Thesis
for
the Degree of Doctor of Medicine
and
Competition Essay
for Gunning Prize in Materia Medica.

Subject

A contribution to the
Pharmacology of curare, curarin,
curin and Methyl-strychninium.

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being an experimental research in the
pharmacological laboratories of the
Universities of Leipzig and Edinburgh.
Curare has for a long time occupied quite a special position in the physiological and pharmacological laboratory as an aid in experimental research.

Although a very large number of papers especially directed to its investigation have been published, and numerous references are made to its uses and actions in the physiological literature of the last thirty years, we still find some very important points about which there are doubts, and some statements which are offered for acceptance without the support of clear experimental evidence.

The circumstance that Curare is not an individual chemical body, but a more or less impure vegetable extract of variable strength, has hitherto been an objection to its employment in precise experiments. This objection has been emphasized quite recently by Boerni, who has shown that, in some varieties of Curare, the alkaloid Curarin is associated with another alkaloid, which he has named Curamin.
He has also shown, that the method of preparing Curarin hitherto employed, is not successful in separating a pure Curarin from these Curares.

It is hoped that the experiments here on Curin, have, by indicating a source of error in the use of some crude Curares, helped to establish the usefulness of a pure Curarin as an aid in research; and, that the extended examination of Curare, Curarin, some of the Strychnos banks of South America, and likewise of the Methyl Strychninium salts, has brought out facts of great pharmacological interest, and established clearly, on experimental grounds, some views of their actions, which have hitherto been overlooked or universally regarded as both improbable and erroneous.
The action of Curarin or Curare on the nervous system of the frog and rabbit.

Especially after Claude Bernard's observations were made on Curare in 1844, its actions were investigated in great detail by many distinguished physiologists, and all agreed that the active principle contained in it interrupted in some way the conductivity of a part of the endings of the motor nerves distributed to the striped muscles.

In addition to this general agreement almost all these early writers, such as Holliker, Vulpian, Martin-Magnon et Quissin, Pelikan, Haber, Reidel, Kühne, and others further concluded, with Bernard, that curare did not paralyse the endings of sensory nerves. But, on the other hand, some contemporary writers, such as Schiff, Bohlender, and later, Lange, and among quite recent authors, Steiner, Brind, and Lauder Brunton, come to the very opposite conclusion, and hold that the sensory nerves are distinctly depressed and paralysed by the poison.

On the important question of the action on the central nervous system...
of a poison derived from the Strychnos family of plants, there is little difference of opinion to be found. The early writers Martin Magron, Ruisson, Mano, Schelske, von Beyold, state that curare has a Strychnos-like action on the spinal cord. Vulpian, too, thinks that it does not paralyse, but rather stimulates the cord. The great majority, however, of the many contemporary and later writers on the subject, are, on the contrary, quite agreed that curare has no such stimulant or tetanising action. Some of them consider that it has no action whatever on the spinal cord, while others believe that the experimental evidence is very distinctly in favour of a paralysing action.

The textbooks on physiology and pharmacology in different countries adopt the general view, that in large doses curare has a paralysing action on the central nervous system, although some favour, or at least quote, the first view, that at the least there is a stimulant action.

Most of the other early accounts of curare are historical, or deal rather with the more general features in the poisoning, than with the precise selective action on the
nervous system - as Condamine, Panereget, Humboldt, Waterton, de Castelnau, Schomburg, Osculati, Brocklesby, Herissant, Fontana, Brodie, Emmet, Virchow, Münster, Logan, Reynolds. Not a few other papers are confined to special points in curare poisoning - such as, the condition of the circulation or with its botanical origin, chemistry, or therapeutic uses; and make no reference, or only incidentally refer to its actions on the nervous system.

As a preliminary to the investigation, a series of experiments were carried out to determine the general action and poisonous activity of the pure alkaloid curarin.

When administered subcutaneously to cold & warm blooded animals the well recognized symptoms of curare poisoning followed, these need not be further referred to than to say that they are identical in kind with those produced by curarin.

In determining the poisonous activity of the alkaloid vigorous specimens of Rana esculenta (male) were selected. The curarin employed was a pure specimen, recently prepared and very kindly supplied to
me by Professor Kocher. The solutions in distilled water varied in strength from 0.000001 to 0.005 gramme per cubic centimetre, although occasionally further dilution was required. The dose was calculated per gramme of body weight and was usually injected into the anterior thoracic and abdominal lymph spaces by passing the hypodermic needle through the floor of the mouth from the inside and along beneath the skin for the necessary distance. When the paralysing dose was exceeded precautions were taken to keep the skin moist and freely exposed to the atmosphere, as thus the extmuous respiration is also interfered with, fatal paralysis of the cerebral nervous system and heart soon sets in from want of oxygen, especially during summer when the vitality is high. When the dose was so large that the circulation was paralysed these precautions were necessary unless as extmuous respiration was almost entirely suspended. The results of numerous experiments are summarized below. The onset, intensity and duration of the symptoms produced by similar doses, administered under the same conditions of season, temperature, time, were, on the whole, uniform. The irregularities were probably due to variations in the rate of
absorption, excretion & other conditions in
different animals which cannot be estimated,
of, considering the minute quantity of curarin
employed, to slight differences in dosage in
making the injections.

**Dose of Curarin per**
**1 gramme of body weight**

0.0000002 gramme
winter.

0.0000004 gramme
winter & summer.

No result. The daily administration
of this dose for 35 days had no
apparent effect on the frog.
In a period varying in different cases
from 15 to 40 minutes unmistakable
signs of muscular weakness appeared,
so that frequently the frog, when
placed on its back, could not
turn over. After moments continued
good, but voluntary movements were
incomplete. Respiration good. Return
to normal took place in from 1½
to 5 hours. The daily administration
of this dose to the same frogs
during 36 days produced similar
effects. The first dose had the least
effect, but, after the third dose, there
was no special increase in the action,
but rather an inconstant variation
in the onset & duration of the weakness.
In summer the action was slightly longer
than in winter.
In from 10 to 20 minutes on an
average symptoms of muscular weakness
appeared, and the frog could not turn over,
when placed on its back. Voluntary
movements were rare. Reflex movement
followed strong stimulation of the skin.
Precipitation continued. In winter return
to normal took place in from 10 to 24
hours; in summer in from 5 to 10 hours.
The administration of this dose daily for
20 days in summer, and every alternate
day during 40 days in winter, acted
similarly, except that the first dose or
two had the least action.
In from 30 to 60 minutes every
movement had ceased except respiratory
movements of the throat muscles. The
reflexes consisted in an occasional slight
muscular twitch.
All voluntary and reflex movements were
abolished by this dose, except a reflex
respiratory movement of the throat muscles.
Recovery took place in summer before
24 hours, and in winter, in from
1 to 2 days.
Dose of 0.0000028 grammes was found to be the minimum complete paralyzing dose. In about 30 minutes general voluntary movements were quite suspended. By 60 minutes all trace of reflex movement had disappeared, except as before, the throat muscles of respiration which were not completely to reflex stimulation until about 2 hours after the administration of the poison. Recovery took place in the inverse order, and was usually complete in summer by 24 hours, and in winter by 2 or 3 days.

On increasing the dose, it was found that an interval of 18 days might elapse before the reflexes returned, and recovery occurred finally. When the dose exceeded about 30 times the minimum paralyzing dose recovery did not take place until the temperature at an average of 15°C. During warm weather even the smallest paralyzing doses not infrequently proved fatal, the cutaneous respiration being...
apparently insufficient to support life

Experiments illustrating the onset, duration of symptoms result on administering multiples of the minimum paralyzing dose at a temp of 15° Celsius (~59°F)

<table>
<thead>
<tr>
<th>Dose for grams of body weight of male frog</th>
<th>Recovery after</th>
<th>Recovery after</th>
<th>Recovery after</th>
<th>Recovery after</th>
<th>Recovery after</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00000028</td>
<td>52 minutes</td>
<td>90 minutes</td>
<td>5 hours</td>
<td>2nd day</td>
<td>3rd day</td>
</tr>
<tr>
<td>80</td>
<td>180</td>
<td>5½</td>
<td>2</td>
<td>3½</td>
<td>14</td>
</tr>
<tr>
<td>0.00000028 x 2</td>
<td>25</td>
<td>30</td>
<td>1 day</td>
<td>1½</td>
<td>5</td>
</tr>
<tr>
<td>27</td>
<td>30</td>
<td>1½ days</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>0.00000028 x 4</td>
<td>15</td>
<td>27</td>
<td>4½</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>0.00000028 x 8</td>
<td>10</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>0.00000028 x 16</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>x 32</td>
<td>10</td>
<td>14</td>
<td>18</td>
<td>18½</td>
<td>25</td>
</tr>
<tr>
<td>0.00000028 x 32</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>x 32</td>
<td>9</td>
<td>15</td>
<td>Heart stopped on 14th day - no urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.00000028 x 48</td>
<td>6</td>
<td>6</td>
<td>Heart stopped on 13th day - late no urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>Heart stopped on 13th day - no urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.00000028 x 50</td>
<td>5</td>
<td>6</td>
<td>Heart stopped on 2nd day - no urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.00000028 x 100</td>
<td>3</td>
<td>3</td>
<td>Heart stopped on 2nd day - no urine or late on 14th day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the cases which recovered there was a considerable secretion of urine which was suppressed from the bladder from time to time during the experiment.
Rate and force of the cardiac contractions during prolonged paralysis at 15°C.

<table>
<thead>
<tr>
<th>Dose of curare</th>
<th>Condition when motor fasciculations</th>
<th>After 2 days</th>
<th>After 4 days</th>
<th>After 6 days</th>
<th>After 8 days</th>
<th>After 10 days</th>
<th>After 12 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00000028</td>
<td>40 strong</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0000018 x 2</td>
<td>40 strong</td>
<td>36 strong</td>
<td>36 strong</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0000018 x 4</td>
<td>38 strong</td>
<td>30 strong</td>
<td>29 strong</td>
<td>28 strong</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0000018 x 8</td>
<td>30 strong</td>
<td>28 weak</td>
<td>28 weak</td>
<td>26 weak</td>
<td>26 weak</td>
<td>26 weak</td>
<td>27 weak</td>
</tr>
<tr>
<td>0.0000018 x 16</td>
<td>42 strong</td>
<td>28 medium</td>
<td>28 medium</td>
<td>26 strong</td>
<td>24 weak</td>
<td>24 weak</td>
<td>26 weak</td>
</tr>
<tr>
<td>0.0000018 x 32</td>
<td>40 strong</td>
<td>28 weak</td>
<td>28 weak</td>
<td>26 weak</td>
<td>24 weak</td>
<td>24 weak</td>
<td>26 weak</td>
</tr>
<tr>
<td>0.0000018 x 48</td>
<td>40 strong</td>
<td>28 weak</td>
<td>28 weak</td>
<td>26 weak</td>
<td>24 weak</td>
<td>24 weak</td>
<td>26 weak</td>
</tr>
<tr>
<td>0.0000018 x 50</td>
<td>40 strong</td>
<td>28 weak</td>
<td>28 weak</td>
<td>26 weak</td>
<td>24 weak</td>
<td>24 weak</td>
<td>26 weak</td>
</tr>
</tbody>
</table>

Note: Heart stopped for 1 day.
In poisoning with the large doses of curarin there seemed to be at least two conditions which determined the recovery or death of the frog, when the temperature was moderate or low.

In the first place, the heart, as observed on the unopened thorax, becomes slow and feeble and may finally stop. If the urine is carefully expressed from the bladder before administering the poison it may be found that although the heart continues to beat for several days no urine is secreted, and consequently recovery is impossible. If the state of the circulation is examined it is found that the blood pressure is at zero, and practically no blood is passing through the heart. The cutaneous respiration must therefore be reduced to a minimum, and death have resulted before the contractions of the empty heart have ceased.

In the second place, if the dose is not so great, as in some of the cases indicated, and if the skin is kept moist, the heart continues to act efficiently, the bladder gradually becomes greatly distended. The urine is not actively expelled during the period of general paralysis, but the accumulation may be so great that the mechanical pressure forces an escape for part of the fluid. If this does not occur the pressure in the overdistended bladder must hinder the evacuation...
of the former and delay recovery, or may cause suppression of the renal secretion. Large doses of curarin seemed to be less fatal when overdistention of the bladder was prevented by expressing the urine daily. That the urine contained no curarin was readily shown by evaporating it, treating the residue with alcohol, evaporating & administering a watery solution of the solids to a frog. Analysis of motor nerve endings set in & was followed by recovery in a day or two.

The minimum fatal dose for the rabbit has been determined by Asshun to be 0.38D milligrams (0.0038) per kilo of body weight. In the case of dogs & cats the minimum fatal dose by subcutaneous injection was only approximately determined. In the dog it was about the same as in the rabbit (0.3D mg. per kilo) & in the cat slightly greater. When the dose was just a fatal one, death was slow, convulsive movements & twitchings, especially of the muscles of the neck & chin, occurred. When the dose was large, the muscles were quickly paralysed, & death occurred without spasms. When a dose slightly less than the minimum fatal was administered daily for 16 days the symptoms of paralysis were least marked during the first day or two. The onset & duration of the symptoms after that varied inconstantly, a circumstance which would readily be accounted
for by a slight difference in the rate of absorption from the different points of injection, since the difference between a moderately active and a fatal dose was about 0.05 mg, the marked symptoms of paralysis lasted only from 10 to 90 minutes.

In order to ascertain in a curarized frog the condition of the sensory nerves and of the central nervous system it is of course necessary to secure some part of the body from the paralyzing action of the poison. This end is not safely attained by the ligature of bloodvessels only, for, unless the dose is small, or the experiment of very short duration, the curarin is apt to diffuse gradually from the adjacent uninterrupted tissues and lymph spaces. In the experiments to be described protection was usually secured by adopting, with some modification, the mode of preparation employed by Bernard*(p345) viz: dissecting out and removing the posterior part of the sacral bone, ligaturing the abdominal aorta below the renal vessels passing a double cord through the lower part of the abdomen and tying all the tissues on each side to the iliae bones, the lumbar nerves
being excluded and carefully protected from exposure, but especially from pressure. Frogs which have been successfully prepared in this manner continue active for a considerable time, and in the main, resemble normal animals. After a number of preliminary observations on the reflexes it was found that this mode of experimenting introduced no unrecognised fallacies which could complicate the investigation.

The effect of the operation & tying of the tissues, the total suspension of the circulation in the lower extremities was tested in a frog whose one half of the spinal cord had been transversely divided below the medulla on the previous day. On testing the reflexes with dilute sulphuric acid (.3%) every 5 minutes or so during an hour, it was found that the foot on the divided side was withdrawn in 2 seconds & on the undivided side in 4-5 seconds. The operation was then carried out as described, everything being ligatured except the lumbar nerves. At 11.57 a.m. - two minutes after the preparation was finished - the reflexes were tested as before with the dilute acid, when the foot on the divided side was...
withdrawn in 12 seconds and on the undivided side was not withdrawn during one minute.

For the next 2 hours the reflexes were tested every 5 minutes, the feet being rubbed with warm water after each immersion in the acid. On the divided side the foot was withdrawn in 4–6 seconds but on the undivided side was not withdrawn at all after 60 seconds immersion.

On both sides the reflexes to pinching the toes were good and fairly regular.

At 4.50 p.m., 5½ hours after suspension of the circulation, the reflexes could be obtained much as before. Although therefore the reflex on the side connected with the brain became weakened and irregular, pinching still produces active movements.

When the spinal cord has been previously divided, the stoppage of the circulation in the lower extremities of the frog is seen, during an ordinary experiment of several hours duration, not to affect their power of movement or the sensibility of the skin to systematic and delicate chemical and mechanical stimulation in any very marked or irregular manner (Rutland, p. 152).

On the day after the stoppage of the circulation most of the sensory nerves in the legs are found to be paralysed and the
muscles furthest from the trunk rigid and acid. It is very important to recognise that in a frog with divided eard, the simple stoppage of the circulation, does not cause irregularity or paralysis of reflexes for hours, because, as will be seen, confusion has arisen by attributing to this certain irregularities in the reflexes which follow the administration of curare. On the other hand, fallacious conclusions on the action of curare on the sensory nerves have been come to by experimenting with frogs where the higher centres were in free connection with the eard. In experiments with curare, the early paralysis of the voluntary muscles necessarily limits the transfusion of gases in a poisoned frog to the skin surface in which the circulation is kept up. It was found however, that when respiration by the lungs was artificially prevented (the frog being fastened to a piece of wood and the nostrils only kept under water), the skin surface meanwhile remaining exposed to pure air, there was, during several hours, no decided impairment of sensibility or motor power. When the skin
respiration was also stopped, as when the frog was completely covered with water, or the circulation paralyzed by ligature of the aorta, administration of adrenalin acting body (heart) or of curare (bloodvessels) death occurred in an hour or two according to the season temperature.

The mode of experimenting, therefore, and the simple stoppage of respiration by the lungs introduce no serious fallacities into experiments of a few-hours duration, more or less, but any action on the circulation may have an important influence on the central nervous system.

It may further be stated that the particular questions at issue here do not depend on the perfect purity of the preparation, for the results about to be described can be obtained with any specimen of curare whose motor paralyzing activity has been determined, just as with pure curarin.
The ordinary symptoms of curare poisoning seem at first sight to point strongly in the direction of general nervous paralyses, and much of the misunderstanding as to the pharmacology of this substance has arisen from not distinguishing clearly between its direct and indirect effects and the obelaxes which one action may produce in the way of another.

After the administration of a small dose of curarin or curare, of say twice the minimum paralysing dose, motor weakness of the unprotected parts appears in a short time, and by 15 minutes the last reflex twitch of the throat muscles has ceased. The protected lower extremities continue meanwhile to maintain their normal position of flexion, and generally exhibit active reflex movements when either the poisoned or the unpoisoned skin is stimulated. It is noticeable, that, although the protected parts are capable of active motion, true voluntary movements in the unprotected parts are rarely seen after the first few minutes. After nearly half an hour the reflexes become distinctly more and more difficult to obtain.
(Kolliker, p. 39) a circumstance hardly sufficiently recognized by Kelkian and others. Martin Magron & Quisson (p. 526) Kelkian (p. 288) and many later writers have all observed, that, as the reflexes in this early stage of the poisoning gradually fail, they become irregular, and stimulation of the poisoned skin ceases usually to produce any effect, while yet stimulation of the skin of the unpoisoned part causes some reflex movement. Martin Magron & Quisson (p. 329) however, in addition, state that sometimes stimulation of the poisoned skin may not only act quite well, but may act when a stimulation of the unpoisoned skin fails. I have repeatedly observed this last fact in frogs where the higher centres were intact. Irregularity of response to the stimulation of any part is indeed almost as marked a feature as depression. The details of the results of stimulation of the poisoned and unpoisoned skin in one experiment are often quite contradicted by the next. Even if we conclude with Bernard, that curare does not paralyse the sensory nerves, the facts are not so simple as would appear from his statement (p. 353) "Mais la sensibilité y sera conservée car toute excitation portée sur cette partie paralysée..."
"au revoir dans la partie preservée des mouvements réflexes énergiques." Holliker, (p. 26) Martin-Magnon et Dussor, (p. 327) et Vulpius, suggérèrent de prouver que le reflexe de réaction et l'irrégularité décrite ne furent pas du à des paralysies des nerfs sensoriels en administrant strychnine et en induisant la stimulation de la peau du membre antérieur reflexes et réflexes t赞美 in the protected leg. Lange, (p. 397) found on the contrary, in agreement with Schiff, that when the aceta abdominals was ligature in a frog & also the right femur, with the excision of its nerve, and a small dose of curare given, and a few minutes later a small dose of strychnine, the stimulation of the uninjured anterior extremity gave reflexes in the protected posterior extremities, while stimulation of the poisoned anterior extremity failed to act. Stein, (pp. 33, 34) repeated these experiments by Schiff and Lange. He stimulated the two anterior extremities in an exact manner by electricity & came to the same conclusion as Lange. He then entirely destroys this statement by remarking "nur muss ich erwähnen dass die Resultate manehmal inkonstant sind."
and offers, in explanation of the inconstancy of the results, the circumstance that the unpoisoned extremity has no blood supply; a condition which we have already seen does not, in such a brief period, lead to paralysis of the sensory nerves.

Bing in his lectures on pharmacology (Bonn 1884 pp. 135, 136), reviews these symptoms in curare poisoning, and concludes that the sensory nerves are undoubtedly paralysed, because, after a time, stimulation of the unpoisoned skin only produces reflexes. "Man glaubte infolge dessen längere Zeit das Curare beschränkte seine lähmende Wirkung auf die motorischen Nerven und lasse die Sensibilität bestehen. Das aber ist nicht richtig. Nur im Anfang des Versuches ist die gesamte Haut des Thiers noch sensibel erregbar; später muss man die Haut des arteriell abgeleiteten Unterschenkels reizen, wenn man von den Hautnerven aus Reflexbewegungen erzielen will. Die zeigt deutlich, das mittlerweile auch die Empfindungsnerven der Haut überall, in welches das Curare dringen konnte, gelehmmt werden, und dass also die auf Grund der Autorität von Claude Bernard viel verbreitete Ansicht von dem dauernden "Unverschüttblieben dieser Nerven ungenau ist"
Lauder Brunton also concludes in a similar manner in the last edition of his text book on Pharmacology (1887 pp 155-6)

"At first it is found that pinching the poisoned foot will cause movements in the non-poisoned leg. As the poisoning becomes deeper however pinching the poisoned leg produces much less effect. This might be due to paralysis of the spinal cord but it is shown that this is not the case by pinching the ligatured leg just above and below the ligature. It is found that a pinch just below the ligature causes marked reaction, while a pinch just above has little or no effect. In this experiment all the structures concerned in the movement have been alike subjected to the action of curare with the exception of the ends of the sensory nerves below the ligature. It is thus evident that the diminished reaction from pinching above the ligature is due to paralysis of the ends of the sensory nerves in the part of the body to which the poison has had access."

This is a perfectly accurate statement of what may occur in any experiment but does not hold good for a number
of experiments. The interpretation therefore is not admissible. I have often observed, at this stage of the poisoning, that pinching the unpoisoned skin of the protected extremity produced a reflex, but, on pinching the poisoned skin no movement followed. On allowing an interval of rest & repeating this order of stimulation several times the same result followed, & apparently there was no other conclusion but that the sensory nerves in the poisoned skin were paralysed. On the other hand, it was often observed, in many different experiments, that if the order of stimulation was simply reversed, the poisoned skin pinched first, a reflex movement followed and then on pinching the unpoisoned skin there was no result. The first stimulation therefore after an interval of rest caused a reflex which applied, but further successive stimulations to any part failed to produce any movement. Many irregularities occur however. The circumstances that stimulation of the unpoisoned skin produces the best reflexes is also less significant than it seems, for it is quite in agreement with the laws of reflex action, that, as only the protected leg can move, stimulation of its own coverings should produce a greater effect.
than when the same stimulation is applied to an equally sensitive area not connected with the same spinal segment. In addition, one must not overlook the fact, that experiments on the reflexes in intact frogs take no account of the possible action of the drug on the higher centres. The influence of voluntary inhibition. Romano (p. 301), who performed experiments on medusae, has also concluded that curare can paralyse the sensory nerves. The animal was divided almost into two parts, so that, when one half was allowed to float in poisoned sea water (1 in 2500) it was connected on the edge of the vessel by a bridge of undivided tissue with the other half floating in unpoisoned water. His experiments show very clearly that motor paralysis results in the half floating in the poisoned sea water while the transmission of impulses is unaffected, because, when it is stimulated, it remains motionless, but the unpoisoned half contracts. Romano however does not stop here but goes on to say, that (p. 301) "a very slight degree of over poisoning paralyses the transmitting system as well as the responding one." We are led to infer
For there is no proof of this assertion—that after a time stimulation of the paralyzed half in the poisoned beaker fails to cause any movement in the formerly active half floating in the unpoisoned water. It is not stated that on stimulating this half directly, it continues to contract but does not do so when the poisoned half is stimulated. We have no experimental evidence therefore that the strip of muscle tissue, where there is no hindrance to the circulation or diffusion of fluids, has not acted as a channel by which any excess of poison not taken up by the one half passes over into the originally unpoisoned half. Indeed this must inevitably happen, and in the absence of any statement to the contrary, we are justified in thinking that when the eurax solution is stronger, the half in the unpoisoned side does not contract after a time when the poisoned half is stimulated because it is really paralyzed by diffusion of the excess of poison. This clearly precludes the proof that the transmitting system was paralyzed, for, without the possibility of motion in any part one could not say whether there was transmission of stimuli or not.
So far, therefore, we have seen that the view that curare paralyses the sensory nerves rests on doubtful proofs, and the character of the experiments leaves considerable room for error.

On tracing the symptoms of the poisoning further we find that frequently after 45 to 60 minutes (½−1½ hours. Kolliker, p. 55) practically no reflex movement can be obtained on stimulating either the poisoned or the unpoisoned skin, while yet stimulation of the lumbar nerves causes vigorous movements in the protected extremities. These symptoms have been concluded to indicate a direct reflex paralysis of the cord by the poison.

Demar's makes no special reference to the cord but he evidently considered that the poison had no direct action at all. Kolliker, p. 55) found that when ½−1½ hours after the poisoning, the reflexes were entirely suspended, movements in the protected parts readily followed a direct stimulation of the upper part of the cord up to 2−3 hours after poisoning. He concluded therefore, with some hesitation, that the grey matter of the cord was paralysed before the white. Haber, p. 41, states that the reflex movements disappear.
in 6 to 10 hours but gives no decision as to the cause. (Biddulph, p. 338) does not think there is any action on the spinal cord. Armstrong (p. 151) concludes that the nerve centres are paralyzed as the poisoning progresses, and other writers on pharmacology & physiology, in this country at least, generally hold the same view. (Rutteford, p. 152) Landois & Schlesier, p. 1701) Foster, p. 2396)

One cannot but observe in reading most accounts of experiments that positive conclusions are often drawn without actual experiments on the divided cord, that confusion exists between the action of small and large doses because no common basis of multiples of a minimum paralyzing dose is adopted, although it is well known that curares differ often considerably in strength, and that little or no account is taken of the circulation, on which the larger doses of curare act strongly.

In direct opposition to the previous statements are the conclusions of Kiindt, Schelske, Martin-Magen, Aunison, von Aegdol, & Vulpian, that the curare acts like strychnine, but this can best be considered after the action of small doses has been discussed.

The latest writers therefore, with the exception of Vulpian, believe that curare paralyzes the sensory nerves of the cord,
while the early writers hold that the sensory nerves are not paralyzed, some believe that the cord is paralyzed, & others that it is excited. The necessity for further work is apparent, when reference is made to the subjoined list.

1. Humboldt & Schletz (1859)  
2. Martin-Maynor & Buisson (1859)  
3. von Rezzold (1860)  
4. Vulpian (1862)

That the spinal cord is excited  
That the cord is paralyzed or unaffected

That the sensory nerves are paralyzed  
That they are not affected

1. Schüff  
2. Buchner (1866)  
3. Lange (1874)  
4. Steiner (1877)  
5. Binnig (1884)  
6. Lauder Brunton (1887)  
7. Romaniello (1875)

It is evident that there must be some serious difficulties or fallacies in the investigation, otherwise so many authors could not agree after time express different opinions, & these I shall now endeavor to clear up.

After many general, and some 97 special, experiments directed to the condition of the spinal cord, and sensory nerves after the administration of curare or curarin, the
following results & conclusions, in this section, have been arrived at.

I

Experiments with small doses of curarin of about 2 to 5 times the minimum paralysing dose.

A. If, in an intact unprotected frog, the same dose of curarin be administered as in B & D, and, about 15 to 60 minutes after poisoning, when the reflexes are very irregular and depressed or have disappeared, to stimulation of either the poisoned or the unpoisoned skin, the spinal cord be successfully divided below the medulla, the condition of reflex depression and irregularity, and apparent sensory or spinal paralysis, quickly changes, and active movements of the protected parts regularly follow every stimulation of either the poisoned or the unpoisoned skin.

Exp. No. 57 Oct. 1887. Temp. 15°C.

Minutes after poisoning.

0 Preparation of lower extremities as usual, after recovery, administration of 0.00003 g/1m curarin, equal to twice the minimum paralysing dose, in 0.3 cc rate, by injection into ant. thoracic lymph sac.
Minute after poisoning.

17. A spontaneous movement. No further spontaneous movements throughout the experiment.

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

18. Reflex to dilute sulphuric acid 0.3% Left 1 sec. Right 1 sec (?)

28. do

38. do

Reflex to pinching either the poisoned or unpoisoned skin continue good & fairly regular.

46. Reflex to pinching becoming rather difficult to obtain. Pinching the protected foot gives naturally the best reflex.

50. Reflexes further impaired, very irregular, sometimes pinching the poisoned skin acts when the unpoisoned skin fails, & sometimes both act, or 20 successive stimulations to all parts failure no movement. When systematically applied the first stimulation as a rule causes a reflex, irrespective of the skin being poisoned or not.

60. Strong acetic acid twice applied to the unpoisoned skin of the feet without any reflex movement following pinching usually entirely fails to act. Extremities kept fixed.

65. The spinal cord now carefully exposed above the level of the brachial nerves. During the cutting of the tissues & bones not the least sign of life occurred in this experiment, as if the nerve centres were paralysed. Complete section of the cord with very sharp knife without dragging or bruising & with very slight haemorrhage. Vigorous ejection of some extremities on making incision.
Minutes after poisoning:

68. Reflexes found to have quite altered. For now every pinch of either the poisoned or the unpoisoned skin immediately causes a reflex movement.

The reflexes to dilute acid have reappeared.
Right foot withdrawn in 22 seconds.
Left foot " " 11 "
Right " " 10 "
Left " " 7 "

95. The same results but the movements becoming very feeble in this case.

In numerous similar experiments with vigorous frogs, where the spinal cord was successfully divided without much hemorrhage or bruising during this stage of reflex depression, the same results were always obtained. When the poisoned anterior extremities were allowed from time to time to hang into the dilute acid after the spinal cord had been successfully divided reflex movements regularly followed in the unpoisoned posterior extremities, although, previous to the section, no form of stimulation produced any effect. In one case, notwithstanding the mutilation and the depression caused by the successive severe operations, the spinal cord retained its vitality for 7 hours after section.

Stimulation of either the poisoned or the unpoisoned skin caused reflex movements. These experiments occasionally failed from different causes (1) Imperfect ligation of the
vessels or tissues at the lower part of the abdomen.
(2) Pressure of the ligatures or compressed tissues or
displaced organs (kidneys) against the trunks of the lumbar nerves (3) Rapid paralyses of
the cord after section was often very rare taken
in the operation. This seemed especially to
occur in warm weather in winter frogs that
had been kept a long time in the laboratory.

The following experiments however removed
all chance of error.

B. If the spinal cord in the frog be success-
fully divided below the medulla on the
day previous to the experiment, and the
same relative dose of curarin be administered
as in A and D, the early irregularity and
depression or disappearance of reflexes which
is usually such a marked feature of curare
poisoning in ordinary experiments on the
intact animal does not occur at all,
for it is observed that the poison exercises no
direct depressing influence on the cord or upon
the sensory nerves.

Exp. No 444    Sep 1887    Temp 17°C. Cels.

The spinal cord successfully
divided on the day previous to the experiment
and the lower extremities protected in the
usual manner one hour before poisoning.
Minutes before poisoning. Reflects to .3% Sulphuric Acid.

<table>
<thead>
<tr>
<th>0</th>
<th>Both feet withdrawn in 2 - 4 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>(d_0) 2 - 4</td>
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<tr>
<td>6</td>
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<td>9</td>
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<td>15</td>
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<tr>
<td>18</td>
<td>(d_0) 2 - 4</td>
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<tr>
<td>21</td>
<td>(d_0) 2 - 4</td>
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</tbody>
</table>

0 Administration of same relative dose of eurain as in experiments on intact frogs.

<table>
<thead>
<tr>
<th>Minutes after poisoning.</th>
<th>Both feet withdrawn in 2 - 4 seconds</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>(d_0) 2 - 4</td>
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<tr>
<td>5</td>
<td>(d_0) 2 - 4</td>
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<td>8</td>
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<td>47</td>
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<tr>
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<td>56</td>
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<td>(d_0) 3 - 4</td>
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<tr>
<td>68</td>
<td>(d_0) 3 - 4</td>
</tr>
<tr>
<td>95</td>
<td>(d_0) 1+</td>
</tr>
<tr>
<td>2 hours</td>
<td>(d_0) 1+</td>
</tr>
</tbody>
</table>

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

These results were repeatedly confirmed and show that the conclusions drawn from experiments where no account has been taken of the possible disturbing influence of the higher centres on the reflexes are very fallacious, altho' they look conclusive enough. When the action of higher doses is considered, additional direct and
indirect actions will have to be taken into account. The fact that the sensory nerves are not paralysed by curarin receives confirmation from experiments of a different kind.

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

Exp. No. 70 Decem. 1887 Temp. 13° Cels.
Spinal cord divided just above brachial nerves on 10th Decem. On 13th Decem. the lower extremities prepared in the usual manner, an extra ligature at pelvis preventing diffusion between the isolated extremities.

Minutes after poisoning.

0. Subcutaneous injection into the right leg of 0.0015 gm. of curarin dissolved in 25 c.c. water.
A dose sufficient to paralyse 90 frogs of the same weight as the one experimented upon was thus introduced into a part of one extremity 30 minutes. Motor paralyses of the whole right lower extremity.
Time after poisoning.
1 hour. Slight stimulation of any part of the skin of the paralyzed extremity causes active reflex movements in the rest of the body. When no stimulation is applied the frog remains perfectly still.
3 hours. The same result.
8 hours. The same result - the reflex movement instantly follows the stimulation of the paralyzed extremity (skin).

It is probable that the curare reached the endings of the sensory nerves in the skin since it was administered subcutaneously and diffused to all the deep motor nerve endings but, at all events, the negative result that the sensory nerves were not paralyzed, is of value.
Experiments of this kind were repeated several times, but the saturation of the skin with overwhelming doses, or their injection into the sciatic artery had no apparent influence on the sensibility. When experiments similar to those carried out by Köllicker (p. 56), Martin-Magnon (Anaison 1870, p. 527), Melpian (p. 288) were adopted the previous results as to the condition of the sensory nerves were still further confirmed (D).
D. If, in an intact protected prog, the
same relative dose of curare be administered
as in A & B, and, about 15 to 30 minutes after
poisoning, when the reflexes are depressed or have
disappeared to stimulation of either the poisoned
skin some strychnine be administered, the
reflex depression disappears and reflex
tetanus of the protected extremities rapidly
follows stimulation of previously apparently
insensible parts.

Exp. 91 by Martin Magen Bruisson, June 15, 1905.

12 am Left iliac tied in prog. Injection of curare

solution beneath skin of back.

12.25 Paralysis of unpoisoned parts

1.30 pm Still movements in left posterior (unpoisoned)

extremity on strongly pinching the skin of the back.

2. No reflexes when part is stimulated

2.12 while the heart continues to beat.

Solution of strychnine injected beneath skin

of back.

2.12 Slight stimulation of any part of the body

causes convulsive movements in the left

posterior (unpoisoned) extremity.

Also, when one posterior extremity is protected

the prog poisoned with curare, when the poisoning is

complete the result of the other, the paralyzed posterior

extremity are ligatured, so that the poisoned and the
unpoisoned skin are under the same circulatory conditions, the result is the same. This demonstrates that the sensory nerves, to which only the curare had access, are not paralysed. Now, in the case where only a single extremity was paralysed, it is obvious that, since neither the curare nor the strychnine could enter it, and since between one and two hours after the administration of the curare, but prior to the administration of the strychnine, stimulation of this unpoisoned skin produced no reflex movement, but after the administration of the strychnine, the same stimulation or a much weaker one applied to the same part produced reflex tetanus, the previous absence of reflexes could not possibly be due to any local change in the sensory nerves but was due to some change in connection with the nerve centres. Taking it for granted then that the sensory nerves are not paralysed by curare, three experiments by Martin-Mag��on, Quinon, Gollner, and Velhun" still leave unexplained the spinal depression which the mere necessity to administer strychnine seems to bring out clearly as the cause of the irregularity and failure of reflexes. This marked depression of the spinal reflexes after comparatively small doses of curare is quite different to that which is found after the administration of large doses. In the absence
of any other explanation, it is almost universally held that curare paralyzes the cord.

The statement made long ago by Wendt, Schelske, Martin, Magron, Viguier, and von Arxold, that curare stimulates the cord has been, almost naturally, held to be inconsistent with this frequently observed feature, and there has been a sort of tacit understanding, that, when these eminent physiologists obtained the interesting results on the spinal cord described by them, they had, as Kühne (Pflüger, p. 334) suggested, the misfortune to be experimenting with a curare, which, unknown to them, contained strychnine—a convenient supposition with which to reconcile such apparently contradictory results.

Curiously enough, no experiments with small doses of curare seem to have been made on the isolated cord, and from these we learn that the reflexes are practically unaffected by a dose which in the same time causes their disappearance in the intact animal as a rule.

It has been made clear, therefore, by the preceding sets of experiments, that the symptoms in the intact frog are not due either to sensory paralysis or paralysis of the cord, but to an inhibitory influence of
some kind" exercised on the spinal reflexes when the higher centres are present.

The reason of the depression is not to be found in the operation or the tying of ligatures on the body alone, for, although this certainly depresses and disorders the reflexes in the intact frog, yet, even when the operation is comparatively slight, as in ligature of the sciatic vessels, the frog has apparently returned to its normal condition, the administration of curarin produces the reflex irregularity and depression all the same.

A number of experiments were next carried out to ascertain if the condition of the reflexes was due to a direct stimulation of inhibitory centres by the poison.

The cerebral lobes were removed in 7 or 8 frogs, and in the following days those were selected which showed an entire absence of reaction, but whose immediate movement followed slight stimulation. The posterior extremities were then protected in the usual way. After about an hour, when all the movements caused by the early irritation of the ligatures had ceased, the experiment was begun.

The reflexes were carefully tested for an hour by dipping the feet every 10 minutes into dilute acid recording the time in the usual way.

In administering small and medium paralyzing doses practically no impairment of reflexes occurred during the following hour.
As the frog is suspended during an experiment of this kind, the greatest care is necessary to see that all the tissues at the lower part of the abdomen are thoroughly ligatured, with the exception of the nerves, otherwise the poison is almost sure to diffuse into the lower extremities.

At the end of the hour the bones covering the optic lobes were removed. The lobes were then picked with a needle. On testing the reflex to the dilute acid now, the jet did not withdraw from tickling, pinching, the application of facial acetic acid to the skin had not the least effect for several minutes.

Sometimes when a drop of a strong solution of curarin was applied to the optic lobes marked depression of reflexes occurred, and very soon other symptoms, which will presently be described, set in. This has no bearing however on ordinary cases where small doses are administered subcutaneously.

Since therefore the optic lobes were functionally capable of acting during these experiments the direct action of curarin on inhibitory centres after subcutaneous injection was nil.

As the reflex depression during the first hour is only to be observed when the cerebral lobes are intact it must proceed from them. It must be due to some direct or indirect action of the poison.
Owing to the fact that undoubted voluntary movements are very generally absent a few minutes after poisoning (Kolleher, p. 58), Steiner inclined to the view that the cerebrum is directly affected. He latter observed that in some kinds of fish voluntary movements disappeared a considerable time before motor paralysis set in.

On the other hand Demaré, Nolpein (1859) observed that when a dog was poisoned with an eau of signs of intelligence when spoken to (mord t'ai) as long as motor power remained.

The loss of volition in poisoned frogs is, thus, a large number of experiments are tried; not absolute (Martin-Magon, Buisson, p. 341, Nolpein, p. 381) altho it is difficult to distinguish between purely voluntary movements and movements due to quite another cause. And also, when eau has been administered subcutaneously in man, (Vosin of Evnville, de Cazal) very distinct effects produced on the motor nerves, the circulation, temperature, 

A second explanation of the voluntary or reflex depression might be found in the fact that
the poison paralyses the muscles of the eye, respiration, general movement but does not affect the sensory nerves. The frog is probably conscious after the first few minutes of its inability to make definite movements with most of its body, ceases to make unintelligent attempts with the protected parts, voluntarily resists stimulation. When the cerebrum is removed the reflexes are no longer depressed in the early part of the experiment although every other condition remains the same. This seems all the more likely because poisoning with tetra methyl ammonium tetra ethyl ammonium and small doses of methyl strychnium salts the same condition seems to occur when the cerebrum is intact. Often when a stimulus is applied a slight tremor in the legs may show that the stimulus has been felt but movement is repressed.

The only other explanation that seems possible (excepting unknown reflex influences on the cerebrum) is a disturbance of the circulation in the brain. Anger and Seawell give some data of the effect on frogs of the mechanical arrest of the circulation. When the brain was present, the arrest caused a strong reflex depression of the cord, apart from any direct action. This was very marked in experiments in September. "For whilst in entire frogs reflex action was lost on an average in 5 minutes, in
brainer's frogs is persisted on an average 59 mm.
Small doses of curarin do not paralyse the
circulation, therefore, if the reflex depression in
intact frogs is due to cerebral anemia it
must arise from vaso motor spasm. I
do not know of any experiments on frogs where
the condition of the vaso motor centres has been
determined in eunurized frogs. Ellis, who employed
the plethysmograph in experiments on eunurized
frogs, mostly directed his attention to the effects
of stimulating the divided nerve [Remarks 15448]
sufficient evidence was not obtained in these experiments
to show that stimulation of the skin produces a
reflex contraction or dilatation of the vessels of the leg.
Fennow [19] does not definite conclusions can be drawn from
these tracings regarding spontaneous vascular changes.

Whateve the explanation of the
reflex depression is regularity may be it is
directly connected with the presence of the cerebrum.
These authors who concluded from experiments
on intact frogs that the sensory nerves were
paralyzed the reflexes depressed could not but
fail into error.
II

Experiments with large doses of curarin of from 50 to 100 times the minimum paralyzing dose (0.0005 to 0.001 g.m. in a frog weighing 30 g.m.)

When a large dose is administered by subcutaneous injection motor paralyses of the unprotected parts occur in a minute or two. Purpose-like voluntary movements quickly disappear in the protected extremities, although markedly irregular spontaneous movements occasionally occur at this stage of the poisoning. The reflexes to chemical and mechanical stimulation of the poisoned or unpoisoned skin usually quickly disappear become difficult to obtain and for a time indeed are practically suppressed.

Early reflex depression of this kind in the intact frog is not due to any direct paralyzing action of the poison on the sensory nerves or the spinal cord, for just as in the case of small and medium doses, it does not occur at all at the same period when the cord is divided before the experiment; nor does it disappear when the cord is divided during the experiment. It is advisable when these large...
doses are administered not to delay the section of the cord beyond about an hour, otherwise the reflexes may not be increased for reasons which will immediately be shown.

The latter symptoms differ very distinctly in the following particulars from those produced by small doses.

1. The reflex depression in intact frogs continues usually for a period of from 70 to 90 minutes and then spontaneously disappears.

2. It is followed by a period of very variable duration during which the reflexes are either simply improved, or, in addition, spontaneous and reflex movements of a spasmodie character occur. This period of relative nervous excitement is as a rule of brief duration; its symptoms, the unmistakable ins character, are slight, and depression of reflex excitability rapidly follows, as from 3 to 5 hours usually passes into total paralysis of the spinal cord. Even 20 hours however may elapse before reflex paralysis is complete. The onset of the paralysis is hastened by a large dose of curare and a high temperature. Stimulation of the poisoned skin causes reflexes as
long as the cord retains vitality & the protected muscles remain contractile.

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

In about 5% of these cases well-marked tetanus occurs.

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

Expt. No. 80 Intact frog. Dec. 88

10 minutes after administration of 75 times the minimum paralyzing dose.

2. Complete motor paralysis of unprotected parts.

15. Disappearance of reflexes to dilute acid.

30. Progressive impairment of reflexes to pinching.

62. No voluntary movement during the last 47 minutes. Spontaneous movements now occur from time to time. These movements are incoordinated and consist of a jerky extension of the lower extremities or a slow sprawling movement or a slow spasmodic like extension the web of the toes being outstretched.

80. Reflex to pinching much more easily obtained now.
A slight touch on either the poisoned or unpoisoned skin causes a quick, jerky extension of the lower extremities. When the stimulation is slight, crossed reflexes are well seen. 3 hours: Feet withdrawn from the dilute acid in 6 seconds. Moderate tetanus can be induced from time to time on pinching the skin or tapping the body. 4 hours: Spontaneous movements ceased & reflexes no longer obtained on stimulating the skin in the upper end of the divided sciatic nerve or the upper end of the cord. Stimulation of the lower end of the divided sciatic nerve or the lumbar nerves of other side causes active movements of the lower extremities.

Exp. No. 81  Intact Freq. Temp. 16° Cels. Jan. 88

Time after poisoning. Administration of 70 times the minimum fatal dose.

25 min:反射s distinctly depressed
80 min: Slight improvement of reflexes
2 hr: Occasional slight spontaneous movements
6 hr: Reflexes distinct but pubic & early exhausted.
16 hr: Pinching the poisoned skin of back & anterior extremities causes pubic contractions in the upper thigh muscles, the rest of the extremity having become dry and rigid. Heart beat not to be observed on thorax.

26 hr: Condition unchanged
40 hr: Paralysis

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

Minutes before poisoning: Tend withdrawn from 3% Sulph. Acid in 4 seconds, 10, 60, 5.

On finishing the frog the reflex is very active.

Minutes after poisoning: Injection of 1 cc. soln containing 0.001 gm.

Frog weighs 88 gm. — about 140 times the minimum.

5 Complete motor paralysis of unprotected parts.

13 Frequent slight spontaneous movements in lower extremities.

15 Reflex to dilute acid in 5 sec. to finishing immediate.

18 Both lower extremities frequently flexibly extended or flexed. While in the position of flexion, extensor fauntly uneasy movements of muscles.

30 Frequent spontaneous movements. No diminution of reflexes as in intact frog.

40 Distinct tetanus following stimulation. The lower extremities often quite rigid for 5-10 seconds. This condition with intervals of rest continued for 30 minutes.

60 Spontaneous movements less frequent. The tetanus when induced is brief & the necessary intervals of rest longer.

Right foot 18 sec. but difficult to estimate.

80 Reflexes much weaker; tetanus more difficult to obtain.

95 A brief tetanus on touching the foot.

120 No further reflex. Direct stimulation of lumbar nerves causes active movements in the lower-
Many of the experiments were without decided evidence of tetanic action, but showed some suspended symptoms—partly paralytic, partly convulsant.


Small eard divided in frog on 24th. Oct. at 5 pm. y. at 5.15 pm. on the following day the lower extremities prepared as usual.

6.41 pm. Injection of 0.00025 gm. in .55c. water (about 30 x. professional).

Paralysis complete in unprotected parts.

62  Reflexes continued good without cessation.

19  After the reflex movements has taken place some twitchings shown in legs. occasionally spontaneous jerks of extension occur.

89  Reflexes very acute but no tetanus.

69  Reflexes slowly becoming less acute.

49  Distinct maxims of reflexes.

109  The slightest movement only obtained.

2 hours complete paralysis of the eard.

After many such experiments it became absolutely certain that the subcutaneous administration of relatively large doses of curarin (.00025 — .001 gm.) caused in intact frogs the disappearance of the primary reflex depression, and produced, in a proportion...
of cases, symptoms (increased reflex excitability and
tetanus) generally understood to signify distinct
"stimulation" of the spinal cord.

In experimenting with curare about
30 years ago Martin, Magron, Perisso, Wendt
v. Schelske v. von Arndt came, as we have
seen, to a similar conclusion, while Vulpius
has also held that the symptoms in both
cold and warm-blooded animals pointed to
a preliminary stimulation of the cord. But
since the experiments of these authors were
made with crude curares, that is to say
with substances consisting of a mixture of
extracts derived from plants, most of which
were unknown, there must always have been
a doubt as to what caused the tetanus
and what the paralysis. Some progress
has up to this point been made in
proving that the paralyzing and the tetanizing
principle are one. The same, and some of the
differences between the actions of small and large
dooses of definite strength, and between the
direct and indirect actions of the poison have
been made clear.

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

The explanation of these facts is almost undoubtedly to be found in the great change produced by the poison in the circulation. It is well known that large doses of curare impair the diastolic filling of the heart, (Kulpmor's p. 3574) which, after several hours (von Avgold's 1887) ceases to beat. It has been noted, in the preliminary observations on the activity of curarin, that medium doses produced slowing, large doses caused stoppage of the heart after a good many hours or even days in cases where the thorax was not opened.

If, in an ordinary experiment where a small dose of curarin has been administered the heart is exposed and watched, little immediate change occurs in its condition, if the frog during the observations is under
the same conditions of temperature as before the experiment. After a time the blood becomes dark owing to the muscular paralysis having stopped the respiration by the lungs, or, especially in warm weather, a distinct slowing of the heart's action sets in. This cannot be attributed to any direct action of curarin for simple artificial stoppage of respiration by the lungs slows the heart in summer frogs.

When large doses of curarin however are administered there may be a quickening of the heart's action for a minute or two, soon followed by a marked slowing. The inhibitory action of the vagus is suspended. But what is most noticeable is a distinct diminution in the size of the heart, the diastolic filling becoming very imperfect, although the rate is not at first affected much. A change in this direction occurs several minutes after the poison has begun to act, and in a variable time, which it is difficult to estimate correctly, but often within 30 minutes, it is really an empty ventricle that for the time being continues its regular contraction. It is well known that in warm blooded animals large doses greatly lower the blood pressure. Since in the frog the heart continues to act well, though more or less empty, it is evident
that the bloodvessels are in some way paralyzed. If the abdominal visera be examined, it will be found that the veins are greatly distended with blood. If the spinal cord be divided there is practically no haemorrhage, and the blood is very dark in colour. It is evident that the supply of oxygen is cut off, for not only is the pulmonary respiration of necessity stopped, but the extraneous respiration is also practically at an end, for the blood is no longer actively circulating throughout the skin of the paralysed animal. This is confirmed by the fact that in deeply curarized frogs the gas analyses (Valentin p.99) shows a marked sinking of the oxygen absorbed and carbonic acid given off, & the muscles have no longer a red colour, whereas in frogs paralyzed by small doses of curare & more consequently the circulation in the skin is not profusely. The gas analysis shows that the oxygen absorbed is not diminished.

Under these circumstances, the quantity of oxygenated blood which can reach the central nervous system must usually be
be very small. It has often been shown that when the aorta is compressed, or the heart paralyzed, or the frog surrounded with an inrespirable gas ½, or in other words when the blood can obtain oxygen but cannot circulate, or circulates but cannot obtain oxygen, the central nervous system becomes after a time paralyzed. On trying the reflexes in unpoisoned frogs for purposes of comparison I found the period which elapsed, after ligation of the aorta, before paralysis of the cord was complete to be about 4½ minutes in very hot weather, and from 1½ to 3 hours at lower temperatures in winter.

Curare in large doses produces, after a short time, a condition of the circulation similar to that which would be caused by the ligation of all the veins entering the heart. In experiments where the spinal cord has been previously divided the circulatory paralysis is if possible accentuated. It is certain therefore that the alkaloid is not only very imperfectly circulated, but that it must be causing this great dilatation of the bloodvessels, indirectly weaken and paralyze the central nervous system. This secondary paralysis must occur no matter what the
direct action may be of that part of the
dose which may reach the brain & cord.

Since, impairment of the circulation
sets in with the subcutaneous administration
of such a large dose of Curarin as one-
milligramme. It is impossible to say how
much of it is ever carried to the spinal
cord. Telfourn (p. 289) points out that
in curarized frogs the action of digitalin,
strychnine, Upre Antiac, Silicium, Murexine
is very much less in degree, & the symptoms
are much later in appearing than when
similar doses are given to non-curarized
frogs. In the absence of any special
action by curarin on the heart this
may be held to indicate delayed
absorption & defective circulation "p. 289 En
"tout cas, elles pourraient bien noter demen
"ce que nous avons déjà établi, à savoir
"que la curarisation préalable retarde et
"ralentit notablement l'absorption"

Assuming for the moment that the
direct action of curarin or curare on the
cord is a stimulating one, then the
infrequency of tetanus after subcutaneous
injection shows that the part of the dose
which does reach the cord is generally
either insufficient to produce the tetanus,
or it reaches too late to overcome the
weakness produced by the want of oxygenated blood. It may possibly also be the case that the circulation of the alkaloid is limited by the nerve ends, muscles or other tissues retaining in some special way a further part of the dose in addition to what lies in the dilated veins.

It will presently be seen, when the action of curarizum on the eord is more fully worked out, that the simple spinal paralysis which follows the subcutaneous administration of large doses, and the infrequency of tetanics, can only be explained by the failure of the circulation.

Central paralysis is not very generally recognised as the secondary action of substances which, in the dose employed, cause complete paralysis of bloodvessels, although it is evident that the absence of oxygenated blood, in whatever way it is brought about, must weaken and finally paralyse the eord & heart. It is known that the cardiac contractions may continue in the frog for a considerable time without blood. It would obviously therefore be a mistake to assume at the beginning of pronounced curare poisoning that, because the heart movements were to be observed on the thoracic wall, the circulation was being efficiently maintained.
We may now proceed to the further statement, that, when the inevitable fallacies which attend subcutaneous administration of the larger doses of the poison are avoided, by applying the poison directly to the cord and by injecting solutions into the aorta, the symptoms are constant and quite unmistakable and show that the direct primary action of curarin on the spinal cord is that of a convulsant poison allied to strychnine.

A. The local application of solutions to the spinal cord.

Before applying a solution of curarin it is necessary to an unprotected frog, to suspend the circulation by ligature of the aorta or heart to prevent the poison being conveyed to the muscles. Experiments are most completely satisfactory in winter, as the cord retains its vitality far from 1½ to 3 hours after the circulation is stopped.

Exp. No 86 Jan 8th 1888. Temp. 12° Cels.

Minutes
0 Ligature of heart. Exposure of cord commenced.
10 Brain destroyed to prevent voluntary movements.
15 Whole cord exposed without injury. No movements.
During the last 30 minutes, 30 drops of a solution (1 in 10000) allowed to trickle over the spinal membranes which are mostly intact. Most of the solution has necessarily escaped. Not the faintest movement has occurred.

During the last 15 minutes 15 drops of a solution (1 in 1000) of curarin applied as before.

Violent tetanic spasm of whole body lasting 15 seconds on accidentally shaking table.

Tetanus follows every stimulation—often successive shocks occur lasting 5 sec. each.

Frequent spontaneous tetanic shocks during the last 10 minutes, some of them last almost continuously for a minute.

Frequent twitching of individual muscles.

Violent tetanus lasting 20 sec. on pinching foot.

2 hours: Tetanus very brief and relatively pellae.

3½ " Refleex very weak.

9 " Paralysis of cord having remained active without blood jet about 8 hours.


Minutes
1 Heart ligatured.
15 Brain destapred and cord fully exposed.
35 Terg has been left undisturbed for 20 minutes to see if any signs of excitement from injury exposure or any imaginary
combination of circumstances could act. Not the least movement has occurred. On finishing the foot the reflex is simple and not at all strong.

After perforating Application of 2 drops of water containing 0.0005 gr. quinine in solution. The membranes lining the spinal canal were free from all parts unbroken, the cavity was partly filled with lymph and blood, so that the quinine could not come into direct contact with the cord.


23. Spontaneous attacks often begin slowly, the extremities being moved about in various directions according to the muscles most in action, finally all parts become affected and intense tetricus sets in lasting for a minute perhaps. Reflex tetricus immediately follows a stimulation.

2½ hours. Spontaneous movements have ceased. Reflex tetricus very feeble.

Note. When the spinal cord is carefully completely divided into two parts before applying the solution it is found that tetricus occurs in the muscles supplied from both parts showing that the symptoms are directly due to an action on
the cord. When the dose is very large - several milligrammes - tetanus of the most violent kind sets in after a few minutes but the cord is soon exhausted.

These experiments demonstrate that the local application of say half a milligramme of curarin produces marked and true tetanic symptoms, when a healthy frog is used. The cord is not seriously injured in the preparation the appearance of tetanus is invariable.

Since the subcutaneous injection of a solution of curarin or curare in a warm-blooded seems absolutely non-irritating, and since the solutions employed were very weak, (average 1 in 1000 rats) neutral in reaction, and free from foreign bodies of any kind, it is quite improbable that a tetanus of the nature described could result from any local irritating action, as ordinarily understood by that term. The symptoms are the same in kind as those which follow the application of strychnine, but are of shorter duration, because the dose which tetanises greatly weakens or paralyses the circulation.

At the same time it would be a satisfactory proof, if the tetanising action of curarin could be further demonstrated by
conveying it to the cord through the blood capillaries

Injection into the aorta.

It has already been shown that the complete absorption and adequate circulation of a dose of curarin sufficient to produce tetanus cannot be hoped for by subcutaneous injection, since paralysis of a part of the circulatory apparatus follows. Tetanus only occurs, as we have seen, in those exceptional cases where presumably the quantity of curarin that reaches the cord is greater than usual, where the depression caused by the impaired circulation is less.

It was obvious in making these experiments that if a large dose of curarin were injected into the abdominal vein matters would only be slightly improved, since most of the solution would pass to the tissues by the large arteries, and, as paralysis of the blood vessels would at once follow, it would be doubtful how much reached the nerve centres. Tetanus was however obtained in this way on repeating the injections, & also on simply injecting the solution into the aorta von eirulating a curarin containing fluid through the vessels of the unprotected part.
Very speedy and entirely satisfactory results were always obtained when the experiment was made in the following manner—ligature of the common abdominal aorta above the origin of the large common intestinal artery (celiacus mesentericus), ligature of one aorta at its origin & one pulmonary trunk. On making the injection by means of a cannula in the intiated aorta close to the heart, the only important vessels through which the solution can pass are the carotid & oecipito-mesobrachial arteries of one side, that is to say the vessels which supply the central nervous system. If the subclavian artery on the arm be also ligatured the great part of the solution passes directly to the brain and cord. The spinal veins are not obstructed although the circulation is stopped.

Exp. No. 90. Jan. 8th, 1867. 13 Cels.

30 mins after poisoning Preparation as described.

0. Slow injection of 8cc 50* containing 0.0008 gm. curarin into left aorta.

Almost immediate appearance of fits & spasms which continued nearly without interruption for 50 minutes.

1. Severe spontaneous tonic convulsions (epiphlebitic) followed by constant spasm of individual
minutes after poison. Muscles and groups of muscles the extremities
being jerked about in all directions

15. The tetanic spasms still continuing with
considerable violence, when these abate every muscular
fibre is in a state of constant twitching.

25. The violence of the spasms abating somewhat.

55. Gradual cessation of spasms. Very almost
complete exhaustion. Only feeble movements on
stimulation.

The same results were obtained in every
experiment. When several milligrams were
injected the tetanus was exceedingly violent. The
complete exhaustion of the nerve centres was no
doubt greatly hastened by the want of any
blood supply. The instant appearance of tetanus shows
that there is no delayed action on the cord.

It is important that the conclusion
that curarin acts on the cord in a strychnia-
lke manner should be substantiated by
experiments on the crude poison. If this
conclusion is true of the active principle of
curariz, then every active motor paralysing
specimen of that substance must, in virtue of its
containing curarin or some closely allied body, produce
unmistakable tetanus when a dose of the
necessary strength is applied in solution to
the spinal cord or injected into the aorta.

The following specimens were examined.

Six specimens in the Materia Medica Museum
of the University of Edinburgh

1. Poisoned darts of the Macusi tribe of Indians
   in British Guiana. From Sir Andrew Halliday
   Army Medical Service presented to Professor
   Christison in 1889.

2. Poisoned arrows from same source

3. Poisoned darts from British Guiana
   obtained by Professor Simpson in 1848

4. Poisoned arrows from same source

5. Uruzi poison in gland from same source.

6. Uruzi poison in gland from Dr. Ewan
   Cameron, Buiriee 1849

I am much indebted to Professor Fraser for specimens
from the following four curares as well as
those mentioned above.

7. Curare from "Agassiz leased, Brazil"
   presented to Prof. Fraser in 1870 by Dr. Heir
   Mitchell.

8. Curare from "Pot from Ooya from Agassiz"
   from same source

9. Curare from "Pot from Pera" from same source.

10. Curare from "Pot from Academy of Natural
    Sciences now in possession of Sir Hammond"
    from same source

The next four specimens were purchased in
Decem. 1888.

11. Curare (source unknown) from Messrs. Hopkins
    & Williams, London.
As different specimens of curare vary considerably in moter paralysing power, a solution in distilled water was made, filtered, and the activity of the filtrate approximately determined on two or three frogs. Taking the dose which was found to be the minimum paralysing to contain about 0.00000028 gramme curarin per gramme weight of frog, the filtrate was evaporated on the water bath until about 0.5 cc. would contain 0.001 gramme.

The details of the experiments were the same as with curarin. It is only necessary to state the conclusion, namely that on applying the solution to the eard, or preferably making a direct injection into the aorta in the manner previously described, tetanus was in every case obtained readily just as with curarin. When a larger dose, corresponding to several milligrammes of curarin, was injected instantaneous tetanus of the most intense character set in.

It has therefore been shown...
that all the curares examined have a marked tetanising action which is readily seen when the indirect actions of the poison are guarded against. These curares were selected quite at random, one of undoubtedly authenticity, one obtained from at least three different sources — Brazil, British Guiana and Venezuela — one therefore of representative character. The specimen dated from 1837 to 1888 included two commercial varieties of curarin, that by Merek being of fairly good quality. The cause of the tetanus produced by the crude arrow poison we have already found in its essential active principle — curarin — an alkaloid having at the same time an intensely active paralysing action on motor nerve ends.

It would perhaps be advisable to consider now if the symptoms observed in warm blooded animals support the previous conclusions. Obviously, as the most prominent action of the poison is a paralysing one on motor nerve ends, tetanus can only be shown by special experiments. In addition however to this positive proof, there are important
negative proofs in the other direction which enable us to say that where the poisoning is not greatly in excess of what is required to produce motor paralysis, the cord is still active.

Kelpman\(^\text{1}\) (p. 332) has especially drawn attention to the view of the case that the cord is not paralyzed. The various points may be briefly summarized as follows:

1. After the subcutaneous injection slight twitchings \(\text{refl} \) occur in various muscles, especially the skin muscles, \(\text{dis} \) disappear as paralysis progresses.

2. Although convulsive movements due to \(\text{asphyxia} \) do occur in animals poisoned with small fatal doses (when the dose is large the motor nerves are paralyzed too quickly to permit of movement) the \(\text{spasm} \) movements referred to are not due to this cause, for several reasons.

(a) They may occur while yet voluntary respiration is good.

(b) They occur despite active artificial respiration.

(c) Spasms due to \(\text{asphyxia} \) do not occur in a chloralised animal but spasms appear in a chloralised animal poisoned with \(\text{curare} \) (Kelpman\(^\text{1}\) p. 332).

(d) I have several times seen spasms occur...
mi a rabbit after the injection of curarin into the jugular vein, altho' artificial respiration was adequately maintained before the injection, the animal was deeply under the soporific influence of urethane: the movements only last for a few seconds after intravenous injection as the nerve ends are almost immediately paralyzed. The pupils dilate & contract reflexly to light & stimulating the sensory nerves of the paralyzed animal.

H. On stimulating nerves reflex contraction & dilatation of bloodvessels follows. When the action of the poison comes to be considered it will be shown that curarin acts on the vasomotor centres in a very special manner which is in harmony with its other actions.

5. Reflex contractions of stomach, intestines & bladder may follow stimulation of the skin, upper end of sciatic or vago-sympathetic (Kulmorin® p.357 &c). Alteration in causes vomiting (Kulmorin®).

6. Reflex increase of salivary secretion on stimulating the skin or sciatic nerve &c. (Kulmorin® &c).

7. Reflex sweating of feet in cats on stimulating upper end of sciatic (Kulmorin® &c).

8. Continuation of rhythmic movements of recters. (Kulmorin® &c).

9. Rarely frequently observed that small & medium doses of curarin, which certainly do not paralyse the splanchnic nerve, frequently induce very marked intestinal peristalsis, all respiration being meanwhile adequately maintained.
Positive proof that curarins not only does not produce paralysis but actually produces a condition of the cord which would ordinarily result in tetanus, if the motor nerve ends were not paralyzed, was obtained by repeating an experiment described by Martin Magron and Buisson (p. 359) where the spinal cord in guinea pigs was exposed at the middle of the back and divided. Care was then taken to see that all voluntary movements in the posterior extremities were abolished and reflex movements preserved. On injecting water into the thickness of the cord no tetanus occurred. On injecting curare solution without letting a drop escape in the neighborhood of the cord, tetanic symptoms set in after a few minutes (3 to 5) lasted for an hour or more without the respiration becoming embarrassed. When any curare escaped round about the cord, it was rapidly absorbed into the general circulation and respiratory failure might set in by 10 minutes. Martin Magron and Buisson found tetanus to occur in 10 successive experiments.

In one experiment of my own, a rabbit weighing 1700 grammes was anaesthetized with ether. The spinal cord exposed at the middle of the back. As the animal was recovering
from the effects of the ether the needle of the hypodermic syringe was passed in a slanting direction fully into the substance of the cord and 0.001 grammes of eurinm dissolved in 0.2 cc of distilled water injected. As the needle entered the cord the animal started violently, on the injection being made struggled several times and emitted several cries. It then rested quietly for 2 minutes, but by the end of this time the spinal muscles were seen to be in a state of spasm, the left side (probably from the seat of injection) being more affected than the right. The spasmotic condition rapidly spread up and down the cord, and by the end of the 14th minute after the injection, there was a universal condition of mixed tetanic and clonic spasms. The fatal dose for a rabbit of this weight is 0.005 grammes of eurinm, but, as the whole 0.001 grammes was fairly injected into the cord substance, it seemed to be taken up by the nerve cells, but at least it did not pass into the general circulation at any time in sufficient quantity to cause any evident impairment of motor nerves or of respiration.

From the 14th minute after the injection a condition of incessant spasm existed which involved every muscle in the body. The animal was never still for more than a second or two, and on several occasions these convulsions seemed
likely to cause death by asphyxia. The tonic spasms mostly affected the muscles of the neck, the head being drawn forcibly backwards, the clonic spasms mostly affected the facial muscles, the limbs, the forelimbs making constant movements as if digging, the hindlimbs kicking out behind in a jerky manner. Even when a few seconds rest occurred, the tail exhibited ceaseless movement. Little opportunity occurred to test the reflex irritability, but, during the momentary pauses, a slight touch seemed at once to renew the movements.

This condition continued unaltered for 14 hours, and then the animal was killed. Such symptoms do not follow the administration of mere local irritants. Although such a method of experiment is not free from objection, it is nevertheless of value when taken in conjunction with the other proofs brought forward throughout the paper.

When administered subcutaneously only a small part of a milligramme dose would normally be received by the cord, but by this mode of administration it received the whole dose without serious injury.

By the two methods of demonstration markedly different symptoms result, for, by causing suitable doses of the poison to act primarily in the one case on the cord, in the other on the motor nerve ends, we see that tetanic spasm is produced, the latter being no longer able to obscure the former.
Some progress has now been made with the proofs that curare acts in a strychnine-like manner on the cord, and some attention may therefore be given to those points which still stand in the way of a clear view of the nature of the poison.

In the first place, the fact that Helkama's experiments with curare when the cord was divided, that Bernard applied it locally to the cord, without observing tetanus, may, in the absence of explanation, be considered to lessen the value and completeness of the previous conclusions. It is not so, however. In Helkama's experiments (p. 30) the curare was administered subcutaneously. When the reflexes had disappeared, the cord was divided & strychnine immediately applied. It was found that the reflexes returned & that reflex tetanus could be obtained. As the strychnine was applied immediately after the division of the cord, no observations were made on the effect of the simple division, or the action of the poison by itself on the divided cord. The experiments were liable to all the fallacies which attend the subcutaneous administration of the poison. The strength of the dose was indefinite, but probably small or medium.

Bernard (p. 30) describes his experiment as follows: "Je, la moelle épineère d'une"
"grenouille a ete demidee dans une certaine etendue et tempee dans le curare. L'excitation galvanique faite sur elle, determine encore dans les muscles des convulsions energiques ce qui prouve qu'elle se comportait comme le trone nerveux."

The expression 'determine encore' shows the expectation that if curare had any action on the spinal cord it would probably be a paralyzing one. The experiment has this value, that the cord was not depressed, but, as a proof that curare does not produce tetanus it is quite valueless because the strength of the dose is unknown. One curare may be 10 or 20 times stronger than another, very different parts of the same specimen, owing to the presence of inert matter, vary considerably in strength; therefore, thus one author speaks of administering 0.1 gms. another 0.01 gms. Bernard uses the expression 'tempee dans le curare,' we have only the vaguest idea of the dose actually employed. In working with a crude poison it is absolutely necessary to make a filtered solution and determine the minimum quantity per gramme of body weight which produces some definite action. By diluting or concentrating this solution testing it from time to time to see that its activity continues unchanged, a considerable degree of precision in dosage is secured.
Bernard does not state if only one or more than one experiment of this kind was tried. The time the frog was under observation is not stated. Indeed, when we find that various other experiments with curare are described in detail, 4 at some length, while this is briefly dismissed it becomes evident that Bernard never seriously experimented in this direction. It is remarkable that since Bernard's experiments some 140 years ago, any form of direct experiment on the cord has been, as far as I have observed, entirely passed over by the many workers with curare, with the exception of those writers who in 1859-1865 came to the conclusion that curare acted in a strychnine-like manner on the cord. As the errors which attend the usual methods of examination have already been fully shown, there is therefore no further opposing experimental evidence to consider. Even granting that the indirect actions of the poison have not been fully appreciated by the later, as also by the early writers, there must have been some strong reasons why the striking experiments of Martin, Mayron,quisson, 5 von Bezold, 6 were not thought worth repeating, 7 why the conclusions they arrived at have been generally ignored. These reasons
seem to be of three kinds.

1. The idea that any tetanus produced by the curares used by the early investigators was due to the presence of strychnine as an impurity.

2. The idea that an alkaloid which has a strong paralysing action on motor nerves cannot have a tetanizing action on the cord.

3. The idea that the active principle of curare is a methyl-strychninium salt and therefore does not produce tetanus.

These views have received support from the experimental difficulties of the subject. The fact that most workers have failed to find that curare has any strychnine-like action, but that strychnine itself is an incomplete knowledge of the pharmacology of strychnine itself. The new body which can be obtained by the addition to it of iodide of methyl (iodide of methyl strychninium or)

The second view, which stands in the way of a clear knowledge of the action of curare, is that strychnine is present in curare or in some curares.

In order to conveniently explain away the unexpected experimental evidence brought...
forward in 1859 by Martin Magron & Bixson. Evidence which did not at all harmonise with the general opinion — Kühne (p.385) & later Husman (p.529). Advanced the statement that the experiments with a strychnine-containing substance and not with a true curare. It has already been shown that curare acts in a strychnine-like manner, that this action is produced by the larger doses of the active principle of the arrow poison. Chemically it has never been found that curare contains the least trace of strychnine. Theoretically it has been assumed to be present, partly under the idea that strychnine should have the monopoly of producing tetanic symptoms, & that strychnos plants ought to furnish strychnine in their backs no matter in what part of the world they grow. The latter view was evidently entertained by Bernard for he remarks, (p.312) that the absence of convulsions in animals which are killed in several minutes by curare is difficult to reconcile with the accounts of several travellers who think that it derives its activity from the concentrated juice of a strychnos. Cogswell in a paper read before the Physiological Society expressed the same view that "the physiological action of woocara is
opposed to the view that it owes its chief 
ingredient to a plant of the genus strychnos

In the discussion which followed one 
speaker remarked "It could scarcely be 
supposed that the effects of one species of 
Strychnos would differ greatly from those 
of another." This is exactly what I hope to prove.

Of course it is well known that plants 
belonging to the same genus do not necessarily 
produce the same active principles (e.g. Atropine, 
Nicotine)

Whenever it was definitely shown 
that curare was derived, in part at least, 
from species of Strychnos, some writers jumped 
to the conclusion that specimens of curare 
might contain Strychnine.

Huxham, in agreement with all other authors 
who base their statements on a practical acquaintance 
with the subject, states (p.327) that the chemical 
examination of curare has only yielded a 
more or less pure curarin, but never Strychnine.

The following investigators have subjected 
quantities of curare to a thorough chemical 
examination, and in no instance, although 
it was carefully sought for, was any 
trace of Strychnine or Quinine ever found.
Chemical Reports

1861. Buchner. " Doubtful experiments by Hettstein led to the conclusion that some S. Brazilian Uraii contained strychnine but a new analysis by Buchner (1861) showed that it contained curare. Physiol. exp. confirms this."

- Niesman, Handbuch der Physiologie, Berlin, 1862 p28


The formula assigned to curare by Preyer was C₁₀H₁₃N and that by Sachs C₁₈H₃₅N. The final results of Boehm's investigation have not yet been published. Curare therefore appears to contain no oxygen whereas the formula of strychnine is C₁₅H₂₁O₂-C₆H₅ (50%) and of brucine C₁₅H₂₁N₂O₂-C₆H₃ (OCH₃)₂ (50%).

There are in addition marked & fully recognized chemical differences between the two alkaloids. Curare is soluble with great ease in cold water (Strychnine 1 in 6660) is permanently yellow in colour, neutral in
reaction, cannot be any known means be
got to combine with acids to form crystalline
salts (tryptamine crystal readily) (Sach's, Bachn'). The
crystalline curarin described by Graeff 71 (loc. cit.)
was according to Sach's (Liebig's Annal. 1877, 191, p. 257) composed of
phosphate of calcium & carbonate of
calcium with admixt. amorphous curarin. &
certainly by Graeff's method a crystalline
curarin can not be obtained. Curarin
gives with cold concentrated sulphuric acid
a violet red colour (Beauv.ault & Recun 71
Sach's, Bachn'). Considering these & other
differences it is hardly possible that strychnine
could fail to have been detected, had it
been present. On the other hand, the statement
that strychnine may & does exist in curarin
is not only entirely unsupported by practical
evidence, but is an addition quite contrary
to all the evidence available. The necessity
for these suppositions & theories has been removed
by showing that the apparently irreconcilable
differences of the authors tabulated in the
early part of this paper are not due to the
poison, but to the absence of any common & accurate
system of dosage, overlooking the sources of
error in ordinary experiments. We shall see
later that a much closer relationship in the
kind of pharmacological action exists
between strychnine & curarin than has been
generally imagined. That the latter produces tetanus is a fact quite in harmony with its botanical origin.

We must conclude therefore that the curares used in 1859 were not impure or exceptional, and that the tetanising action of curare has been discredited on grounds which are either fanciful or erroneous.

Even if it is admitted that strychnine has never yet been found in the curares of the South American continent there is a third serious source of error to be cleared up, namely, that a crude curare which has an active paralysing action on motor nerve ends may contain some tetanising principle other than strychnine. Obviously this is a serious if not fatal objection to the conclusions drawn from experiments with the crude poison, or even to those with an alkaloid which cannot be obtained in a crystalline form that has been prepared from this crude mixture of the extracts of a number of plants, most of which are unknown.

Condamine thought that many plants entered into the composition of the curare of the Ticunas tribe (Upper Amazon) but Martyrs (Nusserman p. 526) believed that this poison was
was at least partly prepared from a Menispermaceous plant Uraci Sepo or Coccus Amazonum. Herberger experimented with an extract from the bark of this Uraci Sepo brought by Martinus * and found that it produced tetanus. Huseman* thinks it possible therefore that various curarecs may contain picROTOXIN.

De Castelnau* (p.140-150) also states that the Yacamas Indians of the upper Amazon district (Yapura river) mainly employ two plants in the preparation of curare. These have been named by Weddell, Strychnos Castelnana and Coccus Toxicoforus. The latter is stated to be a Menispermaceous plant (synonym Eko. Panie Sec. Coccus Amazonum). Dentu et al. et al.* (p.159) state that they have experimented with Coccus Toxicoforus and found it to be a convulsant poison resembling picROTOXIN and nicotine in action.

It is not at all certain however that this plant really enters into the composition of the curare of the upper Amazon. As Hanceh* (p.105) points out, its flowers are not known and the species therefore doubtful. He thinks that the leaves resemble other genera (Chondrodendron &c) rather than Coccus. * Robert* in a communication
to the French Academy (4th Jan. 1848) repeats that probably Trychmus Castelmausa (Hedw.) and Ekeo (Prob. Ececlus escefeus (Hedw.) enter into the composition of this curare. Here again however it is very much a matter of conjecture. While it is possible that a feverish, acting body may be present in this particular curare, it has not been proved that a botanically identified Ececlus is used; it has not been separated chemically from any curare, although large numbers of experiments have been made with all sorts of curares during the last 40 years or so. Titanic spasms or convulsions are only described by the three authors who have already been referred to more than once. There is one exceptional case mentioned by Gubler (p. 28) where small doses of a Venezuelan curare caused symptoms indicating stimulation of nerve centers, large doses being required to paralyse the nerve ends - the very opposite to what occurs with most curares as what always occurs with curarins.

Absolutely conclusive proofs that the titanic symptoms produced by curare are due to curarin, and to this active principle (curarin) will presently be brought forward.

On referring to other accounts of the preparation of curare in different regions we find considerable differences.
a good deal of vagueness. We have no accurate knowledge therefore that curarin is the single active principle present, that the tetanus paralysis is produced by the same body derived from one plant. Experiments with crude curare therefore can give no satisfactory solution of the difficulty.

Perhaps the most accurate account of the preparation of any curare is that given by Schomburgk (18450). Even this is indefinite, for, in addition to 3 species of Styphnolobium, it is stated that 3 other plants were added, "which, to all appearance belonged to the same order as the Styphnolobium." It is impossible therefore to say that the curare of British Guiana is solely an extract from Styphnolobium plants. The results of any experiments with this curare also might fairly be called in question, on the ground that the three plants whose origin was only "to all appearance" identical with the Styphnolobium might contain some tetanising principle.

On the other hand it is improbable that the tribes once a vast region would add the same extra plants (tetanising) in addition to the essential one (paralysing) yet we find that all curares produce both paralysis and tetanus. It has been
further shows that the tetanising power of curare (with a small allowance in some cases in the dosage owing to the possible antagonistic action of some of the constituents) increases and decreases with its paralysing power. The same holds good with perfect precision in the case of curarin. We may therefore strongly suspect that the two actions are produced by an extract from a single bark by a single active principle.

All the evidence points to a strychnos bark as the basis of curare.

1. Strychnos Castelnaeana: (Kiddell) the basis of the curare of the Timanas, Oraros, Redas & Jaguars tribes in Upper Amazon District. Perhaps Strychnos de Castelnae. Plancheon (p. 491).

2. Bajo de Manaure, a kindseed of the Strychnos family, basis of the curare of the Maquisitaires and Aroxas in the upper Orinoco district. Humboldt & Bonpland (p. 579).


4. Rechamons Guyanensis (Aublet) or Strychnos Guyanensis (Martius) the basis of the curare of some Guianan tribes. Needham (p. 338).
5. *Strychnos toxifera* (Schomburgk) (Benth.) Hooker (p. 230)
6. *Strychnos Schomburgkii* (Molisch)
7. *Strychnos cagens* (Benth.)

Three of these species are stated by Schomburgk to form the basis of the curare of the Macauí Indians in British Guiana. Schomburgk (p. 144)

8. *Strychnos Crevaeusii* (Planchon) basis of the curare of the Assunquemés & Drios Indians in French Guiana. Found on the banks of the Parau or an affluent of the Amazon.

Brevané: p. 1023  Planchon (p. 693)

A number of experiments have been made with extracts obtained from the backs of South American *Strychnos* plants. The symptoms observed have been those ordinarily attributed to curare - paralytic symptoms only.

Schomburgk mentions an experiment made by his brother with the back of *Strychnos toxifera*. Part of a concentrated decoction was administered to cheliers (two) symptoms of poisoning after 5 minutes & death occurred in about half an hour. The symptoms are not described and nothing is proved except that the extract is a poison.
M. Couty et de Saavedra (1858) made experiments with an extract obtained from the bark of a common Brazilian Strychnos plant - *Strychnos triplinervia* (Martins). This plant is not known to enter into the composition of any curare. It was found to have a feeble curare action. In December 1888 I obtained a quantity of the bark + wood of this plant through the house of Dr. Schuchhardt, Geissen. I found the extract to have a very feeble paralysing action, which was not exactly of the same character as curare, for often great depression, depression + weakness occurred, without complete paralysis of motor nerve ends. Also (p607) also found that *Strychnos triplinervia* acted in this manner. The first mentioned authors remark (p688) that "Jeus ces extraits ont été beaucoup moins toxiques que le curare" + as this is the case, it was obvious that this plant was not the true basis of curare, & its pharmacology was not investigated any further.

M. Couty et de Saavedra (1867) also made some experiments with an extract from parts of *Strychnos backeiana* (Medel) & found that it had a curare action
(p.179) "De Strychnos caesalpinae, quoique plus
riche que le Strychnos triplicium, est moins
actif qu'on aurait pu le supposer, et le
produit d'bullition de 50 gms. de fragments
de tige n'ont pas suffi à euratiser un
chien de petite taille."

It must be noted that this extract was
with an extract obtained from the wood.
To judge from the results obtained by (p.1028)
Dobell, these parts of the plant, most
probably the bark, are much more active.
In the case of Couty et de Jacqal's experiments
with this species of Strychnos there seems
to have been only some simple observations
made to determine that the extract acted
like curare. Simple observations on warm
and cold blooded animals cannot possibly
demonstrate the tetanising action of a
body which has both a tetanising and a
paralysing action, where the latter is the
stronger of the two.

Dobell (p.646) also states that
his experiments with extracts from the
South American Strychnos plants show that
they act as paralysing but not as
tetanising poisons. "J'ai experimenté
avec des extrait de toutes ces Strychnees.
Leur action physiologique est la même;
elles n'agissent pas comme tetanisant
"... contrairement aux Strychnées de l'Asie..." Les Strychnées américaines du Sud agissent d'une façon identique. Elles ne sont point tétanisantes."

The "I have experimented" of Roberts, uncompromised by any explanation cannot by any means be accepted as proving that these Strychnos banks "are not at all tétanising". We have no guarantee that his method of experimenting would overcome the difficulties of the investigation, or that, when paralysis was observed, anything further was specially looked for, in place of being assumed to be absent.

Crevaux\(^57\) (p703) states that the single bark of the Strychnos Castelnau of the upper Amazon yields a curare 10 times more active than that of the Indians.

He also states that the active ingredient of the curare of French Guiana is, among many plants, for the most part useless, a new Strychnos (Crewxii) (named & described by Planchon\(^53\), p693). Its mother extract has a weaker action than that of the Strychnos Castelnau of the upper Amazon.

Here again we can find no record of any experiment other than some simple test to show that the extract is a poison causing death after the manner of curare. There is
nothing to show that the extract has not a tetanising action which is concealed by the paralysis.

Lastly, Villiers' (p. 63) states that extract derived from the bark of the *Styphnolobium de l'Orinoco* (Plancheon) brought from the Amisco district in 1887 by Crevaux has the chemical physiological actions of ecuraine. No experiments are described. Although Villiers' paper is headed 'Styphnolobium toxiferum,' the bark he examined was not, got from ecuraine, nor does it agree with the *Styphnolobium toxiferum* (Berth.) described by Saker (1861) by Plancheon (p. 60). It is evidently closely allied to it (Plancheon p. 30).

Through the kindness of Mr. Holmes, the curator of the Pharmaceutical Society's museum in London, I received in January 1889 a small quantity of undoubted *Styphnolobium toxiferum* bark, sufficient however to settle this complication.

It is admitted that a *Styphnolobium* bark is the basis of ordinary ecuraine. It is also admitted that the active principle obtained from crude ecuraine is chiefly ecuraine. Therefore we may expect that the bark will yield ecuraine.

But I have shown that ecuraine produces both paralysis obtains. It must be an error (if this is true) on the part of these authors to say *Styphnolobium* bark...
which have a truly curare like paralyzing action, have only this action & do not cause tetanus.

In the first experiments the strychnos toxifera bark obtained from Mr. Hobbs was treated in the simplest manner. Two grammes were powdered and an infusion made with cold distilled water. After several hours it was filtered & a yellowish fluid was obtained having all the appearance of a solution of curarin. On evaporating some of the filtrate it acquired a distinctly bitter taste & on continuing the evaporation an amorphous residue was obtained of a yellow colour at first parts, but orange red when thicker. Here there among the yellow granules were some crystals (lime) more or less concealed usually with adherent granules. On adding some strong sulphuric acid to a portion in the cold a distinct reddish violet colour was produced.

On determining the poisonous activity of the filtrate it was found that about the twenty thousandth part (50,000th) caused in a frog (pithed) weighing 26 grammes distinct weakness in 15, & complete reflex paralyses in 45 minutes. Larger doses caused paralyses in a minute or two and this was found in a protected frog to be due to action on the endings of motor nerves. As the motor paralysing dose of curarin for a frog of this weight
is 26.3 x 0.0000028 gm = 0.0000736 gramme
this x 20000 = 0.14720 gramme which would
show nearly 1% per cent of curarin per the
2 grammes of bark a quantity which of course
could not be obtained chemically.

The remaining 2 grammes of bark
(I could only obtain 4 grammes) I sent
to Professor Bohm at Leipzig. A few
weeks later he wrote confirming the
extraordinary activity of the specimen,
stating that it contained at least from
10 to 5 per cent of curarin

A frog was now prepared by tying
the heart, abdominal aorta & one aorta % at
the heart as described in the experiments on
Curarin

 damp 89.  Experiment by injection into an artery
11.35 am.  About 1/50% of filtrate = 0.00008
gramme Curarin made up to 5cc. with water
injected into the united aorta
11.40  Occasionally a slight spasmodic movement,
otherwise quite quiet.
11.43  Injection of about the 50% of filtrate =
0.003 gm. curarin made up to 5cc. with water
11.45  Marked spasmodic movements of all the
unparalysed parts - especially the legs
11.50  Unmistakable tetanus the lower extremities
being absolutely, then a general spasm of the
unparalysed muscles is not present, individual
muscles or groups of muscles are attacked by frequent spasms. Reflex tetanus easily induced.

These results confirm the repeated several times but it is unnecessary to enter into details as the action of the extract was found to be identical with that of curarin.

I could get no crystalline to form from the chemical examination, so far as the small substance available would allow, showed the active principle to be identical with curarin. Rehm's conformation made this certain.

M. Sim Zhang, B. author of 'Among the Indians of British Guiana,' states that Strenchus toxiferus is to be found on the Demerara river in Demerara; he has written stating that he is forwarding a quantity of the plant. The chemical examination of such a mixture as crude curarin is exceedingly unsatisfactory; but there is now a prospect of obtaining proper material thus of getting rid of all unnecessary difficulties.
All suppositions and misgivings therefore as to the possible action on the
ceist of the active principles of plants
other than certain species of Strzybinsch may
be dismissed for a single Strzybinsch bark (S. c.)
is sufficient to yield large quantities of
a curarin which is chemically pharmaco-
ologically identical with the pure
curarin separated from curare by
Bekm. The various conclusions in the
previous part of the paper have thus been further substantiated.

There is still a fourth series of
statements which declare that curare contains
Strzybinsch combined with some organic body
in the form of an ammonium salt.

Valentin (p. 382) believes that curare
contains Strzybinsch because, in the
first place, it is derived from Strzybinsch
plants (Schomburgk) & in the second place,
because it gives reactions which show that
it contains the alkaloid (Wittstein, Koch).
The first reason we have seen to be quite in-
sufficient. The second is only partly acceptable,
some of the reactions are similar to Strzybinsch but
others are not. & many chemical features are
very different. Valentin at the same time
asserts that no variety of curare gives reflex tetanus like strophanine does. We have seen that this is the opposite of what may be found when it is searched for. Valentin refers to the local twitchings which may precede the paralysis in curare poisoning as "wechselkrämpfe" which are always weak, soon disappear, and are not true tetanic spasms. Such local twitchings do occur, but their appearance is not at all regular, they are quite different from the true tetanus which can be observed later.

In explanation of the fact that curare contains (according to Valentin) strophanine yet that its administration does not produce tetanus, it is suggested that the strophanine is combined with some organic body after the manner of methyl or ethyl strophaninum but that curare is not actually methyl or ethyl strophaninum, since the muscle curvatures and symptoms after poisoning with these substances do not quite correspond with those obtained after the administration of curare.

Gubler 55 (p.392) makes a statement somewhat similar in kind. He suggests that the reason why curare, a substance certainly derived from the
Strophine family of plants in South America, acts as a paralysing and not as a tetanising poison, is that methyl or ethyl strophinine is formed, that these as shown by the experiments of Cumm-Brown & Fraser & Dolget & Caleurs are paralysing but not tetanising poisons. Ploss in les remarquables résultats obtenus en France et en Angleterre à l'aide des dérivés de la strophidine résultats dont personne, à notre connaissance, n'a vu jusqu'ici l'idée de s'emparer pour en faire l'application à l'interprétation des effets du curare. Ainsi les propriétés de l'ethyl-strophidine offrent une singularité analogie avec celles du curare. Elle nous apparaît dans les expériences de Cumm-Brown et de Thomas Fraser aussi bien que dans celles d'André Caleurs et de Dolget. Bartholomé 53 (1558) pratiquement exprès the same idea (1581) "that a remedy obtained from members of the strophinos family of plants and a paralyser in action should antagonise strophidine is a remarkable fact. In the process of preparation employed by the Indians it is in a high degree probable that methyl strophidine is formed. This substance, as was originally shown by Cumm-Brown & Fraser, is a paralyser and acts precisely like curare."
Now, in answer to the statements of these authors, there is to begin with no reason why every member of the strychnos family of plants, more especially plants growing on different continents, should produce the alkaloid \textit{strychnine}. The well-known fact has already been referred to, that different species of the same genus may produce different alkaloids, which may agree or differ more or less in action.

What is this preparation which it is suggested may result in the formation of a methyl \textit{strychnium} body?

Here are six accounts by eye witnesses of the native preparation of curare.

1. \textit{Condamine} \textit{Mém. de l'Acad. des Se.} \textit{t. XIIi}


3. \textit{Catalano} \textit{Relation d'une expé. dans la part ecu. de l'Amér. de l'Oré} \textit{1823 p. 1830.}


6. \textit{In Humb.} \textit{Among the Indians of (British) Guiana.} \textit{London. 1883 p. 311.}

These accounts agree in describing the process.
as the concentration of an infusion or decoction made from a number of barks. Humboldt and Schomburgk give very complete details. The essential barks were pounded, packed in a slaty funnel, and cold water allowed to percolate slowly through the mass. The yellow colored percolate was then concentrated by gentle boiling for a number of hours. Various barks were added from time to time to the evaporating liquid. The completion of the concentration was decided by the bitterness on tasting. A second filtration was then carried out. As the concentrated watery extracts are not adhesive, a glutinous vegetable juice was finally added, so that the poison would stick to the ducts. The addition of this glutinous matter changed the color of the fluid to black. Further concentration was obtained by exposure to the heat of the sun (Schomburgk).

The accounts of some of the early writers are evidently absurd. Foreign matter - ferrets' teeth - has been found in some curares, and it is not unlikely that some tribes through custom, superstition, or ignorance add various unnecessary substances.

While admitting, therefore, the possibility that the original active principles of the barks might be decomposed more or less by the process of concentration.
less by the boiling, it is difficult to see in such elementary processes the high probability of the formation of the hypothetical methyl or ethyl strychninium, and perhaps it is not surprising to find that such a body is not described by the practical chemists who have examined curare. According to this idea the strychnos bark to begin with must contain strychnine, but we have seen that the simple addition of some cold water to a little of the bark of strychnos toxifera gives a solution having an intensely active paralysing action on motor nerves, which is not the primary action of strychnine. The basis does not therefore exist from which the methyl or strychninium could be formed.

Neither does it exist ready formed in the bark, because the chemical properties of the alkaloid obtained from it are evidently not those of methyl or strychninium, the curarin being a yellow amorphous substance, not forming crystalline salts, paying with strong sulphuric acid in the cold a red-violet colour (Bocni, 1870) whereas the methyl strychninium differs entirely on these points (Stahl, 1852).

But what is equally conclusive is the physiological test. The minimum
paralyzing dose of the sulphate of methyl strychnium (a very soluble salt & much more active than the iodide - (Esmm Brown \textit{Brazil} \textit{p} 160) was found to be 0.0008 gramme for a frog weighing 314 grammes (\textit{Puechmann & Leos} \textit{p} 206) that is to say 0.000024 gramme for gramme weight of frog. But the same quantity of pure curarin produces tetanus and \underline{850} times less has an equal paralyzing effect.

Methyl \& strychnium salts are generally considered not to act on the spinal cord, whereas it has been proved that curarin does act in a strychnine like manner. One cannot use this as a further argument against the supposition that curarin is methyl \& strychnium for reasons which will presently be brought forward.

The whole of the first group of statements which were opposed to the conclusions I brought forward have therefore been shown to be imperfect, incorrect or purely theoretical.
The second kind of difficulty which stands in the way of a clear view of the actions of this alkaloid is the view, or rather the prejudice, that a substance having a strong paralyzing action on motor nerve ends does not act as a tetanizing agent on the cord & sacral area. This is very well shown by Inetuto's conclusions on Akakya (M'bondo) bark, which was found to cause tetanus in small doses & paralysis with larger. It was held therefore (Fulpanp621) that if principles were present, one causing tetanus & the other paralysis. Niekel & Schlengenduff showed on careful analysis that its only active constituent was strychnine which produced tetanus or paralysis according to the dose.

Now the fact that strychnine produces tetanus in small doses & paralysis of the motor nerve ends like curare in large doses has been repeatedly demonstrated since 1844, but has not even yet received adequate recognition by most pharmacological writers. Wood (p337) gives most of the bibliography.

If a perfectly pure strychnine salt causes tetanus in small doses & paralysis of motor nerve ends in large, the paralysed part being in violent tetanus, there can be no objection to the alkaloid of
another species of Strychnine causing paralys
in small doses & tetaus in large doses
(The unprotected parts being paralysed.)

Kolliker\(^3\) (p.339) strongly contests the
view that strychnine has any action on
motor nerve ends, but, as he does not give
the details & dose in any experiments which
prove the contrary, we must assume that he
employed relatively small doses.

E. May\(^2\) (p.313) & Pelikan\(^6\) (p.408) speak
of strychnine & curare acting in an opposite
manner, but, obviously, they only speak
of the prominent actions of the poisons.

Rumour & experiment do not give 
proof to show that strychnine
does not in large doses paralyse the
motor nerves.

Vallot\(^8\) (p.315), in a paper in the Journal of
Physiology for 1880, states that he has
satisfied himself that strychnine does not affect
the motor nerves, but his experiments only
justify the conclusion that a dose which causes
convulsions is fatal does not cause paralysis
of motor nerves. But this is a small dose!

There is unfortunately no record of the doses
employed, a circumstance which makes the
conclusion. Vallot therefore concludes that
there is no similarity between the actions
of curare & strychnine—an altogether

incorrect conclusion.

As none of these authors state that they have
tried large doses, these conclusions have really no value on this question.
Now, the proofs on the opposite side are absolutely conclusive, and as the matter is very important in connection with any companion of curarin, I shall as briefly as possible go over the evidence.

The following authors believe that the larger doses of strychnine paralyse the ends of motor nerves in a manner identical with curarin—or at least that large doses paralyse.


*Lecons sur les Subst. ton fléchir.***


(Consider Vulpian p. 571)

All the evidence produced may be summarized in three sets of experiments.

1. See the sciatic artery and vein in one extremity of a frog, and—what the paralyzing action may be very clearly seen—inject subcutaneously from 0.005—0.01 gramme of sulphate
of strychnine. In a few minutes convulsive movements appear in the whole body, but quickly diminish in all the unprotected parts, and by 10 minutes or so have entirely ceased. The protected leg however continues in a state of violent tetanus. All parts are equally connected to the nerves centres. On stimulating the sciatic nerve in the unprotected extremity with a moderate electric current no movement follows. The muscles everywhere contract purely on direct stimulation.

(2) In one sciatic artery & vivis and cut both sciatic nerves & poison as before. Conditions occur for brief period in all parts except the lower extremities where nerves are divided. After 10 minutes or so there is complete cessation of movement. On stimulating the divided nerve on the unprotected side no movement follows, but on the protected side stimulation causes active movements. Both nerves are equally cut off from the nerve centres, but only only on one side from the local action on the nerve ends. The muscles contract freely on direct stimulation.

3) Cut one sciatic nerve without protection of any part. After poisoning every nerve on electrical stimulation is found to be paralyzed.
It is clear, from these experiments, that this peripheral paralysis has nothing whatever to do with any imaginary paralysis passing from centres to periphery or from muscular exhaustion from continued tetaus. As, when protection is not afforded, it occurs equally whether the nerves are connected with the centres or not. When protection is afforded, the nerves left intact, the protected part continues in a state of tetanus while the rest of the body is paralysed.

In warm blooded animals the ends of the motor nerves *the inhibitory fibres* or action of the vagus on the heart can be paralysed by injecting a large dose of strychnine (about 0.05 mg per kilo in the dog) into a vein (Richet & Jullian). The convulsions quickly disappear, and artificial respiration requires to be maintained to prevent death, just as in curare poisoning. The heart and circulation continue good for few hours. When artificial respiration is stopped, the heart continues to beat for several minutes *as asphyxia causes no convulsions.* On reopening the Sciatic nerves *vagus is not the least effect is produced by strong electrical stimulation but the muscles readily contract on direct stimulation.* Some writers say that the *vagus is not paralysed, but no doubt it is a question of dose.*
When artificial respiration is not maintained, death immediately follows the injection of a large dose (Spitzka cited as confirmed by Mied, p. 300). Wood remarks "such doses probably kill the nerve centres just as large doses of a cardiac stimulant overwhelm and paralyze the nerves." The experiment referred to however gives us no information as to the condition of the nerve centres. Kulpian and Richet's experiments show that the heart circulation continue good after the motor nerve ends are completely paralyzed. The experiments on protected frogs show, further, that the protected part continues in active tension long after the unprotected parts are paralyzed. The immediate cause of death therefore, after the injection into a vein of a very large dose of strychnine, is paralysis of motor nerve ends.

Eventually such doses would probably paralyze the nerve centres after the stage of excitation had passed away, r, in any case, must prove fatal.

Curare and strychnine have often been contrasted as examples of substances derived from the same botanical family but possessing totally different actions. Some attempts — notably that by Martin-Magon and Guissone — have
on the other hand, been made to show that
t heir actions are very similar, but this view
has practically met with no acceptance owing
to the number of objections left unanswered.

On comparing them carefully however we find that they agree very closely
in the quality of their actions, but differ in the order of symptoms, and in the doses
required to produce them. Small doses
of strychnine of 0.0001 gramme produce
tetanus in small frogs without any
paralyzing action on the ends of motor
nerves, while 0.0001 gramme of curarin
produces complete paralysis of the ends of
motor nerves without any tetanizing action
on the cord. On the other hand, in
protected frogs, 0.001 gramme of curarin (less)
causes immediate paralysis of the unprotected
parts, while when fallacies are avoided, violent
tetanus of the protected parts, while 0.005
gramme of strychnine causes violent tetanus
of the protected parts, and complete paralysis
of the motor nerve ends of the unprotected
part.

It has therefore been shown that the
difference between the pharmacological actions
of the two alkaloids is in some of its
main features, rather a quantitative than
a qualitative one. An analogous case
to curarin has been brought forward, &
there can be no less theoretical objection to
the convulsant poison producing paralysis,
than to the paralysing poison producing convulsions.

there is no more ground therefore for
saying that, if sulphate of strychnine causes,
in large doses, paralysis of nerve ends
it must contain curarin, than that
curarín must contain strychnine, if large
doses cause tetanus.
The third, last kind of difficulty which throws doubts, of a theoretical kind, on the previous conclusions is the statement that strychnine, the type of convulsant poisons, loses this characteristic action when it is converted into a saturated ammonium base by the addition of iodide of methyl. If this is so, then it seems a little strange, that a saturated ammonium base like curarin, the type of those poisons which paralyse the ends of motor nerves, should at the same time be a convulsant poison of considerable activity.

Even the simplest compound ammonium salts have some special properties of their own, apart from that paralysing action on motor nerve ends which Crum Brown and Fraser showed to be so general. For example, tetra-methyl-ammonium in a dose of 0.02 gramme of the iodide causes, in a few minutes after the subcutaneous injection, stoppage of the heart (chiefly the ventricle) in diastole; an action which is apparently due to stimulation of the inhibitory apparatus, for it is prevented by the administration of atropine.

Tetra-ethyl-ammonium iodide has not this action, but causes, before paralysis
in a dose of 0.02 gramma in the frog, marked fibrillary muscular twitching, which is apparently due to a preliminary stimulation of the nerve ends, for it occurs although the nerve trunk is divided, but does not occur when curarim is administered.

In some of the modified alkaloids, where it is unnecessary to carefully consider the changes introduced by the increased paralysing power, the protection of parts, alterations in the time of appearance, order & strength of symptoms, the fatal dose \( \frac{1}{3} \), it is easy to determine that there are characteristic actions - for example, methyl atropin dilates the pupil, just as atropin does. (Crum, Brown & Travers 65, 740f.)

It is necessary therefore to examine carefully the nature & completeness of the experimental evidence upon which is founded the prevailing view, that strychnine, an alkaloid well known to have a powerful characteristic spinal action, loses this on the addition of methyl, & retains only its paralysing action.

An analysis of this evidence shows that such a wide conclusion is not quite warranted, and there is ground therefore for testing its correctness.
Stahlpeimüttt prepared experimentally with the methyl strychninium salts in 1859. He found (p. 623) that doses which were very large, when compared with active doses of strychnine, (0.15 gramme in a rabbit) were without poisonous activity and concluded thence that the new body was inert.

Schroff experimented in 1866 with the nitrate of methyl strychninium. He found that it caused symptoms of paralysis of a curious like kind. Reflex tetanus sometimes occurred at recovery, (De Vir- 

num's Direct) and Schroff sought to explain this by the supposition that strychnine was liberated in the body by the decomposition of the methyl strychninium salt.

I have not been able to get the paper by Schroff for further reference.
Crum Brown & Fraser made in 1867 an extended series of observations on the ammonium salts obtained from some of the more important alkaloids. These observers found that the methyl & ethyl strychnium salts were much less poisonous than strychnine, that a true curare-like paralysis of the ends of motor nerves was the cause of death, & not tetanus. Doses less than the minimum complete paralyzing dose were not fatal, & caused a greater or less degree of paralysis but no convulsive symptoms.

On pages 195, 196, & 197, the authors give a summary of their experiments with the iodide, nitrate and sulphate of methyl strychnium, and with the hydrochlorate of ethyl strychnium.

The recorded experiments with these bodies are 34 in number, of which 25 were on rabbits, 2 on cats, 1 on a dog and 6 on frogs.

In estimating the value of experiments, as a demonstration of the fact that a poison which paralyses the ends of motor nerves has or has not, in addition, a convulsant action on the eard, several circumstances must be considered. If the toxic substance...
has both actions, then, it is obvious that
simple experiments on warm-blooded
animals can only demonstrate the
convulsant action, when it is prior to,
or when it is produced by smaller doses
than the paralysing one—as in the case
of strychnine itself. Then, as in the
case of eurain, the reverse condition
exists—The paralysing action being produced
by smaller doses, and being an earlier
symptom than the convulsant action.—
The paralysis in simple experiments in
warm-blooded animals necessarily causes
death; & in any case prevents observations
on the convulsant action.

Paralysis of motor nerve ends is
admitted to be the earliest & strongest
action of methyl strychnium salts & the
experiments clearly prove this; we have only,
therefore, to see if their experiments likewise
prove that no later convulsant action occurs.
In this direction we can at once, out
of the 314 experiments recorded, set aside
the 28 on warm-blooded animals. These
consisted in the administration of the methyl
strychnium, by the stomach & subcutaneously,
to rabbits; & terminated in the mere or
less speedy death of the animal, when the
minimum dose which paralyzed the motor
nerves was reached.

Our whole attention may therefore be
directed to the 6 experiments on frogs,
for the full pharmacology of the substance
can only be arrived at by special
experiments on cold blooded animals.

As 2, out of the 6 recorded (XXXVI + XXXVII)
experiments on frogs, were on unprotected
animals, only the nature of the evidence, (for
the mere number of experiments, of the same
kind, is not of very great importance, r no doubt
more experiments were performed than are noted.)
afforded by the other 4 need be considered.

The bearing of the experiments on
any spinal action of methyl strophantidion
salts depends entirely on the different details
of dosage, duration of observations + r I
shall therefore quote them at length, for the
purpose of drawing special attention to their
very brief duration, + to the important fact that
the poison was administered only by subcutaneous injection.

Page 162 " The sciatic artery and vein
were tied at the knee of a frog + one-tenth
of a grain of sulphate of methyl strophantidion
dissolved in distilled water was injected
under the skin of the back. Eight minutes
afterwards the frog was lying in a perfectly
flaccid state, + in ten minutes irritation of
any portion of the skin produced energetic movements of the tied limb below the points of ligature, but nowhere else. The sciatic nerve of the untied limb was now exposed and stimulating it with a weak interrupted galvanic current, movements occurred in the tied limb only; not the slightest effect occurred in any part to which the poison had access. At the same time the muscles were everywhere active and freely contracted when directly stimulated. The sciatic nerve was then exposed in the tied limb above the points of ligature, and stimulating it energetic movements occurred below the knee of that limb, nowhere else. The heart was at this time acting at the rate of 50 per minute.

This experiment was repeated with one grain of iodide of methyl strychninum, the same general results were obtained.

The evidence thus acquired in favour of an action on the peripheral terminations of motor nerves was strengthened by a modification of this method of experiment.

The right gastrocnemius muscle of a frog was carefully dissected from its connections, cutting that its origin & insertion, & the nerve fibers entering it were untouched that all its bloodvessels were ligatured. One-tenth of a grain of sulphate of methyl strychninum dissolved in 5 minims of distilled water was then injected under the skin of the back. Twenty minutes
afterwards the animal being in a perfectly relaxed and motionless condition the two sciatic nerves were exposed. Galvanism of the left produced no movement in the left limb, while galvanism of the right produced energetic movements of the right limb which were seen to be due solely to contractions of the right gastrocnemius muscle the other muscles remaining motionless. At the same time direct stimulation by galvanism caused contractions as freely in the poisoned muscles as in the non-poisoned gastrocnemius.

In an experiment in which iodide of methyl strychnium was substituted for sulphate the effects were the same. This concludes the 14 experiments.

It is impossible to read this account without observing that it was the action on nerve ends with which the authors were most, if not entirely, occupied. In the first 2 experiments the sciatic nerves were exposed 10 minutes after the dose was administered, and after the necessary stimulations the experiment was as described concluded. In the last 2 experiments, one muscle was protected 4 and 20 minutes after the dose was administered the experiments were as in the first two concluded. The authors have noted, on pages 195-196, that in these
experiments the duration of the symptoms was not specially observed.

In the first experiment the frog weighed 53·4 grammes, received therefore about 6 times the minimum paralyzing dose. In the second experiment the frog weighed 39·8 grammes, received about 7 times the minimum paralyzing dose of the sulphate.

Brun, Brown & Fraser have demonstrated very clearly, by these experiments, the great change which the addition of iodide of methyl has produced in the symptoms — paralysed of the ends of motor nerves being prominent.

This, so far as I can judge, was the main object of their research. One cannot, however, conclude from these experiments, that methyl styphehum salts do not act upon the cord at all, for we do not know what the action may be after rather more than 10 minutes, where one leg is protected, or 20 minutes or so where one muscle is protected.

A tetanizing action may exist, but be delayed for some reason. The question therefore of the action on the cord, beyond the initial stage of the poisoning, is an entirely open one; there is no experimental evidence on the subject. No other method of experimenting besides subcutaneous injection has tried. This, as we have seen in the case of one body acting on motor nerve ends, (Curarin), is not free from fallacies.
Salkel and Caheur (p. 904) experimented in 1868 with methyl strychnine salts. They found that pure preparations could be obtained as iodide of methyl acted readily strongly (p. 110) on strychnine. Small doses caused paralysis in unprotected frogs in 15 to 30 minutes. Larger doses produced (p. 905) tetanic symptoms in the protected part "quelque temps après que les nerfs moteurs ont perdu leur excitabilité." These tetanic symptoms were worse of much shorter duration than those produced by strychnine.

Brunn Brown and Fraser (p. 560), in criticizing this conclusion, suggest that the convulsive movements could readily be explained by the presence of strychnine, as an impurity, in the methyl strychnine salt. They remark, further, that some of the specimens first employed by them were found to give similar symptoms. This was due to the presence of strychnine as an impurity, for on treating the salt a second time with iodide of methyl, the convulsive symptoms were removed.

No doubt, if a methyl strychnine salt causes tetanic symptoms soon after an ordinary dose has been administered subcutaneously, it is impure. Brun Brown and Fraser do not mention any new experimental evidence, apparently therefore,
refer to what they have already shown in the
refinements that have been examined at length,
that is to say, that a pure methyl strychnium
salt does not produce tetanus, at the
commencement of its action after subcutaneous injection.

Assuming that Jefrey's calcium methyl
strychnium was impure, it is yet to be
ascertained how a pure specimen does act,
at later stages of the poisoning.

Buchheim (1856) experimented in 1870
with a large number of substances which
acted as paralyzing agents on motor nerve
ends. Among these were methyl and ethyl
strychnium salts, which were found not to
cause tetanic symptoms.

On carefully examining the experimental
evidence, it is at once evident, that it can
have no weight in this particular question,
being evidently in the full belief that there
was no action on the cord.

They found, in experimenting with the
sulphate of methyl strychnium, that the
minimum paralyzing dose for a frog weighing
34 grammes was 0.0008 grammes, and that
when 0.01 grammes was administered the
paralysis was not recovered from for 8 days.

Nine experiments on frogs are described
with this salt, but as no part was protected,
they give no information as to the state of the
cord, but only show a more or less rapid motor paralysis, with recovery after some hours or days.

There are 11 recorded observations on ethyl strychnium. Of these 10 were on unprotected frogs. Here again nothing further could be learned than that convulsions did not precede paralysis or follow recovery.

The remaining experiment consisted in the ligation of the tissues of one extremity, with the exception of the sciatic nerve. On injecting 0.01 gramme subcutaneously in a frog weighing 47.5 grammes paralysis occurred in the unprotected parts after 20 minutes! On stimulating the sciatic nerves active contractions occurred only in the protected leg.

No observations are recorded later than the onset of complete motor paralysis.

The observers have only reaffirmed the paralysing action on motor nerve ends.

Buchheim found that the sulphate of ethyl strychnium had a minimum paralysing dose about 3 times larger than that of the methyl salt. They occasionally observed, 5 or 6 hours after the administration of incomplete paralysing doses of the former, some titanic
like symptoms. This was not observed after the methyl strychnium salt. They therefore attributed the increase of reflexes to the presence of strychnine as an impurity. — a practical point about which one can offer no opinion, & which a supposition, however convenient, did not settle.

Valentin experimented in 1873 with an iodide of methyl strychnium obtained from Hückege & a sulphate of methyl strychnium obtained from Fraser.

He found, before recording the muscle curves, that the iodide (p.229) in small doses, in unprotected frogs, caused feeble strychnine-like spasms. Larger doses caused paralysis.

The sulphate (p.342) in a dose of 14 mgm. caused complete paralysis in 9 or 10 minutes, without any appearance of spasm. Then the poison acted more slowly or feebly (1.5 mgm.) it produced symptoms resembling the iodide, the frog shivering, after it had made a strong voluntary movement, a spasm in the posterior extremities, & finally, paralysis sets in the voluntary movements disappearing before the reflex. The muscle curves rather resembled those of eranized muscles.

If even small doses of preparations,
which were presumably pure, produced in unprotected frogs, before paralysis, symptoms pointing to a spinal action; and, if my analysis of the important papers on the subject is correct, then there are strong reasons for making special, more extended observations with preparations, which cannot possibly contain strychnine as an impurity.

There is another paper by Faure 81 on Methyl strychnine. Attention is chiefly directed to the action on the vagus and the spinal cord is not specially referred to.
Before making experiments on the animal action of methyl strychnium, every care was taken to ensure that the preparations used were pure.

The first specimen was very kindly prepared in Oct. 1887 by Professor Boehrni.

An iodide of methyl strychnium was obtained after the method described by Stahlschmidt (p. 511). As iodide of methyl acts very strongly upon strychnine, (Bolger: Calzoni, p. 1108) an experienced chemist should by this process alone obtain a pure preparation.

The iodide of methyl being employed in excess, some precautions were taken to ensure purity. The iodide (2.5 gm.) was mixed with recently prepared chloride of silver (1 gm.) and water (100 gm.) warmed on the water bath. After filtration the iodide of silver was washed several times with warm water and the filtrate evaporated on the water bath until crystallization had begun. All these crystals were rejected, as strychnine is not readily soluble in water and mixed in the iodide of methyl might be expected to be got rid of.

The residue was then crystallized from absolute alcohol in which strychnine is almost insoluble. The crystals shone under the microscope as fine glistering needles. They were readily soluble in water.
After the experiments with this preparation were concluded I got a specimen prepared in April 1889 for purposes of comparison.

Mr. Dott, for Messrs. Duncan & Blackhart Co., Edinburgh, made an Iodide of Methyl Strephehmine for me. It was arranged that every possible precaution should be taken to secure the purity of the salt — such as the use of excess of Iodide of Methyl, the addition of an alkali to it to prevent the possibility of any salt of Strephehmine being formed.

I do not know if finely powdered Strephehmine was treated with the Iodide of Methyl, as in Stahlschmidt’s process, or whether the Strephehmine was dissolved in chloroform, when the Iodide of Methyl added.

When unsaturated alkaline solution was rendered alkaline by means of Sodium Carbonate, allowed to stand for several hours, not the least trace of a precipitate formed, when shaken well with chloroform, the alkaline solution yielded only a trace of substance which was methyl Strephehmine.

As the Iodide is not fully soluble in water a sulphate was prepared by me by mixing a hot solution of Sulphate of Silver with a solution of the Iodide, precipitating the excess of the silver salt with Sodium Chloride.

After evaporation the Methyl Strephehmine
sulphate was extracted with absolute alcohol, or obtained on evaporation in the form of tufts of fine needle shaped crystals.

On dissolving 1.5 grammes in 10 c.c. distilled water (5% sol.), \( \frac{1}{4} \) rendering the solution alkaline with sodium carbonate no precipitate formed, but on the second day a violet red colour began to appear (the hydrate, hydrated \( \text{pH} \)). The greatest quantity of strychnine which 10 c.c. water (cold) could dissolve is about 0.0017 gram. Therefore, assuming that this was present, means were taken to get rid of it, by repeatedly shaking up the solution (1.5 grammes in 10 c.c.) with chloroform, in which strychnine is much more soluble than in water. After each washing the chloroform was fully separated from the watery layer, with the last washing (30 c.c. chloroform), the adjacent part of the watery layer was run off also. The watery solution was then filtered, neutralized with dilute sulphuric acid, evaporated to dryness and extracted with a small quantity of absolute alcohol. Tufts of fine needle shaped crystals were obtained, with a fine powder. When evaporation was rapid, this product weighed 0.25 g gramme.

I can see no possibility of the least trace of strychnine being present, or if so, since the active dose of methyl strychnium sulphate is 0.001 to 0.005 grammes it must be infinitesimal in amount. Therefore devoid of pharmacological action.
The first experiments with the chloride of methyl strychnine consisted in the subcutaneous administration of a somewhat smaller relative dose than those (0.001) employed by Cum, Brown, & Fraser.

Experiment in frog 37 grammes. Temp. 22° C.

Immin after administration: Injection of 0.003 gr. in 3 c.c. water into ant. thoracic sac of frog weighing 37 grammes. The post. extremities extended as usual.

8. Head rests on the table & respiration falt.

10. Respiration ceased. Coma reflex absent. Heart 40 per minute - strong. Then laid on back, the legs kept extended without movement.

14. On pinching fingers 4 or 5 times the lower extremities were moved vigorously. The frog turned over, the paralyzed body & ant. extremities being jolted round.

20. Reflexes much lessened, but good.

30. Reflexes can hardly be obtained. About 4-0 pinches both light & severe, all on the protected non-paralyzed parts caused no movement, just as often occurs with curare, when when it seemed as if the animal was paralyzed, a vigorous reflex movement occurred.

50. During the last 30 minutes not the least spontaneous movement has been seen, & no stimulation has been applied.

55. 1 pinch followed by a single extension of the legs.
56. 2 pinches
57. 6
58. 3½ columns to the right, not legible.
Reflection much more acute now. Every stimulation, especially if sudden, has slight, acts no matter where applied. The reflexes are in the form of sudden jerks, not complete extirpations, of the whole lower extremity, & are best seen on the side opposite to where the stimulus is applied.

80. Drops of water allowed to fall from a height of a few inches on to any part of the body causes, time after time, an instantaneous jerk in the protected extremities. The reflexes are not easily exhausted.

100. Heart feeble. Reflexes exceedingly acute.

102. Reflex tachys lasting 3 or 4 seconds.

105. Several spontaneous jerks & tachys of legs.

110. Distinct tetanus of lower extremities on tapping the head with the forefists. On repeating the stimulation several times the tetanus becomes very brief & feeble. Heart very weak.

This experiment shows that, although motor paralysis was complete in the unprotected parts in 10 minutes, there was not the least sign of exaggeration of reflexes until more than an hour after the poisoning; but on the contrary they were depressed—Distinct reflex tetanus was not obtained for nearly 2 hours & weakness quickly set in.

On administering 0.01 grammes to a frog weighing 43 grammes—a larger relative dose than that employed by Dean Brown
Fracto - motor paralysis followed in about 3 minutes in the unprotected parts. After 30 to 35 minutes after poisoning the reflexes were depressed, but were vigorous when they occurred. They then rapidly became more and more acute and 55 minutes after poisoning marked tetanus could be induced. Half an hour later, there was complete exhaustion and only feeble twitches followed stimulation. The heart as observed on the thorax was extremely feeble.

The experiments with the sulphate led to similar results, but the spasmodic symptoms which followed the subcutaneous injection of 0.005 gramme seldom developed for an hour or an hour and a half after. Signs of weakness soon appeared. While in some experiments the tetanus was quite unmistakable, in others it was feeble and could, without this check, have been easily overlooked. On examination, it became clear that the fallacies which occur in the examination of curare by subcutaneous injection are common, trace or less, to those bodies which paralyse the ends of motor or probably raus-motor nerves.

In all cases the action of the heart seemed greatly affected.

On exposing the heart in a winter frog.
Weighing 25 grammes, it was found beating at the rate of 32 per minute, the energy was good. It was of considerable size during diastole, being well filled with blood. On injecting 0.005 grammes methyl strychnium sulphate dissolved in 0.2 cc water into the thigh (intension), the heart, after a few minutes, began to show some diminution in size. After 15 minutes the heart was much smaller than action feeble. After 30 minutes the diastole was exceedingly small, so that little or no blood could be circulating; the action was very feeble. After 40 minutes the heart was obviously empty, it resembled the heart of a frog which had been bled to death, or whose complete vasomotor paralysis had been caused by the destruction of the spinal cord. After a little more than an hour the reflexes in the posterior leg became decidedly spasmodic. At the same time in another frog, the heart was ligatured, the brain destroyed, the spinal cord exposed at the middle of the back. For 10 minutes the animal remained quite motionless with its legs. The reflexes were then tested, found to be quite simple. On applying 1 cc solution, containing 0.002 grammes of the sulphate, to the cord no effect followed for nearly 7 minutes when sharp tetaurus set in. During the next 30 minutes
the faintest touch to any part renewed the spasm.

At this time a third frog, a solution (25 cc.), containing two or three milligrammes of the sulphate, was injected directly into the acetabulum after the preparation described in the experiments with curarin. V-marked tetanus immediately followed and continued for about three quarters of an hour.

The spasmodic symptoms appeared then in the first case after an hour, in the second case after 9 minutes and in the third case almost instantaneously. The delay, therefore, in the appearance of tetanus after subcutaneous injection of moderate doses, is not due to a tardy action of the poison, but is due, as in the case of curarin, to an impairment of the circulation, and consequent imperfect diffusion of the poison and imperfect supply of oxygenated blood to the nerve centres.

It would seem, therefore, that tetanus is not described as a symptom which is produced by methyl V. strychnium salts, because (1) attention has been chiefly directed to the action on motor nerves; experiments have been terminated before the concomitant action could manifest itself; (2) a spinal action has not been anticipated, and therefore been specially looked for; (3) the impaired absorption and diffusion has been overlooked.
These results show clearly that pure methyl strychnine preparations have a distinct convulsant action on the cord, which is not due to the presence of strychnine, which could not be demonstrated by the brief experiments of the various writers who came to a negative conclusion.

A theoretical objection to the statement that curarin acts in a strychnine-like manner on the cord has been anticipated.

The addition of iodide of methyl to strychnine does not, therefore, as has hitherto been believed, produce any true change in the kind of physiological action, but only to alter the order and intensity of symptoms: the actions, thereby the symptoms, dosage, mode of death. In methyl strychnine, the paralysing action of strychnine on the cord is delayed and diminished, the paralyzing action on motor nerves hastened and increased.

By artificially giving to strychnine the constitution of an ammonium base its characteristic actions are not destroyed, but the order and strength of the symptoms are approximated to curarin, which is perhaps what might be expected on theoretical grounds, since that alkaloid is an ammonium base belonging to the same botanical genus.
Somewhat analogous results to those which in this instance follow the process of chemical addition occur when the process of substitution is employed, as when the H in morphine (C₁₇H₁₈NO₂-OH) is replaced by an alcohol radical (C₁₇H₁₈NO₂-OC₂H₅) = coduphine (Ermauc).

There is a marked decrease of the narcotic action, & an increase of the tetanising action in Codine (C₁₇H₁₈NO₂-OCH₃) or methyl morphine. The effect substitution besides derived from morphine gives tetanus with small doses, but paralysis with large doses (Rochefontaine cited by Schroeder 1877).

In addition to the chemical change having modified the narcotic & tetanising actions the action on motor nerve ends is also affected. This action with very large doses of morphone is just perceptible, but with a large dose of codeine in a 9oz (0.01 gm) it is quite distinct.

Although I have not made many experiments with codeine, yet the paralysis of the unprotected part of the body seemed quite undoubted, the protected part showing tetanic sympotms.
It is hardly necessary, before concluding this part of the examination, to refer to the 
bymeone statement by Bernard (p. 312), that Curare 
paralyses the nerves from the periphery towards 
the centres & strychnine from the centres to 
the periphery. This was obviously due to a 
miinterpretation of experimental facts, since, 
in a frog one sciatic nerve was cut & the 
animal poisoned with curare, the cut nerve 
lost its excitability quicker than the uncut nerve, 
whereas in the case of strychnine the uncut 
nerve lost its excitability first.

In the case of Curare, section of the sciatic 
nerve produces vaso motic paralysis of the 
bloodvessels of that limb, which will generally 
therefore (Kulpain p. 493) receive a greater share 
of Curarin, containing blood than the limb with 
the intact nerve, since, as has been seen, the 
circulation is slowed. The arteries narrowed at the 
beginning of poisoning with small doses 
(Kelleher p. 511) (Ellis).

As the total quantity of curarin necessary to produce paralysis of the whole 
body is only about 0.00001 gramme in a 
frog of 25 grammes weight, it is evident that 
even a very slight difference in the quantity 
of blood entering the two limbs is 
sufficient to account for the earlier depression 
paralysis of the motor nerve endings in the
limb in which the nerve is divided.

Many hours after poisoning with large

doses of curarim. Long after the spinal cord
was paralyzed, I have repeatedly found that
stimulation of the nerve trunks caused active
contraction of the muscles of the protected part
when these had been adequately protected, whereas
the poisoned nerve trunks were not injured at
the seat of the operation by exposure or pressure.

In the case of strychnine, the earlier
paralysis of the nerves on the undivided side
is only apparent, via due (Martin Magon Russell
p. 104, sep. 84) to the exhaustion of the muscles on
that side from tetanus, because, when finally
the stimulation of the undivided nerve produces
no effect while the divided nerve acts, electrical
(weak) stimulation of the muscles on the undivided
side also fails but acts for hours on the
unparalyzed muscles of the other side. (Kalecki, 1903)

Kulekst (1913) in addition suggests that the
violent muscular contractions may favor the
paralyzing action of strychnine on the endings
of the nerves in some way. But this action
is trifling with small doses of strychnine and
the condition is sufficiently explained by the
muscular exhaustion.

This is not a true difference therefore
between curarin and strychnine.
The experimental evidence has therefore led to the following conclusions:

1. That the sensory nerves are not paralysed by curarin, but that the subcutaneous administration of small doses to protected intact frogs causes very generally an early state of (voluntary?) inhibition leading to considerable irregularity and depression of the reflexes, often closely resembling paralysis of the eard or sensory nerves.

2. That the spinal eard is not directly paralysed by curarin, but after the administration of large doses by subcutaneous injection an actual depression of the eard occurs, usually after 2 or 3 hours not from any action of the poison on it, but secondary to collapse of the circulation through dilatation of the bloodvessels.

3. That curarin on the contrary acts as a convulsant poison. Evidence of this is from time to time obtained before the indirect paralysis which follows the subcutaneous administration of large doses occurs, but complete uncertainty exists as to the quantity which is absorbed reaches the eard. When this failure is avoided in experiments, an increase of reflex excitability and tetanus is invariably observed. This conclusion is confirmed by special experiments on warm-blooded animals.
14. That similarly any specimen of crude curare has in definite doses, in addition to its well known paralysing action on the periphery of motor nerves, a very distinct weaker tetanising action on the cord.

5. That this action of curare is not due to the presence of the active principles of unknown plants, because the simple watery extract of the bark of the Strychnos toxifera (Benth) of Schomburgk (British Guiana) readily causes both paralysis of motor nerve ends and tetanus. Nor is it due to the presence of strychnine, but to a body which is identical with the alkaloid curarin obtained from curare.

6. That the differences pharmacologically between the pure strychnine of the East Indian and African Strychnos barks, the curarin of some of the South American Strychnos species are quantitative rather than qualitative—both producing tetanus and both paralysing the ends of motor nerves by the same kind of action but in opposite doses.

7. That the experimental evidence upon which is founded the general conclusion that pure methyl strychninium salts do not act as convulsant poisons is only sufficient to warrant the limited conclusion, that tetanus does not appear as the first symptom as
in strychnine poisoning is not the cause of death. More extended observations show that a marked convulsant action, which is certainly not due to the presence of strychnine as an impurity, follows from \( \frac{3}{4} \) to \( 2 \) hours (according to the dose) after the paralysis of the motor nerve ends. When the poison is injected into the aorta tetanus immediately follows. The delay in the appearance of symptoms, the early appearance of weakness of the cord, is due apparently, as in the case of eurain, to paralysis of the circulation.
The action of Curarin on the Blood Pressure.

An experimental research on the action of pure curarins on the circulatory apparatus should prove of some value and interest because uncontrollable disturbances and obscurities in the results of experiments do appear in the employment of crude curarins in physiological researches.

A clear rule for the action of curare could not be laid down definitely whilst the poison itself remained a variable factor, and it was impossible, when an unusual symptom was described, whether it was really an action of the active principle of the drug which had been overlooked by previous observers, or was due to differences in the composition of the curarins. The absence of any accurate system of dosage.

The observations that I have made are not comprehensive enough to decide all the problems presented but perhaps the most important points have been investigated.

In the year 1863 there appeared almost at the same time the researches of Kraube and von Beyer on the action of the arrow poison on the circulatory organs of warm-blooded animals.
Draube experimented on dogs and found that with the vagus intact injections of 12 milligrams of curare into the jugular vein caused a rapid diminution of the blood pressure and an increase of the pulse rate. The two changes compensated each other when the artificial respiration was regularly kept up. When the vagi were cut before poisoning the injection again produced a fall of blood pressure but now a slowing instead of a quickening of the pulse. These changes compensated each other after a time.

von Bezold, who experimented on rabbits, summarizes his experiments as follows: that, on cutting the vagi and sympathetics the injection of small doses of the arrow poison caused an increase of the blood pressure from 100 to 160 mm. and an increase of the pulse rate from 19 to 25 in 5 seconds. Later injections lowered the blood pressure to 50 mm. The cardiac contractions to 19 in 5 seconds. In this condition no rise of blood pressure followed stimulation of the spinal cord at the neck. After first dividing the spinal cord at the neck, the injection of small doses of curare produced a slight increase of blood pressure and quickening of the heart. Later, on increasing the dose, the opposite occurred.
Stimulation of the spinal cord after poisoning with small \textit{and} medium doses still produced a considerable rise of blood pressure even though the vagi were already paralysed.

Long afterwards (1849), curare was specially employed in some physiological observations on the innervation of the blood-vessels and some very interesting statements are made as to its actions.

Two of these incidental references are of considerable value in view of the results of my own experiments.

In a paper by Fatschmburgher & Dehne, the following passage appears (p. 157) in the introduction to the experiments: "It may be recorded thus—

All animals were without exception curarised, so that all spontaneous respiratory movements were suspended.

The artificial respiration was taken exactly by the beat of the mitrormone. As is known, there is a curare which like strophcrine acts as a stimulant on the centres; we therefore try an injection of the curare, the blood pressure being already recorded on the cylinder. If the blood pressure rose immediately after the injection then this curare was useless \textit{to us}, but if it sank then it was suitable. With the curare of the first kind one does not obtain a regular tracing and cannot tell whether the features are independent or appear as the result of influences. But in spite of..."
good curare. There are rabbits, which on the other hand are so sensitive that one cannot obtain a regular tracing; such animals cannot be used. There are large French rabbits, especially young animals.

In another part of the same paper, the authors directly attribute certain symptoms to a strychnine-containing curare. The stimulation of the centres does not only show itself in waves; strychnine containing curare produces a continuous heightening, changed form of the curve; pointed tips, large oscillations (vagus pulse) appear. Thus, in this case are not only the centres for the bloodvessels stimulated but also the vagus centre (Fig. 22).

Bülbützka Heidenham (p. 54) in the course of experiments in the same direction in 1878, observed in many cases during the action of small and medium doses of curare in rabbits, marked and long continued rises of blood pressure in consequence of exceedingly slight stimulation of the skin (blowing of the breath 38) while strong and painful stimulation of the skin produced no effect. They thought, on first seeing such results, that the curare contained strychnine, but found that four different sorts of curare had the same action. A. H. did not think that the
cause of this strong increase of blood pressure lay in psychic influences, because the same phenomena appeared in rabbits in which the large brain was separated by an incision from the deeper parts—the optic lobes—the two pedunculi cerebri being completely divided at the anterior margin of the pons.

Therefore appeared that it could be nothing else but a reflex stimulation of the vaso motor centres for no such effects followed in non eunarcised rabbits.

Most authors consider that curare does not directly affect the heart, but Regel (1881) and Hufnagel especially draw attention to the fact that a large dose of curare may stop the heart. Hufnagel cannot explain this because as a rule the heart seems unaffected. This symptom is considered in treating curare.

The condition of the vagus nerve during curare poisoning has been investigated in detail by Böhm and his experiments are exclusively on cats. 

1. They show that, after the inhibiting function of the vagus is paralysed, further stimulation produces a quickening of the heart's action through the accelerator fibres which still remain active.

Different authors have made observations on the action of curare on vaso-motor nerves.
Pulfrich (1829, 1830) found that the vaso-motor nerves were only slightly weakened by curare, if excessive doses were not employed, so that one could obtain all those results which could be obtained through experiment on non-poisoned animals. The vaso-constrictor and dilator nerves continue active, and reflex vaso-motor actions can be studied after the motor nerves are paralysed. Pulfrich could only destroy their action (vago-sympathetic brachial) in dogs after exceedingly large doses, doses which readily paralysed the vagus action on the heart.

Sachet (1827) found that when the nerve was poisoned with curare it lost its power of quickening the blood stream almost at the same time that it (sciatic) loses its action on the muscles. The curare paralysed the dilator nerves but left the constrictors intact. He also mentions that Grof "found that a dose of curare just sufficient to prevent muscular contraction, although it did not entirely stop the action of the chorda on the blood flow in the sub-mammary gland, yet greatly diminished that action. He further mentions Eckhardt's statement that stimulation of various parts of the eard produces no action, whatever, as soon as sufficient curare has been given to just paralyse all muscular action, but, instead, that there is a diminution of flow from the eustachian surface of the ceroid carina during the stimulation"
Bernstein, on the contrary, observed in circulating blood through the extremity of a dog just killed by curare, a strong quickening of the blood stream when the periphery of the sciatic nerve of that leg was stimulated. He considered it probable that a dilatation of the vessels of the skin might account for this result differing from that obtained by Yackell in his experiments on the muscle vessels. He also considered that no contraction of vessels occurred (p. 599) resulting of the blood stream — the immediate consequence of the nerve stimulation in the living animals — because the experiment was not under the same conditions as in life.

Vulpian (p. 301) states that he has made many experiments on deeply curarized animals, where, on stimulating the peripheral end of the divided sciatic nerve with a very strong faradic current, a diminution or cessation of the haemorrhage occurred from a wound in the foot without any muscular contractions in the limb — showing therefore a constriction of vessels. On stopping the stimulation, the haemorrhage recommenced, and again ceased on resuming the stimulation.

Robert (p. 105) found, as in Bernstein's experiment, that the stimulation of the sciatic nerve produce, when curarized blood was contracted.
through the hind of a dog an increase of the blood stream. When blood was circulated through the posterior extremity of a dog, even through a horn of a sheep's uterus, 2 curare added, a strong quickening of the blood stream followed.

The experiments by Waters (p.367) show that, when a frog is fully paralyzed by curare, stimulation of individual spinal nerves in the frog with a weak interrupted current caused distinct constriction of bloodvessels in particular areas of the esophagus, stomach, intestines.

Brodick, Warren" and Ellis" (p.37) have applied the plethysmograph to the study of the vasomotor nerves in curarised animals. Their experiments show that when curare is employed, the effects of the stimulation of the peripheral end of the divided sciatic depend, not upon the action of this dose of the poison on the nerves, but upon the character of the stimulation "slow rhythmic electrical stimulation" of the nerve causing in the cat a rapid dilatation of the vessels, while "shocks of a greater degree of frequency cause an immediate contraction."

Cauty & Faden" state that the fall of blood pressure which occurs after large doses of curare is due to a paralisis of the striated muscles of the vessels.
Period of injection of 1 cc of 005 g. solution

Exp. III  Rabbit  2.150 kilo
0.007 grams previously administered.
I shall now state the results of
of my own experiments on the action
of pure curarin on the blood pressure. The
action on the vasa moter cærulea in rabbits is especially interesting.

The injection of rating solutions of curarin
into the blood-vessels (either an artery or a
vein) of rabbits, cats or dogs causes as
a rule an almost immediate fall of
blood pressure. Successive injections
during the same experiment produce the
same result. The amount of the depression
is inconstant & especially in rabbits it
may be followed by an immediate rise
above normal.

When the dose is small or medium
(1 to 20 times the minimum paralysing dose)
this fall of blood pressure is temporary &
the original level of pressure at least
is usually recovered in from ½ to 10 mm.

When the dose is very large 50 to 100 times
the minimum paralysing dose) the immediate
decrease of pressure is marked, of long
duration & the original level of pressure
is not usually regained.

The minimum complete paralysing dose
for the rabbit by intravenous injection was
about 0.0002 mgr per kilo of body weight, but the
action of the minimum dose was very brief.
After 0.0003 - 0.0005 grm. the diaphragmatie
movements reflexes returned in 10 to 15 min. on an average. After 0.001 grm. in 15 to 30 minutes— with doses of 0.001 to 0.005 grammae in from 30 to 90 minutes longer.

Some examples of the fall of pressure are given below.

Table I

<table>
<thead>
<tr>
<th>Animal</th>
<th>Amount (in mg)</th>
<th>Pressure of Injection</th>
<th>Time to reach Maximum</th>
<th>Pressure before injection in mm</th>
<th>Time after injection in mm</th>
<th>Time after injection in seconds</th>
<th>Time after injection in mm</th>
<th>Time after injection in seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>1.001</td>
<td>176 mm</td>
<td>122 mm</td>
<td>134 mm</td>
<td>2.5 minutes</td>
<td>3 minutes</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>2.002</td>
<td>156 mm</td>
<td>122 mm</td>
<td>3.4 mm</td>
<td>40 seconds</td>
<td>6 minutes</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>3.003</td>
<td>140 mm</td>
<td>54 mm</td>
<td>86 mm</td>
<td>3 minutes</td>
<td>164 mm Remainde for 10 min.</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td>Cat</td>
<td>1.001</td>
<td>164 mm</td>
<td>120 mm</td>
<td>144 mm</td>
<td>2 minutes</td>
<td>10 minutes</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>2.0015</td>
<td>140 mm</td>
<td>100 mm</td>
<td>140 mm</td>
<td>3 minutes</td>
<td>164 mm Remainde for 10 min.</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>3.002</td>
<td>140 mm</td>
<td>98 mm</td>
<td>62 mm</td>
<td>40 seconds</td>
<td>144 mm</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>4.001</td>
<td>125 mm</td>
<td>56 mm</td>
<td>76 mm</td>
<td>2 minutes</td>
<td>9</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td>Cat</td>
<td>1.001</td>
<td>180 mm</td>
<td>152 mm</td>
<td>28 mm</td>
<td>65 seconds</td>
<td>5</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>2.0015</td>
<td>167 mm</td>
<td>130 mm</td>
<td>37 mm</td>
<td>40 mm</td>
<td>8</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>3.005</td>
<td>155 mm</td>
<td>87 mm</td>
<td>68 mm</td>
<td>120 mm</td>
<td>Not recovered</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>4.001</td>
<td>135 mm</td>
<td>59 mm</td>
<td>76 mm</td>
<td>40 mm</td>
<td>2 minutes</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td>Dog</td>
<td>1.001</td>
<td>141 mm</td>
<td>146 mm</td>
<td>25 mm</td>
<td>120 mm</td>
<td>14 mm</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>2.005</td>
<td>158 mm</td>
<td>130 mm</td>
<td>28 mm</td>
<td>30 mm</td>
<td>1 1/2</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td></td>
<td>3.001</td>
<td>203 mm</td>
<td>100 mm</td>
<td>103 mm</td>
<td>80 mm</td>
<td>Did not again</td>
<td>164 mm</td>
<td>2.5 minutes</td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.001</td>
<td>125 mm</td>
<td>98 mm</td>
<td>Maximum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.002</td>
<td>121 mm</td>
<td>98 mm</td>
<td>Maximum raised mm lowered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.004</td>
<td>130 mm</td>
<td>93 mm</td>
<td>37 mm</td>
<td>120 mm</td>
<td>8 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.005</td>
<td>142 mm</td>
<td>81 mm</td>
<td>61 mm</td>
<td>60 mm</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.004</td>
<td>143 mm</td>
<td>45 mm</td>
<td>68 mm</td>
<td>60 mm</td>
<td>Not in drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.005</td>
<td>102 mm</td>
<td>23 mm</td>
<td>19 mm</td>
<td>120 mm</td>
<td>Not returned above 66 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In rabbits the initial fall of pressure may not be observed or be very slight when small or medium doses are injected very slowly. This fall of blood pressure immediately on injecting the poison appears under the following conditions:

1. When the injection is made into either a vein (jugular or saphenous) or an artery (upper end of carotid). It cannot therefore be due to any local action on the heart.

2. When the inhibitory action of the vagus is excluded, by previously dividing both nerves or by administering a paralyzing dose of atropine.

3. When all central influences on the heart have been removed by dividing all the nerves passing to it (depressor Y).

4. When the influence of the vasomotor centres is removed by previous section of the spinal cord at the neck.

5. When the central reflexes are paralyzed or depressed by a soporific e.g. ethane.

The cause of the passing fall of pressure would appear to lie therefore in the vessels themselves.

The character of the tracing during this temporary fall of pressure is shown on the accompanying tracings on the next page.
No. 1.

Cat.

Fall of pressure, sudden recovery, hard good.

 condemned before inj. of 0.001 ppm

30 seconds after injection to

Rectal temperature rise. Pulse

in 20 seconds.

2 minutes after injection

Pulse 87

in 20 seconds.

3 minutes after injection sudden recovery

of pressure with a faint convulsive movement.

2 minutes before inj. of 0.005

Pressure (150-75) 170 Pulse 97

30 seconds

3 minutes after injection

Pressure (185+75) 184 Pulse

30 seconds.
The primary fall of blood pressure produced by small, but morer paralyzing, doses, is accompanied in dogs, when the vagi are intact, by a distinct quickening of the pulse.

In the accompanying tracing a dog weighing 4.240 kilo received 0.005 gm. by injection into the external jugular vein. Two minutes before the injection the average blood pressure was 170 mm. The pulse at the rate of 117 per minute. Two minutes after the injection the average blood pressure was 159 mm. the pulse 138 per minute.

In the cat there is a distinct slowing of the pulse, as in the accompanying tracing, where, in a cat weighing 2.320 kilo, the injection of 0.001 gm. reduced the pulse rate from 258 per minute (blood pressure average 176 mm.) to 171 per minute (blood pressure average 62 mm.) 3 minutes afterward. On the pressure regaining its former level the heart rapidly quickened.

In the rabbit there is a marked slowing of the pulse, which is well shown on the accompanying tracing. This slowing of the pulse is independent of pressure, occurring whether it falls or rises. So long as the dose is insufficient to paralyze the vagus, in the dog and cat it seems to depend on the change in blood pressure as well.
In rabbits slight convulsive movements occur usually 15 or 20 seconds after the administration of small doses (0.01 - 0.03) of curarin. These variation has been discussed in the early part of the paper.

After recovery from the primary depression the blood pressure continues about its original level. In rabbits however, after small but motor paralyzing doses, it very frequently rises and may continue even considerably above the original level for a considerable time (10 - 30 - 60 minutes).

In experiments of long duration the pressure finally falls, apparently in consequence of secondary influences - e.g. loss of animal heat - rather than any direct action of curarin.

When somewhat large doses of curarin are administered the vagi are quickly paralyzed, the rate of the pulse varies after a time with the changes of tension produced by further doses, and with secondary causes.

The blood pressure tracing in dogs, cats, is, after the administration of any dose of curarin, very regular and usually free from unexplained variations. In rabbits however the tracing is only regular and constant after the administration of large doses. Small motor paralyzing doses of curarin cause immediately on
the injection long pointed waves (vagus waves) accompanied by a fall or frequently enough a rise of pressure. This is well shown in the tracings in the rabbit. Very soon after the injection an enormous increase of the excitability (especially reflex) of the vasomotor centres takes place. If from 1 to 10 minutes after the injection of say a milligramme of curariz, a slight stimulation be applied to the paralysed animal – such as puffing the breath on the fur covering the abdomen – then usually secured an almost instantaneous sudden enormous rise of blood pressure which continues on an average from 1 to 5 minutes. This sudden rise of pressure amounts in a few seconds to from 50 to 78 millimetres of mercury. The total pressure frequently reaches 170 to 180 mm., an exceedingly high pressure for a medium-sized rabbit. Then the tracing is quite a new marked rise of pressure occur from time to time, without any known stimulation having been applied. But if any great delay takes place, the symptom is readily produced by striking the table with the hand, finding the rabbit’s leg, blowing on or rubbing the fur, & when it is not especially looked for, it sometimes follows stimulation of the lower end of the vagus. The tracing during this period of excitement frequently shows great irregularities. If the pressure is not too high
| Exp: VII | Rabbit: 16 minutes after 0.001 gram
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Poles 30</td>
<td>m 10 sec</td>
</tr>
<tr>
<td>Poles 18</td>
<td>m 10 sec</td>
</tr>
<tr>
<td>N 50</td>
<td>m 10 sec</td>
</tr>
</tbody>
</table>

11. 59 cm  20  20


<table>
<thead>
<tr>
<th>116 mm</th>
<th>130 mm</th>
<th>180 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>91</td>
<td>89</td>
</tr>
</tbody>
</table>
the heart slows under the regulatory action of the cardio inhibitory centre— as for example in accompanying tracing, where, 10 seconds before the stimulation, the pressure was 116 mm, the pulse 80 in 10 seconds and 10 sec. afterwards, with the pressure 88 + 50 = 138 mm, the pulse was about 18 in 10 seconds, resembling a marked vagus type. In 2 seconds later, as the pressure still rose, the regulatory function of the inhibitory centre became weaker, and finally quite set aside when the pressure reached 180 mm (91 + 89), the heart beating at the rate of 445 in 10 seconds. The waves caused by the artificial respiration becoming very slight. In three successive periods of 10 seconds, the rate of the pulse was therefore about 30, 18, 145.

By 3 or 4, as the pressure gradually falls, the tracing shows sudden descending curves as the vagus action succeeds in asserting itself for a moment. After this, when the vagus action is no longer overcome by the high tension, there may be a considerable length of tracing showing a vagus pulse before there is a return to normal. It is possible that some of the breaks in the regularity of the tracing may be due to momentary failure of the heart from the excessive resistance. Some of the more gradual irregularities are certainly due to varying conditions of the vasomotor centres, because, when the vagus action is arrested by Atropin, the changes still occur though only...
Rabbit. Exp III. 11 minutes after 0.001 gramme Curarin
Nag i intext.

177 mm. 156 mm. 144 mm. 128 mm.
92 mm. 85 mm. 78 mm. 82 mm.

Head 18 in 20 sec.
Head 20 in 20 sec.
Head 60 in 20 sec.
Head 20 in 20 sec.

Exp IV. Rabbit. 14 minutes after 0.001 gramme Curarin
(1690 gramme)
to a relatively slight extent.

Examples of action of slight stimule in Rabbits completely paralysed by curarin.shock at the same time artificial respiration is kept up.

<table>
<thead>
<tr>
<th>Exp</th>
<th>Dose of stimul</th>
<th>Max. point of pressure before stimulus (drawn in figures)</th>
<th>Max. point of pressure after stimulus</th>
<th>Max. amount of rise</th>
<th>Time taken before max. point reached</th>
<th>Time before pressure returned to previous level</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>0.001</td>
<td>14.6 mm.</td>
<td>17.4 mm.</td>
<td>28 mm.</td>
<td>4 sec.</td>
<td>4 min.</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>14.2 mm.</td>
<td>18.4 mm.</td>
<td>20 mm.</td>
<td>3 sec.</td>
<td>3 min.</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>13.2 mm.</td>
<td>17.4 mm.</td>
<td>4.2 mm.</td>
<td>2 min.</td>
<td>2 min.</td>
</tr>
<tr>
<td></td>
<td>0.004</td>
<td>13.4 mm.</td>
<td>14.4 mm.</td>
<td>10 mm.</td>
<td>1 min.</td>
<td>1 min.</td>
</tr>
<tr>
<td></td>
<td>0.004</td>
<td>10.0 mm.</td>
<td>11.2 mm.</td>
<td>12 mm.</td>
<td>6 sec.</td>
<td>6 sec.</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td>6.6 mm.</td>
<td>no effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.0005</td>
<td>9.6 mm.</td>
<td>17.2 mm.</td>
<td>7.6 mm.</td>
<td>3 min.</td>
<td>10 min.</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>10.0 mm.</td>
<td>15.3 mm.</td>
<td>5.3 mm.</td>
<td>4 sec.</td>
<td>4 min.</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>8.0 mm.</td>
<td>9.2 mm.</td>
<td>1.2 mm.</td>
<td>1 sec.</td>
<td>1 sec.</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>7.8 mm.</td>
<td>12.6 mm.</td>
<td>4.8 mm.</td>
<td>3 min.</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>0.0025</td>
<td>9.8 mm.</td>
<td>12.4 mm.</td>
<td>2.6 mm.</td>
<td>5 sec.</td>
<td>continued</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>10.0 mm.</td>
<td>15.0 mm.</td>
<td>5.0 mm.</td>
<td>6 sec.</td>
<td>6 sec.</td>
</tr>
<tr>
<td></td>
<td>0.92</td>
<td>11.2 mm.</td>
<td>20.3 mm.</td>
<td>10 mm.</td>
<td>5 sec.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.30</td>
<td>no further rise</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.003</td>
<td>9.9 mm.</td>
<td>10.9 mm.</td>
<td>1.0 mm.</td>
<td>3 sec.</td>
<td>5 sec.</td>
</tr>
<tr>
<td></td>
<td>0.008</td>
<td>8.8 mm.</td>
<td>no effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>0.008</td>
<td>11.4 mm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.22</td>
<td>14.0 mm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.32</td>
<td>spontaneous res.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>0.0005</td>
<td>11.6 mm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0005</td>
<td>9.8 mm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>1.6 mm.</td>
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<tr>
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<td>0.005</td>
<td>9.8 mm.</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXXI</td>
<td>0.005</td>
<td>9.8 mm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Skin burned several times during first 3 minutes without effect.
Rabbit Exp. VII. Vagi cut. 0.001 gm. cocaine

Rabbit Exp. VII. Vagi fully paralyzed by Atropine. Dying 2 minutes at
administering 0.005 grms. cocaine.

Stimul. of right vag.
Stimulated for 9 sec.
Strength: 100 mm.
On the tracing opposite is shown a marked rise of pressure following a puff of the breath on the skin covering the abdomen. There is no sign after the administration of atropine of the marked vagus pulse shown in the other tracings.

Also on the tracing opposite is shown a considerable rise of pressure following the stimulation of one of the divided vagi (lower end) but without any of the marked irregularities already described.

These marked reflex spontaneous rises of blood pressure which in rabbits follow small paralysing doses of curarin are prevented by

1. Division of the spinal cord at the neck
2. The administration of a specific substance e.g. 0.5–1 gm. urethane
3. The administration of a large dose of curarin.

The tracings show only negative features on blowing on the skin. In the first case the influence of the chief vague motor centre is cut off; in the second its reflex excitability is blunted; in the third the reflex...
Sensitibility cannot manifest itself owing to the peripheral paralysis.

This increase of the reflex sensitibility of the vasomotor centres is a distinct feature therefore of the action of the active principle of curare. It is this which was described by Laucheberger & Reunka as due to strychnine containing curare which was the cause of the irregular tracing in "young French rabbits." It is also that which was correctly described by Heinshain & Grützner in curarized rabbits. I have only tried two sorts of curare in this direction, both gave the same results as with curarin.

Only a few experiments with small doses were made in dogs & cats, and no evidence of a quite similar action was obtained. If, as is probably the case, the vasomotor centres are only stimulated with a large dose the result could not well be observed on the tracing owing to the peripheral depression.

It is known that the inhibitory action of the vagus on the heart is suspended by curare. Several milligrammes of curarin (e.g. 0.005) usually cause this. Slight differences occur in different animals in the amount of resistance offered by the vagus to the
Right vagus stimulus: 100 seconds
- 50 mm current - one cell

Pulse 65 in 20 seconds
Pulse 63 in 20 seconds
Pulse 70 in 20 seconds
Pulse 69 in 20 seconds
Pulse 62 in 20 seconds
Pulse 60 in 20 seconds

Exp. III. Cat. after 0.008 grammes curarum

$1/2 (II)$
paralyzing action. The vagus of the rabbit seems most resistant, the cat least so. The dog intermediate.

After paralysis of inhibition in the cat, stimulation of the divided vagus trunk shows a distinct acceleratory action—for example

1. R. Vagus stimulation for 40 seconds with current of 60 m.m. (single somatic cell) in cat after 0.008 g.mn. curarin.

The pulse before stimulation was 56 in 20 seconds. The rate each 20 seconds during and after stimulation is noted below.

I (during stim.) 63. II (during stim.) 70. III (after stim.) 69. IV (after stim.) 63.

2. R. Vagus stimulation for 30 seconds with current of 65 m.m. (single somatic cell) in cat after 0.012 g.mn. curarin.

The pulse before stimulation was 63 in 20 seconds. The rate each 20 seconds during and after stimulation is noted below.

I 63. II 73. III 78. IV 69. V 68.

3. R. Vagus stimulation for 40 seconds with current of 40 m.m. (single somatic cell) in same cat.

The pulse before stimulation was 63 in 20 seconds.

I 67. II 78. III 75. IV 70. V 69. VI 63. VII 62.

Here was therefore a maximum increase of 15 in 20 seconds during the last period of stimulation or the 30 seconds following, when a gradual return to the former rate during the next minute.
In all three animals, the vagus nerve recovers its inhibitory action before the motor nerves distributed to the voluntary muscles.

Even after very large doses of curarine, of 20 to 40 times the paralyzing dose (0.01 - 0.02 ppm), stimulation of the sympathetic nerve in the neck causes in the rabbit dilatation of the pupil.

After the inhibitory function of the vagus is, for the time being, paralyzed in the rabbit (0.005 ppm) the stimulation of the central end of the depressor nerve lowers the blood pressure distinctly, indicating the reflex activity of the vas motor centres.

With this, smaller doses of curarine, stimulation of the central end of the divided sciatic nerve (reflex stim.) the suspension of the artificial respiration cause a distinct increase of the blood pressure. This only occurs however when the vas motor centres are not highly excited. The pressure is not already at a very high level. As the dose is increased to 0.01 - 0.03 ppm, more the pressure sinks, such stimulation no longer produces any effect.

If the spinal cord be divided in the neck in the rabbit between the 8th and 14th cervical vertebræ, a small or medium
Rabbit (1920 g), 3 hours after administration of 0.001 gm curare.
Cord previously divided in neck.

Period during which artificial respiration was suspended.
paralyzing dose be administered, direct stimulation of the spinal vaso moter enters by suspension of the artificial respiration causes a rise, sometimes quite marked, of the blood pressure. In the accompanying tracing, taken from a rabbit (1820 grammes) in which the cord was without any doubt completely severed in the neck, the pressure rose on stopping the artificial respiration for 40 sec from the very low average level of 30 mm. to about 90 mm of an average - 300 percent. The highest point being about 110 mm. The pressure did not again sink to its original low level for nearly 20 minutes. Blowing the breath on the fur & stimulating the upper end of the divided sciatic produced no effect that was visible on the tracing. This fact entirely agrees with the motor symptoms which have been very fully demonstrated on both frogs & rabbits.

I did not observe any spontaneous rise of pressure merely of note after the cord was divided. Schleisinger (cited by Mood, p.382) found that stroptomine produced a rise of pressure after division of the cord. But Klapp (cited by Mood, p.382) in such experiments did not get any rise of pressure.
Tracheal Hering curves

Cat. after 0.007 gramme curarine

Artificial respiration stopped.

Artificial respiration resumed.

(9) after 0.016 gramme curarine.

Artificial respiration stopped.

Artificial respiration resumed.
When the animal is completely paralysed by curarin, the artificial respiration is suspended, the activity of the vaso-motor centres is shown in the Traube-Hering curves. This is shown on the two accompanying tracings.

After the administration of small and medium doses stimulation of the splanchnic nerve readily raises the blood pressure. As the dose of curarin is increased up to 0.01 - 0.04 gm, stimulation has less effect. A still larger dose may be required before direct electrical stimulation of the cord fails to raise the pressure.

When very large doses of curarin are administered to the rabbit we obtain a perfectly regular tracing showing a low pressure, which, as the poison is excreted, shows a constant tendency to recover. If the large dose is administered at once, the pressure shows considerable power of recovery, but may soon even exceed its original level. If an experiment is prolonged, 1 dose after dose be given, until, after 1 or 2 hours a large total has been reached, the lowering of pressure is very great. Here is considerable loss of animal heat in
prolonged experiments, the low tension greatly diminishes the amount of urine secreted & so hinders the excretion of the poison.

During the period of low pressure produced by a maximum dose of ecurain, the following methods of stimulation fail to produce any alteration:

1. *Stimulation of the spinal end of the divided sciatic nerve, blowing on the face.*

2. *Suspension of artificial respiration until death has occurred.*

3. *Stimulation of the splanchnic nerves.*

4. *Stimulation of the spinal cord in the neck.* This is the last to fail. The heart meanwhile continues to act quite regularly, being only secondarily affected through the removal of inhibition, the alterations in tension.

Is the condition of the blood-pressure after large doses of ecurain due to a central or peripheral paralysis?

Any question of the low pressure being due to paralysis of the muscle of the blood vessels may probably be set aside, because, when a solution of chloride of strychnium is injected, there is an immediate rise of pressure, although, previously, stopping artificial respiration stimulating the upper end of
the injured sciatic nerve had no effect. Nor did the initial fall of pressure is not due to any paralyzing action on the vaso motor centres, but to a passing action on the vaso constrictor nerves. The effect of any injection however depends a great deal on the condition of the vascular centres at the moment. For example in Exp XI the gradual injection of a solution containing 0.001 gram eucarmin into the jugular vein of a rabbit produced a steady fall of pressure from 130 mm. to 120 mm. At this point, while the pressure was still falling the animal was quite paralysed, the breath was sharply blown on the foot covering the abdomen for a moment, the pressure almost instantly rose to 172 mm. Meanwhile the injection was being steadily continued and an additional 0.001 gram had no effect in lowering the pressure.

Had no stimulation been applied, the increased reflex excitability of the centres called into action, the pressure would probably have continued to fall. When the vasomotor centres are in a quiet condition, their tonic action on the vessels seems to be overcome by the paralyzing action of eucarmin on the vaso constrictor nerves as it passes along. As the poison reaches the capillaries, tissues and veins, comparatively fresh blood flows along the arteries, they contract again under the normal
action of the centres. Unless the curarin is actually in large quantity in the vessels, the centres can overcome, or greatly reduce, the peripheral paralysis if excited in any way to exert an extra influence. In a blood-pressure tracing taken from a cat, I refused to in the section on the early fall of pressure, the injection of only 0.001 gram caused a fall of pressure from 176 to 42 mm. Then, after three minutes, the pressure in a second or two regained its original level, the centres having probably been stimulated by the absence of blood.

In Exp. XXII the pressure in a rabbit fell on injecting 0.0015 gm. from 160 to 90 mm. At this point the medulla was stimulated with an electric current (the secondary coil being at 120 mm, the stimulus being readily felt on the tongue) and the pressure rapidly rose to between 180-190 mm. as a maximum. When the pressure was at 160 mm. 0.0085 gm. was injected rapidly, the pressure fell to 97 mm. A minute later 0.015 gm. was injected and the pressure fell to 50 mm. The cord was now stimulated with the same strength of electric current as before but no effect was produced. The strength of the current was gradually increased, and at 60 mm. (very strong) the pressure began slowly to rise, and after several minutes, reached 170 mm. On removing the electrodes the pressure did not fall, but kept for
a long time at this high level. Later it was shown that the centres were in a state of activity, because the stimulation of the upper end of the divided sensory nerve raised the pressure from 140 to 170 mm. The injection of 0.01 gm only lowered the pressure from 160 to 130 mm. It recovered almost at once. That the depressing action was not from the centres follows from the fact that strong stimulation of the eed had for a time no effect but that gradually a rise of pressure took place which was sustained by the centres alone.

In Exp. XXVIII the spinal cord in a rabbit was divided at the 4th cervical vertebra. Before the division the pressure averaged from 110 to 130 mm. After the division it fell to 63 mm. On injecting 0.02 gm curare hardly any change occurred in the pressure (11.22 am). On stopping artificial respiration (11.29 am) the pressure fell. The heart slowed. The upper part divided eed was then stimulated 5 times with electric currents (see cord 100 to 120 mm) which could be very distinctly felt on the tongue but no rise of pressure followed. At 11.41 am the pressure was 53 mm. When the electric current was increased in strength (to 70 mm) the pressure rose during a minute. Stimulation to 80 mm 2 minutes later it had fallen to 60 mm.
On increasing the current to the full strength the pressure rose slowly to 109 mm. During the next hour the pressure kept steadily at about 60 mm, but, at the end of that time, stimulation with the full strength of the current instantly almost caused a rise of pressure to 134 mm, with less tendency to fall again quickly.

In Exp. XXV the spinal cord in a rabbit was exposed at the neck, and electrical stimulation (see coil 120 mm.) raised the pressure from 113 to 180 mm. On administering 0.003 gm. curarin the usual reflex excitability followed, but the pressure did not reach a higher level than 170 mm. After 1 minute when a total of 0.013 gramme curarin had been administered stimulation of the cord with the same strength of current (120 mm.) produced about an equal pressure of pressure to stimulation of the upper end of the sciatic nerve and stopping of artificial respiration. On administering an additional 0.005 gm. the pressure was further reduced to 50 mm. Then all three forms of stimulation failed to act.

On doubling the strength of the electric current the pressure rose from 44 to 84 mm. while reflex stimulation was without effect. The effects of stimulating the splanchinic nerve were tested in 14 experiments.
In 2 experiments the nerve was exposed in the thorax, after removal of part of the 9th rib, 
& in other 2 it was exposed in the abdomen between the diaphragm & its distribution above 
the kidney. Before the administration of curarin stimulation of the splanchnic (divided) for from 
5 to 15 sec., with an electric current (see coil 120 mm.) 
called a rather sharp rise of pressure of 
20 - 30 mm. After the injection of .01 gm. 
the pressure quickly recovered, but after .02 gm. 
stimulation of the nerve with the same current 
as before either has no effect or only raises 
the pressure 3 to 5 mm. Minute after minute 
the same stimulation had more and more 
effect, the brief rise after each increasing 
to 7, 10, 15 & 20 mm. The next injection 
again depressed the pressure, & again the 
electric stimulation gradually had more & more effect. At the same time that 
the stimulation of the splanchnic after 
each injection began to have a greater 
effect, the general height of the blood pressure 
gradually rose, showing that the euniceeuse 
was active but could effect nothing as in the case 
of electric stimulation, until the vaso constrictor 
nerve recovered. Then stimulation of the 
splanchnic with this current raised the pressure 
about 10 - 15 mm. & stimulation of the other end 
of the splanchnic raised it 5 mm. The pressure was 70 mm.
Had the general pressure remained low it 
shown no recovery, while yet the same stim-
ulation of the splanchnic produced an effect 
which showed that the nerve ends had more 
or less recovered, there would have been 
some reason for thinking that the nerve 
centres were affected by paralysis.

Although the condition of the 
vascular centres after large doses of curarin 
is concealed by the weakness or paralysis 
of the pass motor nerves some information 
has been gained by these experiments.

It is quite clear that when even very 
strong electrical stimulation of the splanchnic 
nerve spinal cord in the rabbit fails 
to raise the blood pressure the nerve 
centres must also fail to overcome the 
peripheral paralysis even although they 
are in a high state of activity. When 
only electrical stimulation effects a rise of 
pressure nothing can be assumed as to the 
state of the centres, just as in the case of 
a rabbit which dies from asphyxia after the 
subcutaneous administration of curarin nothing 
can be assumed as to the state of the motor 
centres, although electrical stimulation of the motor 
nerves may still cause muscular contraction.

Electrical stimulation effects what the physiological 
stimulus of the living centres cannot. This
seems obvious enough, but is not always taken into account.

There is not only therefore no evidence of any direct paralysis of the vasomotor centres after large doses, but, on the contrary, the usual gradual recovery of the bloodpressure within a comparatively short time from the administration, coincident with the increasing effect of stimulation of the splanchnic nerve or spinal cord shows that the centres are in all probability acting very vigorously indeed.

After the great reactability caused by small doses signs of exhaustion of the nerve centres set in but there is no evidence of any primary paralyzing action.

The vasomotor nerves are fully paralyzed for the time at least by doses of curarin of 100 to 300 times the dose necessary to paralyze the moter nerves, this paralysis is much more quickly recovered from than that of the vagus or moter nerves.

It has already been shown that curarin acts on the moter centres after the manner of strychnine, and these observations on the vasomotor system in the rabbit add an additional and important proof.

One only requires to refer to the quotation taken from Latschunburger & Bakker's paper.
to emphasize the practical importance of this question in experimental work. Observations of the action of poisons on the heart might be made in curarized rabbits, where the excitability of the centres was prevented by some specific fee (curare?) which had no special action, whereas the vagi was not paralysed by a dose exceeding about 0.005 gm. curarin. Accurate observations in curarized rabbits on the vascular nerves of centres must be extremely difficult. Although small doses cause no obscurity by paralysing the ends of vas motor nerves, so rendering the vascular system irresponsible to stimuli from the centres, they produce as we have seen a condition of marked central excitability owing to the rabbit being very susceptible to the "stimulant" action of curarin. Then large doses are given the vas motor nerves are weakened more or less and are probably at the same time strongly stimulated by the centres. It is quite possible that disturbances solely due to curarin may be attributed to the drug under examination, since the source of error is not anticipated or recognised, although Guttmner, Heidenhain* have drawn attention to this action of some curarins.
The conclusion that curare stimulates vascular nerve centres just as it does motor nerve centres seems to be fully borne out by the symptoms produced in man. Liouville-Vécaris' experiments show, (Chapelle p. 1622) that, 15 to 20 minutes after the subcutaneous administration of small doses of curare, there is an increase in the rate of the pulse, quickening of the respiratory movements, a rise of temperature and increase of the secretions. Several times a marked rigor took place, at the end of an hour and a half at the most, blasted three hands at the most. The temperature in the axilla rose even to 104°F. The pulse from the commencement of the rigor was small and frequent, but, after the rigor, was bounding, the rate remaining the same or even increasing, the sphygmographic tracing showing the ascending line as nearly vertical, the summit twice the ordinary height. During the period of vascular excitement, increased temperature, the respirations perhaps reached the rate of 30 per minute. During the period of cold, the skin of the body was pale, but, after the rigor had passed, it became sometimes intensely red, the dyspnea being succeeded by sweating. The urinary secretion was nearly always increased, contained a
large proportion of sugar.

This is typically a vasomotor spasm, & quite agrees in kind with the symptoms that have been described in rabbits - the rise of external temperature, (due precautions being taken to prevent loss of heat during the preparation of experiment) (Kulfman p.376), the polyporia & myemia (Bernard p.342, Beckhard p.166, Vol.9) have been frequently observed. The rise of external temperature referred to however by Kulfman was associated with a fall of internal temperature was due to the vaso motor paralysis, artificial respiration, & other secondary (p.381) causes.

Röhrig & Züllig found that in unanaesthetised rabbits the regulation of warmth was reduced to a minimum. The oxidation processes in the muscles paralysed. They took the blood pressure before & after the poisoning & found that it was not particularly affected. As no continuous observations were made they could not observe the marked rises of blood pressure which occur from time to time, especially after slight intentional or accidental stimulation, during the first hours of the poisoning.

Züllig (p.527) observed later that when equal artificial respiration was kept up the only small doses of urease employed, the oxygen used & carbonic acid exhaled sank to one half
Solger found that the carbonic acid exhaled was even more reduced than this. Valentin observed in frogs that large doses of curare greatly diminished the quantity of oxygen absorbed by carbonic acid exhaled. Observations on animal heat in animals completely paralyzed are not comparable therefore to those made by Poiseuille on man, where the central influences were not neutralized or prevented. As the rise of temperature was not due to convulsions (spasms) it must have depended on a disturbance of a heat regulating mechanism, a conclusion quite in keeping with the central actions of curarin.

The rise of temperature in strychnine poisoning is usually considered to be due to the tetanic contraction of the muscles because it is prevented by curare or chloral hydrate. It may also be due to a central action, because the curare by the motor paralysis of the chloral by paralysis of the nerve centers prevents its development.

On comparing the actions of strychnine and curarin on the blood pressure, there is seen to be a close similarity in kind. The differences are the same as in the case
of the motor nerves. Small doses of strychnine act strongly on the vasomotor centres (0.005-0.01 m. rabbits) without paralysing the vasomotor nerves, while small doses of curarin (0.005-0.01) also stimulate the reflex excitability of the centres, but in dogs this action is not so marked. The same dose of curarin which affects the vasomotor centres paralyses the motor nerves, while the dose of strychnine requires to be increased about 150 times (0.59 grammes of hydrochloride m. dog weighing 12 kilos) before the animal is perfectly paralysed. In this condition the animal remains much as if it had been poisoned by curarin, strong stimulation of the vagi no longer stops the heart, when artificial respiration is stopped, after an hour or so, there is not the least movement, the heart still beats for several minutes. In these experiments, however, small doses of strychnine cause a marked rise of blood-pressure, but it is very noticeable that this rise is followed (Denny p. 189) by a fall in from 20 to 15-20 minutes below normal. Very often the tracing showed no rise of pressure in his experiments during tetanus. When curarin was administered to rabbits or dogs, this rise of pressure, on the contrary, showed after strychnine
marked and continued rise of pressure with no fall below normal for perhaps an hour. Here the stronger action of strychnine on the vascular centres was aided by the weaker action of the dose of curare employed, while the disturbing influence of the convulsions was foreseen. The rise of pressure in Dungs' experiments on rabbits \(\text{VI} \text{VII}\) from 100 - 156 mm 105 - 160 mm after slight stimulation could have been produced in a curared rabbit without strychnine, as has been shown in the training in the earlier part of this section.

Then very large doses of strychnine are injected into a vein the blood pressure first as in the case of curarin immediately falls. This has been attributed by Klappa (514 Wood p333) to an immediate (paralytic) depression of the vasomotor centres. Judging from the fact that with small doses the blood pressure only falls after a period of stimulation one would have fancied that an immediate fall was due to an action on the vaso motor nerves as with curarin.
A number of observations have been made on the polyuria glycosuria which follow the administration of small paralyzing doses of curarin.

When artificial respiration was kept up after these doses sugar quickly appeared in the urine. When periods of vascular irritability with very high tension were induced by slight stimulation of the skin, blood pigment blood constantly appeared in the urine in a short time. Its appearance coincided also with an increase in the amount of urine.

When the same paralyzing dose of curarin was administered but central stimulation was not prevented by a narcotic dose of ether, neither glycosuria or hemoglobinuria occurred while the quantity of urine was increased.

I do not propose further increasing the length of this thesis by adding the results of these investigations which are being continued. I would only add that so far as they have gone they seem to show that the great value of morphine, codeine in the treatment of diabetes mellitus may be due to a specific action on the medullary centre in those cases which are due to central disturbance. This may agree with the fact that the dose requires to be flushed often before much benefit is got. The reputation
of other medicinal agents pursue is of a
very doubtful character. Lactic acid
plus a purely animal diet is credited with
some success in this direction it is perhaps
worth noting that Lactic Acid has soporific
properties (Medical News II, 1892, 205). If this
supportive proves correct on trial then
soporific substances generally will benefit
diabetes, some which have no beneficial
stimulant action may be of decided
value.

The miraculous occurrence of blood blood
pigment in the urine after doses which permit
sudden severe vasomotor spasm, its absence
with larger doses, or when soporifics have
been administered is a very interesting fact.
It shows that in a perfectly healthy animal
with its vascular system paralyzed, a body
which does not act on the blood, but which
in a particular causes great reflex excitability
of the vas motor centres x periods of
tetanus of the vascular systems causes the
appearance of blood blood pigment in the
urine. The change in the urine was
most marked from 1 to 1½ hours after the
administration of a dose of several milligrams
It was only observed in the rabbit. On
section the kidneys were highly congested.
These experimental facts seem so
far as they have yet been followed out to throw considerable light on
the pathology of Paroxysmal Haemoglobinuria.
It is impossible to read the accounts of
this disorder without being struck by
the similarity it presents to a vaso motor
spasm— the fingers turn becoming white and
dead, perhaps with a distinct rigor, spasm over the
kidneys. In some cases the pulse seems to
fall to 50 or lower, in others to rise to 90
or 100 (Ferguson Medicine II p388).
Nervousness is said to play a part in the
disease, as it is seen particularly in persons
whose fingers turn cold on excitement (Ferguson).
Some hold that the disease is
due to the red corpuscles being broken up
readily by the action of cold on the surface
of the body, others that it is due to vaso-
motor spasm, others to this & renal
congestion.
I do not think that any experimental
demonstration has yet been given that
vasomotor spasm may cause the appearance
of blood in the urine.
If this on clinical examination
should prove to be the cause of the symptoms
in Paroxysmal Haemoglobinuria, the treatment
would obviously be to administer central
sedatives, since these prevent the reflex eceadability.
Another disease which is typically one of vasomotor spasm is 

Ague. Here also blood not infrequently appears in the

urine, extensive deposits of blood pigment (Melanuria) occur in different parts.

During the cold stage, when the vasomotor spasm is at its worst the pulse is

small frequent no treatment is usually adopted further than keeping the patient

warm and giving hot drinks.

It would seem only rational since the vasomotor centre is clearly greatly disturbed

to administer a central sedative. Just as the urethane prevents the development

of vasomotor spasm in the rabbit after

the administration of euramine we might

hope that the same results would follow

in diseases where the symptoms indicated

a similar disorder.

In this direction I shone a note in the

last edition of Robert's medicine 97 p 233 "Dr.

Mossman of Greenville U.S. informs me that

full doses of chloral, given just before the

reflex paroxysm of intermittent fever, will

prevent its occurrence." This is exactly

what one would expect since chloral prevents

the reflex excitability of the vasomotor centre.

It is recognized that emetics greatly

assist the action of quinine in ague.
Bromton p375 remarks "indeed cases of ague may be sometimes cured by the use of emetics alone without quinine, while quinine without emetics is not unfrequently of very little use in bad cases." The idea seems to be that the malarial poison is got rid off in the bile which is vomited. It seems to me much more likely that the central vasomotor disturbance is neutralized or prevented by the great circulatory depression caused by general emetics. Large doses of quinine make the heart depress the vasomotor centre, so an attack of ague can be prevented by a soporific dose of choral, just as it prevents vasomotor spasm in experiments on rabbits with strychnine or cocaine. It is a question if the beneficial action is not due to its depressing the circulation more or less. Additional support is given to the view that Ague should be treated by substances which prevent vasomotor excitability by the fact that "the mediamental use of strychnine causes fits in some cases resembling those of tertian ague" (Kew in ed by Bromton p374). Bromton suggests that these "true true Ague fits due to "Malaria, the action of which has been aided by that of strychnine on the vasomotor centre. The reflex excitability of the vasomotor centre
m. Ague has been observed—"a draught of cold air on the surface causing contraction of the cutaneous vessels shivering"; this opinion appears useful in such conditions probably by lessening the excitability of the vasomotor centre" (Bromb. p. 862)

I would before this have tried the effect of sedatives to the vasomotor centres in preventing or stopping attacks of ague and made observations on the pulse in Jaundice, Haemoglobinuria. The effects of similar treatment, but cases are rare. I hope soon to hear the results of observations made by others in this direction.
Curare.

Tulpian (1560-2) speaks of cases where curare paralyzed the heart, the auricles beating twice as fast as the ventricle, which was finally arrested from failure of the cardiomotor ganglia. He only once observed the heart to stop in a dog, but several times it occurred in rabbits. He could not understand this action as curare usually did not seem to act on the heart at all except through the vagus.

Regnard, Paul Buri, Cauty of Lucera (circa 1698) also noted that the quick injection of curare into a vein may lessen or even arrest the movements of the heart.

On several occasions I have observed the heart stop after small doses of curarin, but only during a period when there was an enormous & sudden rise of blood pressure. On exposing the heart the auricles were found beating the muscular substance of the ventricles showed a constant quivering movement. Both were filled with blood. With doses 50 or 100 times larger the heart never showed any sign of failure; apparently because the exceedingly high sudden changes in tension were removed.

Leaving out of account those cases of sudden cardiac failure, (mechanic) the circumstances that a curare may act on the heart is amply
I satisfactorily explained by an examination of curarin.

All the reagents for the alkaloids gave in watery solutions of curare voluminous precipitates. *Bahm* (p.176) observed in addition that metaphosphoric acid gave, in some curare solutions, a voluminous white precipitate which was found not to be curarin—though that alkaloid was usually mixed with it—but a new alkaloid which has been named curarin. *Bahm* found curarin in a variety of curares, but especially in those which left a considerable insoluble residue when treated with water. This residue contained much curarin. It is not very soluble in water, has a bitter taste, is precipitated by the reagents for alkaloids, as a colourless amorphous body, and, unlike curarin, it gives no characteristic reaction with concentrated sulphuric acid (*Bahm* p.179).

When treated with iodide of methyl, the action is found to be that of curarin. The poisonous activity of this new body was very great—1 mg. (0.0004 g) causing the death of a rabbit weighing 1.6 kilo. *Bahm* states, however, that 5 to 10 milligrams of curarin itself is without action in frogs or rabbits. He seems only to have directed his attention to a possible action on motor nerve ends (curarin has not this action) not observed therefore.
the change in the heart.

As Böhm's chemical examination of Curarin is not yet complete, as it is not yet certain that the specimen obtained from different curarized are quite pure, or identical with one another, it is only necessary to examine it sufficiently to show how failacess may arise in working with crude poisons or 

Exps. 1

Frog. 19th Oct. 1887. 11.1 curarin.

3.12 Head erected - regular, well filled, strong.

Rate 34.6 per min.

R. 37 per min.

Respiration of 100 on the minute in see into the throat.

R. 40

4.2 Injection repeated.

A part of the ventricle near the aortic bell bulges during systole.

14 " 4.3 The entire left side of the ventricle contract post - vasmus. The right side valve about red and distended.

17 " 30 Ventricle occasionally deeps with contraction in quite disorganised. Sometimes the contraction is segmental, at other times different parts of the ventricle contract quite irregularly. More regular contraction of ventricle. do.

21 Aumile 44 do.

23 " 4.2 Ventricule 34 do.

30 " 4.4 Ventrile 24 do.

41 " 4.1 Ventile 20 Upper half of ventricle contracts while the apical is bulged out and. During the diastole red lines appear across the ventricle.


Action of the ventricle precipitate.

During the experiment the respiration, reflexes were not affected, except secondarily through impairment of the action of the ventricle. The motor nerves did not seem to be affected. The muscles seemed weakened somewhat on direct stimulation. On 30th Oct., 21st Oct, and Nov., similar results were obtained.

6.30 p.m. Heart exposed. String, well filled regular

31. Rate 20
35. " 32
40. " 32
50. " 28

7.

By 0.01 . . See
10. ". . . .
25. ". . See
26. ". . . .
30. ". . Pause of the ventricle for 10 seconds.
35. Stopped: Occasionally the ventricle makes an attempt to contract.
40. Several drops of 1% solution of atropine caused no change. The respiration reflexes moter power continue good.

25th Feb.

10 a.m. Frag dead. Ventricle small rigid.

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10 a.m. 0.01 gramme in. See ratio injected subcutaneously in frag weighing 50 grammes.

12.30 p.m. Frag has gradually become weaker in its movements, more cannot recover when placed on its back. On exposing the heart it was found to be dilated, the vent. contracting at 8 the auricle at 9 per min.

1.10 p.m. Aur. 8 (table) Perf. 4 (tongue).

30. Aur. 8 Vent. 2 Neither auricle or ventricle contracted.

During diastole on mechanical stimulation the ventricle however after the mechanical irritation became small & contracted at the irritated part.

4. " " Stopped. For dead. By forcing blood into the ventricle it contracts but tends to remain contracted.

On exposing the sciatic nerve & stimulating it the muscles contracted fairly well.
Heart, exposed at 1.30 pm, appeared acting well.

4.30 P.H. 36
5.10 " 38
All parts of the ventricle do not relax at the same time. The systole is long but less perfect than usual.
5.15 " 34
The heart is in a state of complete but feeble peristalsis. The ventricle is always contracting but yet remains large and resists if emptied.
6.20 Vent. 10
The base of the heart contracts, but the blood is driven into the apex which is bulged out.


5.30 Heart 38 per min. Regular. Small.
Injects 0.005 gr. in 1cc into thigh.
6.30 Distinct peristalsis
7.30 Each powerful complete contraction is followed by 2 or 3 peristaltic contractions passing from base to apex and greatly impeding the circulation.

In blood pressure of rabbits the action of Currin on the heart was very clearly shown, although its subcutaneous administration in simple experiments produced no evident symptoms.

In the first experiment 0.244 gr. was injected into the jugular vein: the heart almost immediately stopped. In the second experiment 0.08 grame was injected into the saphenous vein, but the pressure fell to zero, the heart continued contracting for 14 minutes in a feeble irregular way, then stopped.
In 3rd experiment a distinct fall of
Mark 30 m 20 sec

Mark 61 m 20 sec
Pressure reliefing of the pulse followed each injection. The injections followed each other rapidly however so that the pulse had little opportunity of recovering fully, the pressure rising as in later experiments.

**Table on Exp. III** 2nd Aug. 1887

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<thead>
<tr>
<th>Dose</th>
<th>Average pressure before injection</th>
<th>Systolic level of pressure after inj.</th>
<th>Time taken before max. decrease reached</th>
<th>Time taken before recovery</th>
<th>Ratio before to after inj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>0.20 g.m.</td>
<td>84 mm.</td>
<td>67 mm.</td>
<td>50 seconds</td>
<td>3 minutes</td>
</tr>
<tr>
<td>2nd</td>
<td>0.20</td>
<td>86</td>
<td>53</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>3rd</td>
<td>0.40</td>
<td>86</td>
<td>36</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>4th</td>
<td>0.60</td>
<td>85</td>
<td>32</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>5th</td>
<td>0.80 (previous 0.79)</td>
<td>29</td>
<td>120</td>
<td>Q</td>
<td>6</td>
</tr>
<tr>
<td>6th</td>
<td>0.01</td>
<td>49</td>
<td>18</td>
<td>120</td>
<td>6</td>
</tr>
</tbody>
</table>

The tracing at the 4th injection is shown opposite. The injection of 0.60 g.m. reduced the pressure from 85 to 32 mm, the rate of the pulse from 55 to 30 per minute. The amplitude of the contractions during the slowing was marked.

Experiment IV was similar in character. In experiment V both vagi were divided and artificial respiration maintained. On injecting 3 cc. (0.6 g.m.) slowly into the saphenus vein the heart stopped but on pressing the thorax several times it resumed beating. The pressure gradually rose from 100 to 150 mm. with a slow powerful pulse of 55 per minute. On stimulating the lower end of one divided vagus (right) the heart
1st Feb. 1888

Rabbit 1.370 Kilo.
Curare y Atropine

50 mm. 106 mm.
51 mm.

2 minutes after .08
Atropine (no curare)
Heart 93 in 20 sec.
Pressure 106 mm.

10 minutes after 2° injection of Curare.
116 mm.
76 mm.

Artificial respiration 70 mm.

After 2° injection of Curare.
Tracing at 11.5 am.
Heart 53 in 20 sec.
Pressure 116 mm.

1st hr. 10.40 am. .02 gramme.
2nd hr. 10.55 am. .028.
stopped for a second or two as usual. The urine contained no sugar or blood.

In experiment VI a considerable dose (0.8 gms.) of atropine was first injected. The vagi fully paralysed (inhibitory action). On injecting 0.02 gms. curarin the pulse slowed just as before. After a second injection of 0.028 gms. curarin the pulse slowed from original 279 to 159 per minute. The pressure rose from 104 to 146 mm. Hg. The respiration had before this become greatly affected, having slowed to about 12 per minute. The whole abdominal muscles contracting in a laboured manner. Occasionally a slight convulsive jerk of the body occurred as if from asphyxia. Although artificial respiration was carefully maintained the heart continued to beat in the slow, powerful way shown on the accompanying tracing. The natural respiration after a little became powerful very rapid. On giving a third injection of 0.03 the heart stopped completely. On reopening it the auricles were found contracting and continued for 15 minutes. Occasionally an unprofused 'ventricular contraction' occurred. Electrical stimulation did not cause a good contraction. The right ventricle was dilated, the left only partly so.

No further experiments were carried
cut as the immediate purpose had been served, namely to show that experiments with crude curares of unknown composition could not be satisfactory. When the purity of curarin is assured it seems worthy of further examination, but meanwhile its relation to curarin, if any, has not been determined. We do not know if it is derived from the same plant, but Bahl, from various circumstances, thinks it possible that curarin may be converted into curarin at certain seasons, because, when its constitution is artificially altered into that of an ammonium base, it acquires an intensely active paralysing action, though not quite so great as that of the true curarin formed by the physiological activity of the plant itself.

Some South American Strychnos barks were examined in the Pharmacological Laboratory in Edinburgh University in the summer 1888-9. The Strychnos toxifera of Schomburgk has already been referred to. Through the kindness of Mr. Jackson of the Royal Gardens, Kew, I obtained a Strychnos sent from America (Antoquia) as Strychnos toxifera. On examination I found that it did not agree with the descriptions or posse of Strychnos toxifera, but exactly corresponded with the description by
Planchon \(p.327\) of a plant which he has named Strophanthus tumbillici, which was brought from Venezuela by M. Vivier, Consul General, in 1867. This Strophanthus is reputed to be the basis of the cure of the upper Orinoco district, but is not identical. Planchon \(p.327\) thinks with the 'bej conceive de Maracouer' of Humboldt \& Bonpland \(p.327\) from which certainly curare was prepared.

Although this Strophanthus tumbillici doubtless enters into the composition of the curare of this district, Planchon has advanced no proof that it is the basis of the curare. His claims only rest on native reports to the French Consul, \& on the fact that it is undoubtedly a Strophanthus. On experimenting with it, I could observe no curare-like action on the ends of motor nerves. After a few hours the frogs died, but this was found to be due to interference with the circulation, the ventricle being dilated \& acting in a feeble peristaltic manner. The action was not unlike that of curari, \& Professor Adair, \& whom I sent a small piece of a young stem, assured me that it did not contain curari. Only a small quantity of the specimen could be obtained, but sufficient to show that it could not be compared in action or poisonous activity to
Strychnos toxifera.

Here seems to be no doubt that several of the Strychnos barks are cardiac poisons. 

M. Conly v. A. V. (p. 1735) found that an extract from the bark of the Strychnos Gandinni of Brazil caused disorder of the cardiac action, fall of blood pressure, secondary arrest of central excitability and respiration without any apparent action on motor nerves ends.

These authors also record the interesting fact, that, on boiling the extract from Strychnos triphthamines, some curares the paralyzing action on nerve ends was destroyed, and replaced by a paralyzing action on the heart. Other curares were not decomposed by prolonged boiling, showing apparently that the active principle is not always the same. As the natives always prepare the curare by making a decoction and concentrating it by boiling, we have not only different ingredients in different proportions present but also decomposition products in all likelihood. Although the action of curarine is greatly preponderates in curare it cannot be satisfactory to use such a mixture in delicate experiments.

In connection with this action of some Strychnos barks extracts on the heart...
it is interesting to remember that Hammond and Mitchell obtained from New Granada two arrow poisons named Cerronal and Vaco which they found to be varieties of one poison which produced cardiac paralysis, the nerve functions being only secondarily affected through the failure of the circulation. The Strophonos plant obtained from New Gardens came from Antioquia in New Granada.

It would seem therefore that, on the South American continent, the arrow poisons consisted of either pure nerve-paralyzing substances or cardiac poisons ( mk?), or mixtures of these. Both seem to be derived from Strophonos plants although Robert (p.647) states that the Arawic tribe (Piro) use an arrow poison which acts on the heart, it is derived from a Monopetalous plant (Chondropernum). I do not know that such a plant has been identified botanically, though at the same time experimentally to have such an action.

I can only now repeat the hope that these last experiments on curare have (apart from any intrinsic interest) a practical value, so far as they indicate a possible source of error in the use of crude curare as an aid in research, I replace the suspicions which
have sometimes been entertained about different (Palmer 1972) curves by actual facts.
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