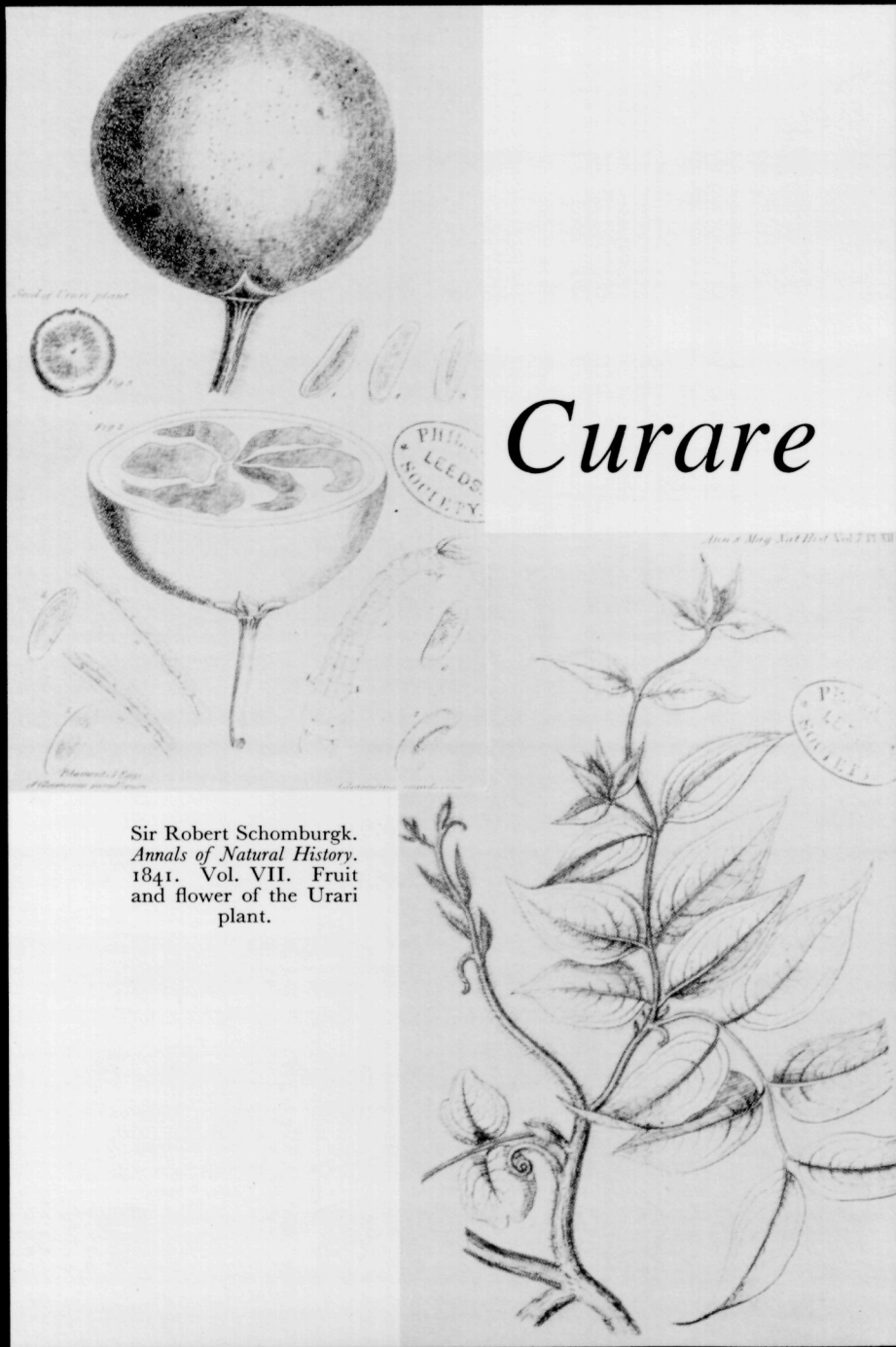


# The History of Anesthesiology

Reprint Series: Part Thirteen



Sir Robert Schomburgk.  
*Annals of Natural History.*  
1841. Vol. VII. Fruit  
and flower of the Urari  
plant.

# History of Anesthesiology

Reprint Series: Part Thirteen

## CURARE

In the long run, the curare compounds may prove to be just as important in the evolution of anesthesia as were the inhalation and local anesthetic agents. And now the opioid derivatives promise to be fourth in line. Each class of substance carries its own fascinating history, extending retrograde toward antiquity — and with a curious conformity as typified by those intrepid individuals responsible for recognition and development of these drugs. Logically, according to the tenor of the times, the inhalation method should have arisen per primum as indeed it did, so that once the concept of pain relief was accepted, the entry for the regional agents was assured. With the many problems created by the original inhalants, curare easily became a welcome adjunct. To be sure these remarks are largely in the nature of hindsight. Nevertheless, according to the selection of reprints offered here, curare in its biography plays as dramatic a role as any other alkaloid introduced to medicine.

L. D. Vandam, M.D.

## SELECTED PAPERS ON CURARE

1. Waterton, Charles: "Experiments in London of the wourali poison." WANDERINGS IN SOUTH AMERICA, ... Fourth edition. London, B. Fellowes, 1839, pp 74-76
2. Brodie, Benjamin Collins: "Experiments and observations on the different modes in which death is produced by certain vegetable poisons." From the PHILOSOPHICAL TRANSACTIONS. London, W. Bulmer & Co., 1811

### *Addendum:*

Brodie, Sir Benjamin C.: PHYSIOLOGICAL RESEARCHES. Collected and Republished from the PHILOSOPHICAL TRANSACTIONS. London, Longman, Brown, Green & Longman, 1851, p 142 — Note G

[This addendum is appended to Paper #2, in which Sir Benjamin acknowledged Mr. Charles Waterton as the source of his supply of "wourali" for the experiments he had carried out.]

3. Vulpian, Alfred Edme-Felix. "The use of curare as an antidote to strychnine and as a treatment for tetanus." *L'Union Médicale*, 11:25-26, Jan. 15, 1857. English translation of this paper reprinted from Faulconer A, Keys TE, FOUNDATIONS OF ANESTHESIOLOGY, Vol. II. Springfield, IL, Charles C. Thomas, 1965, pp 1152-1158
4. Bernard, Claude: LECONS SUR LES EFFETS DES SUBSTANCES TOXIQUES ET MEDICAMENTEUSES. Paris, J. -B. Bailliere et Fils, 1857, pp 311-325  
  
[With English translation from Faulconer A, Keys TE, FOUNDATIONS OF ANESTHESIOLOGY, Vol II. Springfield, IL, Charles C. Thomas, 1965, pp 1142-1150.]
5. West, Ranyard: "Curare in man." PROC ROYAL SOCIETY MEDICINE 25: 1107-1116, 1931-1932

6. West, Ranyard: "The action of curarine on the respiratory mechanism." J PHYSIOLOGY 94: 437-446, 1938

*Addendum:*

[Personal letter of Ranyard West to Richard C. Gill in reference to the subject of their mutual interest — curare, dated January 5, 1948. This 2-page letter is appended to Paper #6.]

7. Bennett AE: "Preventing traumatic complications in convulsive shock therapy by curare." JAMA 114: 322-324, 1940
8. Griffith, Harold R., Johnson G Enid: "The use of curare in general anesthesia." ANESTHESIOLOGY 3: 418-420, 1942



WANDERINGS  
IN  
SOUTH AMERICA,

THE  
NORTH-WEST OF THE UNITED STATES,  
AND THE ANTILLES,

IN THE YEARS 1812, 1816, 1820, & 1824,

WITH  
ORIGINAL INSTRUCTIONS  
FOR THE PERFECT PRESERVATION OF BIRDS, &c.  
FOR  
CABINETS OF NATURAL HISTORY.

BY CHARLES WATERTON, ESQ.

FOURTH EDITION.

LONDON:  
B. FELLOWES, LUDGATE STREET.

M DCCC XXXIX.



*Drawn by T.H. Foljambe.*

*Engraved by J.W. Lewis.*

A NONDESCRIFT.

*See page 27.*

*Published by B. Fellowes, Ludgate Street.*

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## R E M A R K S.

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“Incertus, quo fata ferant, ubi sistere detur.”

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KIND and gentle reader, if the journey in quest of the wourali poison has engaged thy attention, probably thou mayest recollect that the traveller took leave of thee at Fort St. Joachim, on the Rio Branco. Shouldst thou wish to know what befel him afterwards, excuse the following uninteresting narrative. Illness at Fort St. Joachim.

Having had a return of fever, and aware that the farther he advanced into these wild and lonely regions, the less would be the chance of regaining his health; he gave up all idea of proceeding onwards, and went slowly back towards the Demerara, Returns to Demerara. nearly by the same route he had come.

On descending the falls in the Essequibo, which form an oblique line quite across the river, it was Falls of the Essequibo. resolved to push through them, the downward stream



FIRST  
JOURNEY.

being in the canoe's favour. At a little distance from the place, a large tree had fallen into the river, and in the mean time the canoe was lashed to one of its branches.

The roaring of the water was dreadful; it foamed and dashed over the rocks with a tremendous spray, like breakers on a lee-shore, threatening destruction to whatever approached it. You would have thought, by the confusion it caused in the river, and the whirlpools it made, that Scylla and Charybdis, and their whole progeny, had left the Mediterranean, and come and settled here. The channel was barely twelve feet wide, and the torrent in rushing down formed transverse furrows, which showed how near the rocks were to the surface.

Nothing could surpass the skill of the Indian who steered the canoe. He looked steadfastly at it, then at the rocks, then cast an eye on the channel, and then looked at the canoe again. It was in vain to speak. The sound was lost in the roar of waters; but his eye showed that he had already passed it in imagination. He held up his paddle in a position, as much as to say, that he would keep exactly amid channel; and then made a sign to cut the bush-rope that held the canoe to the fallen tree. The canoe drove down the torrent with inconceivable rapidity. It did not touch the rocks once all the way. The Indian proved to a nicety, "*medio tutissimus ibis.*"

Thunder  
and light-  
ning.

Shortly after this it rained almost day and night, the lightning flashing incessantly, and the roar of thunder awful beyond expression.

The fever returned, and pressed so heavy on him, that to all appearance his last day's march was over. FIRST JOURNEY. However, it abated; his spirits rallied, and he Fever returned. marched again; and after delays and inconveniences he reached the house of his worthy friend Mr. Edmonstone, in Mibiri creek, which falls into the Reaches Mibiri creek. Demerara. No words of his can do justice to the hospitality of that gentleman, whose repeated encounters with the hostile negroes in the forest have been publicly rewarded, and will be remembered in the colony for years to come.

Here he learned that an eruption had taken place in St. Vincent's; and thus the noise heard in the night of the first of May, which had caused such terror amongst the Indians, and made the garrison at Fort St. Joachim remain under arms the rest of the night, is accounted for.

After experiencing every kindness and attention Sails for Granada. from Mr. Edmonstone, he sailed for Granada, and from thence to St. Thomas's, a few days before poor Captain Peake lost his life on his own quarter-deck, bravely fighting for his country on the coast of Guiana.

At St. Thomas's they show you a tower, a little St. Thomas's tower. distance from the town, which they say formerly belonged to a Bucanier chieftain. Probably the fury of besiegers has reduced it to its present dismantled state. What still remains of it bears testimony of its former strength, and may brave the attack of time for centuries. You cannot view its ruins, without calling to mind the exploits of those fierce and hardy hunters, long the terror of the

FIRST  
JOURNEY.

western world. While you admire their undaunted courage, you lament that it was often stained with cruelty; while you extol their scrupulous justice to each other, you will find a want of it towards the rest of mankind. Often possessed of enormous wealth, often in extreme poverty, often triumphant on the ocean, and often forced to fly to the forests; their life was an ever-changing scene of advance and retreat, of glory and disorder, of luxury and famine. Spain treated them as outlaws and pirates, while other European powers publicly disowned them. They, on the other hand, maintained, that injustice on the part of Spain first forced them to take up arms in self-defence; and that, whilst they kept inviolable the laws which they had framed for their own common benefit and protection, they had a right to consider as foes, those who treated them as outlaws. Under this impression they drew the sword, and rushed on as though in lawful war, and divided the spoils of victory in the scale of justice.

Leaves  
St. Thomas's,  
and is at-  
tacked by  
a tertian  
ague, and  
returns to  
England.

After leaving St. Thomas's, a severe tertian ague, every now and then, kept putting the traveller in mind, that his shattered frame, "starting and shivering in the inconstant blast, meagre and pale, the ghost of what it was," wanted repairs. Three years elapsed after arriving in England, before the ague took its final leave of him.

Experi-  
ments in  
London  
of the  
wourali  
poison.

During that time, several experiments were made with the wourali poison. In London, an ass was inoculated with it, and died in twelve minutes. The poison was inserted into the leg of another, round

which a bandage had been previously tied a little above the place where the wourali was introduced. He walked about as usual, and ate his food as though all were right. After an hour had elapsed, the bandage was untied, and ten minutes after death overtook him.

A she-ass received the wourali poison in the shoulder, and died apparently in ten minutes. An incision was then made in its windpipe, and through it the lungs were regularly inflated for two hours with a pair of bellows. Suspended animation returned. The ass held up her head, and looked around; but the inflating being discontinued, she sunk once more in apparent death. The artificial breathing was immediately recommenced, and continued without intermission for two hours more. This saved the ass from final dissolution; she rose up, and walked about; she seemed neither in agitation nor in pain. The wound, through which the poison entered, was healed without difficulty. Her constitution, however, was so severely affected, that it was long a doubt if ever she would be well again. She looked lean and sickly for above a year, but began to mend the spring after; and by Midsummer became fat and frisky.

The kind-hearted reader will rejoice on learning that Earl Percy, pitying her misfortunes, sent her down from London to Walton Hall, near Wakefield. There she goes by the name of Wouralia. Wouralia shall be sheltered from the wintry storm; and when summer comes, she shall feed in the finest pasture.

FIRST  
JOURNEY.

No burden shall be placed upon her, and she shall end her days in peace.\*

For three revolving autumns, the ague-beaten wanderer never saw, without a sigh, the swallow bend her flight towards warmer regions. He wished to go too, but could not; for sickness had enfeebled him, and prudence pointed out the folly of roving again, too soon, across the northern tropic. To be sure, the continent was now open, and change of air might prove beneficial; but there was nothing very tempting in a trip across the channel, and as for a tour through England!—England has long ceased to be the land for adventures. Indeed, when good King Arthur reappears to claim his crown, he will find things strangely altered here; and may we not look for his coming? for there is written upon his grave-stone,—

“Hic jacet Arturus, Rex quondam Rexque futurus.”

“Here Arthur lies, who formerly  
Was king—and king again to be.”

Don Quixote was always of opinion that this famous king did not die, but that he was changed into a raven by enchantment, and that the English are momentarily expecting his return. Be this as it may, it is certain that when he reigned here, all was harmony and joy. The browsing herds passed from vale to vale, the swains sang from the bluebell-teeming groves, and nymphs, with eglantine and roses in their neatly-braided hair, went hand in hand

\* Poor Wouralia breathed her last on the 15th of February, 1839, having survived the operation nearly five-and-twenty years.

to the flowery mead, to weave garlands for their lambkins. If by chance some rude uncivil fellow dared to molest them, or attempted to throw thorns in their path, there was sure to be a knight-errant, not far off, ready to rush forward in their defence. But, alas! in these degenerate days it is not so. Should a harmless cottage maid wander out of the highway to pluck a primrose or two in the neighbouring field, the haughty owner sternly bids her retire; and if a pitying swain hasten to escort her back, he is perhaps seized by the gaunt house-dog ere he reach her!

Æneas's route on the other side of Styx, could not have been much worse than this, though, by his account, when he got back to earth, it appears that he had fallen in with "Bellua Lernæ, horrendum stridens, flammisque, armata Chimæra."

Moreover, he had a sibyl to guide his steps; and as such a conductress, now-a-days, could not be got for love or money, it was judged most prudent to refrain from sauntering through this land of freedom, and wait with patience the return of health. At last this long-looked for, ever-welcome stranger came.



**EXPERIMENTS AND OBSERVATIONS**

**ON THE**

**DIFFERENT MODES IN WHICH DEATH IS PRODUCED  
BY CERTAIN VEGETABLE POISONS.**

**BY**

**MR. B. C. BRODIE, F. R. S.**

**FROM THE**

**PHILOSOPHICAL TRANSACTIONS.**

**LONDON:**

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**PRINTED BY W. BULMER AND CO. CLEVELAND-ROW,  
ST. JAMES'S.**

**1811.**



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Gentlemen who are indulged with separate Copies of their Communications, are requested to use their endeavour to prevent them from being reprinted, till one month after the publication of that part of the Philosophical Transactions in which they are inserted.

*By Order of the President and Council,*

W. H. WOLLASTON, M. D. Sec. R. S.

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### III. Experiments with Poisons applied to wounded Surfaces.

#### *Experiments with the Woorara.\**

*Exp. 19.* A small quantity of the woorara in powder was applied to a wound in the side of a Guinea pig. Ten minutes afterwards the animal was unable to walk; then he became quite motionless, except some slight occasional convulsions. He gradually became insensible, the respirations were laboured, and at the end of fourteen minutes from the application of the poison, the respiration had entirely ceased, and he was apparently dead; but on opening the thorax, the heart was found acting seventy times in a minute, circulating dark coloured blood, and it continued to contract for several minutes afterwards. On dissection no preternatural appearances were observed in the brain; nor was there any other appearance in the limb than would have arisen from an ordinary wound.

*Exp. 20.* I made a wound in the side of a Guinea pig, and introduced into it about two grains of the woorara in powder.

\* The Woorara is a poison with which the Indians of Guiana arm the points of their arrows. It appears not to differ essentially from the Ticunas, which was employed in the experiments of the Abbé FONTANA. I am indebted to Dr. E. N. BANCROFT, who not only furnished me with some of the Woorara which he had in his possession, but also lent me his assistance in the experiments which were made with it.

At the end of twenty-five minutes, symptoms took place very similar to those, which occurred in the last experiment, and in thirteen minutes more the animal was apparently dead; but the heart continued to contract one hundred and eight times in a minute, and by means of artificial respiration the circulation was kept up for more than twenty minutes.

The results of other experiments, which I have made with the woorara, were similar to those just described. The heart continued to act after apparent death, and the circulation might be kept up by means of artificial respiration. It is evident that this poison acts in some way or another on the brain, and that the cessation of the functions of this organ is the immediate cause of death.

I found in these experiments, that the best mode of applying the woorara is when it is dissolved in water to the consistence of a thin paste. I first made the wound, and then smeared the poison over it with the end of the scalpel. I found that the animal was more speedily and certainly affected, if there was some hæmorrhage, unless the hæmorrhage was very copious, when it produced an opposite effect, by washing the poison away from the wound. When the poison was applied in large quantity, it sometimes began to act in six or seven minutes. Never more than half an hour elapsed from the time of the poison being inserted, to that of the animal being affected, except in one instance, where a ligature was applied on the limb, which will be mentioned afterwards. The woorara, which I employed, had been preserved for some years, which will account for its having been less active, than it has been described to be by those, who had witnessed its effects when in a recent state.

XI. *Further Experiments and Observations on the Action of Poisons on the Animal System.* By B. C. Brodie, Esq. F. R. S. Communicated to the Society for the Improvement of Animal Chemistry, and by them to the Royal Society.

Read February 27, 1812.

I.

SINCE I had the honour of communicating to the Royal Society some observations on the action of certain poisons on the animal system, I have been engaged in the further prosecution of this inquiry. Besides some additional experiments on vegetable poisons, I have instituted several with a view to explain the effects of some of the more powerful poisons of the mineral kingdom. The former correspond in their results so nearly with those which are already before the public, that, in the present communication, I shall confine myself to those which appear to be of some importance, as they more particularly confirm my former conclusions respecting the recovery of animals apparently dead, where the cause of death operates exclusively on the nervous system. In my experiments on mineral poisons, I have found some circumstances wherein their effects differ from those of vegetable poisons, and of these I shall give a more particular account. Whatever may be the value of the observations themselves, the subject must be allowed to be one that is deserving of investigation, as it does not appear unreasonable to expect that such investigation may hereafter lead to some improvements

in the healing art. This consideration, I should hope, will be regarded as a sufficient apology for my pursuing a mode of inquiry by means of experiments on brute animals, of which we might well question the propriety, if no other purpose were to be answered by it than the gratification of curiosity.

In my former communication on this subject, I entered into a detailed account of the majority of my experiments. This I conceived necessary, because in the outset of the inquiry I had been led to expect that even the same poison might not always operate precisely in the same manner; but I have since had abundant proof, that in essential circumstances there is but little variety in the effects produced by poisons of any description, when employed on animals of the same, or even of different species, beyond what may be referred to the difference in the quantity, or mode of application of the poison, or of the age and power of the animal. This will explain the reason of my not detailing, in the present communication, so many of the individual experiments from which my conclusions are drawn, as in the former; at the same time I have not been less careful to avoid drawing general conclusions from only a limited number of facts. Should these conclusions prove fewer, and of less importance than might be expected, such defects will, I trust, be regarded with indulgence; at least by those, who are aware of the difficulty of conducting a series of physiological experiments; of the time, which they necessarily occupy; of the numerous sources of fallacy and failure which exist; and of the laborious attention to the minutest circumstances, which is in consequence necessary in order to avoid being led into error.

## II. *Experiments with the Woorara.*

In a former experiment, I succeeded in recovering an animal, which was apparently dead from the influence of the essential oil of bitter almonds, by continuing respiration artificially until the impression of the poison upon the brain had ceased; but a similar experiment on an animal under the influence of the woorara was not attended with the same success. Some circumstances led me to believe, that the result of the experiment with the woorara might have been different, if it had been made with certain precautions; but I was unable at that time to repeat it, in consequence of my stock of the poison being exhausted. I have since, however, been able to procure a fresh supply, and I shall relate two experiments which I have made with it. In one of these, an animal apparently dead from the woorara, was made to recover, notwithstanding the functions of the brain appeared to be wholly suspended for a very long period of time; in the other, though ultimate recovery did not take place, the circulation was maintained for several hours after the brain had ceased to perform its office.

*Experiment 1.* Some woorara was inserted into a wound in a young cat. She became affected by it in a few minutes, and lay in a drowsy and half sensible state, in which she continued at the end of an hour and fifteen minutes, when the application of the poison was repeated. In four minutes after the second application, respiration entirely ceased, and the animal appeared to be dead; but the heart was still felt acting about one hundred and forty times in a minute. She was placed in

a temperature of 85 of FAHRENHEIT'S thermometer, and the lungs were artificially inflated about forty times in a minute.

The heart continued acting regularly.

When the artificial respiration had been kept up for forty minutes, the pupils of the eyes were observed to contract and dilate on the increase or diminution of light; saliva had flowed from the mouth, and a small quantity of tears was collected between the eye and eye-lids; but the animal continued perfectly motionless and insensible.

At the end of an hour and forty minutes, from the same period, there were slight involuntary contractions of the muscles, and every now and then there was an effort to breathe. The involuntary motions continued, and the efforts to breathe became more frequent. At the end of another hour, the animal, for the first time, gave some signs of sensibility when roused, and made spontaneous efforts to breathe twenty-two times in a minute. The artificial respiration was discontinued. She lay, as if in a state of profound sleep, for forty minutes, when she suddenly awoke, and walked away. On the following day she appeared slightly indisposed; but she gradually recovered, and is at this time still alive and in health.

*Experiment 2.* Some woorara was applied to a wound in a rabbit. The animal was apparently dead in four minutes after the application of the poison; but the heart continued acting. He was placed in a temperature of 90°, and the lungs were artificially inflated. The heart continued to act about one hundred and fifty times in a minute. For more than three hours the pulse was strong and regular; after this, it became feeble and irregular, and at the end of another hour the circulation had

entirely ceased. During this time there was no appearance of returning sensibility.

The circulation of the blood may be maintained in an animal from whom the brain has been removed for a considerable, but not for an unlimited time. We may conclude, that in the last of these experiments the animal did not recover, because the influence of the poison continued beyond the time during which the circulation may be maintained without the brain.



PHYSIOLOGICAL  
RESEARCHES.

BY

SIR BENJAMIN C. BRODIE, BART., D.C.L., F.R.S.,

CORRESPONDING MEMBER OF THE ACADEMY OF SCIENCES  
OF THE INSTITUTE OF FRANCE.

COLLECTED AND REPUBLISHED FROM THE

“PHILOSOPHICAL TRANSACTIONS.”

LONDON:  
LONGMAN, BROWN, GREEN, AND LONGMANS.  
1851.

## NOTE G. (Page 80.)

The cat which was resuscitated, after being apparently dead under the influence of the woorara, was given to a friend, and lived, as I have been informed, for some years.

Not long after this experiment was made, I repeated it on an ass, with the assistance of Professor Sewell, at the Veterinary College. The animal lay in a state of total insensibility (the lungs being inflated by means of a pair of bellows and a tube introduced into the trachea) for more than an hour. He then recovered, and seemed to suffer no inconvenience afterwards. The poison used on this occasion had been given to me by Mr. Waterton, who had himself brought it from America. The ass had been purchased for the purpose of the experiment, by the late Duke of Northumberland (then Earl Percy), and was afterwards given by his Lordship to Mr. Waterton, in whose island he was allowed to range, and where he was alive many years afterwards.

The method of resuscitation, which is here described, is evidently applicable to all cases of apparent death, in which the action of the heart, so as to maintain the circulation, continues after respiration has ceased. The success of the treatment depends, 1st, in cases of poisoning, on the

dose of the poison, a limit to the period there being during which life can be maintained by means of artificial respiration; 2ndly, on the inflation of the lungs being carefully made\*; 3dly, on the animal being kept in a temperature of not less than 85 or 90 degrees of heat of Fahrenheit's thermometer. This last precaution is of course a matter of greater importance where the animal is of a small size (as in the case of a cat or rabbit), than where it is larger; still it is not to be neglected even in the case of the human subject; otherwise the animal heat gradually diminishes until it reaches that point at which the action of the heart can no longer be maintained, when we have the singular result of an animal perishing from cold in the ordinary temperature of the atmosphere. I have not myself known the circulation to continue where the temperature of the interior of the thorax has been below 78° of Fahrenheit; but an experiment is related by Dr. Chossat, in which it had fallen still lower.

It is needless to multiply examples of the kind. I am, however, induced to record the following experiment, as it derives a peculiar interest from the circumstance of the use of ether and other anæsthetic agents having been lately introduced into the practice of surgery.

\* On this subject I have offered some observations elsewhere. See Lectures illustrative of various Subjects in Pathology and Surgery, page 7.

## The Use of Curare as an Antidote to Strychnine and as a Treatment for Tetanus\*

EDME-FÉLIX-ALFRED VULPIAN, M.D.

Former House Physician to the Hospitals of Paris  
Secretary of the Society of Biology  
Paris, France

*The Medical Union*, in the editions of December 23 and 25, 1856, contained an interesting article by Dr. Thibeaud, of Nantes, on facial paralysis and its treatment. In this paper, Dr. Thibeaud was led, through a consideration of the action of strychnine compounds and the action of curare, to propose the use of the latter substance to combat tetanus. One cannot speak too highly of the seriousness with which he treats this grave subject, and of the advice which he gives on the need to make precise physiologic studies before this drug is used. It is to be feared, however, that some impetuous physicians, misled by the plausibility of the analogy proposed by Dr. Thibeaud, will not restrain themselves, and without attempting to learn more about this subject by means of experimentation, will eagerly take up this hypothesis because of its newness. Over the last two years I have performed experiments on the action of strychnine and curare for the purpose of discovering whether these substances, injected one after the other into the animal economy, would be able to neutralize the effects of each other reciprocally. Recently I repeated these experiments, and although I am not yet able to elucidate all the points of the question, I am at least able to render some useful information.

The concept of a reciprocal neutralizing effect between curare and strychnine is not entirely new in science. In his memoir entitled *Natural Researches; Chemical and Physiological, on Curare*, Alvaro Reynoso wrote: "Virchow, (private communication) has performed a number of experiments for the purpose of finding out whether curare and strychnine neutralize each other; that is, whether they are mutual poisons for each other. Since each of these poisons acts with too much force, these experiments have not given him very conclusive results. However, a dog poisoned to the point of complete paralysis recovered as a result of the use of strychnine, and continued to live without the least difficulty" (Paris, 1854, pp. 48-49). The December, 1856, issue of the *General Archives of Medicine* contained a paper by Dr. Harley, of London, in which this physiologic problem is newly posed. Dr. Harley wrote that these two poisons act positively as antidotes, the one for the other, and in support of this assertion he cited three experiments which seem decisive.

\* Translated from Vulpian: De l'emploi du curare comme antidote de la strychnine, et comme traitement du tétanos. *L'Union médicale*, 11:25-26 (Jan. 15) 1857.

In the first of these experiments he poisoned a frog with  $\frac{1}{500}$  of a grain of curare, and three minutes after the animal had become unconscious he injected  $\frac{1}{120}$  of a grain of strychnine acetate into the abdomen. At the end of five minutes the frog became unconscious [thus in original].

I have repeated this experiment many times, but have obtained the opposite results. Each time, after I have injected  $\frac{1}{500}$  of a grain of curare under the skin of a frog's back and have found the nervous impulse destroyed (verified by touching the sciatic nerves with an electrode), I have injected into the same fold of skin strychnine acetate in variable quantities, both weak and strong, and have never seen it produce the least convulsion. Tetany has always been absent.

In a second experiment, Dr. Harley poisoned a frog with  $\frac{1}{120}$  of a grain of strychnine; three minutes after tetany had appeared he injected under the skin of the back  $\frac{1}{300}$  of a grain of curare: at the end of seven minutes the tetany had disappeared.

This experiment always gave the results which have just been described. It is unfortunate that Dr. Harley did not tell the reader what happened to these animals when the tetany disappeared. In my experiments they consistently died.

Finally, in the last experiment,  $\frac{1}{500}$  of a grain of curare and  $\frac{1}{40}$  of a grain of strychnine were simultaneously injected into the abdomen of a frog at five minutes after 1 o'clock; at ten minutes after one the animal was in a strong tetanic convulsion; at 1:30 it had become perfectly flaccid; the next morning it was getting along very well.

This fact appears convincing, especially since the quantity of strychnine was, in this case, according to the author, more than sufficient to kill the animal. I shall return to that last experiment and try to explain the result, and I shall return to the second experiment in order to add several details.

Must we think, as Drs. Virchow and Harley do, that strychnine is an antidote for curare and that the converse holds true, namely, that curare is an antidote for strychnine?

In order for curare to be rightly called the antidote for strychnine and vice versa, it is necessary that one of these two substances neutralize the other chemically, or else that they both act on the same organ in an inverse manner, so that one is able to counterbalance the effect of the other and annul it. I do not think that the problem is one of a chemical action between curare and strychnine in the depth of the tissues; experimentation has shown just the contrary.

But the second hypothesis merits our attention for a moment. If we are to judge the problem, it is important to recognize the organs upon which strychnine acts, on the one hand, and on the other those which are affected by curare. The numerous experiments of Magendie, Emmert, Van Deen,

Marshall-Hall, Brown-Séguard and Bonnefin have shown that strychnine exerts its action upon the spinal cord. Yet, the equally conclusive experiments of Professor Claude Bernard have shown us that curare does not act upon the spinal cord, but that, on the contrary, it exerts its action exclusively on the motor nerves. Here we come to an experiment which proves that curare and strychnine, introduced successively into the circulation, do not neutralize each other chemically. It is an experiment which establishes the different effects of these two poisons at the same time that it establishes the structures on which these toxic actions are exerted.

**Experiment 1.** The experiment of Professor Claude Bernard is carried out on a frog to prove that sensation remains intact during poisoning with curare; that is to say, a ligature is placed around the entire body of the animal at the level of the lumbar region, excepting the lumbar nerves. The vascular channels between the anterior part of the body and the hindquarters are thus interrupted, but the hindquarters communicate freely with the spinal cord by means of the lumbar nerves. A very small quantity of curare is introduced under a fold of skin in the dorsal region. At the end of several minutes the entire part of the body situated anterior to the ligature is poisoned; the passage of nerve impulses is completely abolished in this region, but sensation remains there, for if one pinches the anterior paw or the skin of the head, the animal moves its hindquarters immediately, since the nerves to this region have been preserved from the effect of the curare by the ligature of the blood vessels. The anterior limbs, head and all that part of the body anterior to the ligature remain immobile, even though muscular irritability remains intact in this region. After several more minutes, a half-milligram of strychnine acetate is injected under the skin in the same place. Two or three minutes after this injection, the hindquarters appear to become more excitable, and sensation in the anterior region thus appears even more developed. The effects of the strychnine become more and more apparent; convulsive tremors appear and tetanic stiffness is evident, both restricted to the posterior members.

This experiment is of the most clear cut type. The two poisons enter the body fluids through the same locus and simultaneously reach the blood stream; however, their effects manifest themselves as clearly and individually as they would had they been employed separately. Since the hind limbs are not paralyzed, curare obviously does not act on the spinal cord, and since sensation remains in the paralyzed parts, the agent must limit its action to the motor nerves. The excitation produced in one of these paralyzed parts passes into the cord and there provokes a particular condition, by virtue of which the excitation is followed by movements which, in general, would spread out through the entire body but which are limited in this case to those parts capable of reacting, namely, the hindquarters. Hence, since

the spinal cord has not been affected by the curare, but remains normal, strychnine affects it according to its own characteristic manner, and convulsions appear which are as violent as in the ordinary case of poisoning by that substance, but which are precisely limited to the posterior limbs.

Therefore, curare is not a *direct* antidote for strychnine, and neither is strychnine a *direct* antidote for curare. Although these two substances do not act on the same organs, might they not work against each other mutually, and *indirectly* neutralize their effects? Since curare paralyzes the motor nerves, particularly at the point at which they make contact with their muscles, and strychnine violently excites the spinal cord, might not the latter substance revitalize latent nervous energy and permit respiratory and voluntary movements to resume? On the other hand, if strychnine is introduced first into the physiologic economy of the animal and there produces its effect upon the spinal cord, might not curare render the convulsions less violent by diminishing the action potentials of the motor nerves, or might not it be antagonistic to the asphyxiation which is produced by tetany of the respiratory apparatus which, it seems, is the cause of death in strychnine poisoning? These two hypotheses seem very probable, at first glance. We shall see later that they will stand up under closer reasoning.

First of all, let us see what experimentation shows. I have already indicated the results which follow an attempt to restore an animal poisoned by curare by the use of strychnine. However weak the dose of curare used, every time the transmission of a nervous impulse in a frog is abolished (as determined by stimulation with an electrode on a motor nerve; the sciatic, for instance, with the finding of no movement in the appropriate limb), strychnine, even in high doses, introduced under the skin does not cause the most fleeting of convulsions, even though the absorption of the latter substance is not impaired, as shown in the first experiment herein. I have shown in another publication that the heart beat remains intact in frogs poisoned by curare, so that it must follow that absorption of these substances continues almost as efficiently as it does in the normal state. If the dose of curare is weak enough so that the transmission of nervous impulses is merely diminished, convulsions are produced by strychnine, although they are weaker. They are, however, as prolonged and as dangerous to life as before.

Let us now first of all inject strychnine.

**Experiment 2.** On a small adult dog at five minutes to 3 o'clock I made a longitudinal incision in the skin of the nape of the neck, and then I introduced into the subcutaneous tissue less than half a centigram of strychnine diluted with water and with a very small quantity of acetic acid. Five minutes later the animal, which already had manifested several generalized tremors in the posterior quarters and a general appearance of apprehensive-

ness, fell on its flank. Very violent strychnine fits ensued. Two drops of a concentrated solution of curare were immediately placed in the same fold of skin. Three minutes later respirations stopped, but the convulsions persisted up to that moment. I exposed the sciatic nerve and clamped it between the jaws of a forceps; there was no longer any nervous impulse demonstrated (although perhaps I might have found some traces of it with the aid of an electromagnetic machine). It was very evident that of all the nerves, the phrenic nerves alone had conserved their nervous impulse.

The amount of curare employed in this experiment was sufficient, and it is seen that death occurred with the same rapidity as it would have done if curare had been introduced into the tissues of a perfectly healthy animal.

**Experiment 3.** At twenty-five minutes to 3 o'clock about a half-centigram of strychnine, prepared as in the preceding experiment, was injected into the subcutaneous tissues of the neck of a small adult dog. At twenty-two minutes to 3 o'clock the animal repeatedly closed its eyes and hung its head, as if to go to sleep. Then a sudden light shaking awakened the dog. At this point, then, we had the first sign that the strychnine was taking effect. At twenty minutes to 3 the dog fell on its side with forceful convulsions, opisthotonus, stiffness of the legs, agitation of the eyes and trismus. Then I injected into the skin a very strong dose of curare. The convulsions continued: after light interruptions the shakings reappeared in the form of rippling contractions of muscles. At fifteen minutes to 3, after an episode of shaking which lasted longer than the others, the animal appeared to be dead. I applied artificial respiration by strongly pressing at regular intervals upon the thorax; and in this way succeeded in re-establishing several spontaneous respiratory movements. Soon the respirations established themselves entirely. I exposed a sciatic nerve. Crushing of this nerve in the jaws of a clamp still excited movements in the limb. I injected more curare into the fold of skin. At the end of one or two minutes, more or less, increasing signs of life reappeared in proportion to the maintenance and regularity of the respirations; then a new fit supervened. It was very violent and prolonged. When it ceased respirations again were suspended, and I was unable to reanimate the animal by means of artificial respiration; I could stimulate nothing but rhythmic movements of the facial muscles. I tested the motor ability of the sciatic nerve; it was entirely abolished, or at least mechanical manipulation was no longer able to reanimate it. I continued the artificial respiration until ten minutes after 3 o'clock; at this time the heart still beat regularly. Then I stopped the artificial respiration; the heart beat was not long in ceasing, also. In this case, the phrenic nerves still maintained an appreciable nervous energy.

In this experiment it is seen even better than in the second experiment to what degree the two toxic substances exert independent effects. Although



the dose of curare injected the first time was strong enough, and although it appeared to contribute to the suspension of respiration, we saw, nonetheless, that the animal displayed signs of reanimation, but was then taken with a fit at least as violent as the one which had preceded it. A new quantity of curare was then introduced which exerted an effect on the animal in the midst of a tetanic convulsion, and without any period of transition that I could perceive, death supervened. I draw attention to a period of transition because if curare is indeed a counterpoison to strychnine, there must be a moment in which the two substances reciprocally neutralize each other, the functions resuming their regular order in a normal manner. There is none of this, for as long as there remains any trace of nervous energy, strychnine tetanizes the animal. Its effect becomes hidden only when the nervous energy is abolished completely.

I might add that I have repeated these experiments a number of times. They always give the same results. In the cases in which the quantities of strychnine and curare were too small to cause death, the tetany produced by strychnine continued for as long a time as was required for the elimination of that substance; curare did not appear to have any obvious influence on the convulsive state. Perhaps, however, it rendered the convulsions a little less violent than would have been the case if the doses were in suitable strength.

Experimentation shows, therefore, that curare is not an *indirect* antidote for strychnine. It could not be otherwise. Strychnine stimulates and perverts the reflex activity of the spinal cord: the least stimulation coming from outside through the senses or through the voluntary or respiratory muscles summons this faculty immediately into action. The spinal cord, diseased, in a manner of speaking, replies to this stimulation by a series of movements produced by means of a prolonged discharge which constitutes the tetanic fit. Among the muscles subject to the convulsion are those of the respiratory apparatus, and asphyxia, imminent on several occasions, eventually becomes established in a final convulsion more violent and prolonged than the others. Then cessation of respiration is seen. Curare diminishes and abolishes nervous activity. If the quantity is large enough to annihilate that nervous energy, then death is the immediate and inevitable result of it; if the quantity is small enough so that the nervous energy is merely weakened, then it must be conceded that the morbid state of the spinal cord remains the same, and that the convulsion produced by the strychnine will not change in character or in duration. Only the violence of the convulsion will be somewhat diminished. But what will be the advantage obtained? Tetany of the respiratory apparatus, even though it has become enfeebled, will be just as complete, just as long, and just as pernicious as it would if the nervous energy were intact.

In the performance of these experiments on frogs, if a certain quantity of strychnine is first introduced under the skin and then, when tetany supervenes, if a little quantity of curare is introduced in the same place, the frog will be found the next day in the same state of flaccidity which prevailed on the evening before. The heart beat not only is still apparent, but has even conserved normal rhythm. Action of the heart might thus persist for several days, and I am sure that in certain cases, at the end of twenty-four hours (in the experiment of Dr. Harley) or in two, four, eight or ten days, the frog might still be able to recover from that lethargy. I have seen this occur when frogs were poisoned solely with curare. What would have happened in such a case? Certainly, it is permissible to assume that strychnine would have been eliminated at the same rate as curare, and that at the time of recovery there no longer would have been any convulsive state.

Strange as it may appear, in dogs which have been poisoned first by strychnine and then by curare it is seen that movements of the heart persist and maintain their regularity even at the moment of death. This shows definitely that strychnine does not act on that organ directly. If artificial respiration were applied, it might be possible to keep up these movements for a long time. It is probable that one might also, by placing the animal in a warm atmosphere and by maintaining artificial respiration for a long time, restore the animal to life; this presumption is founded upon the very conclusive evidence supplied by the experiments of Brodie and Waterton (cited by Reynoso), the first of whom described the return to life of a cat at the end of two hours of artificial respiration, and the second of whom reported the restoration to life of a female ass at the end of four hours. The question remains, however: would this amount of time be sufficient for the complete elimination of strychnine?

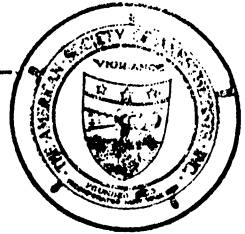
In summary, then, I do not think that the available evidence will sustain the notion that curare is an antidote for strychnine poisoning.

Now, if we apply to tetanus the considerations developed in this paper, it is seen that there is slight basis for the use of curare as a therapeutic agent against affliction. Whether tetanus is spontaneous or traumatic, it certainly has for its direct cause some state of the spinal cord analogous to that which is induced by strychnine. Curare merely acts on the structures not involved in strychnine poisoning; if we administered it in tetanus, we would simply weaken these structures and render them susceptible to abolition of their function, and thus merely compound another hazard in the presence of a prognosis which, in tetanus, is already grave.



*Claude Bernard*

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Nous allons maintenant aborder l'étude des phénomènes plus intéressants qu'offre le curare dans son action sur le système nerveux.

Vous savez, messieurs, que les poisons qui agissent sur le système nerveux peuvent l'affecter tantôt en produisant l'anéantissement de ses fonctions, tantôt, au contraire, en les exaltant; que, dans les deux cas, lorsque l'action toxique a été portée assez loin, la mort arrive produite par deux mécanismes différents.

Vous avez tous été témoins des convulsions violentes, de la surexcitation nerveuse considérable qui succède à l'administration de la strychnine. Le curare, au contraire, abolit les propriétés du système nerveux avec une netteté qu'on ne retrouve dans les effets d'aucun autre poison. Il supprime physiologiquement ce système important sans porter directement atteinte à l'intégrité des autres, et permet ainsi de juger de ce que deviendrait l'organisme si, à un moment donné, les nerfs qu'il paralyse cessaient d'exister.

Cette action du curare permet aussi de s'en servir pour analyser les propriétés des systèmes moteur et sensitif, et savoir si l'irritabilité musculaire et l'excitabilité nerveuse sont deux ordres de phénomènes distincts, ou s'ils peuvent être, théoriquement au moins, séparés l'un de l'autre et être envisagés isolément.

Nous vous avons dit que, lorsqu'un animal était tué par le curare, il mourait sans convulsions. C'est vrai, lorsque la dose est suffisante pour le faire périr rapidement; mais si elle le laisse succomber lentement, vous avez pu remarquer des frissons, qui sont

de véritables convulsions des muscles peauciers.

Toutefois il pourrait bien aussi se faire qu'il y eût du curare dans lequel il entrât des strychnées. Parmi les flèches empoisonnées que m'a communiquées M. l'amiral Du Petit-Thouars, il y en avait provenant de la Polynésie, qui développaient chez les grenouilles des mouvements convulsifs sans tuer spécialement les nerfs moteurs. La strychnine et le curare agissent en sens exactement opposé; le curare tue les nerfs de la périphérie au centre, et la strychnine du centre à la périphérie. Si l'on coupe le nerf sciatique, par exemple, chez une grenouille et qu'on l'empoisonne par le curare, le nerf coupé perdra plus vite son irritabilité que les autres; pour la strychnine, c'est l'inverse, le nerf coupé conservera bien plus longtemps ses propriétés.

L'absence de convulsions chez les animaux qui meurent en quelques minutes par le curare, est difficilement conciliable avec les récits de quelques voyageurs, qui pensent qu'il n'entre pas de venin dans sa préparation, et qu'il doit son activité au suc épaissi d'une strychnée.

D'une autre part, le fait de l'empoisonnement des oiseaux par suite de l'introduction du curare dans leur jabot, en ne permettant d'admettre qu'avec réserve son innocuité dans les voies digestives, admise d'abord comme un fait général, pouvait faire repousser l'idée qu'il doit ses vertus toxiques à du venin de serpent. Cependant j'ai lu tout récemment dans Fontana, qui a fait de nombreuses expériences sur les poisons d'origine animale, que le venin de la vipère empoisonne les pi-

geons quand on l'introduit dans leur jabot. Jusqu'ici le curare semblerait encore, par ses effets et les particularités relatives à son absorption, pouvoir se rapprocher des venins.

Une expérience vous fera saisir nettement les différences symptomatiques des effets du curare d'avec ceux de la strychnine, en même temps qu'elle vous rendra sensible cet anéantissement de l'innervation déterminée par le poison.

Sous la peau de cette première grenouille, nous introduisons un peu de curare solide. Au bout de trois minutes à peu près, elle succombe sans avoir offert le moindre mouvement convulsif.

Sous la peau d'une seconde grenouille, nous introduisons un peu d'extrait de noix vomique. Vous la voyez presque aussitôt s'étendre et se roidir avec assez de force pour soulever la cloche dont nous l'avons recouverte. Bientôt les mouvements convulsifs deviennent moins énergiques, et l'animal succombe au bout de cinq minutes environ.

La différence des symptômes est bien prononcée; mais la comparaison peut être poussée plus loin encore.

Si nous voulons nous rendre compte des modifications apportées dans l'exercice de l'innervation, le moyen le plus simple est de comparer notre grenouille empoisonnée par le curare à une grenouille tuée par décapitation. Or, nous préparons chez toutes deux le train postérieur : la colonne vertébrale est coupée de manière que le fragment supérieur *a* (fig. 19) serve à



fixer un crochet, et que sa séparation d'avec le fragment inférieur laisse un espace libre, dans lequel apparaissent seulement les nerfs lombaires *b*, que j'ai respectés.

Cette pile en forme de pince (fig. 20) va nous servir à porter l'excitation galvanique en rapprochant ses deux pôles (fig. 21). Il y a environ six ou sept ans que nous avons fait faire cette pince à M. Pulvermacher, et aujourd'hui la plupart des physiologistes l'ont adoptée comme étant d'un usage très commode. Cette pince est une pile en fil de cuivre C et de zinc Z.

On voit que les muscles de la grenouille tuée par le curare sont d'une couleur plus rouge, comme s'ils contenaient plus de sang que ceux de la grenouille morte par décapitation.

Lorsque je galvanise les nerfs lombaires de la grenouille tuée par décapitation, immédiatement les membres auxquels se rendent ces nerfs entrent en convulsion.

La même excitation portée sur les nerfs lombaires de la grenouille tuée par le curare ne détermine aucune contraction des membres postérieurs.

L'excitabilité nerveuse a donc été détruite.

Si maintenant, au lieu de galvaniser les nerfs, je galvanise directement les muscles auxquels ces nerfs se distribuent, je détermine dans les deux cas des contractions très vives. Chez la grenouille empoisonnée par le curare, la contractilité musculaire existe quand l'irritabilité nerveuse a complètement disparu. Ces deux phénomènes sont donc bien distincts, puisqu'ils peuvent exister l'un sans l'autre.

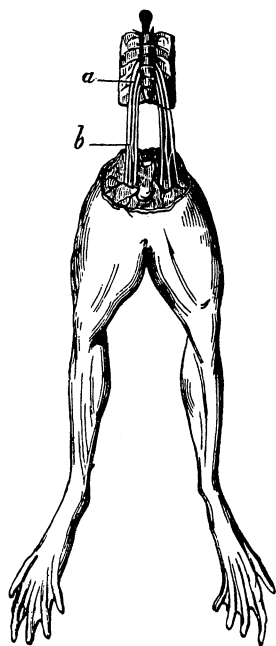


FIG. 19.

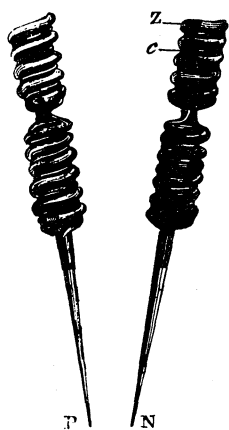


FIG. 21.



FIG. 20.

Lorsqu'on tue une grenouille par décapitation, la contractilité musculaire peut être mise en évidence par les excitations galvaniques pendant assez longtemps pendant plusieurs jours, quand la température est basse. Il en est de même de l'irritabilité nerveuse.

Quand on empoisonne une grenouille par le curare, nous avons vu que l'irritabilité nerveuse disparaît tout de suite. Il n'en est pas de même de la contractilité musculaire : vous venez de le voir ; je dois ajouter que, dans ce cas, les muscles conservent pendant un temps plus long la propriété de se contracter.

Le curare, qui anéantit l'action nerveuse sur les muscles, conserve au contraire plus longtemps la contractilité musculaire. Preuve que ce sont là deux actes bien distincts.

Bien que cette expérience, répétée souvent, nous ait toujours donné les mêmes résultats, savoir, l'augmentation de l'irritabilité musculaire après l'empoisonnement par le curare, on pourrait objecter à nos conclusions que l'inégale excitabilité des grenouilles peut avoir été la cause de la conservation de la contractilité musculaire que nous attribuons à l'action du curare.

Pour nous mettre à l'abri de cette cause d'erreur, nous avons lié sur une grenouille les vaisseaux qui se rendaient à l'une des pattes postérieures ; après quoi, nous l'avons empoisonnée avec le curare. L'expérience était la même ; seulement, le membre lié représentait la grenouille morte par décapitation ; l'autre, l'animal empoisonné. Ce que nous avons observé sur

deux grenouilles envisagées séparément, nous l'avons réalisé sur la même. Nos conclusions étaient donc parfaitement légitimes, ainsi que nous allons le voir par les expériences faites il y a déjà longtemps, et que je vais vous rapporter.

*Expérience.* — Sur une première grenouille, le 6 décembre 1854, on fait la ligature de la veine et de l'artère crurales droites; après quoi, on fait une plaie à la peau du dos, par laquelle on introduit un fragment de curare. Cette opération fut faite à deux heures cinq minutes, et, à deux heures vingt minutes, l'animal est complètement immobile. Quand on lui pince la peau du corps, celle des deux pattes antérieures celle de la patte droite postérieure, et la patte postérieure gauche, dont les vaisseaux ont été liés, il y a des mouvements réflexes, et l'animal retire ce membre. Mais on remarque, quand on pince la patte antérieure que, la patte dont les vaisseaux sont liés remue seule.

A deux heures et demie, l'animal est dans le même état, et les mouvements réflexes de la patte postérieure deviennent plus évidents quand on l'a laissée reposer pendant quelque temps.

A deux heures quarante minutes, si l'on pince d'abord la patte postérieure intacte, les autres ne remuent pas; mais si l'on pince une patte antérieure, la patte postérieure opérée se meut.

Quand, après quelque temps de repos, on imprime un mouvement à l'assiette sur laquelle se trouve la grenouille, cet ébranlement produit des mouvements

dans la patte qui a été opérée. Mais si aussitôt on remue de nouveau l'assiette, le phénomène n'a plus lieu. Enfin, on laisse reposer la grenouille un quart d'heure, et quand on pince la patte postérieure intacte, l'autre, dont les vaisseaux sont liés, remue. Il en est de même lorsqu'on pince les pattes antérieures.

Après avoir observé ainsi tous ces phénomènes, qui montrent, comme nous le verrons, que les nerfs moteurs seuls sont affectés et les sensitifs conservés, on lascia la grenouille dans l'assiette jusqu'au lendemain. Elle était placée sous une cloche pour empêcher son dessèchement par évaporation, la température était de 8 à 10 degrés.

Le 7 décembre, à onze heures du matin, et à deux heures et demie du soir, en pinçant la patte dont les vaisseaux sont liés, on y observe des mouvements réflexes. On laisse la grenouille dans les mêmes conditions que la veille.

Le 8 décembre, quand on pince un membre quelconque, il ne se produit plus d'action réflexe; ces mouvements ont partout disparu. Mais, en galvanisant les deux membres antérieurs, sans enlever la peau, on obtient des contractions énergiques. En galvanisant le membre postérieur intact, on a également des contractions énergiques; tandis que lorsqu'on galvanise, avec le même courant de la pince électrique, le membre dont les vaisseaux ont été liés, les contractions sont relativement beaucoup plus faibles.

Le 9 décembre, en galvanisant les quatre membres de la grenouille sans enlever la peau, on obtient des

contractions dans tous, excepté dans celui dont les vaisseaux sont liés. D'où il résulte que les contractions sont encore très fortes dans les trois membres dont les muscles ont été empoisonnés par le curare, tandis qu'elles ne sont plus sensibles dans les muscles que le curare n'a pas atteints, en raison de la ligature des vaisseaux.

Le 10, les phénomènes sont toujours les mêmes.

Le 11, de même : les trois membres empoisonnés se contractent, tandis que, dans le quatrième, il n'y a pas de contraction sensible.

Le 12, même état; seulement les contractions, dans les membres, sont moins intenses; le cœur battait toujours.

Pendant trois jours, la grenouille n'est pas observée.

Le 15, la grenouille, qui était d'abord d'une couleur noirâtre, est devenue verte, et il y avait une espèce de roideur cadavérique qui avait succédé à la résolution des membres qui existait précédemment. Cette roideur est plus forte dans les membres antérieurs.

On écorche alors la grenouille, et l'on remarque que les muscles de la patte liée sont un peu plus roses, ce qui tient probablement à la ligature des vaisseaux. En galvanisant les muscles mis à nu dans les trois membres empoisonnés, il y a encore de faibles contractions fibrillaires, particulièrement dans les muscles postérieurs et intérieurs de la cuisse. Il y a dans les membres des muscles qui perdent plus rapidement leur contractilité que les autres, et quand il faut comparer, on doit toujours agir sur les mêmes muscles. Il n'y a plus de contraction du tout dans les muscles non

empoisonnés. Ce qui prouve que c'est bien au poison qu'est due cette persistance, c'est que dans le membre lié, les muscles sont contractiles au-dessus de la ligature et ne le sont pas au-dessous. Le cœur ne bat plus ; l'oreillette est gorgée de sang.

Le 16, la contractilité persiste encore dans le gastrocnémien et dans le muscle droit antérieur de la cuisse du membre postérieur où les vaisseaux n'avaient pas été liés.

On cesse d'observer la grenouille.

Nous voyons, d'après cette expérience, qu'au bout de dix jours, il y avait encore des contractions dans les muscles empoisonnés, tandis qu'au bout de trois ou quatre jours, la contractilité avait déjà complètement disparu dans le membre où le curare n'avait pas agi, puisque la ligature l'avait empêché d'y pénétrer. — On voit donc clairement, par cette expérience, que l'action du curare augmente la persistance de la contractilité musculaire.

*Expérience.* — Le 6 décembre 1854, sur une seconde grenouille, on isole le nerf sciatique N; on passe au-dessous un fil, avec lequel on lie le membre en entier par-dessus la peau (fig. 22). Le nerf se trouve ainsi isolé et en dehors de la ligature.

A deux heures vingt minutes, on introduit un fragment de curare par une incision I faite à la peau du dos : peu à peu la grenouille ressent les effets du poison. Quand on lui pince la patte liée, elle la remue ; quand on pince une patte antérieure, elle remue également le membre lié. La grenouille devient peut à peu

insensible dans les trois membres intacts, c'est-à-dire que lorsqu'on pince ses pattes, elle ne remue pas; mais il en résulte des mouvements dans la patte liée.

A deux heures et demie, on a les mêmes phénomènes; à deux heures quarante minutes, quand on pince la patte postérieure intacte, aucun mouvement ne se manifeste. Mais quand on pince les pattes antérieures, on a des mouvements dans la patte postérieure liée.

Au bout d'un certain temps de repos, lorsqu'on pince la patte postérieure intacte, on observe des mouvements dans la patte postérieure liée;— quand on remue la plaque de liège sur laquelle la grenouille est fixée, il survient des mou-

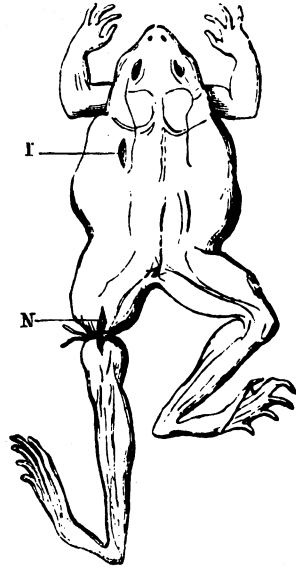


FIG. 22.

vements dans la patte liée. On observe alors une différence de teinte singulière dans la peau de la grenouille : la peau de la patte liée est d'une couleur plus claire que celle du reste du corps.

On laisse alors reposer la grenouille pendant un quart d'heure, et après ce temps, quand on vient à pincer successivement les trois pattes empoisonnées, on a toujours des mouvements dans la patte liée, non empoisonnée.



Le 7 décembre, à onze heures du matin, il n'y a plus de mouvements dans la patte liée quand on pince les autres. On découvre les muscles du mollet sur les membres postérieurs droit et gauche ; on excite par la pince électrique, et on constate une contraction très évidente et à peu près égale dans les deux membres.

On conserve la grenouille dans une assiette, sous une cloche, dans l'amphithéâtre; la température est de 8 à 10 degrés.

Le 8 décembre, les muscles des mollets sont contractiles; mais les muscles du côté de la patte liée le sont plus faiblement que ceux du côté où le curare a agi.

Le 9 décembre, le muscle du mollet de la patte liée n'est plus excitable au courant électrique; l'autre réagit très énergiquement encore sous un courant de même intensité.

Le 10, les mêmes phénomènes continuent.

Le 11, également; — le 12, la contractilité du membre empoisonné existe encore, mais faible.

Le 15, toute trace de contractilité a disparu.

Nous voyons, dans cette expérience, le même résultat qui s'est produit sur une grenouille un peu moins vivace: la contractilité a duré pendant six jours dans le membre empoisonné, tandis qu'au bout de trois jours elle avait disparu dans le membre non empoisonné.

Quelle pourrait être la cause de cette durée plus considérable de la contractilité musculaire dans les muscles empoisonnés par le curare? Est-ce l'effet du poison lui-même, ou bien la possibilité qu'ont ces

muscles de recevoir encore du sang, grâce à la persistance des battements du cœur, et à la possibilité, peut-être, de la respiration cutanée de ces animaux? Car ici les muscles non empoisonnés ne recevaient plus de sang, tandis que les autres continuaient à en recevoir.

Pour examiner cette question, nous avons fait l'expérience suivante :

*Expérience.* — Le 6 décembre 1854, on lie encore la patte postérieure gauche d'une grenouille, sauf le nerf. L'animal est empoisonné par le curare.

Le 7, l'animal ayant été conservé, comme les autres, sous une cloche et à la même température, on découvre les muscles des mollets dans les deux membres. On constate qu'il y a des contractions énergiques des deux côtés.

Le 8, les muscles sont encore contractiles dans les deux membres, mais plus faiblement dans le membre lié que dans l'autre.

Le 9, mouvements énergiques dans la patte empoisonnée, mouvements à peine sensibles dans la patte préservée.

Le 10, mouvements énergiques dans la patte empoisonnée, absence complète de contractions dans la patte liée.

On découvre le cœur, qui bat encore; on l'enlève, de manière à empêcher la circulation dans les muscles.

Le lendemain 11, il n'y a plus de contractions du tout, ni dans le membre empoisonné, ni dans l'autre.

Il semble donc que, dans cette expérience, l'ablation

du cœur, en empêchant le sang d'aller dans les muscles, ait fait cesser leur contractilité, puisque, dans les expériences précédentes, nous avons vu la contractilité durer une fois plus dans les muscles empoisonnés que dans les muscles non empoisonnés. Ici, il n'en a pas été de même, puisque, dès le lendemain, la contractilité musculaire a disparu après l'ablation du cœur.

Il semblerait donc résulter de là que le curare conserverait la contractilité musculaire en conservant plus longtemps les mouvements du cœur. Toutefois, nous verrons plus tard si cette cause est la seule.

Nous avons encore fait une dernière expérience, pour savoir si la destruction des centres nerveux avait une influence sur la durée de la contractilité.

*Expérience.* — Le 6 décembre 1854, on détruit une partie de la moelle épinière à une grenouille.

Le 10, on s'aperçoit que la moelle épinière n'est pas complètement détruite. — On la détruit alors complètement.

Le 12, les muscles sont encore contractiles sous l'influence du galvanisme.

Le 15, ils le sont encore, mais surtout dans les membres postérieurs; les contractions ont à peu près disparu dans les membres antérieurs.

Il faudra répéter cette expérience pour être autorisé à en tirer des conclusions nettes.

Sous l'influence du curare, il y a donc abolition de toute manifestation nerveuse.

Il y aura cependant lieu, dans cet anéantissement

fonctionnel, de distinguer deux effets bien différents, et qui ne se produisent pas en même temps. L'innervation n'est pas détruite en masse.

La motilité et la sensibilité ne disparaissent pas toujours en même temps. Mais comme la manifestation des phénomènes nerveux ne peut pas être comprise sans l'exercice des deux ordres de nerfs, il en résulte que l'animal se trouvera privé de toute manifestation nerveuse dans les deux cas. Ainsi, bien que le résultat soit identique, le mécanisme est différent et du plus haut intérêt à déterminer pour le physiologiste.

Nous entrerons dans l'examen de cette question dans une des prochaines leçons. Mais avant nous devons chercher par quelle voie et par quel mécanisme le curare peut être porté à agir sur le système nerveux.

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**On the Effects of Toxic and Medicinal Substances\****(Course in Medicine, College of France)*

CLAUDE BERNARD

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We shall now begin the study of those most interesting phenomena which are produced by curare in its action on the nervous system.

You know, gentlemen, that poisons which act on the nervous system may do so either by diminishing its functions or by accentuating them, and that in both cases, when the toxic action is of marked degree, death ensues, produced by two different mechanisms.

You have all witnessed violent convulsions, produced by the considerable nervous hyperexcitation which follows the administration of strychnine. Curare, on the other hand, abolishes these convulsive properties of the nervous system with a completeness found in no other poison. Curare suppresses physiologically this important system without directly attacking the integrity of others, and thus permits the observation of what becomes of the organism if, at a given moment, the nerves which it paralyzes cease to exist.

This action on the part of curare also permits utilization of the agent for analysis of the properties of the motor and sensory system, and for determination of whether muscular irritability and nervous excitability are two orders of distinct phenomena or are, theoretically at least, separate one from the other, and are to be regarded separately.

We have already told you that when an animal is killed by curare, it dies without convulsions. This is true when the dose is sufficient to make the animal die rapidly; but if the dose permits it to die slowly, you may note some quivering—true convulsions of the muscles of the skin.

There is, however, always the possibility that the curare contained some impurity in which some strychnine compound was present. Among the poisoned arrows sent to me by Admiral Du Petit-Thouars were some from Polynesia which produced convulsive movements in frogs without especially killing motor nerves. Strychnine and curare act in exactly opposite senses; curare kills peripheral nerves toward the center and strychnine from the center to the periphery. If one cuts, for example, the sciatic nerve of the frog and then poisons it with curare, the cut nerve will lose its faculty of irritability more quickly than will others. In the case of strychnine, the converse is true: the cut nerve will conserve its properties much longer.

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\* Translated from Bernard, Claude: *Leçons sur les effets des substances toxiques et médicamenteuses*. Paris, J. B. Ballière et Fils, 1857, pp. 311-325.

The absence of convulsions in animals which die within a few minutes after the injection of curare is difficult to reconcile with the tales of some travelers who think that no venom enters into the preparation of curare, and that it owes its activity to the thick juice of a strychnine compound.

Moreover, the fact that poisoning of birds follows the introduction of curare into their crops caused the view that it is innocuous in the digestive tract to be embraced with uncertainty—although the view at first was thought to be a general fact. This, then, may help to change the idea that curare owes its toxic qualities to serpent's venom. However, I have read quite recently in the writings of Fontana, who has made numerous experiments on poisons of animal origin, that viper venom poisons pigeons when it is introduced into their craws. Thus far, curare would seem to simulate venoms, because of its peculiar absorption effects.

An experiment will clearly point out the symptomatic differences between the effects of curare and those of strychnine, and at the same time will clarify this weakening of innervation produced by the poison.

Under the skin of this first frog we shall introduce a little solid curare. At the end of approximately three minutes, the frog will die without the least indication of a convulsive movement.

Under the skin of a second frog we shall introduce a little *nux vomica* extract. Almost immediately, you see the frog extend and stiffen itself, with enough force to lift the bell jar with which we have it covered. Soon the convulsive movements become less energetic, and the animal succumbs at the end of about five minutes.

The difference between the symptoms is very pronounced, but the comparison can be carried even further.

If we wish to take into account the changes brought on by exercise in innervation, the simplest means would be to compare our curare-poisoned frog with a frog killed by decapitation. Then we prepare both frogs in the following manner: the vertebral column is cut in such a way that a hook may be placed around the upper portion (*a* in Fig. 19), and that separation of the upper part of the vertebral column from the lower portion leaves a free space, through which course the lumbar nerves (*b* in Fig. 19) alone.

This battery in the form of a pincer (Fig. 20) will serve to carry galvanic excitation when we bring its two poles (Fig. 21) together. It is now six or seven years since we had Mr. Pulvermacher make this pincer for us, and today most physiologists have adopted it, finding it of very considerable use. This pincer is a battery composed of copper C and zinc Z wire (*c* and *z* in Fig. 20).

One can see that the muscles of the frog killed by curare are redder, as if they contained blood for a longer time than those of the frog killed by decapitation.

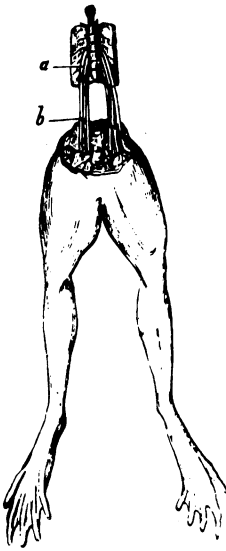


Figure 19



Figure 21



Figure 20

When I stimulate galvanically the lumbar nerves of the frog killed by decapitation, immediately the limbs which are innervated by the stimulated nerves go into a convulsion.

The same excitation, brought to bear on the lumbar nerves of the frog killed by curare, produces no contraction of the hind limbs.

The nervous excitability has thus been destroyed.

If, now, instead of galvanizing the nerves, I stimulate directly the muscles to which these nerves are distributed, I bring about very strong contractions. In the curare-poisoned frog, muscle contractility remains when the nervous irritability has completely disappeared. Thus, these two phenomena are very distinct, since they may exist one without the other.

After one has killed a frog by decapitation, muscular contractility may be made evident for a fairly long time; for several days, even when the temperature is low. It is the same relative to nervous irritability.

After one has poisoned a frog by curare, we have seen that nervous irritability disappears immediately. But it is not so relative to muscular contractility, as you have just witnessed, and I must add that in this case, the muscles maintain their property of contracting for a longer time.

Curare, which weakens the nervous action on muscles, preserves, on the contrary, the muscular contractility for a longer time. Here is proof that both acts are completely distinct.

Although this experiment, often repeated, has always given us the same results, namely, the augmentation of muscular irritability after poisoning with curare, one may object to our conclusions that the unequal excitability of the frogs may have been the cause of the preservation of muscular contractility which we attribute to the action of curare.

In order to avoid making this type of error, in one of the frogs we tied off the vessels leading to one of the hind feet, after which we poisoned the frog with curare. The experiment was the same except that the tied limb resembled that of the frog killed by decapitation and the other, that of the poisoned animal. That which we had observed in two frogs observed separately, we observed in only one. Our conclusions were thus perfectly legitimate, as we shall see, proved by experiments carried out a long time ago, which I am going to relate to you now.

**Experiment.** On a first frog, on December 6, 1854, a ligature was placed around the crural artery and vein, after which we made a fold in the skin of the back, through which we introduced a particle of curare. This operation was made at five minutes past 2 o'clock, and by 2:20 the animal was completely immobile. Pinching the skin of the body, of the front feet, of the right hind foot, and of the left hind foot, produced a reflex movement in the limb in which the vessels had been ligated, manifested by retraction of this limb. Moreover, it was noted that on pinching the forefoot, there was retraction only of the limb in which the vessels had been tied off.



At 2:30 the animal was in the same state; the reflex movements of the hind foot became more evident after they had been left in a state of repose for a while.

At 2:40, if the intact hind foot was pinched first, there was no movement of the others; but if the forefoot was pinched, the operated hind foot moved.

When, after a short period of rest, one agitated slightly the dish on which the frog lay, this shaking induced movement of the operated limb. But if one jerked the dish again immediately, this phenomenon did not take place. If, finally, after having let the frog rest for a quarter of an hour, one then pinched the intact hind foot, the other, the vessels of which had been tied off, moved. The same thing happened when the forefeet were pinched.

After having thus observed all these phenomena, which show that the motor nerves alone are affected and that the sensory ones are spared, the frog remained on the dish until the next day. It was placed under a bell jar to prevent evaporation, at a temperature of 8 to 10°.

On December 7, at 11:00 a.m. and at 2:30 p.m., the foot in which the vessels had been ligated was pinched and reflex movements of that limb were observed. The frog was allowed to remain in the same condition as the night before.

On December 8, when any limb in which there was no reflex action was pinched, these movements had completely disappeared. But, when galvanic energy was applied to the two forefeet, without elevation of the skin, energetic contractions were obtained. When galvanic energy was applied to the intact hind foot, equally strong contractions were obtained, whereas when galvanic current was applied to the limb in which the vessels had been tied off, the contractions observed were relatively much weaker.

On December 9, when all four limbs were galvanized without lifting the skin, contractions in all were obtained, except in the one in which the vessels had been ligated. Hence, it resulted that the contractions were still quite strong in the three limbs which had been poisoned by curare, whereas those muscles which were no longer sensitive had not been so poisoned because of the barrier provided by the ligature.

On the 10th, the phenomena were still the same.

The 11th, the same: the three limbs which had been poisoned contracted, while in the fourth, no contraction was noted.

On the 12th, the same situation, only the contraction of the limbs was less intense; the heart was still beating.

For the next three days, the frog was not observed.

On the 15th, the frog which at first had been a blackish color became green and some sort of cadaveric rigidity followed resolution of the condition of the limbs which existed previously. This rigor was stronger in the forefeet.

The frog was then skinned, and it was noted that the muscles of the tied

foot were a little pinker than the rest, this hue probably was due to the ligature around the vessels. When the exposed muscles of the three poisoned limbs were galvanized, weak fibrillary contractions were still observed, especially of the posterior and interior muscles of the thigh. Some muscles of the limbs lose their contractility more rapidly than do others, so that when a comparison is made, the same muscles must always be employed. There was no contraction at all of the muscles which had not been poisoned. Proof that this persistence of contractility was due to the poison is seen in the fact that in the ligated limb the muscles were contractile above the site of ligature and not below. The heart beat no longer; the auricle was engorged with blood.

On the 16th, the contractility still persisted in the gastrocnemius and in the right anterior muscle of the thigh of the limb in which the vessels had not been ligated.

No further observations were made on the frog.

We see then, that according to this experiment, after ten days there were still some contractions in the poisoned muscles, while at the end of three or four days contractility had completely disappeared from the limb in which curare had not acted, since a ligature had prevented penetration of the curare. One sees clearly, then, by this experiment, that curare augments the persistence of muscular contractility.

**Experiment.** On December 6, 1854, a second frog was employed; the sciatic nerve was isolated; under it was passed a thread which was then tied around the rest of the limb on the skin (Fig. 22). The nerve thus was isolated and not affected by the ligature.

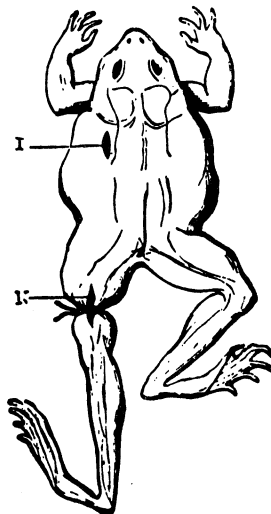


Figure 22

At 2:20 o'clock, a fragment of curare was introduced into the skin of the back by incision (*I* in Fig. 22); little by little the effects of the poison became apparent. When the tied limb was pinched, it moved; when a fore-foot was pinched, the ligated limb also moved. The frog became less and less sensitive in the three intact members; that is to say, when these intact limbs were pinched they did not move, but this did result in movement of the ligated limb.

At 2:30, the same phenomena were observed; at 2:40, when the intact hind foot was pinched, no movement was manifest; but when the forefeet were pinched, movement was observed in the ligated hind limb.

At the end of a certain amount of rest, it was observed that pinching the intact hind limb produced some movement also in the ligated limb. When the cork board to which the frog was fixed was moved, movement was observed in the ligated limb. Then we observed a singular difference in the hue of the frog's skin: the skin of the ligated limb was much brighter than that of the rest of the body.

We allowed the frog to rest for a quarter of an hour. At the end of that time, whenever the three poisoned limbs were pinched, movement in the ligated limb was noted, but not in the poisoned one.

On December 7, at 11:00 a.m., there was no longer any movement in the ligated limb after the others had been stimulated. We exposed the muscles of both calves and excited them electrically; we then noted evident contractions, almost equal, in the two limbs.

The frog was preserved on a dish under a bell jar, in the amphitheatre at a temperature of 8 to 10°.

On the 8th of December, the calf muscles were contractile; the muscles of the tied limb were weaker than those of the side on which the curare had acted.

On the 9th of December, the calf muscles of the ligated limb were no longer excitable with electric current; the muscles of the other limbs still reacted very energetically when they were stimulated with a current of the same intensity.

On the 10th, the same phenomena continued.

On the 11th, the same; on the 12th, the contractility of the poisoned limb persisted still, but it was feebler.

On the 15th, all trace of contractility had disappeared.

In this experiment we see that the same result occurred in a less lively frog: the contractility lasted six days in the poisoned limb, while at the end of three days it had disappeared in the limb not poisoned.

What is the possible cause of this considerable increase in duration of muscular contractility in curare poisoning? Is it the effect of the poison itself, or could it be that these muscles still receive blood, on account of the persistence of the heart beat, or is it perhaps related to the cutaneous

respiration of the animal? For in this experiment the nonpoisoned muscles no longer received any blood, whereas all other muscles continued to receive it.

To examine this question, we have carried out the following experiment.

**Experiment.** On December 6, 1854, we tied the left hind leg of a frog, excepting the nerve. The animal was then poisoned by curare.

The animal was preserved, as were the others, under a bell jar, and at the same temperature. On the 7th we exposed the calf muscles bilaterally. There were energetic contractions on both sides.

On the 8th, the muscles were still contractile in the two limbs, but were feebler in the ligated one than in the other.

On the 9th, energetic movement was noted in the poisoned foot, but movement was scarcely discernible in the ligated one.

On the 10th, energetic movement in the poisoned limb was seen, but contractions in the ligated limb were completely absent.

The heart was exposed. It was found to be still beating; it was removed to prevent further circulation into the muscles.

On the next day, the 11th, there were no longer any contractions in the poisoned limb or in the other.

It seems, then, from this experiment, that ablation of the heart, by preventing the passage of blood into muscles, caused cessation of their contractility, since in the preceding experiments we observed that the contractility lasted longer in the poisoned muscles than in those not poisoned. This experiment indicates an entirely different phenomenon, since from the next day after ablation of the heart, muscular contractility disappeared.

Thus, it would seem that this phenomenon results from the fact that curare preserves muscular contractility by preserving the heart beat. In any case, we shall see later if this is the sole cause.

**Experiment.** On December 6, 1854, a portion of the spinal cord of a frog was destroyed.

On the 10th it was perceived that the cord was not completely destroyed. It was then destroyed completely.

On the 12th, the muscles were still contractile to galvanic stimulation.

On the 15th, they were still contractile, but especially in the hind limbs; contractions of the anterior limbs had almost disappeared.

It will be necessary to repeat this experiment to justify the drawing of hard-and-fast conclusions from it.

Under the influence of curare, there was a complete abolition of all nervous manifestations.

However, in this functional weakening, it will be possible to distinguish two completely different effects which are not produced at the same time. Innervation is not destroyed *en masse*.

Motility and sensitivity do not always disappear at the same time. But,

since the manifestations of nervous phenomena may not be understood without the exercise of two orders of nerves, it follows that the animal is found to be deprived of all nervous manifestations in both cases. Thus, although the results are identical, the mechanism is different, and it is of the greatest interest to the physiologist to determine what it is.

We shall enter into the examination of this question in an early lesson. But first, we must seek the path and the mechanism by which curare may be carried to act on the nervous system.

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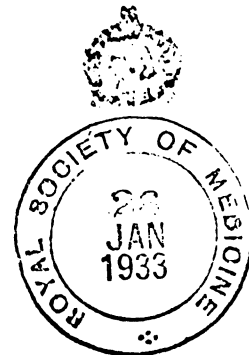
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UNDER THE DIRECTION OF  
THE EDITORIAL COMMITTEE

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tingling and reference sensations, and accompanying this is a restoration of discriminating sensibility in skin, joints and muscles.

Joint and muscle sensations seemed to be restored earlier when re-education exercises had been followed, so that all the delay in the reappearance of these functions cannot be ascribed to delayed regeneration of the nerves involved.

Observations upon thermal sensibility have been incomplete, owing to the difficulties encountered by thermal adaptability. Unless the skin was examined under ideal conditions, i.e., always at the same temperature, such varying results were obtained that we gave up the experiments as, owing to the press of routine work, the necessary time was not available.

Finally, as a result of my experience, I have formed the opinion that changes in the end-organs in the skin and deeper tissues hold the secrets of most of the phenomena encountered.

Differing, as they probably do, in their various recovery rates, some perhaps never being restored, and many connected after suture to heterogeneous pathways, we have a double source of error possible. If the distance receptors of our special senses can be specific in their selection of stimuli, why not the various end-organs on the surface of the skin?

Varying excitabilities and interference effects are possible at the periphery. Dissociation of sensation is possible in the skin. The experiences related and certain histological findings, as yet incomplete, lead to the view that these varied phenomena of regeneration in the sensory nerves may be explained more completely by a full study of the endings rather than by an assumption that certain classes of nerve fibres exist which would modify the conducting pathway in the nervous system.

### Curare in Man.

By RANYARD WEST, M.D.

*Introduction.*—Since the classical experiments of Claude Bernard [1] and Kolliker [2] curare had been considered to produce its pharmacological action exclusively upon the end-plates of the motor nerves. When the chemistry of curare was subsequently undertaken (Boehm [3], Lewin [4], Spath, etc. [5]), the various active principles isolated were classified according to the presence or absence of their peripheral effects. It was considered unlikely that curare could have a useful place in medicine, in view of the undesirable nature of its action. Curare was indeed used in one or two desperate cases of hydrophobia and tetanus (Hunter [6]), when it was difficult to choose between paralysis and convulsions, but there appeared no place for it in normal therapeutics. It was not until the electrical properties of the nerve, nerve-ending and muscles came to be studied (Lucas [7]) that a differential action of this drug was discovered. Recently Bremer, Titeca and Van der Meiren in Brussels, and Hartridge and the author in London, recorded a selective removal of certain rigid conditions in the experimental animal. Bremer, Titeca and Van der Meiren [8, 9, 10, 11, 12] recorded a selective abolition of decerebrate rigidity and of local tetanus in the cat. Hartridge and the author [13] recorded a selective abolition of the tonic, clonic and fibrillary fits of dogs suffering from parathyroid tetany, and suggested a number of possible sites a lesion of which might produce this effect. What emerged from our work was that tetany in the dog could be abolished by a dose of curare which was only half of the minimum dose required to produce signs of paresis. A dog so treated would pass from the violent, continuous convulsions of tetany into an apparently normal state and would so remain for some hours.

At the time this work was undertaken, I was engaged in an investigation of the neurological mechanism involved in tetany, and the possible association of tetany with certain other diseases of the central nervous system suggested to me a trial of

curare in other conditions. The margin of dosage in the dog seemed to me to justify the cautious trial of the drug in man.

*Method of administration.*—The curare used in this series of cases was given to me by Sir Charles Sherrington, who obtained it from South America some thirty years ago. It was a resinous mass of the consistency of hard toffee, and was incompletely soluble in water. Messrs. Burroughs Wellcome filtered it and sterilized it by autoclaving, and supplied me with the drug in ampoules of suitable strength. Doses corresponding to from 2 to 20 milligrammes of the original curare were the final quantities used. The drug was given hypodermically. Thirty patients have been treated.<sup>1</sup>

*Symptoms and signs.*—For about ten minutes after injection no symptoms are recorded. At the end of this period, or between it and thirty minutes after the injection, headache and slight giddiness were described by most patients. These symptoms were aggravated on standing. They were found invariably to be associated with a fall of systolic blood-pressure of some 20 millimetres of mercury. This could be counteracted and the headache entirely relieved by administering 5 or 10 minims of adrenalin with or shortly after the curare injection. The headache was found to vary directly with the fall in blood-pressure. Accompanying this fall, and commensurate with it, was a fall in pulse-rate, the pulse frequently reaching 60 or a lower figure in patients whose normal was about 80. [In the dog, extreme slowing of the heart-rate, with extrasystoles and marked sinus arrhythmia occur.] With the giddiness a non-persistent lateral nystagmus could be elicited in some cases on lateral fixation of the eyes. In the cases in which the giddiness was most marked, an irregular ataxia was noted and these patients would describe their condition as being "stupid" or "fuddled." No other abnormalities of the central nervous system were detected. There was a tendency for all these symptoms to diminish as treatment was continued, but in the earlier stages the palpitations and discomfort of adrenalin were preferred to the headache and giddiness caused by curare.

*Observations on rigidity.*—Observations on muscular rigidity were divided into two groups: (1) General change in rigidity, including general clinical observations, the patient's ability to perform movements, his symptoms and the observations of the nursing staff. (2) Specific measurements of changes in rigidity of certain muscles.

Rigidity or spasticity involving the flexors of the elbow or of the knee was chosen for measurement whenever possible, and in these cases I used a simple apparatus designed for me by Professor Hartridge, an illustration of which is given. It consists of a wooden board 18 or 20 in. long and 3 or 4 in. wide to which is hinged a similar board 14 in. long. The hinge is 4 or 5 in. from one end of the first board. In the case of the knee this latter is strapped along the extensor surface of the thigh so that the hinge lies over the knee-joint with the patient sitting in a chair. The second board will lie along the dependent lower leg. Extension is applied by means of a spring balance tied to the ankle and the force required to produce a given extension (which is most readily measured by a set square of appropriate angle inserted between the two boards) is measured in pounds. Care is taken to take the same time over the movement of extension on each occasion. In cases of spastic paraplegia or hemiplegia the initial movement registers a high tension, in view of the phenomenon of "clasp knife" rigidity. In extrapyramidal rigidity there is at first a bewildering irregularity in the degree of rigidity, but it is surprising how this settles down if rapid rhythmical movements of extension and flexion are made. The strength of the spring balance and the proportions of the wooden instrument can be altered to suit the requirements of the case.

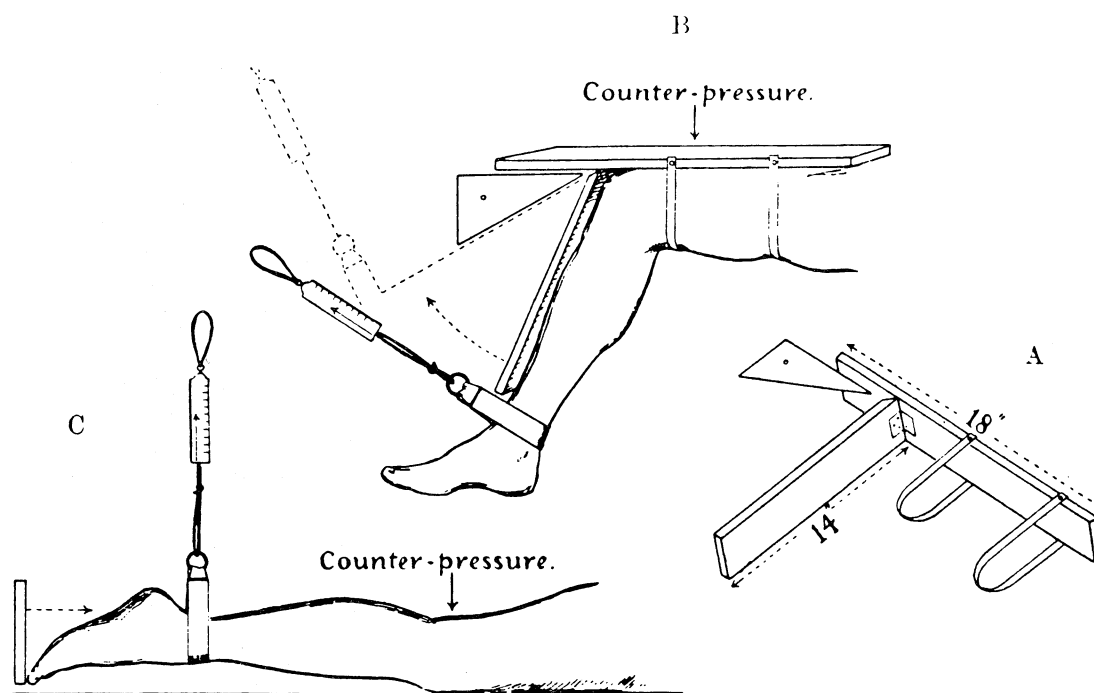
*Diseases studied.*—As curare in safe and controlled dosage is a new drug in medicine, I am trying it in a wide series of cases. In this paper, I wish to present

<sup>1</sup> I am indebted to the staff of the Hospital for Epilepsy and Paralysis, Maida Vale, for a number of the cases investigated.



the results in a preliminary series of seventeen patients, including two cases of epilepsy, five of rigidity due to pyramidal lesions, and five patients suffering from rigidity of the Parkinsonian type. The remainder comprise certain positive results among a variety of investigations suggested by various hypotheses of the action of curare.

*Epilepsy.*—The results in epilepsy have hitherto been entirely negative, and in view of one critical observation, I have for the time being abandoned curare in these cases. This critical observation was on a patient who, for months, had suffered five or six fits during each night between 8 p.m. and 8 a.m. Curare was given hypodermically each evening and as it made no difference to the frequency or character of the attacks, the dose was gradually increased. Finally, a point was reached at which the patient complained that half an hour after his injection his neck muscles were so weak that he was unable to lift his head from the pillow. I examined him when he was in this condition and found a considerable difference in



Apparatus.—A for measuring rigidity in paraplegia, B in flexion, C in extension.

the power of various muscles. He felt not the slightest embarrassment to respiration and this confirmed observations made on dogs. His heart, though slow, was regular. The flexor muscles of the neck were definitely weak. The patient could rotate his head but could not lift it. Muscular power in the limbs appeared normal. While I was moving his right arm about the limb began to jerk spontaneously and a Jacksonian fit spread to the face and became generalized. If higher dosage becomes possible, however, I propose to investigate selected cases of epilepsy further.

*Pyramidal disease (hemiplegia, paraplegia).*—

*Case I.*—A case of paraplegia in flexion, due to syphilitic myelitis of seven years' standing, with a very severe and constant flexor contraction of both legs at the knee. A much less severe degree of flexion spasm occurred at the hips. The spasm had been present without intermission, other than momentary—for instance, in a hot bath—for eight months.

*First observations.*—Passive extension of left and right knee-joints was possible to about thirty degrees from full extension. Active extension was possible to a less degree. Four

milligrammes of curare extract were administered hypodermically. After ten minutes a little giddiness was felt by the patient. After twenty minutes the patient declared her legs to be "looser." The right knee could now be extended to ten degrees short of full extension, the left a little short of this. The patient was able to walk with the assistance of a stick in a way which was not possible before. After twenty-four hours the legs were still observed to be "looser" by the patient, the ward sister and the masseuse. After forty-eight hours the legs were stiff again and declared by the patient to be "worse than ever." Five subsequent injections of approximately the same dose were each followed by decreased rigidity for from twenty to forty-eight hours. On the nineteenth day of treatment and on the occasion of the seventh injection, the apparatus described above was introduced. Extension of the left leg to thirty degrees from full extension required a force of 30 lb. (an average of six readings) before the injection, and 8 lb. (an average of six readings) after the injection (Table I). This patient improved considerably on injections of curare two or three times a week. Removal of curare for three days led to an increase in spasticity.

TABLE I.—CURARE "A" ABOUT 10 MGM.: REDUCTION OF RIGIDITY.

Patient	Disease	Joint movement	Rigidity		Control	
			Before lb.	After lb.	Before lb.	After lb.
P1, M.M.	Paraplegia in flexion	Left knee extension (1)	30	8	—	—
		" " (2)	32	8	—	—
		" " (3)	28	8	—	—
		Right knee extension	20	6	—	—
					Right side	
P2, E.S.	Hemiplegia (left)	Left knee flexion (1)	16	10	—	—
		" " (2)	11	10	8	8
P3, H.E.	Left hemiplegia	Left elbow extension	11	4	3	2½
E4, F.I.	Post-encephalitic rigidity	Left knee flexion	10	6	—	—
		Left elbow flexion	6 → 4	2 → 1	—	—
		Left elbow extension	9 → 6	2½ → 1½	—	—

This patient was troubled with giddiness following the injection of curare only when she was standing or sitting. Observations of blood-pressure gave a reading of 140/82 before curare, and 130/80 forty minutes after the injection was given (Tables II and III).

TABLE II.—CURARE "A" 5 TO 10 MGM. VASCULAR CHANGES.

Patient	Initial blood-pressure	Reduced to	After	Initial pulse-rate	Reduced to	Headache or giddiness
P3	128/90	128/90	45 minutes	76	70	Giddiness only
P2	125/70	110/60	40 "	108	90	Headache* Giddiness*
E1	150/90	124/80	c. 35 "	—	—	—
P4	120/60	94/60†	c. 35 "	74	60†	Headache* Giddiness*
E4	140/75	106/60‡	40 "	—	—	—

†Hypotension persisted for 12 hours. ‡For 3 days. \*Cardiac extrasystoles.

TABLE III.—FALL OF BLOOD-PRESSURE WITH CURARE.

Average of 30 observations.			Fall of blood-pressure		Fall of pulse-rate
After 15 minutes	...	17 systolic fall, 7 diastolic fall	...	9	
" 15-30 minutes	...	12½	7	5½	
" 30-60 "	...	10	5	6½	
" 2-12 hours	...	7	4	—	

*Case II.*—A case of vascular hemiplegia five months previously occurring in a woman aged 45. The patient was unable to walk, the left leg was spastic in extension; the left arm had very slight flexion spasticity, but was still very weak. Leg-flexion to thirty degrees from full extension required a force of 16 lb. on the left side, and 8 lb. on the right side, this latter being due to the weight of the limb. Eight milligrammes of curare extract were given as an initial dose. Forty-five minutes later the patient complained of a headache, and said that her paralysed arm "felt very light." Ten minutes later a force of 11 lb. was required to flex the left leg, 8 lb. being still required for the right. The patient moved her leg more readily than previously. She was much troubled by headache, and said that she felt "muddled," but she soon went to sleep. Forty-eight hours later the force required for

flexion of the left leg was 18 lb., that for the right being 10 lb. Six subsequent observations with the spring balance showed similar results. Within three weeks from the commencement of treatment with curare a definite improvement from her previously static condition was noted; she walked better, and could turn herself over in bed from shortly after the time the injections started. Improvement was noted until the injections were stopped, when walking was definitely worse. She improved three days after recommencing the injections. After individual injections headache and giddiness occurred from twenty to forty minutes after administration of the drug. On standing, at the height of the giddiness, a general ataxia was noted. The cardio-vascular system of this patient was more thoroughly investigated than in Case I. The initial blood-pressure was 125/60. Forty-five minutes after curare it was 110/60. The pulse-rate had fallen from 108 to 90. As treatment continued there was a tendency for lower blood-pressure levels to be obtained, but on each occasion a fall of systolic pressure occurred at the time of the giddiness and headache, and this fall was accompanied by a fall in pulse-rate. On adding 20 minims of adrenalin to the injection, the blood-pressure rose in five minutes from 118/78 to 132/90, and in fifteen minutes to 170/90 (Table IV). Palpitations and slight headache occurred, but there was not a trace of giddiness. A quarter of an hour later the blood-pressure had fallen to 126/80. Subsequent reduction of the dose of adrenalin to 5 or 10 minims enabled me to keep the blood-pressure comparatively constant and to avoid all headache and giddiness, though there was usually some palpitation.

TABLE IV.—CURARE "A" 5 TO 10 MG. + ADRENALIN m 10 TO 20.

	Blood-pressure initial	Adrenalin m	Blood-pressure after			Symptoms		Headache and giddiness with Curare alone	
			5 min.	15 min.	30 min.	Palpitation	Headache or giddiness		
P2 (i) ...	118/78	xx	132/90	170/90	126/80	Slight	O	+	+
(ii) ...	130/82	x	150/90	135/80	130/80	O	Slight headache after 30 minutes	+	+
Pulse-rate ...	76	—	—	86	96				
Control 1 (normal)	125/80	xv	180?	180?	135/80	+	O		
Control 2 (curare hypotension)	110/52	viii‡	110/52	112/45	120/50				

*Case III.*—Left-sided vascular hemiplegia of four years' duration in a woman aged about 45. The arm was in considerable rigidity, passive extension could move it only to within ten degrees of full extension. The hand was flexed to ninety degrees on the forearm and the fingers were adducted. It was quite impossible to extend the fingers passively, though the patient said that they became relaxed when she yawned. The extension of the left forearm on the arm required a force of 11 lb., while the same movement on the right side required only 3 lb. The blood-pressure was 138/90, the pulse-rate 76. Six milligrammes of curare were given hypodermically. After forty minutes the left arm could be extended with a force of 6 lb., the right requiring 4 lb. The blood-pressure was 128/90, the pulse-rate 70. A second injection of the same quantity was given. Ten minutes later extension of the left arm required a force of 8 lb. and 40 minutes later one of 4 lb. The blood-pressure was 132/80, the pulse-rate 64. The fingers could be extended passively but not actively.

*Case IV.*—Right-sided hemiplegic contraction, lasting since birth, in a girl aged 13. Spontaneous athetoid movements occurred from time to time and the arm would take up unusual postures sometimes for a considerable period. Curare in increasing doses up to 12 milligrammes was given and it was not until this dosage was reached that symptoms were noticed. The injection was followed by nystagmus on fixing the eyes to the left. There was no diplopia. The child was a little giddy on walking, the arm hung almost flaccid by the side. Passive flexion encountered no resistance, extension was met by a temporary clasp-knife rigidity, which gave way to allow full extension in a manner which had not been possible before. The first dose in this case produced a marked fall in blood-pressure from 120/60 (pulse 74) to 94/6 (pulse 60) and this hypotension remained for over twelve hours. Four days later the blood-pressure was 122/64 and the pulse 84. Cardiac extrasystoles occurred when the pulse-rate was at its lowest.

*Case V.*—Spastic paraplegia from disseminated sclerosis of long standing. The condition was one of paraplegia in flexion with a great deal of adduction spasm. Injections of curare produced very varying results on this patient, but at no time was the reduction of spasticity very obvious. The best record was a reduction of from 14 lb. to 8 lb. in the force required to separate the knees by 6 in. In the former case a force of 6 lb. was required to keep the

knees separate, and in the latter 5 lb. It was impossible to place much reliance on the figures obtained. The patient's subjective improvement is to be accepted with caution.

*Extrapyrarnidal disease, Parkinsonian rigidity.*

*Case I.*: A case of stationary chronic encephalitis with a well-marked tremor rigidity syndrome. The patient was a man aged 24 years. The tremor was more marked than the rigidity. The left leg shook violently from time to time. This was the first case of other than desperate illness in which I gave curare. The drug was started in minute doses, and it was not until 7 milligrammes were given that definite symptoms appeared. Twenty-five minutes after this dose the rigidity in the arms was almost abolished, but the tremor was increased in amplitude. The patient mentioned a sensation of pins and needles in the palm of the left hand, spreading upwards to the elbow. Rigidity remained in abeyance for two and a half hours. With larger doses headache was noticed. 13 milligrammes produced a sensation of slight weakness in the legs. The effective dose for the removal of rigidity was ultimately found to be between 5 and 7 milligrammes. This patient found hyoscine given hypodermically to be his best relief, in view of tremor, rather than rigidity, being his chief disablement.

*Case II.*—An established case of Parkinsonian rigidity in a woman aged 59. This patient's disease had reached a disabling stage, she was unable to walk unsupported, had not been able to write a letter for six months and was unable to turn in bed at the time treatment commenced. "Cogwheel" rigidity was considerable and a slight pill-rolling tremor was present. Twelve milligrammes was the minimum effective dose. Ten minutes after injection the rigidity in the arms was reduced, but the tremor remained; there was no apparent weakness. After half an hour the patient was able to walk, though very poorly and with much assistance. Reduction of leg rigidity was apparent at this time. Forty minutes after the injection there was some return of rigidity. On the next day 12 milligrammes of curare were combined with 1 100th grain of hyoscine by mouth. Subsequently the patient walked unsupported but with a tendency to propulsion. On this occasion improvement was maintained for a longer period. There was no doubt about the improvement in walking on the subsequent day, but the patient had been transferred from hyoscine by mouth to hyoscine hypodermically, and this rendered the significance of her improvement uncertain. She was now kept on hyoscine hypodermically, and subsequent experiments with curare were made in addition to this. Days on which curare was given were reported as better walking days by the massage department. The patient improved steadily, becoming able to walk alone and to write letters. She ultimately regarded hyoscine alone as being as helpful to her as hyoscine with curare, but there was no doubt about the relaxation which curare gave her in the earlier stages of treatment.

*Case III.*—A post-encephalitic aged 27. A case with moderate tremor and slight rigidity and also with oculo-gyral and static crises. Cogwheel rigidity of the right leg was found suitable for measurement. The patient was placed on his face and the force required to flex the extended lower leg at a given speed was measured. Constant readings were not obtained but an average of the readings was 10 lb. Fourteen milligrammes of curare were given, and one hour later an additional 6 milligrammes. Ten minutes after the second injection renewed measurements gave readings averaging 6 lb. for the same movement of the leg. The blood-pressure had fallen from 130 systolic to 104 systolic, the patient walked better with a longer stride and with an easier movement. Three days later 20 milligrammes of curare again improved his movement and lessened his rigidity for some hours. The patient had not been on adequate treatment and subsequent replacement of curare by hyoscine and belladonna led to a further improvement in walking.

*Case IV.*—A youth, aged 18, with a history of acute encephalitis in 1924 and rigidity of arms and legs from 1929 to 1931. The patient has advanced—and advancing—Parkinsonism and has had large doses of hyoscine, balladonna and stramonium without much improvement resulting. At 3.30 on one afternoon his walking was tested and his rigidity measured (Table I, E4). At 3.35 8 milligrammes of curare was given. At 3.55 he rose quickly from his chair and walked across the room swinging his arms in a way quite different from his previous performance. Measurement of rigidity showed a decrease (Table I, E4). He was sent home on his usual treatment. A week later his mother reported that he had dressed himself and had washed up the tea-things throughout the week, things which he had not done for many months previously. On the strength of this improvement the boy was admitted to hospital and given daily injections of curare. The first excellent results were not

maintained however, and after some weeks in which he became very depressed and suffered from increasing oculo-gyral and static crises, he was found to do better on stramonium than on curare. Stramonium improved him for a short time only however, and was in its turn eclipsed by hyoscine. This then proved to be one of those cases which respond excellently to a standard treatment of chronic encephalitis, but only do so for a short time. Curare, in the form in which I was using it, appeared to have taken its place amongst these treatments. The marked vascular hypotonia resulting from curare in this case is shown in Table 2, E4.

Table IV (Control 2) shows the subsequent response to adrenalin, which was delayed and poor, and in marked contrast to that of a normal individual.

*Curare in other conditions.*—(1) "*Causalgia*" (?)—A case not unfamiliar in type, of pain down the left arm and in the palm and fingers of the left hand, with "pins and needles," and tenderness at the root of the neck "for years." There had been little relief with thyroid extract, bromide mixtures and radiant heat therapy. There was no apparent vascular spasm. The patient was a woman aged 57. Four milligrammes of curare partially removed the pain and paræsthesia in fifteen minutes and both were absent after thirty minutes. The patient volunteered that she could move her fingers about better. A fall in blood-pressure and pulse-rate accompanied the improvement, which lasted one and a half hours. A second experiment is shown in the following table:—

Time	Injection	Blood-pressure	P	Symptoms
2.30	—	160 100	80	Pain severe and continuous from shoulder to fingers throughout the day
2.38	Curare 8 mgm.			
2.50	"	135-138 80	64	Pain less in shoulder.
3. 0	"	143-150 80	66	No pain above elbow
3.15	"	—	—	Pain remains in hand only. Severe headache
3.25	"	—	58	Pain in one spot in the palm and in the fourth and fifth fingers. Severe headache
3.40	Adrenalin mxx			
3.45	"	158 70	—	Headache suddenly vanished
4. 0	"	152?	80	A little pain in fifth finger. "Fingers move more easily." Relief: two hours. Dull ache only: one day

Inconstant from beat to beat, with extrasystoles.

There was total relief of pain for two hours, and a dull ache only for a day. The patient was used to severe pain.

(2) *Spasm of the orbicularis oculi*, of intermittent but daily occurrence was relieved for five days following one injection of curare. Subsequent injections had effects for shorter periods.

(3) *Arterial hypertension with arterio-sclerosis*.—Two cases with systolic pressures of 270 and 280 mm. Hg respectively. Both failed to respond to curare by a fall in pressure. Instead, both underwent a rise of arterial pressure of from 10 to 16 mm during the fifteen minutes after injection. It would not then appear probable that falls in blood-pressure are due to cardiac weakness.

*The possibilities of curare therapeutically.*—A forecast on this subject demands a survey of a number of aspects of a most interesting problem. The first of these involves an answer to the question "What is curare?"

Curare (or "urali," to give it the best known of its many alternative names) is a resinous arrow-head poison which kills by muscular paralysis and consequent asphyxia. It occurs under various names in many wild areas of the world, but the best known of these are the Amazon basin, the Orinoco basin and Guiana; and it is

only from these areas that the specimens in the Royal Botanical Gardens come. It is a matter of interest to learn that Sir Walter Raleigh [14] described the action of the poison and hoped to find an antidote.

In the first half of last century Humboldt [15], Waterton [16] and the Schomburgks [17, 18] saw the poison prepared by evaporation and mixture of plant extracts and it was Sir Robert Schomburgk who identified the chief plant ingredient as a member of the strychnos species to which he gave the name *Strychnos toxifera*.

In 1897 Quelch [19] recorded the preparation and the ingredients of the mixture as described by Waterton and Schomburgk and compared them with his own observations in the same areas of the Kanuku mountains of Guiana. He found that from three to eight plants entered the brew. The majority of the plants were poisonous, and in one curare four plants were apparently of the strychnos species. But the most constant ingredient of the varied brews was the bark of the ligneous vine, *Strychnos toxifera*.

The black resin of the curare is put up in various ways for transit and protection; notably in gourds containing some two ounces, in earthenware pots of varying sizes and in bamboo sticks. It is said that these varying vehicles are related to varying strengths of curare.

Boehm [3] has described three separate alkaloids as being present in "pot" curare, two further ones in "tube" curare and two, different again, in "gourd" or "calabash" curare. These vary very much in their paralysing properties, and at least one alkaloid—curine—is lacking in paralysing power in its naturally occurring form (Spath, etc. [5]).

But while various curares have various strengths of paralytic action, Prof. Hartridge and I found only two specimens out of seven to possess the power of removing tetany in the dog, without causing paralysis. It is one of these two successful specimens which has the action I have just described in man.

The second question before us then is: Does curare contain a second active principle for the removal of these rigid states? Such a second substance might act as a central depressant or might still act peripherally but in some way selectively.

I thought that possibly some light might be thrown on this matter by employing one of the synthetic preparations of quaternary ammonium bases, which have a curare-like action in regard to paralysis. I used octyl-trimethyl ammonium iodide, very kindly prepared for me by the Wellcome Physiological Research Institute according to the formula of Dr. Ing, who has recently described the action of this base [20]. It has unfortunately been impossible to carry these tests very far. The drug caused severe vomiting and prostration in the dog and it was impossible to press the dosage to the point of obtaining any specific pharmacological effect. Small ascending doses have been given to man, but these again produced nausea and had to be abandoned.

The question of an action of curare at the periphery, which is selective in its removal of these varied forms of rigidity, and also of the clonic and the tonic states of tetany in the dog, is both an interesting and a difficult one. In the case of decerebrate rigidity in the cat, Bremer and his colleagues think that curare produces its selective action by affecting more readily nerve-endings which are continuously in action than those which are resting. These authors cite the Wedensky phenomenon in which partial narcosis will permit the passage of one electrical stimulus of threshold strength, but inhibits succeeding stimuli. They found that with curarization of a degree which diminished tone but left the tendon reflexes intact, the muscle responded fully to isolated stimuli, but when repeated stimulation reached a certain frequency—which might be quite low—the muscle response "showed the sinking down typical of Wedensky inhibition." They suggest that "the tonic impulses, continuously arriving at the neuromuscular junctions of the fibres engaged in postural tone, are similarly blocked" by weak curare. Dr. Bremer thinks that

the selective removal of tetany in dogs, which Hartridge and I have described, can be explained along similar lines. There are, however, difficulties in accepting such an explanation, particularly in view of the removal of the short-duration, clonic contractions which are a common feature of dogs in tetany, and even more in the fact that these are removed in doses which leave intact the power of normal voluntary movements, such as walking.

In the event of our being forced to regard this selective action of curare as peripheral, certain possibilities call for consideration.

In the first place, there calls for elimination the possibility of afferent impulses from the periphery being affected. For all these rigid states, including tetany [21], are modified by deafferentation. It must be noted, however, that Mathews [22] finds no modification in the ascending discharge from the muscle spindle resulting from curarization in any doses inadequate to cause paralysis.

Secondly, there is the possibility of the myoneural junction being a more selective apparatus than it is usually considered to be. I have in mind a structure upon which curare could actually act selectively, removing discharges of certain electrical patterns, while allowing others to pass. Dale and Gaddum [24] have shown with great clearness that stimulation of the nerves to the blood-vessels of the tongue, by the local production of acetyl choline, can cause the contraction of this organ when its motor innervation has been removed. If such an action is upon the remaining myoneural junctions (as it seems it may be) these would appear to have become sensitized by denervation to the peculiar form of stimulation presented. Whether some such mechanism could involve the autonomic nervous system as offering to these pathological rigidities a contribution which is specifically removed by an action of curare on the myoneural junction, is entirely speculative. But the relationship of curare—or rather of the active principles which it contains—to the autonomic system deserves investigation.

The next step in the elucidation of the pharmacological problem is, I think, a renewed attempt to separate the various constituents of curare. The approach is twofold: by obtaining the ingredient plants separately and assaying them, and by chemical analysis of the final product as it reaches this country. I am glad to say that investigations along both these lines are already in progress.

From the therapeutic point of view this communication is preliminary and tentative. The rigidity-reducing—or “lissive”<sup>1</sup>—agent is apparently absent or inadequately present in some samples, and there is still difficulty in guaranteeing supplies of suitable curare. There are, however, all too few drugs with lissive properties, and it appears worth while exploring this somewhat intricate new one. It is hardly necessary to issue a warning against the rough and ready trial of unstandardized preparations in which the presence and the range of dosage of the lissive factor have not been determined. Hitherto I have found the dog the best subject for standardization of the various curares I have recently tried.

From the pharmacological aspect, we have in curare a drug which presents new subtleties for study, and from the point of view of neurological theory much of interest depends on whether the selective action described proves to be central or peripheral in its site.

#### SUMMARY.

(1) A specimen of curare has been administered, as a sterilized hypodermic injection, to man in thirty cases. Seventeen cases are here reported.

(2) In doses which produce no detectable signs of weakness of voluntary muscular power, a definite, measurable reduction in the muscular rigidity resulting from diseases of the pyramidal and the extrapyramidal motor systems is recorded.

<sup>1</sup> O.E., *lithe* = soft. Cogn. with *L. lentus* = pliant. (Cf. *lissom*.)

Rigidity became lessened in from ten to forty minutes after administration of the drug and this reduction lasted for from two to forty-eight hours.

(3) Clinical improvement coincided with the registrable changes, and massage and physical exercises were facilitated while the patients were under the influence of the drug.

(4) Certain other events are recorded. This curare produced a fall in blood-pressure and in pulse-rate, accompanied by headache and giddiness, coincidentally with its reduction of muscular rigidity. These events were prevented by an adequate injection of adrenalin with the curare. Adrenalin did not appear to modify the "lissive" action of the drug.

(5) The actions described appear to forecast a place for curare, or for one or more of its derivatives, in therapeutics. Opportunity has not occurred for a trial of curare in tetanus, hydrophobia or strychnine poisoning.

(6) Certain theoretical aspects of the action of curare are considered, and the fact that it is not a unity, or even of constant composition, emphasized.

(7) A need of further chemical and physiological assay of curare is stressed.

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Dr. C. P. BLACKER read a paper on "Human Pedigrees." He explained the schedule prepared and published by the Eugenics Society and entitled, "How to Prepare a Family Pedigree."

[October 15, 1931.]

### Herpes Zoster<sup>1</sup> involving Left Quadratus Lumborum and Oblique Muscles, with Complete Reaction of Degeneration. Lumbar Pseudo-Hernia in Region of Scars.—A. DICKSON WRIGHT, M.S.

Patient, a man, aged 60, three months and a half ago had a typical attack of herpes zoster on the left side, involving the tenth and eleventh dorsal segments. Since then the muscles on the left side of the abdomen have shown marked weakness, with the development of a lumbar pseudo-hernia, for which he wears a support.

*Present condition.*—Well-marked recent herpetic scarring on left side of abdomen and back from middle line of front to back, as high as the navel and extending nearly to the groin.

On exertion, as in rolling over towards the right, the ventral hernia through the weak quadratus lumborum and external oblique can be seen.

On electrical testing, there is well-marked complete reaction of degeneration of these muscles.

<sup>1</sup> Publication of these notes was held over owing to the illness of the author.





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**A.M.A. Session. NEW YORK. June 10-14, 1940**

## Wiener & Alvis' New Eye Surgery

The Journal of the American Medical Association, in its review of Wiener and Alvis' new book, says: "For many years the American ophthalmologist has awaited a surgery of the eye which would give in simple but descriptive words, a practical treatise that could be used in everyday work. The authors of this volume have achieved such an ideal. *No ophthalmologist can afford to leave such a book off his 'must' list!*"

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**See also SAUNDERS ADVERTISEMENT on Pages 3, 4, 5**

## PREVENTING TRAUMATIC COMPLICATIONS IN CONVULSIVE SHOCK THERAPY BY CURARE

A. E. BENNETT, M.D.

OMAHA

Convulsive shock therapy has been very enthusiastically endorsed by many workers and critically condemned by others. Its exact status as a permanent therapeutic agent in neuropsychiatry is yet to be determined. The follow-up studies after convulsive shock treatment of schizophrenic reaction types are not very encouraging, since relapses are frequent. Hypoglycemic shock therapy seems preferable. However, in chronic affective disorders of both the depressive and the manic types, the favorable sustained improvements from convulsive shock are more encouraging.<sup>1</sup> Midlife and presenile depressive states are terminated in the large majority of cases by convulsive therapy.<sup>2</sup> The cases of schizophrenia that respond best to this type of treatment are likewise admixture types with affective components.

For convulsive shock most workers use a convulsant dose of metrazol (pentamethylenetetrazol). Other convulsant drugs in use are triazol,<sup>3</sup> picrotoxin<sup>4</sup> and coriamyrtin.<sup>5</sup> Preliminary reports<sup>6</sup> indicate that all these methods are therapeutically effective.

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From the Psychiatric Department of Bishop Clarkson Memorial Hospital and the University of Nebraska College of Medicine.

1. Bennett, A. E.: Convulsive (Pentamethylenetetrazol) Shock Therapy in Depressive Psychoses: Preliminary Report of Results Obtained in Ten Cases, *Bull. Menninger Clin.* **2**: 97 (July) 1938 and *Am. J. M. Sc.* **196**: 420-428 (Sept.) 1938.

2. Bennett, A. E.: Metrazol Convulsive Shock Therapy in Affective Psychoses: A Follow-Up Report of Results Obtained in Sixty-One Depressive and Nine Manic Cases, *Am. J. M. Sc.* **198**: 695 (Nov.) 1939.

3. Walk, Alexander, and Mayer-Gross, W.: Observations of Convulsion Therapy with Triazol 156, *J. Ment. Sc.* **84**: 637-663 (Sept.) 1938.

4. Low, A. A.; Blauroch, M. F.; Sachs, Mandel; Wade, Chester, and Ross, Edward: Picrotoxin as a Convulsant Treatment of Certain Mental Illnesses, *Arch. Neurol. & Psychiat.* **41**: 747-754 (April) 1939.

5. Swanson, E. E., and Chen, K. K.: The Pharmacological Action of Coriamyrtin, *J. Pharmacol. & Exper. Therap.* **57**: 410-418 (Aug.) 1936.

6. Ebaugh, Franklin, and Johnson, G. S.: Status of Chemotherapy in Schizophrenia and Affective Reactions, *Am. J. M. Sc.* **197**: 862-873 (June) 1939.

One of the serious drawbacks to this therapy has been the occurrence of traumatic complications in the form of fractures of the spine and extremities.<sup>7</sup> This hazard is sufficiently serious, in spite of excellent obtainable results, that many workers have given up convulsive shock therapy. Insulin shock also carries this risk, but in a lesser degree than other convulsant drugs.

Up to date, none of the measures advocated for prevention of fracture complications can be accepted as universally prophylactic. Various orthopedic restraint devices, hyperextension of the spine, preliminary insulin coma and even spinal anesthesia along with metrazol<sup>8</sup> give no constant assurance that fractures can be prevented. Preexisting pathologic conditions of the bone may explain the tendency to fracture in some instances, but the fundamental problem still remains; namely, the severity of the tonic muscular contraction producing skeletal fracture by direct muscle pull.

If shock treatment is to survive, the incidence of fracture complications must be reduced to a minimum. Since the fundamental cause of fracture complications is the severity of the muscular contractions occurring from the convulsive attack, the proper theoretical approach in prevention should be toward lessening the severity of the convulsion. The principle of curarization, or blocking the neuromuscular junction, seems to be the proper approach.

Since the time of Claude Bernard, curare (Indian arrow-poison) has been the ideal laboratory drug for blocking nerve impulses between the nerve fiber and the muscle. This peripheral motor paralysis in general affects nerve endings of all striated musculature. While systems other than the neuromuscular apparatus are undoubtedly affected to some extent, the chief action resulting in death is one of peripheral paralysis of the muscles of respiration. Cardiac muscle is relatively little affected until after asphyxia.

Curare has not as yet gained a definitely useful application in clinical medicine. Attempts from time to

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7. Palatin, Philip; Freedman, M. M., and Harris, M. M.: Vertebral Fractures Produced by Metrazol Induced Convulsions, *J. A. M. A.* **112**: 1684-1687 (April 29) 1939. Bennett, B. T., and Fitzpatrick, C. P.: Fractures of the Spine Complicating Metrazol Therapy, *J. A. M. A.* **112**: 2240-2244 (June 3) 1939. Hamsa and Bennett.<sup>8</sup>

8. Hamsa, W. R., and Bennett, A. E.: Traumatic Complications of Convulsive Shock Therapy: A Method of Preventing Fractures of the Spine and Lower Extremities, *J. A. M. A.* **112**: 2244-2246 (June 3) 1939.

time have been made to apply the curarization principle in treatment of spasmodic disorders. West<sup>9</sup> reported partial success in tetanus. The most encouraging report is that of Burman<sup>10</sup> in infantile cerebral palsies, spastic pyramidal states and extrapyramidal rigidity states which are associated with involuntary movements, athetosis and tremor.

For the past six months I have been using curare at the Nebraska State Orthopedic Hospital on a large number of spastic paralytic children, with encouraging results similar to those reported by Burman. These observations, after convincing me of the safety of the drug, have pointed the way to its application in convulsive shock therapy of mental disorders.<sup>11</sup>

One of the reasons, I believe, for previous inconclusive clinical application of the drug has been inability to obtain a sufficient quantity of proved pure crude curare (authenticated curare).<sup>12</sup> Through the courtesy of Mr. Richard C. Gill, of New York, and E. R. Squibb & Sons, we were given the opportunity of standardizing a large quantity of the crude drug for experimental purposes.

#### THE TECHNIC OF CURARIZATION PRELIMINARY TO CONVULSIVE SHOCK THERAPY

Either an infusion or an alcoholic extract from crude curare is prepared and the smallest lethal dose (per kilogram) for mice is determined. The lethal dose (different with each batch) is then determined; about one-tenth the lethal dose (per kilogram) is the beginning dose for human beings. The drug must be sterilized<sup>13</sup> and slowly injected intravenously or given intramuscularly. The active physiologic reaction of curarization is noted at about one-fourth to one-half the estimated lethal dosage.

---

9. West, Ranyard: Intravenous Curarine in Treatment of Tetanus, *Lancet* 1: 12-16 (Jan. 4) 1936; The Pharmacology and Therapeutics of Curare and Its Constituents, *Proc. Roy. Soc. Med.* 28: 565-578 (March) 1935.

10. Burman, M. S.: Therapeutic Use of Curare and Erythroindine Hydrochloride for Spastic and Dystonic States, *Arch. Neurol. & Psychiat.* 41: 307-327 (Feb.) 1939.

11. These results, with more extended observation on combined curare and metrazol therapy, will be reported elsewhere.

12. Gill, R. C.: Curare, The Flying Death, *Natural History*, November 1935, pp. 279-292.

13. Dr. A. R. McIntyre, professor of pharmacology at the University of Nebraska College of Medicine, is now carrying out biologic standardization experiments, and a safe commercial preparation should soon be available.

When the physiologic dosage is reached, the physiologic effects noted immediately after intravenous injection and fifteen minutes after intramuscular injection are as follows: First, there is a subjective heaviness of the eyelids, then bilateral ptosis, slight nystagmus and strabismus with diplopia. Weakness of the muscles of the neck with inability to raise the head, loss of facial expression from weakness of the muscles, slow hesitant speech, weakness of the throat and jaw muscles rapidly follow. Next occur weakness to complete paresis of the spinal muscles, preventing the patient from raising himself, and, last, complete paresis of the arms and legs. These symptoms follow the same order as



Fig. 1.—The patient in a straight metrazol convulsion.

the progressive symptoms of a patient with myasthenia gravis. Double ptosis and nasal smile simulate the appearance of the myasthenic patient.

When, within five minutes after the intravenous injection of curare, this effect is produced, the estimated convulsant dose of metrazol is given. I still hyperextend the patient's back by placing between the scapulas a firm folded blanket fastened on a pillow. Care must be used not to allow the patient's head to fall backward, as his neck muscles are powerless. The usual metrazol convulsion ensues immediately, but with very much less tonic and clonic contraction—no special precaution except tongue gag need be used.

By the time the patient regains consciousness the effects of curare have disappeared. Although patients

are not able to thrash about after administration of metrazol, they should be watched carefully.

While we have not seen any side effects from the combination of the drugs except for a few instances of transient urticaria, nor any respiratory embarrassment, these should be watched for. Ampules of epinephrine and prostigmine should be available for injection as an antidote. If respiratory failure should occur, artificial respiration should be effective, since the excretion of the drug is rapid and the patient will spontaneously regain breathing power within a short time. It is doubtful whether respiratory failure need be feared unless too large a dose of curare is employed. The criterion to be followed is sufficient curare to para-



Fig. 2.—Same patient as shown in figure 1 after curarization followed by metrazol, illustrating the remarkable diminution of muscular contraction.

lyze the muscles of the neck and back. When the patient is unable to raise the head, sufficient motor paresis has been produced for metrazol to be given.

I have not noted any tendency to increased tolerance of curare on repeated injections. Neither am I sure that larger doses of metrazol are necessary to induce a convulsion after curarization. It may be wise to use a slightly larger dose of metrazol, however.

I have noted the same therapeutic effectiveness in depressive states by this combined method as from previous metrazol treatment. Curare in no way interferes with the therapeutic effect of metrazol. It may possibly allay somewhat the anxiety of the patient. So far, I have found that patients do not dread this convulsive shock as much as that from metrazol alone.

Figure 1 shows a patient in a straight metrazol convulsion. Figure 2 shows the same patient after curarization followed by metrazol, illustrating the remarkable diminution of muscular contraction.

I am convinced that fracture complications resulting from a metrazol convulsion in a properly curarized patient are almost impossible unless there is a serious pathologic condition of the bone.

#### CONCLUSIONS

Aqueous or alcoholic extract of curare given parenterally in physiologic dosage sufficient to produce flaccid generalized motor paresis adequately protects the patient from traumatic complications of convulsive shock therapy.

So far, no danger or drawback to this combination treatment has been encountered. The therapeutic effectiveness of convulsive shock is still maintained.

Further experimentation is indicated before this procedure can be safely recommended for general psychiatric practice. More detailed experiences with this method will be reported elsewhere.

1204 Medical Arts Building.





615.785.3:612.2

THE ACTION OF CURARINE ON THE  
RESPIRATORY MECHANISM

By RANYARD WEST

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## THE ACTION OF CURARINE ON THE RESPIRATORY MECHANISM

By RANYARD WEST

*From the Department of Pharmacology, Oxford*

*(Received 3 November 1937)*

CURARINE is the type alkaloid of Guianese curare: it has the classical curare action of neuromuscular paralysis. When given subcutaneously, the respiratory muscles are often among the last affected. But this is not always so, and in a number of species, notably in rodents and in dogs, animals whose general musculature is not yet noticeably weakened by the drug may be seized with respiratory embarrassment leading to cyanosis, and thence rapidly to fatal asphyxia [West, 1935].

The attacks of difficulty in breathing are as follows. The injected animal suddenly commences to breathe slowly and with effort, the difficulty appearing to be inspiratory rather than expiratory. At the same time a characteristic feature of curarization of the respiratory mechanism may develop, namely a long maintenance of the chest in the expiratory position, the inspiratory phase being represented by a short deep gasp sometimes divided into two stages, due to lack of synchronization of the intercostal muscles with the diaphragm, the former usually contracting first. Small animals (rats or guinea-pigs) will make pawing movements at their throats such as occurs with histamine, and respiration becomes audible as well as effortful in a way strongly suggesting bronchial spasm. In dogs, the independence of this respiratory attack from general curarization may be striking. The hitherto normal animal suddenly stands still, braces its forelegs, and breathes stertorously, slowly, and with inspiratory difficulty. The attack may remit after a few seconds, recur, and finally pass off, or else it may lead to a fatal asphyxia, in which case it is usually accompanied by some degree of general curarization. In two such cases it was found impossible to induce an air current in the trachea when artificial respiration was attempted by compression of the chest. Abductor paralysis of the vocal cords was considered as a cause of the

respiratory embarrassment, but was ruled out because tracheotomy did not remedy the condition [West, 1935]. Post-mortem examination of the lungs showed a remarkable degree of general collapse, the lungs appearing almost airless, though in fact the alveoli contained air and the lung floated on water. Curarized rabbits, killed before respiration is arrested, have collapsed, dark pink and almost airless lungs, in contrast to the partly distended, light pink, air-containing lungs of a normal control. An air-pressure of 8 cm. of water is required to distend the curarized rabbit lung, as opposed to a pressure of 2 cm. of water in death from a blow, or 3.5 cm. in death from ether anæsthesia.

#### *Drug antagonism of curarine in its respiratory action*

(1) Respiratory spasm in cats, produced by curarine, yields to adrenaline, and returns when the transitory effects of that drug have passed [West, 1937].

(2) Isolated rings of the trachea and large bronchi of the cat were examined in oxygenated Ringer-Locke solution. Curarine causes strong muscular contraction after a long latent period. This is only found with high concentrations of the drug (1 : 3000 and upwards). The spasm is unaffected by atropine (1 : 250,000), but removed by adrenaline (1 : 250,000) [West, 1937].

(3) With the collaboration of Dr J. W. Thornton, a few experiments were performed using his technique of perfusing the exposed lung of the guinea-pig and recording the perfusion-pressure as an index of bronchoconstriction. By this method also curarine produced measurable bronchoconstriction only when perfused through the lung at a concentration of 1 : 3000, in contrast with histamine which caused profound constriction at dilutions of 1 : 100,000.

The subject for investigation was twofold. First, in what ways can curarization, in its ordinary sense of myoneural paralysis, affect the mechanism of respiration? Secondly, to what extent has curarine an action on the respiratory mechanism other than by curarization?

#### METHODS

*Passive collapse of the lung* was produced by phrenic nerve section and by curarization, and studied by X-ray and records of intrapleural pressures. The effects of anæsthetics were compared with those of curarine. The effects of posture on artificial respiration were also studied in this connexion.

The element of *bronchial spasm* was studied in the exposed lung of the guinea-pig by direct observation, and by records of distension pressures from a manometer attached to the tracheal tube. Curarine was compared with histamine by these methods.

*Passive collapse of the lung*

*Diaphragmatic paralysis—phrenic nerve section.* Complete motor paralysis of the rabbit's diaphragm was produced by bilateral section of the phrenic nerves in the neck. Ether anaesthesia was continued for 15 min., and the animal then killed by a blow on the neck. The lower lobes of both lungs were partially collapsed. In response to internal pressure, the upper lobes expanded as in the normal control, the lower lobes with greater difficulty. Diaphragmatic paralysis by motor nerve section does not produce the general collapse of the lung which occurs in curarine poisoning.

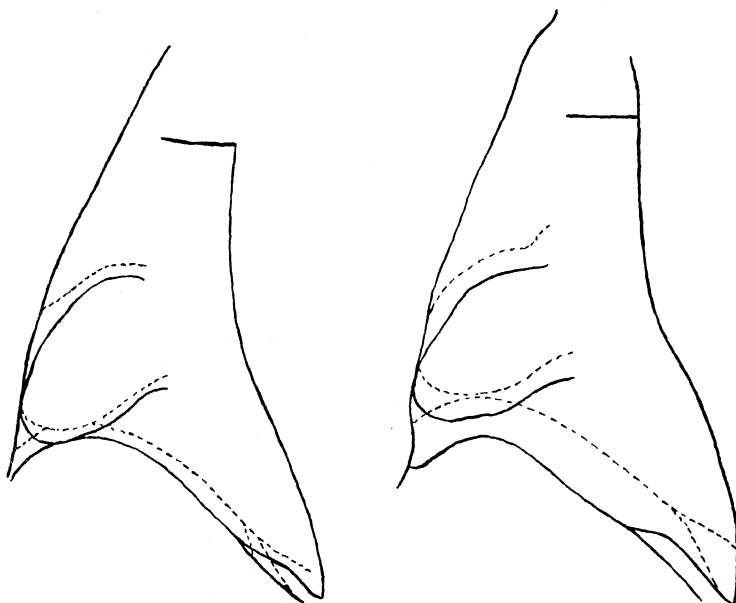


Fig. 1.

Fig. 2.

Line drawings from a tracing of X-ray photographs. Decerebrate cat in horizontal position, lateral view. Dotted lines show reduction in size of thoracic cavity in curarization. Fig. (1), expiration. Fig. (2), inspiration.

*X-ray observations: effect of posture.* By the courtesy of the Director of the Nuffield Institute of Medical Research, Oxford, and the kind cooperation of the Honorary Radiologist, Dr A. E. Barclay, X-ray obser-

vations were made and X-ray cinematograph records taken, of rabbits and cats, under curarine, and in various postures. If a normal rabbit held with the head up is photographed, the chest appears elongated, and respiratory movements appear to be almost entirely diaphragmatic. If held inverted, the diaphragm advances a little into the chest cavity, the cavity widens laterally and the intercostal muscles take an increased part in respiratory activity. After curarization, the diaphragm rises into the chest by about one intercostal space with the head held up: its cephalic displacement being more with the head down. Further, with the head up, the chest cavity becomes diminished in all its measurements: inverted there is no lateral expansion adequate to compensate for the altered position of the paralysed diaphragm. The volume of the thoracic cavity must be markedly reduced by such curarization (Figs. 1 and 2).

*Posture and artificial respiration by compression.* If the chest wall of the curarized rabbit or curarized decerebrate cat be compressed with the animal lying on its side, little or no air can be expelled from the lungs. If the animal be inverted, this form of artificial respiration becomes impossible; no air passes. If, on the other hand, the animal is suspended with the head up, it is possible to expel air by compression, and there is enough suction to draw air in again. For the relaxed diaphragm has fallen, and has so reformed to some degree the "negative" pressure system which is abolished in the other postures, when the weight of the abdominal contents transmits a positive pressure to the thoracic cavity, as is shown in the following section.

*A study of intrapleural pressures.* Intrapleural pressures may be registered, in rabbits and cats, after the induction of a minimal artificial pneumothorax, by the introduction of a hollow needle into the space behind the sternum at level of the 4th intercostal space, with the animal in the supine posture. In these experiments the needle used resembled in design a standard artificial-pneumothorax needle, as used clinically, except that it had a somewhat wider bore, a firmer stillette, and a longer stem beyond its bifurcation and tap. It thus gave greater protection against obstruction and at the same time a greater security against the adventitious introduction of air through the main stem. Before its insertion the needle was connected with a water manometer by a narrow-bore pressure-tube. The needle was introduced with a "negative" pressure of about 1 cm. of water already in the closed system, so that very little air entered the pleural cavity. Free oscillations were obtainable without difficulty. In the cat, under moderate ether or chloralose anaesthesia, pressures in expiration varied from  $-0.5$  to  $-1.5$  cm. water,

in inspiration from  $-1.5$  to  $-2.5$  cm. In the rabbit, under ether alone, the pressures were more variable. In expiration there was seldom less than  $-1$  cm. on induction, and, under light anæsthesia, inspiratory pressures reached  $-4.5$  cm. Average established pressures for the rabbit were: expiration  $-0.5$  cm., inspiration  $-3.5$  cm.

*Posture and intrapleural pressures.* Variations of intrapleural pressure with posture were studied in both rabbit and cat under light and deep ether anæsthesia. The *rabbit*, with a more fragile bony thorax, and a thinner, and much less muscular, diaphragm, responded with a much greater variation than did the cat. Average readings are shown in Table I.

TABLE I. Posture and intrapleural pressures, inspiratory : expiratory.  
Average pressures in cm. water

Animal	State	Horizontal (dorsal)	Vertical (head up)	Inverted (head down)	Number of animals included in average
Rabbit	Light ether	$-0.5$ to $-3.5$	$-2.5$ to $-4.5$	$+0.5$ to $-3.0$	8
	Respiratory arrest by ether	$-0.75$	$-2.5$	$+0.75$	7
Cat	Light ether, chloralose	$-1.0$ to $-2.0$	$-1.5$ to $-2.5$	$0$ to $-1.5$	4
	Respiratory arrest by ether	$-1.0$	$-2.0$	$-0.5$	4

With the head held up the expiratory negative pressure is increased, probably by traction on the diaphragm as the abdominal viscera tend to fall away from it. Inspiratory pressures alter in the same direction. When inverted, the rabbit is unable to maintain a negative pressure in expiration. Respiration becomes embarrassed and rapid, inspiration is effected with effort, so that inspiratory pressures are almost as great as usual. They may even be greater; in one instance an excursion of from  $-1.5$  to  $-3.5$  cm. in the horizontal position became one of  $0$  to  $-6$  cm. when the head was lowered.

When respiration was arrested by deep ether anæsthesia, a negative pressure resulted in the dorsal and head-up postures; but a positive pressure ( $0.25$ – $1.5$  cm.) was obtained when the animal was inverted.

The *cat* shows similar but smaller variations of pressure with varying body posture. A negative pressure is usually maintained on arrest of respiration by ether anæsthesia, even in the inverted position.

*Curarine and intrapleural pressures.* In uncomplicated curarization, respiration is arrested as a result of paralysis of the respiratory muscles. X-ray observations showed that in both rabbits and cats respiration is largely longitudinal (i.e. diaphragmatic) in type, and also showed paralysis

of the diaphragm as the chief factor in respiratory failure from curarization. Records of intrapleural pressures show that, with this paralysis of the diaphragm, the curarized *rabbit* may fail to maintain a negative pressure, even in the horizontal position. In some cases the diaphragm loses its "tone" to such a degree that positive pressures as high as 2 cm. water are recorded. Otherwise, and throughout in the *cat*, the intrapleural pressures in curarization resembled those of fatal anaesthesia (Table II).

TABLE II. Curarine and intrapleural pressures. Average figures

Animal	Horizontal	Head up	Head down	Number of animals included in average
Rabbit	0	-1.25	+1.0	4
Cat	-1.5	-2.0	-0.75	3

*Retraction of the exposed lung: bronchial spasm*

Failure to maintain intrapleural "negative" pressure might be solely responsible for the collapse of the lung found at post-mortem in curarine poisoning. Reduction of intrathoracic volume would produce a relative broncho-constriction, and this might perhaps be alleviated by adrenalin in its broncho-dilator function. The direct bronchial action of curarine was therefore studied upon the exposed lung, and for this purpose guinea-pigs were chosen. They suffer from curarine respiratory "spasm", and in addition are notoriously sensitive to the true bronchial spasm produced by histamine.

*Exposed lung in pithed guinea-pig.* The lungs of pithed guinea-pigs were exposed from below by opening the abdomen widely and incising the diaphragm. The lungs were ventilated by a pump, under a measured air-pressure, and injections made direct into the right ventricle of the exposed heart. Curarine in doses which varied from 0.1 mg. upward, caused the lungs to retract, decrease the amplitude of their movement, and blanch. The lungs appear to lose their elasticity, and the minimum pressure required for distension rises. The action resembles and yet differs from that of histamine. Whereas 0.1 mg. of histamine completely arrests lung movement by its action on the bronchial muscles, and smaller doses cause a temporary decrease in lung movement, large doses of curarine were never found to abolish expansion of the lung completely, at any normal air pressure. Again, while small doses of histamine (0.02 mg.) cause a slight retraction and a diminution of lung movement resembling that caused by curarine, with the latter the lung surface



becomes a greyish white colour which coincides in onset with a severe general cyanosis absent in the comparable histamine experiments. The appearance is as if effective oxygenation ceased at a lesser reduction of lung movement with curarine than with histamine (Table III).

TABLE III. Minimal lung distension pressures

Initial pressure cm. H <sub>2</sub> O	Drug	Resultant pressure cm. H <sub>2</sub> O	Condition of lungs	Effect of adrenaline
1-2	Histamine 0.02-0.1 mg.	Over 10 (usually very high)	Respiration arrested	Re-expansion with large doses
1-2	Curarine 0.1-0.5 mg.	7-10 (never very high)	Lung retracted. Blanching of sur- face. Expansion re- duced	Retraction removed. Blanching removed. Re- expansion with large doses

These appearances were taken to indicate that curarine causes a bronchial spasm. The spasm resembles that caused by histamine. But it was difficult to attribute the blanching of the lung, and the high degree of cyanosis which occurs (when the lung is retracted only some 10 or 20 p.c. and still has considerable movement) merely to the weaker action of curarine. It is possible that curarine has a greater action, proportionately, on the minute terminal bronchioles than has histamine.

The bronchial spasm caused by curarine has a response to bronchodilator drugs similar to that of histamine. Intracardiac adrenaline (0.1 c.c. of 1 : 1000) causes the lungs to re-expand instantaneously, and to become pink of hue. The effect is transitory, lasting 1 or 2 min. only. Atropine must be given in large doses to have any dilator effect: its action is then prolonged. Large preliminary doses of atropine protect against the spasm.

*Retraction of the lung in situ.* Guinea-pigs were used as in the above experiments. But instead of the lungs being exposed, they were viewed through the transparent diaphragm, after opening the abdominal cavity. At the onset of the curarine spasm the bases of the lungs withdraw slightly, diminishing the area of their contact with the diaphragm. As the diaphragm itself rises into the chest cavity as a result of its loss of "tone", this further shrinking of the lungs must represent a very considerable decrease in lung volume. Further, it appears that, at least in these animals, loss of the suction normally applied to the lungs by the "negative" intrathoracic pressure, combined with the broncho-constrictor action of curarine, and whatever natural elastic "recoil" the lungs themselves may possess, causes the separation of the lungs from the chest walls, and a corresponding increase in the size of the pleural cavity.

## DISCUSSION

The collapse of the lungs which is characteristic of curarine poisoning is brought about by a combination of the factors considered below. (1) *Curarization of the muscles of respiration*, and particularly of the diaphragm, leads to a reduction of the normal "negative" pressure in the pleural cavity, and a consequent reduction of the volume of the thoracic cavity (Figs. 1 and 2). The whole lung is reduced in size, and, in as far as the "negative" intrapleural pressure can be regarded as bronchodilator in effect, broncho-constriction may be regarded as an element of respiratory curarization proper. In the rabbit, which lacks a rigid chest wall and a powerful diaphragm, the effect of curarine is to abolish the "negative" intrapleural pressure, unless the animal is suspended vertically from the head. But in the more strongly built cat, the reduction of negative intrapleural pressure produced by curarine does not exceed that produced by arrest of respiration by ether anæsthesia (Tables I and II). Thus a fall of intrapleural negative pressure, produced by curarization of the respiratory muscles, does not alone explain the difficulty of artificial respiration by external compression in certain postures. For these changes of intrapleural pressure occur with ether arrest of respiration, and the difficulty of artificial respiration does not. (2) *Posture* measurably affects intrapleural pressures in normal cats, and greatly alters them in rabbits. It is probably this effect of posture which renders artificial respiration by compression possible in curarized animals held vertically with the head up, when it has become ineffective in the horizontal position (Table II). Curarine further causes (3) *active retraction of the lung*, probably as a result of a constricting action on the smaller bronchi, as is evidenced by the observations on exposed lungs in guinea-pigs. This effect is antagonized by adrenaline and by atropine in large doses.

The broncho-constrictor action of curarine resembles, but is not identical with, the action of histamine on the lung (Table III). Large doses of curarine never produce the intense histamine bronchial spasm, while small doses of histamine seem to produce less blanching of the lung surface, and less general cyanosis, compared with the reduction of lung movement than does curarine. The general pharmacological action of curarine does not show resemblances to that of histamine, for instance upon blood pressure or intestinal movements [West, 1937]. Curarine bronchial spasm has been recorded in man [West, 1936]. It was not accompanied by flushing of the skin, nor did the blood pressure fall.

The fact that the broncho-constrictor action of curarine is associated

with inspiratory difficulty and pulmonary collapse, instead of with the expiratory difficulty and pulmonary distension which occurs with broncho-constriction from other causes (e.g. histamine, asthma), may be attributable to two causes: (1) the weakness of power of contraction, and of maintenance of contraction, of the respiratory muscles produced by curarine; (2) the factors, tending towards pulmonary collapse enumerated above, and which result from a loss of "tone" in the muscles of respiration and particularly in the diaphragm. Both causes are properties of normal curarization as it affects these particular muscles.

Curarine has come to be regarded as the characteristic active principle of the "calabash" Macusi curare of British Guiana. It has been prepared both from this "calabash" curare and direct from its plant ingredient, *Strychnos toxifera* [Boehm, 1895; King, 1935]. Boehm attributed to it the formula  $C_{19}H_{25}ON_2$ . Both Boehm and King noted that this alkaloid was amorphous; it could never be obtained in crystalline form. Recently, Wieland *et al.* [1937] have published an investigation of a "calabash" curare from which they have isolated an alkaloid "Toxiferin", of a curariform potency many times that of curarine, as judged by its minimal lethal dose in the frog. Further reports of the pharmacological properties of this new alkaloid have not yet been communicated, but its potency renders it a more acceptable essential alkaloid of Guianese curare than curarine has proved to be. It will be of interest if this new alkaloid proves to be obtainable direct from *S. toxifera*. It is possible that it may prove not only more potent in its curariform action, but purer, and in particular, free of the broncho-constrictor action of curarine.

#### SUMMARY

An enquiry into the actions of curarine upon the respiratory mechanism was undertaken, because it causes a sudden fatal respiratory embarrassment, which can be observed in the absence of full general curarization, and which is characterized by (i) an apparent bronchial spasm, (ii) the failure of artificial respiration by chest compression, and (iii) a tendency to collapse of the lung as a post-mortem finding.

The action of curarine on the respiratory mechanism may be summarized as follows:

There is a direct constrictor action upon the bronchi and bronchioles. Normally this would probably lead to expiratory dyspnoea, but this effect of broncho-constriction is prevented by the other action of curarine, which is to curarize the muscles of respiration. Partial curarization produces two effects upon muscle: there is (a) a reduction

in the power of muscular contraction, particularly in the power of maintained (i.e. tetanus) contraction, and (b) a reduction in the normal tone of the muscle. When these two actions of curarine affect the respiratory muscles, and, in particular the diaphragm, they cause respectively, (a) a weakened and poorly maintained inspiratory effort, (b) a reduction of the thoracic volume (Figs. 1 and 2) and a fall in the normal "negative" intrapleural pressure (Table II). The result is a partial collapse of the lung. It is even possible that the reduced intrapleural pressure resulting from loss of muscular tone in the diaphragm, assisted by the normal elastic recoil of the lungs, may convert the "potential" pleural cavity, which probably normally contains a little air, into an "actual" cavity, the lungs shrinking away from the chest-wall. Finally reduction of negative intrapleural pressure causes a *passive* broncho-constriction.

The cause of the sudden failure of respiration in curarization with curarine is thought to be acute pulmonary collapse. The sequence of events is: (1) loss of tone in the respiratory muscles, particularly in the diaphragm; (2) consequent reduction in chest volume, and fall in intrapleural negative pressure. The resulting retraction of the lung is assisted by (3) an active broncho-constriction produced by curarine, (4) the passive broncho-constriction produced by a rise in intrathoracic pressure, and (5) a loss of power of contraction and a failure of maintenance of contraction in the inspiratory muscles.

Of these factors the active broncho-constriction (3) may be due to the presence of an impurity. The recent report of the isolation for the first time of a crystalline alkaloid ("Toxiferin") from calabash curare [Wieland *et al.* 1937] suggests that the amorphous curarine hitherto isolated may be impure. "Toxiferin" is reported to have a curarizing power many times greater than that of curarine.

I am indebted to Dr J. W. Thornton for his collaboration in the lung-perfusion experiments mentioned in the introduction to this Paper; to the Director and Assistant Directors of the Nuffield Institute of Medical Research, Oxford, for the X-ray facilities referred to; to Dr K. J. Franklin for the loan of apparatus and for suggestions, and to Sir Henry Dale for advice throughout the work, which was done while in receipt of an Expenses Grant from the Medical Research Council.

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Richard C. Gill,  
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5th January, 1946

Dear Mr. Gill,

I was most interested to get your letter and to learn that our work had quite a close historical connection with your own. I had ~~always~~ hoped that this was so and that a rather unwelcome publicity, which my work received in the public press round about 1936 had had the good ultimate effect of drawing attention to the curare problem among a wide public ~~and among~~ <sup>including</sup> a few determined adventurers like yourself.

I am afraid I too am very short of reprints in this subject. I am, however, sending you a copy of the one to which you particularly refer, "The Action of Curarine on the Respiratory Mechanism", and if I can possibly do so I will also enclose a reprint of the paper which I published in 1935, and which includes the map which you so carefully carried into the Amazon with you!

I do most heartily congratulate you on your energetic and successful pursuit of your quarry. I knew very well that an expedition was necessary. I advised it as early as 1932 but

*Tell me more about it!*

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without success except for the one highly efficient collection of plants, whose action I analysed in my 1937 paper, and which gave us the considerable supplies of strychnostoxifera "curarine" on which I worked.

Have you I wonder come across any reports of bronchial spasm? One or two reports have reached me from people using d.tubocurarine chloride. It was a real danger with strychnostoxifera "curarine" and I have never fully understood the method of its production.

Yours very sincerely,

Ranyard West

Ranyard West.



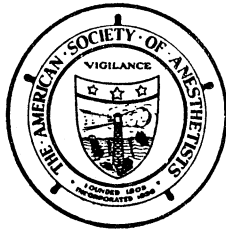
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## THE USE OF CURARE IN GENERAL ANESTHESIA

HAROLD R. GRIFFITH, M.D., AND G. ENID JOHNSON, M.D.\*

*Montreal, Canada*

EVERY anesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anesthesia. This is a preliminary report on the clinical use of a drug which will give this kind of relaxation, temporarily and apparently quite harmlessly.

The physiological action of curare as an interrupter of the neuromuscular mechanism has long been recognized, and its best known practical applications have been by South American Indians as an arrow poison and in the physiological laboratory. The crude curare of the South American forests contains numerous toxic substances, but it has been possible so to refine the drug that the elements of cardiac and respiratory depression are removed and only the "pure" curare effect remains.

For several years this purified curare has been used experimentally in psychiatric hospitals to prevent traumatic complications in convulsive shock therapy. Bennett (1), Gray (2) and others have reported on the efficiency and harmlessness of curare when used for this purpose in quite a large number of patients.

In January, 1942, at the suggestion of Dr. L. H. Wright, we began using Intocostrin (Extract of Unauthenticated Curare, Squibb) in order to increase skeletal muscular relaxation in patients under general anesthesia. So far, we have given it to 25 patients, and in each case there has been rapid and complete muscular relaxation, which develops within one minute after intravenous injection of the drug and gradually disappears in from ten to fifteen minutes. In none of our patients has there been any serious depressing effect on respiration, pulse or blood pressure, and there was no demonstrable postoperative effect of any kind. Apparently the drug is very rapidly broken down and excreted almost as rapidly as it acts, although there is some evidence from the psychiatric experience that patients who are given a second injection on the same day require a smaller dose to produce the physiological effect.

We administer the Intocostrin intravenously with a dosage of 10 to 20 mg. of the active curare per 20 lbs. of body weight. Intocostrin is prepared in solution containing 20 mg. of the active curare substance per cubic centimeter, so that an average adult dose is 4 to 5 cc. We have

\* From the Department of Anesthesia, Homeopathic Hospital of Montreal.

not given to any one patient more than 5 cc., and we make the injection rather rapidly, in less than a minute.

It has not been necessary to administer artificial respiration or stimulants in any of our cases. As our patients are all under gas anesthesia, with means of resuscitation by oxygen immediately available, we do not fear this complication. Since prostigmine is used as an antidote to curare, an ampule of this drug should always be available.

The operations during which curare was given have been as follows:

Appendicectomy .....	12
Cholecystectomy .....	4
Laparotomy .....	3
Curettagc of Uterus .....	2
Hemorrhoidectomy .....	2
Colostomy .....	1
Nephrectomy .....	1
	1
Total .....	25

All the patients were under cyclopropane anesthesia, and ranged in age from 18 to 70 years. Since we do not ordinarily have difficulty due to inadequate relaxation during cyclopropane anesthesia, in many of these cases the anesthesia was purposely lightened to the point of abdominal straining in order to test the effect of the curare. Several cases, however, have illustrated the possible real usefulness of this drug to the surgeon.

One case was that of a man weighing 250 lbs. who insisted on general anesthesia for hemorrhoidectomy. Under cyclopropane anesthesia, relaxation of the anal sphincter was unsatisfactory. Immediately after the administration of 5 cc. of Intocostrin, complete relaxation was obtained, and the operation was easily performed.

Several of the cases of appendicectomy were in healthy young adults undergoing operation for an acute infection, and who were particularly resistant to anesthesia. When the surgeon began to close the peritoneum the abdominal muscles became tense, a situation which arises at times in the experience of every anesthetist. We administered 5 cc. of Intocostrin, and within one minute the abdomen was "soft as dough," and the surgeon was able to finish the operation without any difficulty.

In one case of curettagc the Intocostrin was given to see if there would be any effect on the muscular tone of the uterus or cervix, and no effect was observed. The other case of curettagc was an extremely obese woman on whom the surgeon found it difficult to make a satisfactory bimanual examination. The Intocostrin gave such complete relaxation of the abdominal musculature that he was able to feel the pelvic organs without difficulty.

It seems to us, as the result of these preliminary clinical investigations, that curare may prove to be a drug which will occasionally be of great value, and will give us a means of providing the surgeon rapidly

with excellent muscular relaxation at critical times during certain operations.

Its scope of usefulness is limited because of its somewhat fleeting action, and because it is in no sense an anesthetic agent. It is potentially a dangerous poison, and should be used only by experienced anesthesiologists in well-equipped operating rooms; but we have been so much impressed by the dramatic effect produced in every one of our patients that we believe this investigation should be continued.

The Intocostrin used has been supplied through the courtesy of E. R. Squibb & Sons, to whom we are grateful also for friendly assistance.

#### SUMMARY

A purified extract of curare (Intocostrin) has been administered intravenously to 25 patients under light general anesthesia. In each case temporary but complete muscular relaxation was rapidly produced with apparently no harmful effect.

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