A variety of curara acting as muscle-poison / Joseph Tillie.

With D: Tillie's compliments.

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TILLIE, Joseph

A Variety of cura

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A VARIETY OF CURARA ACTING AS A MUSCLE-POISON.

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AFTER the publication of my paper[1] "On an Arrow-Poison from New Granada, and on its Botanical Source," Dr James Whiteford of Greenock very kindly presented to me a bamboo quiver containing 13 poisoned blow-pipe darts, which he had also obtained personally in 1862 from the chief of a branch of the Rio Verde tribe of Indians at a village named Musinga, situated about 50 to 60 miles to the west of the city of Antioquia (New Granada, South America), between the watersheds of the rivers Atrato and Cauca.

The curara on the darts was stated by the Indians to be solely of vegetable origin, and to have been obtained from climbing plants (Spanish, *bejucos*). The Indians also informed Dr Whiteford that they never used curara of animal origin, as they could obtain in their own neighbourhood climbing plants which yielded curara, some plants yielding stronger curara than others.

Dr Whiteford informs me that, in the district of Antioquia at least, the word *curara* and its variations, is simply the Indian term for the generic *poison* (Spanish, *veneno*), and that the word is applied to any poisonous substances, whether of vegetable or of animal origin. He was, for example, informed, without however being able to verify the statement, that the Indians in the upper valley of the Atrato obtained a poison from a small *frog*, and that this was "*muy buen curara*" (very good curara), an expression which illustrates the real meaning attached to the word. It would seem therefore that the poison is not called "curara from the plant *curari* from which it is obtained," as Taylor[2] mentions, but rather that various plants are called curari, woorali, &c., because they yield curara (*i.e.*, poison).

The only reference I have found concerning the curara of New

[1] *Jour. Anat. and Phys.*, vol. xxvii. p. 402, 1893.

[2] *Pharm. Jour.*, Dec. 1877, p. 424 (cit. *Taylor on Poisons*).

Granada occurs in Hammond and Mitchell's paper[1] on "Two New Varieties of Woorara, &c.," brought from the Rio Darien region in 1859, and is as follows:—"Our friend Mr Trautbine, late chief engineer of the Panama Railway, informs us that the arrow-poison employed by the Indians of the Rio Atrato, on the eastern[2] side of New Granada, is not at all powerful. He states that he has frequently wounded birds, pigs, and other animals with it without producing any marked result. The Indians, however, told him that they used a more virulent poison when they went to war, but, if this be true, he was unable to obtain any of it." Dr Whiteford also experienced no special difficulty in obtaining in the Antioquia district specimens of ordinary curara, but he informs me that he obtained the darts, which are here described, with considerable difficulty. This circumstance alone might lead to the suspicion that the darts are smeared with some special curara, or possibly with, as Mr Trautbine was informed existed, a "more virulent poison," used in warfare.

The 13 darts are similar in appearance. They are made of a light and somewhat flexible wood; the colour, both externally and on section, is a deep brownish-black. The average weight of a dart is 1·7 grammes (26·2 grains); and the average length is 23 centimetres (9 inches). The one end is sharpened to a fine point; the other is blunt, and has a diameter of 1·5 millimetres. The shaft is roughly rounded, and attains a maximum diameter of 3 millimetres at a distance of 8 centimetres from the pointed end, and gradually tapers to the blunt end. The tips of the darts have, for a distance of about 3 centimetres ($1\frac{1}{4}$ inch), a thin coating of a greyish-coloured firmly-adherent substance.

These New Granada blow-pipe darts resemble specimens of blow-pipe darts in the Materia Medica Museum of the University of Edinburgh, obtained in 1839 from the Macusi Indians, who inhabit districts about the Upper Essequibo, British Guiana. The Macusi darts are made of a light straw-coloured wood, and are much more neatly finished than the New Granada specimens. They are of three sizes, 23, 30, and 34·5 centimetres long respectively. They have a maximum diameter of 3 millimetres; the

[1] *American Jour. Med. Sciences*, vol. xxxviii. p. 25, 1859.

[2] The Rio Atrato is on the western, not the eastern side of New Granada.

longest size of dart weighs 2 grammes; and the tips of the darts are thinly covered, for a distance of 4 centimetres (1½ inch), with a black coloured substance which possesses the usual pharmacological actions assigned to curara.

On completely immersing the tips of 6 of the New Granada darts in 10 c.c. of distilled water, an almost perfectly clear solution of a deep yellowish-red colour was obtained after a few minutes. The darts were left in the water for 24 hours, and on their removal a dull yellow-coloured undissolved layer remained on the tips.

A few particles scraped from the tip of one of the remaining darts and placed on the tongue imparted a slightly bitter taste. The solution yielded by the 6 darts had a faintly acid reaction, and was tasteless. This solution, after filtration, was divided into two equal parts, one of which was evaporated to dryness at a temperature not exceeding 138° F., and yielded 0·024 gramme of a dark yellowish-red coloured substance having the form of an amorphous film, and possessing a slightly bitter taste. The other part of the solution was employed in carrying out the pharmacological examination, and was not subjected to heating or to any chemical process.

The 6 darts yielded to 10 c.c. of distilled water 0·048 gramme (0·024 grm. × 2) of substance. The moist undissolved residue was easily entirely removed from the tips of the darts in the form of flocculent particles and pieces, and weighed when completely dried 0·039 gramme. The total amount of substance on the 6 darts was therefore 0·087 gramme, of which 55·1 per cent. was readily soluble in water.

The undissolved substance showed, on microscopical examination, numerous amorphous yellowish-red particles, a few broken crystals and a few entire crystals (apparently oxalate of calcium), some globules (oil), and fragments of vegetable tissues.

A few colour reactions were tried with the small amount of dried soluble substance available. A drop of distilled water added to a few minute particles almost immediately produced a light yellowish-red coloured solution. A drop of solution of potash (*Ph. Brit.*) added to a few particles in the cold almost immediately produced a reddish-yellow colour slightly yellower than that produced by water. A drop of strong sulphuric acid

added to a few particles in the cold produced within a few minutes a dark red colour, changing within 15 minutes to a muddy brown colour. Strong nitric and strong hydrochloric acid, similarly added, each produced almost immediately a dark yellowish-red solution, changing in a few minutes to a light yellowish-red colour, which only differed slightly in shade from the solution in distilled water. When a few particles were gradually heated from 110° to 120° F. along with a drop of strong sulphuric acid, the very dark red colour at first produced changed within 15 minutes to a muddy brownish-red colour, having a tinge of green at the edge, and within 40 minutes a very faint olive colour was developed. When 10 per cent. sulphuric acid was employed the green tinge was within 30 minutes more marked, but no other distinct colour change was detected.

As the quantity of curara which was soluble in water and pharmacologically active only amounted, for the 13 darts, to 0·104 gramme, no chemical processes could be adopted for the isolation of the active principle. But, as the toxicity was considerable, it was possible to carry out a sufficient number of experiments to determine the prominent signs of poisoning and the cause of death, and to render evident that this curara possesses an altogether different action from what is expected, and is found, with singular uniformity, in the crude mixture of substances bearing the name curara, woorara, &c., and used as an arrow-poison by Indian tribes scattered over vast and widely separated regions in the north of South America.

The minimum-lethal dose, by subcutaneous injection, of that part of the curara which was soluble in water, was determined for the frog (*R. temporaria*) to be, according to the following table, about 0·000013 gramme per gramme weight of frog, the experiments being made at a temperature of 70° to 77° F.

The general effects produced by the poison were of a nearly uniform character in the experiments (Nos. 6, 7, 9, 10, 11) where death resulted one or two hours after the subcutaneous injection of more than the minimum-lethal dose.

Before 30 minutes usually the frog showed signs of uneasiness, and when at rest the anterior extremities were extended, and the attitude was erect. The volume of the respiratory movements then became irregular; deep respirations became less and

MINIMUM-LETHAL DOSE OF WATERY EXTRACT FOR FROGS.

No. of Experiment.	Weight of Frog in Grammes.	Dose in Grammes.	Dose per Gramme of Frog.	RESULT.
1	14	0·000100	0·000007	No effects.
2	13	0·000140	0·000010	Very slight effects. Recovery.
3	19	0·000240	0·000012	Very slight effects. Recovery.
4	13·2	0·000158	0·000012	Death before 23 hours. Time not known.
5	14·7	0·000192	0·000013	Death in 25 hours. Probably a small part of the dose was lost or entered the stomach.
6	17	0·000238	0·000014	Death in 1 hour and 20 minutes.
7	12·5	0·000187	0·000015	Death in 2 hours and 37 minutes.
8	20	0·000330	0·000016	Death before 12 hours. Time not known.
9	22	0·000480	0·000021	Death in 1 hour and 10 minutes.
10	20	0·002400	0·000120	Death in 55 minutes.
11	22	0·004800	0·000218	Death in 55 minutes.

less frequent; and within about 40 minutes irregular pauses in respiration occurred, and the rate soon fell to 5 or 6 per 60 seconds, with prolonged periods of total arrest. The mouth gaped during the period of interrupted respiration in experiment No. 11 only, where a large dose was administered. Meantime the frog leaped about vigorously, but soon the head sank to the ground, the leaps became uncertain, the extremities remained in any position, and, finally, the extension of the posterior extremities was too feeble to produce any change in the animal's position. At this time no cardiac movement was to be observed on inspection of the thoracic region. The feeble voluntary movements soon ceased, but, on stimulation, reflex movements were still readily obtained, and also movements of the respiratory muscles at the lower jaw. Very slight fibrillary twitches of those superficial muscles brought into contact with the injection were observed in Experiment No. 10 only.

On immediate *post-mortem* examination, the veins were found to be distended, and the muscles very pale in colour. On opening the thorax the heart was found to be motionless. The auricles were distended with blood, and dark in colour. The ventricle was usually empty, and in a condition of marked systole, the colour being pale or a mottled red. At this stage, neither mechanical stimulation of the heart, nor electrical stimu-

lation by means of a very strong interrupted current caused any pulsation ; but, when the ventricle was somewhat relaxed and red in colour, the stimulation caused it, within a minute or two to gradually pass into permanent contraction and to become pale.

A moderately strong current from a single bichromate cell and Du Bois Reymond's induction apparatus, applied to the upper end of the spine, immediately after all voluntary and reflex movement had ceased, caused general tetanus. Also, when one sciatic nerve was divided, stimulation of the upper end caused no reflex movement, but stimulation of the lower end readily caused tetanus of that lower extremity.

The disappearance of voluntary and reflex movements is due to paralysis of the central nervous system, because, when, in a brainless frog, one leg is protected by ligature of the vessels before the poisoning, the movements of both legs and the reflex effects produced by stimulation of the skin of either leg are equal, and the voluntary and reflex movements disappear in both the poisoned and the unpoisoned leg at the same time. The period at which the paralysis of the central nervous system occurs indicates that it is secondary to the arrest of the circulation.

Muscular rigidity set in very early, especially in the thoracic muscles. On the day following the experiment the frog was always in a state of strong general rigor, and the muscles were acid in reaction, and (with the exception of a protected part and sometimes of the unprotected muscles of the foot) were inexcitable to mechanical or electrical stimulation.

Stimulation of a motor nerve, after death, continued to cause muscular contractions until the muscles themselves, by only responding to stronger and stronger direct electrical stimulation, showed distinct signs of poisoning. In one experiment (No. 13), where a small dose of curara was employed, the sciatic nerves were found to be excitable 12 hours after the heart was paralysed, but, 10 hours later, the muscles were paralysed.

When, in pithed frogs, the poison was applied directly to the heart, after removal of the pericardium, the results varied according to the dose employed. When the dose was about the exact minimum-lethal, the heart continued to pulsate for several hours, the rate then became very slow, and the rhythm, owing to

prolonged periods of stoppage in extreme diastole, became very irregular. During the period of arrest in diastole, the heart readily contracted on stimulation. For example—0·00015 gramme of the poison, in solution in about half a minim of distilled water, was applied at 3.48 p.m. to the heart of a frog, the rate being 56 per minute, and the systole and diastole normal. In 17 minutes, the rate was 44 per minute, and the heart was acting more vigorously, the diastolic expansion being greater and the ventricle paler during systole. In 42 minutes, the rate had fallen to 24 per minute, the slowing being due mainly to the lengthening of the pause in diastole. The diastolic expansion was a little less, and the systole more complete than before. In 58 minutes, the rate was 16 per minute, and, then, for 2 hours the rate varied quite irregularly, but rarely exceeded 5 per minute. Pauses in complete diastole continuing for from 40 to 100 seconds frequently occurred, both auricles and ventricle being greatly distended. When the heart resumed pulsating, sometimes the auricular contractions took place first, sometimes the ventricle acted alone during a few minutes, and sometimes the whole heart seemed to contract at once. The infrequent ventricular contractions were extremely vigorous. After 4 hours the rate rarely exceeded 1 per minute, but, at any time, slight mechanical stimulation during a pause caused contraction, although after stimulation had been several times repeated the diastolic expansion seemed smaller. On the following day the heart was found motionless, with the ventricle moderately contracted, but not affected by mechanical or electrical stimulation.

When the dose was considerably in excess of the minimum-lethal, the ventricle was arrested within 10 or 20 minutes, but retained its excitability for about 20 minutes longer, when it passed into a condition of extreme and permanent systole. The auricles were affected after the ventricle. For example:—In a frog weighing 19 grammes, 0·00096 gramme of curara in solution in 3·5 minims of distilled water, was applied in small drops, during 5 minutes, to the exposed heart, which was acting normally at the rate of 40 per minute. In 9 minutes, the rate was 32 per minute; the ventricle was paler during systole than before, and the diastole was less complete, one side of the

ventricle looking a little paler during the diastole than the other; the auricles looked larger, not apparently being fully emptied during systole. In 11 minutes, the ventricle suddenly stopped in medium diastole—the cavity being fairly well filled, and the colour of the ventricle quite red. The auricles meantime continued to pulsate at the rate of 36 per minute. After a pause of 45 seconds, the ventricle resumed contracting for 1 minute at the rate of 12 per minute, then stopped in medium diastolic expansion for 7 minutes; then it contracted quite regularly, without any stimulation having been applied, for 32 seconds at the rate of 32 per minute, when it permanently ceased to contract spontaneously. The auricles all this time were acting regularly at the rate of 32 per minute, they then stopped for 70 seconds, 2 minutes after the permanent arrest of the ventricle, and during the next 3 minutes, 4 contractions occurred, and then the auricles ceased to pulsate spontaneously. The auricles still responded to mechanical stimulation for 2, and the ventricle for 8 minutes longer. At this time slight fibrillary twitchings of the thoracic muscles were occurring, and the general reflexes produced by stimulating the skin were excellent.

These few experiments suffice at least to indicate that the most prominent features of the pharmacological action of small and moderate doses of this curara in the frog are :—

1. Rapid and absolute paralysis of the muscle of the heart, the respiration continuing.

2. Absolute paralysis and rigidity of the skeletal muscles at a much earlier period than happens in the case of an animal whose circulation has been artificially arrested.

3. Exemption of the motor nerves from paralysis until after death, and until the muscles show signs of poisoning.

A sufficient quantity of the curara remained after the experiments on frogs to allow of the administration to a rabbit of a dose which was lethal, and which, since it was approximately the minimum-lethal dose per gramme weight of frog (0·000013 gramme) multiplied by the weight of the rabbit in grammes (1814 grammes), was probably near the minimum-lethal.

At 4.40 p.m., 0·024 gramme of curara dissolved in 1·5 c.c. of water was injected subcutaneously, the temperature of the room

being 80° F., and the animal's respirations 60 per 15 seconds. During the next 20 minutes (up to 5 p.m.), the respirations continued at the same rate, the rate of the heart being 70 per 15 seconds; and nothing unusual was noticed in the animal's attitude or movements. In 30 minutes (5.10 p.m.), the respirations slowed for a second or two occasionally; the animal either rested in an extended position on the thorax or in a sitting position; and the lips were licked occasionally (salivation ?) and rubbed with the paws. In 34 minutes, the respirations were 55; in 39 minutes, 46; and in 50 minutes, 40 per 15 seconds. At this point (5.35 p.m.), signs of asphyxia set in, the respirations quickly becoming extremely shallow and slow, the rate varying from 6 to 10 per 15 seconds, with intervals when apparently little or no air entered the lungs, but inspiratory attempts continued, as shown by gaping and snapping movements of the mouth; and slight movements of air were indicated by whistling laryngeal sounds, chiefly with expiration. Coincident with the onset of marked respiratory difficulty, the exact time relation not being determined, the rate of the heart was found, by palpation of the thorax, to be only from 20 to 25 per 15 seconds, and the rhythm to be irregular and the impact feeble. During 22 minutes (until 5.57 p.m.), the slow, laboured, extremely shallow respiration continued. The heart, however, distinctly recovered during the first half of this period, the rate increasing to 40 and then to 50 per 15 seconds, and the rhythm becoming regular, and the impact fairly strong; but, during the second half, the action of the heart became irregular, rapid, and so feeble that only a fluttering movement was perceptible. During the whole 22 minutes the animal was able at will to maintain a sitting position, with the head and ears erect, or to move about. In 77 minutes, the respirations consisted only of snapping movements of the mouth and mere quiverings of the muscles of the abdomen; the heart movements were scarcely perceptible to palpation; the head began to sink to the ground; and urination occurred. In 82 minutes, the animal lay prostrate on its side, but could still rise voluntarily; the heart movements seemed to palpation to be mere quiverings; the respirations entirely failed; and no fibrillary twitchings were observed. A minute later violent tetanus set in, and the pupils dilated widely.

At 6.4 p.m., about 84 minutes after the administration of the curara, three gasping inspiratory movements occurred; no cardiac impact could be felt; contraction of the pupils soon began; and the motion of the abdominal walls showed the occurrence of intestinal peristalsis.

Six minutes after death the heart was exposed. The auricles contained some blood; the right ventricle was distended with blood, and the left was empty. Slight mechanical stimulation of the auricles caused no movement, but, when applied to either ventricle, the stimulation caused, on three or four occasions, a few quivering movements, but no complete pulsations. About 16 minutes after death, one sciatic nerve was exposed, and stimulated by means of the strongest current from a single bichromate cell and Du Bois Reymond's induction apparatus, without any result, but on testing the muscles themselves, it was found that, with the exception of some of the facial muscles, they did not contract on direct stimulation. About 41 minutes after death rigidity had distinctly commenced, but some of the facial muscles still contracted on electrical stimulation; the blood in the right ventricle was found to have coagulated, and the muscle of the left ventricle was very hard. About 54 minutes after death (7 p.m.), the reaction of the heart muscle and of the muscles of the thigh was taken, and found to be acid.

The absence of motor weakness until near death, the marked action upon the heart, and the early total paralysis of muscles and onset of rigidity, at once distinguish the prominent actions of this curara from those of ordinary curara, which, as is well known, causes death by producing an asphyxia due solely to paralysis of the motor nerves, and does not affect the heart or muscles. In the case of this curara, one experiment on a warm-blooded animal is quite insufficient to show the exact cause of the prolonged respiratory difficulty, but phenomena quite similar in kind occur after the administration of other muscle-poisons.

This specimen of the South American curara resembles in action, therefore, the Strophanthus[1] type of the African arrow-poisons. It possesses a similar action to the "Woorara, variety Corroval," and the "Woorara, variety Vao," investigated very

[1] Fraser, *Trans. Roy. Soc. Edin.*, vol. xxxvi. part ii., 1891.

fully by Hammond and Mitchell[1] in 1859, but the botanical origin of which is unfortunately unknown.

Although it is not known from what plant or plants this curara from Antioquia which I have described is derived, it is highly probable that, like the curara of Guiana, Venezuela, and Brazil, it is got from one or more species of *Strychnos*, for, of course, it is not at all necessary that the members of the same botanical genus should yield the same active principle. My reason for coming to this conclusion is that, in 1889, I obtained from the Herbarium of the Royal Gardens, Kew, a piece of stem of an unknown but unmistakable *Strychnos* plant which had been collected in the same district (Antioquia) from which these darts were obtained, and had been forwarded to Kew as the source of a curara. I found,[2] however, that a watery extract prepared from the bark had, in frogs, no primary action upon motor nerves, but caused cardiac paralysis. In these actions the extract agreed with that obtained from the *Strychnos Gardnerii* of Brazil,[3] but differed altogether from the extract prepared from the bark of the *Strychnos toxifera*[4] of British Guiana.

In view of the fact that it is now definitely known *by experiment* that curara may consist of curarine-acting or digitalin-acting principles, or of mixtures[5] of these in unknown strength and proportion, it is impossible, without a careful preliminary experimental examination of each specimen, to employ crude curara, in place of the alkaloid curarine,[5] in accurate physiological experiments on the circulation or upon muscle, much less (as is unfortunately recommended in several works of Materia Medica, and by the British Pharmaceutical Conference[6]) as a therapeutic agent to be administered by hypodermic injection.

[1] *Loc. cit.*, pp. 34 and 58.
[2] *Jour. Anat and Phys.*, vol. xxv. p. 57, 1890–91.
[3] MM. Couty et De Lacerda, *Compt. rend.*, vol. lxxxix. p. 1035, 1879.
[4] *Jour. Anat. and Phys.*, vol. xxiv. p. 403, 1889–90.
[5] Boehm, *Chem. Stud. über das Curare*, p. 180, 1886, Leipzig.
[6] *Unofficial Formulary*, 1888, p. 14.