysed extremity* causes active reflex movements in the rest of the body. When no stimulation is applied the frog remains perfectly still.
3 hours.	The same result.
8 hours.	The same result. The reflex movement instantly follows the stimulation of the poisoned skin.

Experiments of this kind were repeated several times, *but the saturation of the skin with overwhelming doses had no apparent influence on the sensibility.*

It is probable that the curarine, in an experiment of this kind, reached the endings of the sensory nerves in the skin, since it was administered subcutaneously and diffused to all the deep motor endings. At all events, the negative result is of some value.[1]

The preceding three sets of experiments bring out clearly that the early reflex depression and irregularity in an intact protected frog, after small doses of curarine or curare, are due to an "inhibitory" influence exercised by the higher centres, and not to a paralysis of the sensory nerves or of the spinal cord.

When the cerebrum was removed, the administration of small and medium paralysing doses of curarine produced, during the following hour, practically no impairment of the reflexes; but, when in the same experiment, the optic lobes were pricked with a needle, the reflexes were at once suspended for several minutes to every form of stimulation.

Sometimes when a drop of a relatively strong solution of curarine was applied to the optic lobes, marked depression of reflexes occurred, but very soon other symptoms, presently to be described, set in.

The reflex depression caused by small doses of curarine, in addition to that caused by the operation itself in intact frogs, would seem to proceed from the cerebrum therefore.

[1] The administration of strychnine during the stage of depression in the intact frog (Martin-Magron and Buisson (4), p. 527) shows that stimulation of the previously apparently insensible parts, poisoned and unpoisoned alike, readily causes reflex tetanus of the protected part.

It has also already been noted that in protected frogs poisoned by curarine or curare, impairment or loss of volition is one of the earliest symptoms.

The depression of voluntary and reflex movement may be due to a reflex influence on the cerebrum. The frog is probably conscious, after several attempts, of its inability to make definite movements with most of its body, ceases to make ineffectual attempts with the protected part, and resists stimulation. This seems all the more likely, unless there is a common direct cerebral action, because in poisoning with paralysing doses of Tetra-methyl, and Tetra-ethyl-ammonium and Methyl-strychnium salts, I have noticed much the same condition in intact protected frogs.

The only other explanation that occurs to me, apart from a possible direct action on the cerebrum, is a possible disturbance of the circulation in the brain. Ringer and Murrell (21) give some data of the effect on frogs of the mechanical arrest of the circulation. When the brain was present the arrest caused a strong reflex depression of the cord, since, in experiments in September (p. 73) " in entire frogs reflex action was lost on an average in 5 minutes, and in brainless frogs it persisted on an average 59 minutes."

Small doses of curarine do not paralyse the circulation; therefore, if the reflex depression in intact frogs is due to cerebral anæmia, it must arise from vasomotor spasm. I do not know of any experiments where the condition of the vasomotor centres has been determined in curarised frogs. Later experiments on the blood-pressure in rabbits will show, that, after the administration of small doses of curarine, stimulation of the skin of the paralysed animal causes intense vasomotor spasm. It is possible that the same condition exists in frogs.

Passing now to the consideration of the action of large doses of the poison, I shall try to show that its direct and indirect effects, and the obstacles which one action may throw in the way of another, have not been clearly defined, and that consequently almost all the experiments that have been made have pointed in one direction—to an erroneous view of the direct action of the poison on the spinal cord.

II. *Experiments with Large Doses of Curarine of from fifty to one hundred times the Minimum Paralysing Dose (0·0005 to 0·001 gramme in a frog weighing 36 grammes).*

When a large dose is administered by subcutaneous injection, motor paralysis of the unprotected parts occurs in a minute or two. Purpose-like voluntary movements quickly disappear in the protected extremities, although, at this stage of the poisoning, markedly irregular spontaneous movements occasionally occur. In the intact frog the reflexes to chemical and mechanical stimulation of the poisoned or the unpoisoned skin usually quickly become difficult to obtain, and for a time indeed are practically suppressed. This early reflex depression is not due to any direct paralysing action of the poison on the sensory nerves or spinal cord, for, just as in the case of small and medium doses, it does not occur at all when the spinal cord is isolated from the higher centres. If, when a large dose has been given, the spinal cord be divided *during* and not *before* the experiment, it is advisable not to delay the section beyond about an hour, otherwise, for reasons which will immediately be shown, a direct weakness of the cord may have set in.

The later symptoms differ very distinctly in the following particulars from those produced by small doses:—

1. The reflex depression in intact frogs continues usually for a period of from 70 to 90 minutes, and then spontaneously disappears.
2. It is followed by a period of very variable duration, during which the reflexes are either *simply improved* slightly, or, in addition, spontaneous and reflex movements of a *spasmodic character* occur.

   This period of relative nervous excitement is as a rule of brief duration, and the spasmodic symptoms, although unmistakable in character, are, when present, slight and easily exhausted.

   Marked depression of reflex excitability rapidly follows, and, in from 3 to 5 hours usually, passes into *total paralysis* of the spinal cord. Even 20 hours, however, may elapse before reflex paralysis is complete. The *larger the dose* of curarine, and the *higher the*

temperature, the quicker the paralysis as a rule. Stimulation of the *poisoned* skin at this stage causes reflexes as long as the cord retains vitality, and the protected muscles remain contractile.

3. In a *decided minority* of cases the period of early reflex depression is followed by a *marked increase* of the nervous excitability, passing an hour or two later into complete spinal paralysis.

In about 5 per cent. of these cases *well marked tetanus* occurs.

Perhaps the precise significance of these symptoms can best be considered after one or two experiments have been described.

Exp. No. 80. *Jan.* 1888. *Intact* frog.

Time after poisoning.	
	Administration of *seventy-five times* the minimum paralysing dose.
2 min.	Complete motor paralysis of unprotected parts.
15 ,,	Disappearance of reflexes to dilute acid.
30 ,,	Progressive impairment of reflexes to pinching.
62 ,,	No voluntary movement during the last 47 minutes. *Spontaneous* movements now occur from time to time. These movements are *inco-ordinate*, and consist of a jerky extension of the lower extremities, or a slow sprawling movement, or a slow, spasmodic-like extension, the web of the toes being outstretched.
80 ,,	Reflexes to pinching are *much more easily* obtained now.
100 ,,	A slight touch on *either the poisoned or unpoisoned* skin causes a quick, jerky extension of the lower extremities. When the stimulation is slight crossed reflexes are well seen.
3 hrs.	Feet withdrawn from the dilute acid in 6 *seconds*. *Moderate tetanus* can be induced from time to time on pinching *any part* of the skin or tapping the body.
4 ,,	Spontaneous movements ceased, and reflexes no longer obtained on stimulating the skin, the upper end of a divided sciatic nerve, or the upper end of the cord. Stimulation of the lower end of the divided sciatic nerve, or the lumbar nerves of the other side, causes active movement of the lower extremities.

Exp. No. 81. *Jan.* 1888. *Intact* frog. *Temp.* 16° C.

Administration of seventy times the minimum paralysing dose.

Time after poisoning.	
25 min.	Reflexes distinctly depressed.
80 „	Slight improvement of reflexes.
2 hrs.	Occasional slight spontaneous movements.
6 „	Reflexes distinct, but feeble and easily exhausted.
16 „	Pinching the poisoned skin of back and anterior extremities causes *feeble* contractions in the upper thigh muscle, the rest of the extremity having become dry and rigid. The heart beat not to be observed on the thorax.
26 „	Condition unchanged, but, when next observed, paralysis was complete, the cord having retained vitality for a much longer time than usual.

Exp. No. 82. *Jan.* 1888. Frog with *divided cord.* *Temp.* 18° C.

Spinal cord successfully divided on the day previous to the experiment.

Minutes before poisoning.	
10	Feet withdrawn from ·3 per cent. sulphuric acid in 4 to 5 seconds.
0	Feet withdrawn from ·3 per cent. sulphuric acid in 4 to 5 seconds.
	On pinching the feet the reflex is very active.

Time after poisoning.	
	Injection of 1 c.c. solution containing 0·001 gramme curarine. Frog weighs 88 grammes—about *forty times* the minimum paralysing dose.
5 min.	Complete motor paralysis of the unprotected parts.
13 „	Frequent slight spontaneous movements in the lower extremities.
15 „	Reflex to dilute acid in 5 seconds—to pinching immediate.
18 „	Both lower extremities frequently forcibly extended and flexed. While in the position of flexion and extension, faint, irregular movements of muscles.
30 „	Frequent spontaneous movements; no diminution of reflexes as in the intact frog.
40 „	*Distinct tetanus* following stimulation. The lower extremities often quite rigid for 5 to 10 seconds. *This condition, with intervals of rest, continued for* 20 *minutes.*
60 „	Spontaneous movements less frequent, and the tetanus when induced is brief, and the necessary intervals of rest longer.
	To dilute acid, { Right foot in 15 sec. / Left „ 9 „ } But difficult to observe the exact time of true reflex.
80 „	Reflexes much weaker, and tetanic movements difficult to obtain.
95 „	A brief tetanic spasm on pressing the foot.
2 hrs.	No further reflex. Direct stimulation of the lumbar

nerves causes active movements in the lower extremities.

Many of the experiments were without decided evidence of tetanic action, but showed some suspicious symptoms—partly paralytic and partly convulsant.

Exp. 59. *Oct.* 1887. *Divided cord.* *Temp.* 15° C.

Cord divided on previous day.

Time after poisoning.	
	Injection of 0·00025 gramme curarine in 0·25 c.c. water = thirty times the paralysing dose.
7 min.	Paralysis complete in unprotected parts.
32 „	Reflexes have continued good — no exaggeration of reflexes.
49 „	After the reflex movement has taken place, some twitchings shown in the legs, and occasionally spontaneous jerks occur.
59 „	Reflexes very acute (but no tetanus) on touching any part.
69 „	Reflexes slowly becoming less acute.
79 „	Reflexes distinctly feeble.
109 „	Only a faint reflex movement obtained.
2 hrs.	Complete paralysis of the cord.

After many such experiments it became absolutely certain that the subcutaneous administration of relatively large doses (0·0005 to 0·001 gramme) of curarine caused in intact frogs the disappearance of the primary reflex depression, and produced in a proportion of all the cases symptoms generally understood to signify "stimulation" of the spinal cord. I especially repeated the experiments over and over again as the result was quite contrary to the general belief.

Without a pure curarine such a question could never be settled, for, in experiments with a doubtful mixture like curare (assuming meanwhile that the same results are obtained), there must always have remained with it an uncertainty as to *what caused the tetanus, and what the paralysis.*

Now, while the "stimulation" of the spinal centres shows itself, on the one hand, in the early spontaneous disappearance of the reflex depression, and on the other hand in the appearance more or less of reflex spasm, it remains to be explained why in the first place *total paralysis* of the spinal cord occurs in the *majority of cases* in a few hours, and why, in the second place, if stimulation of the cord is a true action of the larger doses of

the poison, *the appearance of reflex tetanus after subcutaneous administration is inconstant, and occurs only in a relatively small proportion of cases.*

The explanation of these important negative facts is, I think, undoubtedly to be found in the great change produced by large doses of the poison (·001 gramme) in *the circulation.*

It is known that large doses of curare impair the diastolic filling of the heart (Vulpian (3), p. 354), which may, after several hours (Von Bezold (7), p. 168, &c.), cease to beat. In my own experiments where large doses of curarine were given, and the thorax not opened, the heart continued to beat for a good many hours, or even for a day or two.

If in an ordinary experiment where a small dose of curarine has been administered the heart be exposed and watched, little immediate change occurs in its condition, if the frog during the observations is under the same conditions of temperature as before the experiment.

After a time the blood becomes dark owing to the general muscular paralysis having stopped the respiration by the lungs; and, especially in warm weather, a distinct slowing of the heart's action sets in. This cannot be attributed to any direct action of curarine, for simple artificial stoppage of respiration by the lungs slows the heart in summer frogs.

When large doses of curarine, however, are administered, there may be a quickening of the heart's action for a minute or two, soon followed by a marked slowing. The inhibitory action of the vagus is suspended. But what is most noticeable is a distinct diminution in *the volume of the heart.* The diastolic filling becomes very imperfect, although the rate is not at first affected much. A change in this direction begins several minutes after the poison has begun to act, and in a variable time which it is difficult to estimate correctly, but often within 30 minutes, it is practically an empty ventricle that for the time being continues its regular contractions. It will be shown that in warm-blooded animals large doses of curarine greatly lower the blood-pressure, just as curare does. Since in the frog the heart itself continues to act well, though more or less empty, it is evident that the blood-vessels are in some way paralysed. If the abdominal viscera be examined, it will be found that the

veins are greatly distended with dark coloured blood. If the spinal cord be divided, there is practically no hæmorrhage.

It is evident that the supply of oxygen is cut off, for not only is the pulmonary respiration of necessity stopped, but the cutaneous respiration is also practically at an end, for the blood is no longer actively circulating throughout the skin of the paralysed animal. This is confirmed by the fact that in deeply curarised frogs the gas analysis (Valentin (22), p. 99) shows a marked sinking of the oxygen absorbed and carbonic acid given off, and the muscles have no longer a red colour, whereas in frogs paralysed by small doses of curare, and where consequently the circulation in the skin is not so much influenced, the gas analysis shows that the oxygen absorbed is not diminished.

Under the conditions of the circulation therefore brought about by a large dose of curarine, the quantity of oxygenated blood which can reach the central nervous system must usually be very small.

It has often been shown that when the aorta is compressed, or the heart paralysed, or the frog surrounded with an irrespirable gas, &c., or, in other words, when the blood can obtain oxygen but cannot circulate, or circulates but cannot obtain oxygen, the central nervous system becomes after a time paralysed. In control experiments I generally found that the paralysis of the cord was *complete* in about 45 minutes in very hot weather, and in from 1½ to 3 hours at lower temperatures in winter.

Now curarine, in large doses, produces, in a short time, a condition of the circulation *similar to that which would be caused by the ligature of all the veins entering the heart.* In experiments where the spinal cord has been previously divided the circulatory paralysis is, if possible, accentuated by the vasomotor centres being cut off.

It is certain, therefore, that the alkaloid is not only imperfectly circulated, but that it must, by causing this great dilatation of the blood-vessels, indirectly weaken and paralyse the central nervous system; and this secondary paralysis must occur, no matter what the direct action may be of that part of the dose which may reach the brain and cord.

Since marked impairment of the circulation sets in with the subcutaneous injection of such a large dose of curarine as 0·001

gramme, it is impossible to say how much of it is ever carried to the spinal cord.[1]

Assuming for the moment that the direct action of large doses of curarine on the cord is a "*stimulating*" one, then the *infrequency of tetanus* after subcutaneous injection shows that the part of the dose which does reach the cord is generally either insufficient to produce tetanus, or it reaches too late to overcome the weakness produced by the want of oxygenated blood.

It is known that the cardiac contractions may continue in the frog for a considerable time without blood, and it would therefore be a mistake to assume at the beginning of pronounced curare poisoning that, because the *heart movements* were to be observed on the thoracic wall, *the circulation* was being efficiently maintained.

Later experiments show that the infrequency of tetanus and the spinal paralysis can only be explained by the failure of the circulation.

We may now proceed to the further statement that, when the inevitable fallacies which attend the subcutaneous administration are avoided, by applying the poison directly to the cord, and by injecting a solution of it into the aorta, *the symptoms are constant and quite unmistakable, and show that the true primary action of at least the larger doses of curarine on the spinal cord is that of a convulsant poison allied to strychnine.*

A. *The Local Application of Solutions to the Spinal Cord.*

Before applying a solution of curarine it is necessary, in an unprotected frog, to suspend the circulation by ligature of the aorta or heart, to prevent the poison being conveyed to the muscles. Experiments are most completely satisfactory in winter, as the cord retains its vitality for from $1\frac{1}{2}$ to 3 hours after the circulation is stopped.

Exp. No. 86. *Jan.* 1888. *Temp.* 12° C.

Brain destroyed to prevent voluntary movements. Heart ligatured.

[1] Vulpian (3) (p. 359) shows that in curarised frogs the action of Digitalin, Strophanthin, Upas Autiar, Jaborandi and Muscarin is much less in degree, and the symptoms much later in appearing, than when similar doses are given to non-curarised frogs, and that this indicates delayed absorption.

Minutes after poisoning.	
15	Whole cord exposed without injury. No movements when undisturbed.
30	During the last 30 minutes 30 drops of a solution (1 in 10,000) allowed to trickle over the spinal membranes, which are mostly intact. Most of the solution necessarily escaped. Not the faintest movement has occurred.
50	During the last 15 minutes 15 drops of a solution (1 in 1000) of curarine, applied as before.
51	*Violent tetanic spasm* of the whole body, lasting 15 seconds (about), on accidentally shaking the table.
52	*Tetanus follows every stimulation.* Often successive shocks occur, lasting about 5 seconds each.
65	*Frequent spontaneous tetanic shocks during the last* 10 *minutes*, some of them lasting almost continuously for a minute.
75	Frequent twitching of individual muscles.
95	Violent tetanus, lasting 20 seconds, on pinching the foot.
2 hrs.	Tetanus very brief, and relatively feeble.
2½	Feeble reflexes only.
3	Paralysis of cord, having remained active without blood for about 3 hours at this temperature.

Exp. 87. *Jan.* 1888. *Temp.* 13° C.

Minutes before poisoning.	
35	Brain destroyed, heart ligatured, and cord fully exposed.
15	Frog has been left undisturbed for 20 minutes to see if any signs of excitement from injury, exposure, or any imaginary combination of circumstances could act. Not the faintest movement has occurred. On pinching the foot the reflex is simple, and not at all strong.
Minutes after poisoning.	
	Application of 2 drops of solution, containing 0·0005 gramme curarine. The membranes lining the spinal canal were in great part unbroken, and the cavity filled with lymph and some blood, so that the curarine did not come into quite immediate contact with the cord.
16	*Violent tetanic convulsion*, lasting for 16 seconds (about), and the faintest touch or vibration renews the spasm.
23	*Repeated spontaneous tetanic spasms.* These often begin slowly, the extremities being moved about in various directions, according to the muscles most in action, and, finally, all parts become affected, and a *most intense tetanus* sets in, lasting for a minute perhaps.
	Reflex tetanus immediately follows a stimulation.
2¼ hrs.	Spontaneous jerks, &c., have ceased. Reflex tetanus very feeble and brief.

When the spinal cord is carefully and completely divided into

two parts before applying the solution, it is found that tetanus occurs in the muscles supplied from both parts, showing that the symptoms are directly due to an action on the cord. When the dose is very large—several milligrammes—tetanus of the most violent kind sets in after a few minutes, and the bloodless cord is sooner exhausted; or it may possibly be that the poison finally exercises some direct paralysing action in addition. Such experiments prove that the local application of, say, half a milligramme or so of curarine produces marked and true tetanic symptoms; and, when a healthy frog is used, and the cord is not seriously injured in the preparation, and the motor nerve ends are thoroughly protected, *the appearance of tetanus is invariable.*

Since the subcutaneous injection of a solution of curare or curarine in a warm-blooded animal seems absolutely non-irritating, and since the solutions employed were very weak (average 1 in 1000), neutral in reaction, and free from impurities of any kind, it is quite improbable that a tetanus of the nature described could result from any local irritating action, as that term is ordinarily understood. The symptoms are the same in kind as those which, under the same circumstances, follow the application of strychnine, while the dose of curarine is larger and the symptoms of shorter duration. It is impossible, however, to experiment with large doses of curarine under the same conditions as with strychnine, and they cannot be fully contrasted therefore. Even if the heart be not artificially arrested, the dose of curarine which tetanises must, on absorption, greatly weaken or paralyse the circulation.

B. *Injection into Blood-Vessels.*

A satisfactory demonstration of the tetanising action of curarine is obtained when it is conveyed to the cord through the blood capillaries.

Very speedy results were always obtained when the experiment was made in the following manner:—Ligature of the common abdominal aorta *above* the origin of the large common intestinal artery (cœliaco-mesenteric), ligature of one aorta at its origin, and one pulmo-cutaneous trunk. On making the injection by means of a cannula in the other aorta close to the heart, the only important vessels through which the solution can pass are

the carotid and occipito-vertebral arteries of one side, that is to say, the vessels which supply the central nervous system. If the subclavian artery, or the arm on the same side, be also ligatured, the great part of the solution passes directly to the brain and cord. The experiments are most successful when the temperature is not high, as the cord does not lose its vitality so quickly when deprived of blood.

Exp. No. 90. *Jan.* 1888. *Temp.* 13° C.

Minutes after poisoning.	
	Preparation as described, the cord having been divided to prevent voluntary movements, and the brain destroyed.
1	Slow injection of ·8 c.c. solution, containing 0·0008 gramme curarine, into the left aorta. Almost *immediate appearance of jerks and spasms*, which continued nearly without interruption for 50 minutes.
7	*Severe spontaneous tetanic convulsions*, followed by constant spasm of individual muscles and groups of muscles, the extremities being jerked about in all directions.
15	The tetanic spasms still continuing with extreme violence, and when these abate every muscular fibre is in a state of constant twitching.
25	The violence of the spasms abating somewhat.
55	Gradual cessation of spasms. Only feeble movements on stimulation.

The same results were obtained in every experiment. When several milligrammes were injected, the tetanus was almost *instantaneous* and *exceedingly violent.* The *instant appearance* of tetanus here shows that the late and inconstant appearance of spasmodic symptoms *after the subcutaneous injection* of large doses is not due to any true delayed action on the cord, but to the circulatory difficulties.

Kölliker (2) and Bernard (1) made special experiments with curare *without observing tetanus.* In Kölliker's (p. 39) experiments the curare was administered subcutaneously, and when the reflexes had disappeared the cord was divided and strychnine immediately applied. The first part of the experiment was exposed to the fallacy which attends subcutaneous injection; the strength of the dose is unknown; and the immediate use of strychnine after the division of the cord prevented any further observations.

In Bernard's experiment (p. 329) the curare was *applied locally* to a part of the cord. The experiment has this value that the cord was not depressed, but for several reasons it would be valueless as a proof that curare is not a tetanising poison. In the first place the *strength*

of the dose is unknown. *The time* the frog was under observation is not stated; and we do not know whether *only one*, or more than one experiment was tried. Indeed, the experiment is so briefly dismissed that it is evident that Bernard never seriously experimented in this direction.

So far as I have read, no other special experiments have been made, and there is therefore no further opposing evidence of an *experimental* kind to consider.

III. *Experiments with Curare.*

If curarine is a tetanising poison, it becomes very probable that *every genuine motor paralysing specimen of crude curare* has this action. As it seemed important to substantiate this, I carried out a series of observations on pithed frogs in the Pharmacological Laboratory of Edinburgh University during the winter 1888–89.

The following specimens of curare were examined:—

1. Poisoned darts of the Macusi tribe of Indians in British Guiana. From Sir Andrew Halliday, Army Medical Service, presented to Professor Christison in 1839.
2. Poisoned arrows from same source.
3. Poisoned darts from British Guiana, obtained by Professor Simpson in 1848.
4. Poisoned arrows from same source.
5. Urari poison in gourd from same source.
6. Urari poison in gourd from Dr Ewan Cameron, Berbice, in 1849.
7. Curare from "Agassiz gourd, Brazil," presented to Professor T. R. Fraser in 1870 by Dr Weir Mitchell.
8. Curare from "Pot from Paya, from Agassiz," from same source.
9. Curare from "Pot from Para," from same source.
10. Curare from "Pot from Academy of Natural Sciences, now in possession of Dr Hammond," from same source.
11. Curare (source unknown) purchased from Messrs Hopkin & Williams. London, 1888–89.
12. Curarine from same source.
13. Curare (source unknown) purchased from E. Merck, Darmstadt, 1888–89.
14. Curarine (curin frei) from same source.
15. "Wourali poison of Guiana, presented to Dr Traill from Dr Schomburgk in 1842."

The first six specimens and the last are in the Materia Medica Museum of the University of Edinburgh, and for these and the next four specimens I am indebted to Professor Fraser.

The different specimens were standardized by making solutions in distilled water, filtering, and approximately determining the activity of the filtrate on two or three frogs. Taking the quantity which was found to be the minimum paralysing dose to contain about 0·00000028 gramme of curarine per gramme weight of frog, the filtrates were evaporated at a low temperature until in each case about ·5 c.c. would contain roughly 0·001 gramme curarine.

The details of the experiments were the same as in the case of similar experiments with curarine, and it is only necessary to state the conclusion, viz., that on destroying the brain, and applying these solutions to the cord, or preferably making a direct injection into the aorta in the manner previously described, tetanus was in every case obtained readily just as with curarine. When a larger dose, corresponding probably to 2 or 3 milligrammes of curarine, was injected *instantaneous tetanus of the most marked character* set in.

These curares were selected quite at random, were of undoubted authenticity, and quite representative specimens, dating from 1837 to 1888.

It would appear, therefore, that any genuine motor paralysing curare has a *direct tetanising* action, which is readily seen when a definite dose is employed, and when, above all, the *indirect* actions of the poison are guarded against.

The cause of this tetanus we have already found in the essential active principle of the crude arrow poison—curarine—an alkaloid having, at the same time, an intensely active paralysing action on motor nerve ends.

The statement made thirty years ago that curare acted as a tetanising as well as a paralysing poison gave rise to the opinion (Husemann (24), p. 528) that experiments giving such results could not have been made with *curare*, but with some strychnine containing substance.

As no one since has observed tetanus produced by ordinary curare, it is quite disbelieved that it can have any such action.

This view has been further strengthened by the chemical examination of curare. The following investigators found no trace of strychnine or brucine:—Roulin and Boussingault (28), p. 24 (1828); Pelletier and Petroz (29), p. 213 (1829); Heintz (30), p. 452 (1847); Buchner (31), p. 528 (1861); Preyer (32), p. 1346 (1865); Sachs (33), p. 255 (1878); Boehm (20) (1886).

It is impossible that so many chemists could have failed to detect an alkaloid having the characters of strychnine, and differing in so many respects from curarine.

Curare produces tetanus through containing curarine, not strychnine.

Martius (Husemann (24), p. 526) and De Castelnau (34) (p. 14 *et seq.*) state that the Ticunas tribe employ, among others, a menispermaceous plant (*Cocculus Amazonum, &c.*) in preparing curare. This plant has been found (Couty and De Lacerda (35), p. 719) to be a convulsant poison resembling picrotoxin and nicotine. These accounts are, however, all uncertain, for as Planchon (36) (p. 105) points out, the flowers of this plant are unknown, and the species doubtful.

Admitting that the composition of curare is uncertain, the existence of any specially active body, other than a paralysing one, must be very exceptional indeed, as numerous experiments by many observers have shown apparently that curare only paralyses.

If it be assumed that a picrotoxin acting body may be present in the curare of a particular district, still it is very improbable that the tribes over a vast region would always add to the essential paralysing constituent of curare a *non-essential* tetanising one, and yet we find that all curares produce both paralysis and tetanus. When we see, further, that the *tetanising* power *of curare increases and decreases in proportion to its paralysing power*, and that the same holds good with precision in the case of curarine, we may strongly suspect that the two actions are produced by an extract from a *single bark* and by a *single active principle.*

All the evidence that has been gradually accumulated points to a strychnos bark as this *basis* of curare. Most of the plants discovered by De Castelnau (34), Humboldt and Bonpland (45), Schomburgk (30), Gubler (37), Crevaux (38), and others are fully described or discussed by Planchon (36) (p. 492 *et seq.*).

The authenticity of a number of these, as bases of curare, depends only on native or other reports, and not upon *experimental* evidence.

A number of experiments have, however, been made with extracts obtained from the barks of South American strychnos plants, and the symptoms observed have been those ordinarily attributed to curare, viz., *paralytic symptoms only, and never tetanus.*

1. Schomburgk (30) (p. 445), . .	Strychnos toxifera.
2. Couty et De Lacerda (35) (p. 583), .	Strychnos triplinervia. Strychnos Castelnææ.
3. Crevaux (38) (p. 1023), . . .	Strychnos Castelnææ. Strychnos Crevauxii.
4. Jobert (39) (p. 646), . . .	Strychnos Castelnææ. "Toutes ces Strychnées."
5. Villiers (40) (p. 653), . . .	Plant closely allied to, but not Strychnos toxifera, Planchon (36) (p. 30).

The conclusion that the extracts from the barks of the South American strychnos plants, which form the basis of curare, act as paralysing but not as tetanising poisons may be given in the words of Jobert (40) (pp. 646, 647), as he seems to have examined more than

one. "J'ai experimenté avec des extrait de toutes ces strychnées. Leur action physiologique est la même; elles n'agissent pas comme tétanisant contrairement aux strychnées de l'Asie. Les strychnées Américaines du sud agissent d'une façon identique. Elles ne sont point tétanisantes, &c."

I can find no record of any experiments by these observers other than simple tests on a cold or warm blooded animal, showing that the extract is a poison acting after the manner of curare. There is no guarantee, therefore, that the method of experimenting would overcome the fallacies attending the investigation, or that, when paralysis was observed, anything further was specially looked for.

IV. *Experiments with Extract from Bark of Strychnos toxifera.*

Since a strychnos bark is the basis of curare, curarine must be derived from a strychnos bark, and the extract from the genuine bark must produce, contrary to the opinions just quoted, both paralysis of motor nerve ends and tetanus, since curarine does so. Fortunately, I am in a position to prove this. In the Pharmacological Laboratory at Edinburgh I received, in January 1889, through the kindness of Mr Holmes, Curator of the Pharmaceutical Society's Museum in London, a small quantity (4 grammes) of the bark of the *Strychnos toxifera* (Benth.), discovered by Schomburgk (30) in British Guiana, and described by Hooker (41) (iii. 340) and by Planchon (36) (p. 756), sufficient to enable me to carry out a number of experiments.

The bark was treated in the simplest manner. Two grammes were powdered, and an infusion made with cold distilled water. After several hours this was filtered, and a yellowish, bitter fluid obtained, having all the appearance of a moderately strong solution of curarine.

Experiments were then made on pithed frogs.

On determining the poisonous activity of the filtrate, it was found that about $\frac{1}{20000}$th caused in a frog (*Rana temporaria*), weighing 26·3 grammes, distinct weakness in 15, and complete reflex paralysis in 45, minutes. Larger doses caused paralysis in a minute or two, and this was found, when a part was protected, to be due to an action on the endings of the motor nerves.

As the motor paralysing dose of curarine for an intact frog (*Rana esculenta*) of this weight is 0·00000736 gramme, the 2 grammes of bark would roughly contain—to judge by the physiological test—about 7 per cent. of curarine.

A frog was then prepared by destroying the brain and tying a cannula in the aorta as described in the experiments on curarine:—

11.35 A.M.—About $\frac{1}{180}$th of the filtrate (probably equal to rather less than 0·0008 gramme curarine?) made up to ·5 c.c. with water, and injected into left aorta.

11.40 A.M.—Occasionally a slight spasmodic movement, otherwise quite still.

11.43 A.M.—About $\frac{1}{50}$th of the filtrate (probably equal to rather less than 0·003 gramme curarine?) made up to ·5 c.c. with water, and injected as before.

11.45 A.M.—Marked *jerky spasmodic* movements of all the unparalysed parts, especially the legs.

11.50 A.M.—*Unmistakable tetanus*, the lower extremities being absolutely rigid. When a general spasm of the unparalysed muscles is not present, individual muscles and groups of muscles show frequent spasms. Reflex tetanus readily induced.

It is unnecessary to enter into any further details, as the watery extract was found to be identical in its action with curarine and curare. The quantity of bark available was much too small to allow of a satisfactory chemical examination. The other 2 grammes of bark I sent to Professor Boehm, and a few weeks later he wrote confirming the extraordinary poisonous activity of the specimen, and stating that it contained curarine to the extent of probably at least 4 to 5 per cent.[1]

A *single strychnos bark* from Guiana has been found, therefore, to yield an extract containing a large percentage of an active principle which is pharmacologically, and probably chemically, identical with the pure curarine separated by Boehm from crude curare.

The bark, the crude arrow poison and the alkaloid have been shown to act in the same manner, producing paralysis by a peripheral, and tetanus by a central action.

The various conclusions in the previous part of this paper have been further substantiated, and all suppositions and misgivings as to the spinal action of crude curare being possibly due to the active principle (picrotoxin, &c.) of plants, other than the essential basis of curare, dismissed.

Most of the grounds which would discredit my conclusions have now been discussed.

The later suggestions by Gubler (37) (pp. 683) and by Bartholow (42) (p. 558), that methyl-strychnium is formed in the process of pre-

[1] The examination by Villiers (40) (p. 653) in 1885 of the bark of the *Strychnos de l'Orinoque* (Planchon), brought from the Orinoco district in 1881 by Crevaux, led also to the recognition of a body having chemical characters like curarine.

paring curare is not probable. The preparation (Humboldt (45), p. 518; Schomburgk (30), vol. v. p. 450, &c.) simply consists in the concentration of a decoction of the barks. No such body as methyl-strychnium has been found; and its chemical characters (Stahlschmidt, pp. 513–522) are not at all those of curarine (Boehm, 20). In addition, curarine has eighty-five times the paralysing activity of methyl-strychnium sulphate.

Comparison of Curarine and Strychnine.

The researches of Martin-Magron and Buisson (4) (p. 342), Richet (50) (p. 121), and Vulpian (51) (p. 555) (3) (p. 448) have especially shown, and in quite a conclusive manner, that although small doses of strychnine salts have no particular action on the endings of motor nerves, the larger doses readily cause complete motor paralysis.

It is easy to demonstrate this in a protected frog.

On comparing the two alkaloids, strychnine and curarine, we find then that they agree very closely in the quality of their actions, but differ in the order of symptoms and in the doses required to produce them. Small doses of strychnine of 0·00001 gramme produce tetanus in small frogs, without any paralysing action on the ends of motor nerves; while 0·00001 gramme of curarine produces complete paralysis of the ends of motor nerves, without any tetanising action on the cord. On the other hand, 0·001 gramme or so of curarine causes immediate paralysis of the unprotected parts, and (when fallacies are avoided) violent tetanus of the protected parts; while 0·002, or better, 0·005 gramme of a strychnine salt, causes violent tetanus of the protected parts and complete paralysis of the motor nerve endings of the unprotected parts; and neither paralyses sensory nerves.

The difference therefore between some of the main pharmacological actions of the two alkaloids remains a quantitative rather than a qualitative one.

(To be continued.)

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