Thesis

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Subject.

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

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being an experimental research in the
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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 Boehm, who has shown, that, in some varieties of Curare, the alkaloid Curarin is associated with another alkaloid, which he has named Curin.

He has also shewn, 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 barks of South America, and likewise of the Methyl Strychnium 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 & Rabbit

Especially after Claude Bernard's[2] 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 striped muscles.

In addition to this general agreement almost all these early writers, such as,- Kolliker[3], Vulpian[4], Martin-Magron et Buisson[5], Pelikan[6], Haber[7], Bezold[8], Kühne[9], Bidder[10] & others further concluded, with Bernard[2], that curare did not paralyse the endings of sensory nerves. But, on the other hand, some contemporary writers, such as,- Schiff[11], Bahlenderff[12], and later, Lange[13], and among quite recent authors, Steiner[14], Rinz[15], & Lauder Brunton[16] 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 & Buisson[5]; Wundt & Schelske[17] & von Bezold[8] state that curare has a strychnine like action on the spinal cord. Vulpian[18], 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 text books on physiology and pharmacology in different countries adopt the genral 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 beginning 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,[19] Bancroft,[20] Humboldt,[21] Waterton,[22] de Castelnau,[23] Schomburgk,[24] Osculati,[25] Brocklesby,[26] Herissant,[27] Fontana,[28] Brodie,[29] Emmet,[30] Virchow & Münter,[31] Cogswell,[32] Reynoso[33] &c. &c. Not a few other papers are confined to special points in curare-poisoning - such as, the condition of the circulation - or deal with its botanical origin, chemistry or therapeutic uses, & 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 recognised 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 & very kindly supplied to

me by Professor Boehm. 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 & abdominal lymph spaces by passing the hypodermic needle through the floor of the mouth from the inside & along beneath the skin for the necessary distance. When the paralysing dose was exceeded precautions were taken to keep the skin moist & freely exposed to the atmosphere, as, when the cutaneous respiration is also interfered with, fatal paralysis of the central nervous system & 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 necessarily useless as cutaneous respiration was almost entirely suspended. The results of numerous experiments are summarized below. The onset, intensity & duration of the symptoms produced by similar doses, administered under the same conditions of season, temperature & time, were, on the whole, similar. The irregularities were probably due to variations in the rate of

absorption, excretion & other conditions in different animals which cannot be estimated, or, possibly, 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	
0.00000002 gramme in winter.	No result. The daily administration of this dose for 35 days had no apparent effect on the frog.
0.00000004 gramme Winter & Summer.	In a period varying in different cases from 15 to 40 minutes unmistakeable signs of muscular weakness appeared, so that frequently the frog, when placed on its back, could not turn over. Reflex movements continued good, but voluntary movements were infrequent. 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 slighter & briefer than in winter.

Dose of curarin per 1 gramme of body weight.

0.00000008 gramme Winter & Summer

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 movements followed strong stimulation of the skin & respiration 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.

0.00000020 In from 30 to 60 minutes every movement had ceased except the respiratory movements of the throat muscles. The reflexes consisted in an occasional slight muscular twitch.

0.00000022 All voluntary & 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 curarin per 1 gramme of body weight.	
0.00000028 gramme	This was found to be the minimum complete paralysing dose. In about 30 minutes general voluntary movements were quite suspended. By 60 minutes all trace of reflex movement had disappeared, except, as before, in the case of the throat muscles of respiration which were not completely paralysed 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 & recovery occur finally. When the dose exceeded about 30 times the minimum paralysing dose recovery did not take place with the temperature at an average of 15°C. During warm weather even the smallest paralysing doses not unfrequently 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 paralysing dose at a temp^re of 15° Celsius (^ 2)

Dose per Gramme of body weight of male frog (grms)	Abolition of General reflexes after.	Abolition of reflex mvt. of throat muscles after	Return of reflex temp. mov^t at throat after	Return of Ordinary reflexes after	Return of power to turn over, when placed on back after	Return to Normal after.
0.00000028	52 minutes	90 minutes	5 hours	2nd day	3rd day	3rd day
	80 "	180 "	5½ "	2 "	3½ "	4 "
0.00000028 X2	25 "	30 "	1 day	1½ "	5 "	6 "
	27 "	30 "	1½ days	2 "	4 "	8 "
0.00000028 X4	15 "	27 "	4½ "	5 "	4 "	8 "
	15 "	25 "	5 "	5 "	8 "	9 "
0.00000028 X 8	10 "	20 "	5 "	5 "	8 "	9 "
	15 "	30 "	5 "	5 .	4 "	8 "
0.00000028 X16	10 "	13 "	9 "	10 "	16 "	14 "
X32	10 "	14 "	18 "	18½ "	25 "	26 "
0.00000028 X40	6 "	8 "	10 "	11	14 "	15 "
X32	9 "	15 "	Heart stopped on 4th day			- no urine secreted
0.00000028 X48	6 "	6 "	Heart stopped on 13th day			- little or no urine
	6 "	7 "	Heart stopped on 3rd day			- no urine
0.00000028 X50	5 "	6 "	Heart stopped on 2nd day			- no urine
0.00000028 X100	3 "	3 "	Heart stopped on 2nd day or late on 1st day			- no urine

In the cases which recovered there was a considerable Secretion of urine which was expressed from the bladder from time to time during the experiment.

Rate & force of the cardiac contractions during prolonged paralysis at 15° C.

Dose of Curarin per Gramme of frog	Condition when motor paral. complete	After 24 hours	after 2 days	after 3 days	after 4 days	after 5 days	after 6 days	after 7 days	after 8 days	
0.00000028	40 Strong 42 "	36 Strong 37 "								
0.00000028×2	38 Strong 40 "	30 Strong 34 "	29 Strong 26 "	34 Strong 32 "						
0.00000028×4	38 Strong 38 "	30 Strong 28 "	30 weak 26 medium	28 weak 26 medium	26 weak 26 strong	26 strong 24 "	26 strong 24 "	27 strong 24 "		
0.00000028×8	30 Strong 32 "	28 Medium strength 28 "	28 medium 28 "	30 medium 30 "	28 strong 28 "	30 strong 30 "	28 strong 30 "	30 strong 30 "		
0.00000028×16	42 Strong 38 "	34 Medium 34 "	25 weak 22 "	24 very weak 24 "	32 weak 28 "	not visible 26 weak	22 very weak 24 "	26 weak 28 "	26 weak 30 "	25th day 32 Strong 15th day 32 strong
0.00000028×32	40 Strong 40 "	34 Medium 30 "	26 weak 21 "	24 very weak Heart stopped	not seen	30 weak	34 weak	30 weak	34 weak	14th day 30 medium 11th day Heart stopped
0.00000028×48	40 Strong	28 Weak	22 weak	26 weak	not seen	not seen	19 very weak	not seen	20 very weak	
0.00000028×50	44 Strong	30 Weak	Heart stopped							

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 & feeble & may finally stop. If the urine be 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, & consequently, recovery is impossible. If the state of the circulation is examined it is found that the blood pressure is at zero, & that practically no blood is passing through the heart. The cutaneous respiration must therefore be reduced to a minimum, & 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, & 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 excretion

of the poison and delay recovery, or may cause suppression of the renal secretion. Large doses of curarin seemed to be less fatal when over-distention of the bladder was prevented by expressing the urine daily. That the urine contained the curarin & was readily shewn by evaporating it, treating the residue with alcohol, evaporating & administering a watery solution of the solids to a frog. Paralysis 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 Boehm (1890) at 0·35 milligramme (·00035) 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 (0·35 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 & skin, 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 & a fatal dose was about 0·05 m.g, & the marked symptoms of paralysis lasted only from 10 to 30 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 paralysing 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[2] (p 345) 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 iliac 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, & 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 where 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 am. - 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 washed with 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, in this experiment, not withdrawn at all after 60 seconds immersion. On both sides the reflexes to pinching the toes were good & fairly regular. At 4.50 pm, - 5 hours after suspension of the circulation, the reflexes could be obtained much as before. Although therefore the reflexes on the side connected with the brain become weakened & 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 & delicate chemical & mechanical stimulation in any very marked or irregular manner (Rutherford 34. p152)
On the day after the stoppage of the circulation most of the sensory nerves in the legs are found to be paralysed & the

muscles furthest from the trunk rigid and acid. It is very important to recognise that in a frog with divided cord the simple stoppage of the circulation in the legs 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 cord. 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 paralysed by ligature of the aorta, administration of a digitalis acting body (heart) or of m. large dose 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 introduces no serious fallacies 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 paralysing 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 paralysis, 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 obstacles which one action may throw 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 protected parts are rarely seen after the first few minutes (Kolliker[3] p58. Vulpian[18] p256) Foster[35] p397 After nearly half an hour the reflexes have become distinctly more & more difficult to obtain.

(Kolliker[3] (p39)) a circumstance hardly sufficiently recognised by Vulpian[4] & others.

Martin Magron & Buisson[5], (p526) Vulpian[4] (p288) 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 protected part causes some reflex movement. Martin Magron & Buisson[5] (p527) 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[2], that curare does not paralyse the sensory nerves, the facts are not so simple as would appear from his statement (p353) "Mais "la sensibilité y sera conservée car toute "excitation portée sur cette partie paralysée

"veillera dans la partie preservée des
"mouvements réflexes énergiques". Kolliker[3]
(p 46) Martin-Magron & Buisson[5] (p 527) &
Vulpian[8] p 38 sought to prove that the reflex
depression and irregularity described was
not due to a paralysis of the sensory
nèrves by administering strychnine & finding
that stimulation of the poisoned skin caused
reflex movements and reflex tetanus in
the protected leg. Lange[13] p 397) found
on the contrary, in agreement with Schiff[11].
that, when the aorta abdominalis was
ligatured in a frog & also the right
forearm, with the exception of its nerve,
and a small dose of curare given,
and a few minutes later a small
dose of strychnine, the stimulation of
the unpoisoned anterior extremity gave
reflexes in the protected posterior
extremities, while stimulation of the
poisoned anterior extremities failed to
act. Steiner[14] (pp 33. & 34.) repeated these
experiments by Schiff[11] and Lange[13] We
stimulated the two anterior extremities
in an exact manner by electricity & came
to the same conclusion as Lange. We
then entirely destroys this statement by
remarking "nur muss ich erwähnen dass
"die Resultate manchmal 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.

Binz[15], in his lectures on pharmacology (Bonn 1884 pp 135.136), reviews these symptoms in curare poisoning, and also 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 beschränke seine lähmende "Wirkung auf die motorischen Nerven und lasse "die Sensibilität bestehen. Das aber is nicht "richtig. Nur im Anfang des Versuches ist "die gesamte Haut des Thiers noch sensibel "erregbar; später muss man die Haut "des arteriell abgebundenen Unterschenkels "reizen, wenn man von den Hautnerven "aus Reflexbewegungen erzielen will. Dies "zeigt deutlich das mittlerweile auch die "Empfindungsnerven der Haut überall, "wohin das Curare dringen konnte, gelähmt "wurden, und dass also die auf Grunde "der Autorität von Claude Bernard viel "verbreitete Ansicht von dem dauernden "Unversehrtbleiben 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 shewn 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 wherever applied, but further successive stimulations to any part failed to produce any movement. Many irregularities occur however. The circumstance 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.

Romanes[36] (p299), 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 over the edge of the vessel by a bridge of undivided tissue with the other half floating in unpoisoned water. His experiments shew 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. Romanes however does not stop here but goes on to say, that, (p301) "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 paralysed 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, & in the absence of any statement to the contrary, we are justified in thinking that when the curare solution is stronger, the half in the unpoisoned water does not contract after a time when the poisoned half is stimulated because it is really paralysed by diffusion of the excess of poison. This clearly precludes the proof that the transmitting system was paralysed, 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. Kölliker[3] p55) 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.

Bernard[2] makes no special reference to the cord but he evidently considered that the poison had no direct action at all. Kölliker[3] p55) 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[7] p41) states that the reflex movements disappear

in 6 to 10 hours but gives no decision as to the cause. Bidder[10] p338) does not think there is any action on the spinal cord. Brunton[16] p150) concludes that the nerve centres are paralysed as the poisoning progresses, & other writers on pharmacology & physiology, in this country at least, generally hold the same view; - Rutherford[34] p152) Landois & Stirling[37] p701) Foster[35] p396)

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 paralysing 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 Wundt & Schelske[17] Martin-Magron & Buisson[5] von Aegold[8] & Vulpian[18] 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,[18] believe that curare paralyses the sensory nerves & spinal cord,

while the early writers hold that the sensory nerves are not paralysed, & some belive that the cord is paralysed & others that it is excited. The necessity for further work is apparent, when reference is made to the subjoined list.

That the spinal cord is excited as in Strychnine poisoning.	That the cord is paralysed or unaffected
1. Wundt & Schelske[7] (1859)	
2. Martin-Magron & Buisson[5] (1859)	all other writers
3. von Bezold (1860)[8]	
4. Vulpian[18] (1882)	

That the sensory nerves are paralysed	That they are not affected
1. Schiff[11]	
2. Bahlenderff[12] (1865)	
3. Lange[13] (1874)	All other writers
4. Steiner[14] (1877)	
5. Binz[15] (1884)	
6. Lauder Brunton[16] (1887)	
7. Romanes[36] (1876)	

It is evident that there must be some serious difficulties or fallacies in the investigation, otherwise so many authors could not time after time express different opinions, & these I shall now endeavour 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 curarine, 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 protected frog, the same dose of curarin be administered as in B & D, and, about 45 to 60 minutes after poisoning, when the reflexes are very irregular and depressed or have disappeared to stimulation of either the poisoned or the unpoisoned skin, the spinal cord be successfully divided below the medulla, the condition of reflex depression and irregularity, and apparent sensory or spinal paralysis, quickly changes, and active movements of the protected parts regularly follow every stimulation of either the poisoned or the unpoisoned skin.

Exp: N: 57 Oct: 1887. Temp^re 15° C.

Minutes after poisoning.

0 Preparation of lower extremities as usual, & after recovery, administration of 0.00003 grm curarin, - equal to twice the minimum paralysing dose, - in 0·3 cc water, by injection into ant. thoracic lymph sac.

Minutes after poisoning.

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

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

18 Reflexes to dilute sulphuric acid ·3% Left foot withdrawn 20 sec. Right " " 1 sec (?)

28 do Left foot not withdrawn 70 sec. Right " " " 70 "

38 do Left " " " 70 " Right " " " 70 "

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

45 Reflexes to pinching becoming rather difficult to obtain. Pinching the protected feet 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 cause 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 flexed.

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 extension of lower extremities on making incision.

Minutes after poisoning.

68. Reflexes found to have quite altered for now very touch 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	"
75	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 hæmorrhage 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 & the depression caused by the successive severe operations, the spinal cord retained its fitality 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 ligature of the

vessels & tissues at the lower part of the abdomen (2) Pressure of the ligatures or compressed tissues or displaced organs (kidneys &) against the trunks of the lumbar nerves (3) Rapid paralysis of the cord after section even when very care taken in the operation. This seemed especially to occur in warm weather & in winter frogs that had been kept a long time in the laberatory.

The following experiments however removed all chance of error.

B. If the spinal cord in the frog be successfully divided below the medulla on the day previous to the experiment, and the same relative dose of curarin be administered as in A & 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, & it is observed that the poison exercises no direct depressing influence on the cord or upon the sensory nerves.

Exp: N° 44 Sep 1887 Temp^re 17° 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. Reflexes to .3% Sulphuric acid

0	Both feet withdrawn in	2 – 4 seconds
3	do	2 – 4 "
6	do	2 – 4 "
9	do	2 – 4 "
12	do	2 – 4 "
15	do	2 – 4 "
18	do	2 – 4 "
21	do	2 – 4 "

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

Minutes after poisoning

2	Both feet withdrawn in	2 – 4 seconds
5	do	2 – 4 "
8	do	2 – 4 "
11	do	2 – 4 "
14	do	2 – 4 "
17	do	2 – 4 "
23	do	2 – 4 "
28	do	2 – 4 "
33	do	2 – 4 "
38	do	2 – 4 "
43	do	2 – 4 "
48	do	2 – 4 "
53	do	3 – 4 "
58	do	3 – 4 "
63	do	3 – 4 "
95	do	3 – 4 "
2 hours	do	4 "

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

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These results were repeatedly confirmed & 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: N°. 70 Decem: 1887 Temp: 15° 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 grm. of Curarin dissolved in .25 cc 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 paralysis of the whole right lower extremity.

Time after Poisoning.

1 hour. Faint stimulation of any part of the skin of the paralysed extremity causes active reflex movements in the rest of the body. When no stimulation is applied the frog remains perfectly still.

3 hours. The same result

8 hours. The same result - the reflex movement instantly follows the stimulation of the paralysed extremity (skin)

It is probable that the curarin 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 paralysed 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 Kölliker[3] p56) Martin-Magron & Buisson[5] p527) & Vulpian[18] p288) were adopted the previous results as to the condition of the sensory nerves were still further confirmed (D)

D. If, in an intact protected frog, the same relative dose of curarine be administered as in A + B, and, about 45 to 60 minutes after poisoning, when the reflexes are depressed or have disappeared to stimulation of either the poisoned or unpoisoned skin some strychnine be administered the reflex depression disappears and reflex tetanus of the protected extremities readily follows stimulation of previously apparently insensible parts.

Exp: 91 by Martin-Magron & Buisson. Journ de Physiol. III p527

12 am Left iliac tied in frog. Injection of curare solution beneath skin of back

12.25 " Paralysis of unprotected parts

1.30 pm Still movements in left posterior (unpoisoned) extremity on strongly pinching the skin of the back

2. " No reflexes whatever part is stimulated 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 frog poisoned with curare, & when the poisoning is complete the vessels of the other, the paralysed 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 protected, 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, these experiments by Martin-Magron & Buisson[5], Kölliker[3] & Vulpian[18] 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 paralyses the cord.

The statement made long ago by Wundt & Schelske[7], Martin-Magron & Buisson[5] & von Bezold[8] that curare stimulates the cord has been, almost naturally, held to be inconsistent with this frequently observed feature, & 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 (Buisson[5] p334) 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, & 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 4 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 & 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 & 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, & on the following days those were selected which shewed an entire absence of volition, but where 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.

On administering small & medium paralysing 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 pricked with a needle, ~~both~~ on testing the reflexes to the dilute acid now, the feet were not withdrawn ~~nor~~ ~~tickling~~ pinching ~~the~~ the application of glacial 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, but very soon other symptoms, which will presently be described, set in. This has no bearing however on ordinary cases where small doses are administered sub-cutaneously

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 & 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 (Kolliker[3] p58 · Steiner[14] incline to the view that the cerebrum is directly affected. The latter observed that in some kinds of fish the voluntary movements disappeared a considerable time before motor paralysis set in

On the other hand Bernard[2] & Vulpian[18] (p329) observed, that, when a dog was poisoned with curare it showed signs of intelligence when spoken to (moved tail &) as long as motor power remained

The loss of volition in protected frogs is, when a large number of experiments are tried, not absolute, (Martin Magron & Buisson[5] p341 Vulpian[18] p331) altho' it is difficult to distinguish between truly voluntary movements & movements due to some other cause. Bernard Also, when curare has been administered subcutaneously in man, (Voisin & Liouville[38], du Cazal[39]) & very distinct effects produced on the motor nerves, the circulation temperature & urinary secretion no evidence was obtained pointing to any special action on the cerebrum.

It is not possible to investigate the action of larger doses on warm blooded animals.
On the whole it is improbable that there is any direct action on the cerebrum.

A second explanation of the voluntary & reflex depression might be found in the fact that,

the poison paralyses the muscles of the eye, respiration & genital 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 (intentional) attempts with the protected part, & 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 in poisoning with Tetra-methyl-ammonium Tetra-ethyl-Ammonium & 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. Unger & Mennell[40] (p 73) 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, <u>apart from any direct action</u>. This was very marked in experiments in September "for whilst in entire frogs reflex action was lost on an average in 5 minutes, in

"brainless frogs it 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 anaemia it must arise from vaso motor spasm. I do not know of any experiments ~~in frogs~~ where the condition of the vaso motor centres has been determined in curarised frogs. Ellis[41], who employed the Plethysmograph in experiments on curarised frogs, mostly directed his attention to the effects of stimulating the divided nerve & remarks (p 448) "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" & p 445 "no definite conclusions can be drawn from these tracings regarding spontaneous vascular changes"

Whatever the explanation of the reflex depression & irregularity may be it is directly connected with the presence of the cerebrum. Those authors who concluded from experiments on intact frogs that the sensory nerves were paralysed & the reflexes depressed could not but fall into error.

II

Experiments with large doses of Curarin of from 50 to 100 times the minimum paralyzing dose (0.0005 to 0.001 grm. in a frog weighing 36 grm.)

When a large dose is administered by subcutaneous injection motor paralysis of the unprotected parts occurs in a minute or two. Purpose-like voluntary movements quickly disappear in the protected extremities, although markedly irregular spontaneous movements occasionally occur at this stage of the poisoning. The reflexes to chemical & mechanical stimulation of the poisoned or unpoisoned skin usually quickly ~~disappear~~ become difficult to obtain & 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 & medium doses, it does not occur at all at the same period when the cord is divided before the experiment, & it disappears when the cord is divided during the experiment, & reflexes readily follow stimulation of either the poisoned or the unpoisoned skin.

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 shewn

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

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

(2) It is followed by a period of very variable duration during which the reflexes are either simply improved, or, in addition, spontaneous and reflex movements of a spasmodic character occur. This period of relative nervous excitement is as a rule of brief duration, & the symptoms, 'tho' unmistakeable in character, are slight, and depression of reflex excitability rapidly follows & in from 3 to 5 hours usually passes into total paralysis of the spinal cord. Even 20 hours however may elapse before reflex paralysis is complete. The onset of the paralysis is hastened by a large dose of curarine & 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 excitability 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.

Exp: No 80 Intact frog. Decy 88

Minutes after poisoning

0 Administration of 75 times the minimum paralysing 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 incoordinate and consist of a jerky extension of the lower extremities or a slow sprawling movement or a slow spasmodic like extension the web of the toes being outstretched.

80 Reflexes to pinching much more easily obtained now.

minutes after poisoning

100 A slight touch on either the poisoned or unpoisoned skin causes a quick jerky extension of the lower extremities. When the stimulation is slight crossed reflexes are well seen.

3 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 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: N° 81 Intact Frog Temp: 16° Cels. Jan. 88

Time after poisoning. Administration of 70 times the minimum paral: dose

25 min: Reflexes distinctly depressed

80 " Slight improvement of reflexes.

2 hours. Occasional slight spontaneous movements

6 " Reflexes distinct but feeble & easily exhausted.

16 " Pinching the poisoned skin of back & anterior extremities causes feeble contractions in the upper thigh muscles, the rest of the extremity having become dry and rigid Heart beat not to be observed on the thorax

26 " Condition unchanged

40 " Paralysis.

Exp. № 82 Frog with divided cord. Temp° 18° Cels. Jan. 88.

Spinal cord successfully divided on the day previous to the experiment

Minutes before poisoning. Feet withdrawn from 3% Sulph. Acid in 4 Seconds

10 do 5 "

On pinching the foot the reflex is very active

Minutes after poisoning. Injection of 1 cc sol° containing 0·001 grm.

Frog weighs 88 grm = about 40 times the min: fatal dose

5 Complete motor paral. of unprotected parts

13 Frequent slight spontan: movts in lower extremities

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

18 Both lower extremities frequently forcibly extended & flexed. While in the position of flexion & extension faint weary 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 20 minutes

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

To dilute acid Right foot 15 Sec. but difficult to estimate.
Left " 9 "

80 Reflexes much weaker & tetanic movts difficult to obtain

95 A brief tetanic spasm on pressing the foot

120 No further reflex. Direct stimulation of lumbar nerves causes active movements in the lower

extremities.

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Many of the experiments were without decided evidence of tetanic action, but shewed some suspicious symptoms - partly paralytic, partly convulsant.

Exp: 59 Divided cord. Temp" 15° Cels. Oct. 87.

Spinal cord divided in frog on 24th Oct: at 5 pm. & at 5.15 pm. on the following day the lower extremities prepared as usual.

6.41 pm. Injection of 0.00025 grm in .25cc. water (about 30 × paral. dose)

minutes after poisoning.

7 Paralysis complete in unprotected parts

32 Reflexes continued good without exaggeration

49 After the reflex movement has taken place some twitchings shewn in legs & occasionally spontaneous jerks & extensions occur.

59 Reflexes very acute but no tetanus.

69 Reflexes slowly becoming less acute

49 Distinct weakness of reflexes

109 The slightest movement only obtained.

2 hours Complete paralysis of the cord.

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After many such experiments it became absolutely certain that the subcutaneous administration of relatively large doses of curarin (0.0005 — .001 grm.) 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 & Buisson,[5] Wundt & Schelske,[17] & von Bezold[8] came, as we have seen, to a similar conclusion, while Vulpian[18] has also held that the symptoms in both cold & 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 paralysing & the tetanising principle are one & the same, & some of the differences between the actions of small & large doses of definite strength, & between the direct & indirect actions of the poison have been made clear.

Now, while the 'stimulation' of the spinal centres shews itself, on the one hand, in the early spontaneous disappearance of the reflex depression, & on the other hand, in the appearance

more or less of reflex spasm, it remains to be explained, why, in the first place, total paralysis of the spinal cord occurs in the majority of cases in a few hours, and why, in the second place, if stimulation of the cord is 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, (Vulpian[18] p. 354) which after several hours (von Bezold[8] 165 ff.) 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 be exposed and watched, little immediate change occurs in its condition, if the frog during the observations is under

the same conditions of temperature as before the experiment. After a time the blood becomes dark owing to the general muscular paralysis having stopped the respiration by the lungs, & 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 hearts' 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, altho' 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 paralysed. If the abdominal viscera 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. & 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 cutaneous respiration is also practically at an end, for the blood is no longer actively circulating throughout the skin of the paralysed animal. This is confirmed by the fact that in deeply curarised frogs the gas analysis (Valentin[42] p99) shews a marked sinking of the oxygen absorbed and carbonic acid given off, & the muscles have no longer a red colour, whereas in frogs paralysed by small doses of curare & where consequently the circulation in the skin is not ~~pa~~suspended the gas analysis shews 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 shewn that when the aorta is compressed, or the heart paralysed, or the frog surrounded with an irrespirable gas &c, or in other words when the blood can obtain oxygen but cannot circulate, or circulates but cannot obtain oxygen, the central nervous system becomes after a time paralysed. On trying the reflexes in empoisoned frogs for purposes of comparison I found the period which elapsed, after ligature of the aorta, before paralysis of the cord was <u>complete</u> to be about 45 minutes in very hot weather, and from 1½ to 3 hours at lower temperatures in winter.

Curarin in large doses produces, after a short time, a condition of the circulation similar to that which would be caused by the ligature of all the veins entering the heart. In experiments where the spinal cord has been previously divided the circulatory paralysis is if possible accentuated. <u>It is certain therefore that the alkaloid is not only very imperfectly circulated, but that it must, by causing this great dilatation of the bloodvessels, indirectly weaken and paralyse the central nervous system. & this secondary paralysis must occur no matter what the</u>

direct action may be of that part of the dose which may reach the brain & cord.

Since marked 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. Vulpian[18] (p359) points out that in curarised frogs the action of digitalin, strophanthus, Upas Antiar, Jaborandi & Muscarin 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" p359 En "tout cas, elles prouveraient bien nettement "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 shews 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 curarin on the cord is more fully worked out, that the simple spinal paralysis which follows the subcutaneous administration of large doses, & the infrequency of tetanus, 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, causes 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 cord & 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 & by injecting solutions into the aorta the symptoms are constant & quite unmistakeable and shew 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, in an unprotected frog, to suspend the circulation by ligature of the aorta or heart to prevent the poison being conveyed to the muscles. Experiments are most completely satisfactory in winter, as the cord retains its vitality for from 1½ to 2 hours after the circulation is stopped.

Exp: № 86 Jan^y 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.

Minutes after poisoning.

30. 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

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

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

52 Tetanus follows very stimulation - often successive shocks occur lasting 5 sec. each.

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

75 Frequent twitching of individual muscles.

95 Violent tetanus lasting 20 sec. on pinching foot.

2 hours. Tetanus very brief & relatively feeble.

2½ " Reflexes very weak

3 " Paralysis of cord, having remained active without blood for about 3 hours.

Exp: 87 Jan: 1888. Temp: 13° Cels.

Minutes

1. Heart ligatured

15 Brain destroyed & cord fully exposed

35 Frog has been left undisturbed for 20 minutes to see if any signs of excitement from injury exposure or any imaginary

combination of circumstances could act. Not the least movement has occurred. On pinching the foot the reflec is simple & not at all strong.

Minutes after poisoning
0. Application of 2 drops of water containing 0·0005 gramme Curarin in solution. The membranes lining the spinal canal were for the most part unbroken, & the cavity was partly filled with lymph & some blood, so that the curarin could not come into direct contact with the cord.

16. Violent tetanic convulsion lasting for 16 sec. The faintest stimulation renews the spasm

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 & a most intense tetanus sets in lasting for a minute perhaps. Reflec tetanus immediately follows a stimulation.

2¼ hours. Spontaneous movements have ceased. Reflec tetanus very feeble.

Note. When the spinal cord is carefully & completely divided into two parts before applying the solution it is found that tetanus occurs in the muscles supplied from both parts shewing 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 sooner 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 animal seems absolutely non-irritating, and since the solutions employed were very weak, (average 1 in 1000 water) 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 bloodvessels 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 circulating 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 (coliaco-mesenteric), ligature of one aorta at its origin & one pulmo-cutaneous trunk. On making the injection by means of a canula in the united aorta close to the heart the only important vessels through which the solution can pass are the carotid & occipito-vertebral arteries of one side, that is to say the vessels which supply the central nervous system. If the Subclavian artery or the arm 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: ~~Or~~ N°90. Jan: 8th Temp°: 13° Cels.

Minutes after poisoning — Preparation as described.

0. Slow injection of ·8cc sol° containing 0·0008 gm. Curarin into left aorta.

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

7. Severe spontaneous tetanic convulsion (opisthotonus) followed by constant spasm of individual

Minutes after poisoning.

7. muscles and groups of muscles the extremities being jerked about in all directions

15 The tetanic spasms still continuing with extreme 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. Now almost complete exhaustion. Only feeble movements on stimulation.

The same results were obtained in every experiment. When several milligrammes 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 shews that there is no delayed action on the cord.

It is important that the conclusion that curarin acts on the cord in a strychnia-like manner should be substantiated by experiments on the crude poison. If this conclusion is true of the active principle of curare, then every active motor paralysing specimen of that substance must, in virtue of its containing curarin or other closely allied body, produce unmistakeable 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 1839.
2. Poisoned arrows from same source
3. Poisoned darts from British Guiana obtained by Professor Simpson in 1848
4. Poisoned arrows from same source
5. Urari poison in gourd from same source.
6. Urari poison in gourd from Dr. Ewan Cameron, Berbice 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 Gourd. Brazil" presented to Prof. Fraser in 1870 by Dr. Weir Mitchell.
8. Curare from "Pot from Poya from Agassiz" from same source
9. Curare from "Pot from Para" from same source.
10. Curare from "Pot from Academy of Natural Sciences now in possession of Dr. Hammond" from same source

The next four specimens were purchased in Decem. 1888.

11. Curare (source unknown) from Messrs Hopkin & Williams. London.

12 Curarin from Hopkin & Williams. London

13 Curare (source?) from E. Merck. Darmstadt.

14 Curarin from E. Merck. Darmstadt.

The curares from which Prof. Boehm prepared the curarin used in my experiments were Venezuelan.

As different specimens of curare vary considerably in motor paralysing power, a solution in distilled water was made, filtered & 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 ·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 cord, or preferably making a direct injection into the aorta in the manner previously described, tetanus was in every case obtained readily just as with 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 shewn

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, were of undoubted authenticity, were obtained from at least three different sources - Brazil. British Guiana & Venezuela - were therefore of representative character. The specimens dated from 1837 to 1888, & included two commercial varieties of curarin, that by Merck 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.

Vulpian[18] (p 333) has especially drawn attention to the view of the case that the cord is not paralysed & the various points may be briefly summarized as follows –

1. After the subcutaneous injection slight twitchings & spasms occur in various muscles, especially the shin muscles, & disappear as paralysis progresses
2. Although convulsive movements due to asphyxia do occur in animals poisoned with small fatal doses (when the dose is large the motor nerves are paralysed too quickly to permit of movement) the spasmodic 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 asphyxia do not occur in a chloralised animal but spasms appear in a chloralised animal poisoned with curare (Vulpian[18] p332)
   (d) I have several times seen spasms occur

in 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 paralysed.

3. The pupils dilate & contract reflexly to light & stimulating the sensory nerves of the paralysed animal

4. On stimulating nerves reflex contraction & dilatation of bloodvessels follows. When the action of the poison comes to be considered it will be shewn 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 (Vulpian[18] p 357 Vol) Apomorphine causes vomiting (Vulpian[18] p 357)

6. Reflex increase of salivary secretion on stimulating the skin sciatic nerve V[1] (Vulpian[18] loc cit)

7 Reflex sweating of feet in cats on stimulating upper end of sciatic (Vulpian[18] loc cit)

8 Continuation of rythmic movements - ureters. (Vulpian[18] loc cit)

9. I have frequently observed that small & medium doses of curarin which certainly do not paralyse the splanchnic nerve frequently induce very marked intestinal peristalsis, artif. respiration being meanwhile adequately maintained.

Positive proof that curarin not only does not produce paralysis but actually produces a condition of the cord which would ordinarily result in tetanus, if the moter nerve ends were not paralysed, was obtained by repeating an experiment described by Martin-Magron & Buisson's (p329) where the spinal cord in guinea pigs was exposed at the middle of the back & 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 substance thickness of the cord no tetanus occurred. On injecting curare solution without letting a drop escape in the neighbourhood of the cord tetanic symptoms set in after a few minutes (3 to 5) & lasted for an hour or more without the respiration becoming embarassed. When any curare escaped round about the cord it was rapidly absorbed into the general circulation & respiratory failure might set in by 10 minutes. Martin-Magron & 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 gramme of curarin dissolved in .2 cc of distilled water injected. As the needle entered the cord the animal started violently & on the injection being made struggled several times & 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 spasmodic condition rapidly spread up & down the cord, & by the end of the 4th minute after the injection, there was a universal condition of mixed tetanic and clonic spasm. The fatal dose for a rabbit of this weight is 0.00054 gramme of curarin, but, as the whole 0.001 gm 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 & so of respiration.

From the 4th 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, & on several occasions these convulsions seemed

likely to cause death by asphyxia. The tetanic 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 excitability, but, during the momentary pauses, a slight touch seemed at once to renew the movements.

This condition continued unaltered for 4 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 tetanus & paralysis follows, the latter being no longer able to obscure the former.

Some progress has now been made with the proofs that curarin acts in a strychnine like manner on the cord, & 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 Kölliker[3] made experiments with curare when the cord was divided, & that Bernard[2] applied it locally to the cord, without observing tetanus, may, in the absence of explanation, be considered to lessen the value & completeness of the previous conclusions. It is not so however.

In Kölliker's[3] experiments (p 39) 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[2] (p 329) describes his experiment as follows "Ici, la moelle épinière d'une"

" grenouille a été denudée dans une certaine
" étendue et trempée dans le curare. L'excitation
" galvanique portée sur elle, détermine encore
" dans les muscles des convulsions énergiques
" ce qui prouve qu'elle se comporte comme
" le tronc nerveux "

The expression 'détermine encore' shews the expectation that if curare had any action on the spinal cord it would probably be a paralysing 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, & different parts of the same specimen, owing to the presence of inert matter, vary considerably in strength, therefore, when one author speaks of administering 0·1 grm & another 0·01 grm, & Bernard[2] uses the expression "trempée 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, & 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 of precision in dosage is secured.

Bernard[2] 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, & 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[2] experiments some 40 years ago, any form of direct experiment on the cord has been, so 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 shewn, 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~~ as also ~~as~~ by the early writers, there must have been some strong reasons why the striking experiments of Martin Magnus & Buisson[5] & von Bezold[8] were not thought worth repeating, & 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 <u>Strychnine</u> &c as an impurity.

(2) The idea that an alkaloid which has a strong paralysing action on motor nerves <u>cannot have a tetanising action</u> on the cord

(3) The idea that the active principle of curare is a <u>Methyl &c Strychnium salt</u> & therefore does not produce tetanus.

These views have received support from the experimental difficulties of the subject, & the fact that most writers have failed to find that curare has any strychnine like action. But they originated also in 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 &c (Iodide of Methyl Strychnium &c)

The second view which stands in the way of a clear knowledge of the action of curarin is <u>that strychnine is present</u> in curare or in some curares.

In order to conveniently explain away the unexpected experimental evidence brought

forward in 1859 by Martin Magron & Buisson[45] - evidence which did not at all harmonize with the general opinion - Kühne (cit. by Marsh. Mag. & Buisson (p334))[5] & later Huseman[43] (p538) advanced the statement that the experiments were made with a strychnine containing substance and not with a true curare. It has already been shown that all curares act in a strychniae like manner, & that this action is produced by the larger doses of the active principle of the arrow poisons.

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 barks no matter in what part of the world they grow. The latter view was evidently entertained by Bernard[2] for he remarks, (p312) '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[44] in a paper read before the Physiological Society expressed the same view that "The physiological action of woorara 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 (eg. Atropine, Nicotine)

Whenever it was definitely shewn 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

Husemann,[43] in agreement with all other authors who base their statements on a practical acquaintance with the subject, states (p527) 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, in some cases was any trace of Strychnine or Brucine ever found

Chemical Reports

Year		
1828.	Caulin et Boussingault.[45]	Annal. de Chem. (p34)
1829.	Pelletier et Petroz.[46]	Annal. de Chem. (p213)
1847.	Heintz[47]	(in connection with physiological experiments by Virchow & Münter) Schomburgk's Reisen Bd i p452. 1847
1861	Buchner[48].	" Doubtful experiments by Wittstein led to the conclusion that some N. Brazilian Urari contained Strychnine but a new analysis by Buchner (1861) shewed that it contained Curarin & physiol. exp. confirmed this" - Husemann. Handbuch der Toxikologie. Berlin. 1862 p528
1865	Preyer.[49]	Compt. Rend. vol. 60 p1346. Zeitschrift für Chemie. 8. 381
1878	Sachs.[50]	Liebig's Annalen. vol 191 p 355
1886	Boehm'.	Chem. Studien über das Curare Leipzig (Vogel) 1886.

The formula assigned to Curarin by Preyer[49] was $C_{10}H_{15}N$ and that by Sachs[50] $C_{18}H_{35}N$. The final results of Boehm's' investigation have not yet been published. Curarin therefore appears to contain no oxygen whereas the formula of Strychnine is $C_{15}H_{17}N_2O_2 - C_6H_5$ (~~Acetyl~~) & of Brucine $C_{15}H_{17}N_2O_2 - C_6H_3(OCH_3)_2$ (~~Acetyl~~)

There are in addition marked & fully recognized chemical differences between the two alkaloids. Curarin is soluble with great ease in cold water (Strychnine 1 in 6660) is permanently yellow in colour, neutral in

reaction, cannot by any known means be got to combine with acids to form crystalline salts (strychnine cryst- readily) (Sachs[50]. Boehm). The crystalline curarin described by Preyer[59] (loc. cit) was according to Sachs[50] (Liebig's Annal. 1878. 191. p 254) composed of Phosphate of Calcium & Carbonate of Calcium with adherent amorphous curarin. & certainly by Preyer's[59] method a crystalline curarin can not be obtained. Curarin gives with cold concentrated sulphuric acid a violet red colour (Boussingault et Roulin[65]. Sachs[50]. Boehm). 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 curare is not only entirely unsupported by practical evidence but is in addition quite contrary to all the evidence available. The necessity for these suppositions & theories has been removed by shewing 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, & to 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 to some extent even(?) to those with an alkaloid which cannot be obtained in a crystalline form & has been prepared from this crude mixture of the extracts of a number of plants, most of which are unknown

Condamine[9] thought that many plants entered into the composition of the curare of the Ticunas tribe (Upper Amazon) but Martius[5] (Husemann p536) believed that this poison was

was at least partly prepared from a Menispermaceous plant Urari Sepo ex Cocculus Amazonum. Herberger[43] (Hunefeld loc. cit) experimented with an extract from the bark of this Urari Sepo brought by Martius & found that it produced tetanus. Husemann[43] thinks it possible therefore that various curares may contain picrotoxin.

De Castelnau[23] (p114 et seq) also states that the Ticunas Indians of the upper Amazon district (Yapura river &c) mainly employ two plants in the preparation of curare & these have been named by Weddell - Strychnos Castelnaeana & Cocculus toxicoferus. The latter is stated to be a Menispermaceous plant (Synonym Eko. Pani Icè. Cocculus Amazonum). Couty & Lacerda[52] (p709) state that they have experimented with Cocculus toxicoferus & have found it to be a convulsant poison resembling picrotoxin & 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 Planchon[53] (p105) points out, its flowers are not known & the species therefore doubtful. He thinks that the leaves resemble other genera (Chondrodendron &c) rather than Cocculus. Jobert[54] in a communication

to the French Academy (4th Jan. 1848) repeats that probably Strychnos Castelnaeana (Wedd.) & Ekko (prob. Cocculus toxicoferus (Wedd.)) enter into the composition of this curare. Here again however it is very much a matter of conjecture. While it is possible that a picrotoxin acting body may be present in this particular curare, it has not been proved that a botanically identified Cocculus is used; it has not been separated chemically from any curare; altho' large numbers of experiments have been made with all sorts of curares during the last 40 years or so tetanic 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[55] (p328) where small doses of a Venezuelan curare caused symptoms indicating stimulation of nerve centres, large doses being required to paralyse the nerve ends. - the very opposite to what occurs with most curares & to what always occurs with curarin.

Absolutely conclusive proofs that the tetanic symptoms produced by curare are due to curarin & not to this active principle (Picrotoxin in Cocculus toxi) 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 <u>crude curare</u> therefore can give no satisfactory solution of the difficulty.

Perhaps the most accurate account of the preparation of any curare is that given by <u>Schomburgk</u>[24] (p450). Even this is indefinite, for, in addition to 3 species of Strychnos, it is stated that 3 other plants were added "which to all appearance belonged to the same order as the Strychnos" It is impossible therefore to say that the curare of British Guiana is solely an extract from Strychnos 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 Strychnos might contain some tetanising principle.

On the other hand it is improbable that the tribes over a vast region would add the <u>same extra plants (tetanising)</u> in addition to <u>the essential one (paralysing)</u> & yet we find that <u>all curares</u> produce both paralysis & tetanus. It has been

further shews 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 & 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 Castelneana (Weddell) the basis of the curare of the Ticunas, Oregones, Pebas & Yaguas tribes in Upper Amazon District. Perhaps Str. Yapurensis De Castelnau Planchon[53] (p 492)

2 Bejuco de Mavacoure a bindweed of the Strychnos family basis of the curare of the Maquiritares and Piaroas in the upper Orinoco district Humboldt & Bonpland[21] (p 519)

3 Strychnos Gubleri in the same district (Planchon[53] p 589) brought from Venezuela in 1867 basis of the curare of tribes near the Cassiquiare & Jemi rivers.

4 Rouhamon Guyanensis (Aublet) or Strychnos Guyanensis (Martius) the basis of the curare of some Guiana tribes. Heuseman[43] (p 528).

5 Strychnos toxifera (Schomburgk) (Benth) Hooker (p 710)
6. Strychnos Schomburgkii (Klotsch)
7. Strychnos cogens (Benth:)

These three species are stated by Schomburgk to form the basis of the curari of the Macusi Indians in British Guiana Schomburgk[234] (p 445)

8 Strychnos Crevauxii (Planchon) basis of the curare of the Roucouyennes & Trios Indians in French Guiana & found on the banks of the Parou an affluent of the Amazon.

Crevaux[57] p 1023 Planchon[53] (p 693)

A number of experiments have been, in past years, made with extracts obtained from the barks of South American Strychnos plants, & the symptoms observed have been those ordinarily attributed to curare - paralytic symptoms only.

Schomburgk[234] (p 445 d 34) mentions an experiment made by his brother with the bark of Strychnos toxifera. Part of a concentrated decoction was administered to chickens (two) Symptoms of poisoning appeared 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.

MM. Couty et de Lacerda[52] (p583 1879) made experiments with an extract obtained from the bark of a common Brazilian Strychnos plant - Strychnos triplinervia (Martius). This plant is not not known to enter into the composition of any curare. It was found to have a feble 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 feble paralysing action, which was not exactly of the same character as curare, for often great depression ~~depression~~ & weakness occurred, without ~~without~~ complete paralysis of motor nerve ends. Robert[58] (p647) also found that Strychnos triplinervia acted in this manner. The first mentioned authors remark (p583) that " Tous ces " extraits ont été beaucoup moins toxiques " que le curare &c. " & 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.

MM. Couty et de Lacerda[52] (p721) also made some experiments with an extract from parts of Strychnos Castelnaea (Wedell) & found that it had a curare action

(p 719) " le Strychnos castelnæa, quoique plus
" riche que le Strychnos triplinervia, est moins
" actif qu'on aurait pu le supposer, et le
" produit d'ébullition de 50 grm. de fragments
" de tige n'ont pas suffi à curariser un
" chien de petite taille "

It must be noted that this experiment was with an extract obtained from the Wood so judge from the results obtained by Crevaux[57] (p 1023) (Lobert[58] Mr) other parts of the plant, most probably the bark, are much more active. In the case of Couty et de Lacerda'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 in warm & cold blooded animals cannot possibly demonstrate the tetanising action of a body which has both a tetanising & a paralysing action, & where the latter is the stronger of the two

Lobert[58] (p 646) also states that his experiments with extracts from the South American Strychnos plants shew that they act as paralysing but not as tetanising poisons. " J'ai experimenté
" avec des extrait de toutes ces strychnées.
" Leur action physiologique est la même;
" elles n'agissent pas comme tetanisant

" contrairement aux Strychnées de l'Asie
" ex again p647 " Les Strychnées Américaines
" du Sud agissent d'une façon identique.
" Elles ne sont point tétanisantes ▽ " "

The " I have experimented " of Robert unaccompanied by any explanation cannot by any means be accepted as proving that those Strychnos barks "are not at all tetanising" 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] (p1033) states that the single bark of the Strychnos Castelnæa 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 (Crevauxii) (named & described by Planchon[53] p693) Its watery extract has a weaker action than that of the Strychnos Castelnæa 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 shew that the extract has not a tetanising action which is concealed by the paralysis.

Lastly, Villiers[59] (p653) states that the extract derived from the bark of the Strychnos de l'Orinoque (Planchon) brought from the Orinoco district in 1881 by Crevaux has the chemical & physiological actions of curarine. No experiments are described. Although Villiers' paper is headed 'Strychnos toxifera', the bark he examined was not got from Guyana; nor does it agree with the Strychnos toxifera (Benth) described by Hooker (fil. 240) & by Planchon[53 & 60] (p756). It is evidently closely allied to it (Planchon[60] p30)

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 Strychnos toxifera bark, sufficient however to settle this complication.

It is admitted that a Strychnos bark is the basis of ordinary curare. It is also admitted that the active principle obtained from crude curare is chiefly curarine, therefore we may expect that the bark will yield curarine. But I have shewn that curarine produces both paralysis & tetanus. It must be an error (if this is true) on the part of these authors to say that Strychnos barks

which have a truly curare like paralysing action, have only this action & do not cause tetanus

In the first experiments the strychnos toxifera bark obtained from Dr. Holmes 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 thin parts, but orange red where thicker. Here & there among the yellow granules were were crystals (lime) more or less covered 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 ($\frac{1}{20.000}$ th) caused in a frog (pithed) weighing 26 grammes distinct weakness in 15', & complete reflex paralysis in 45 minutes. Larger doses caused paralysis 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 0·00000028 grm. = 0·00000736 gramme this X 20.000 = 0·14720 gramme which would shew nearly ¼ per cent of curarin for 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 Boehm at Leipzig. A few weeks later he wrote confirming the extraordinary activity of the specimen, stating that it contained at least from 4 to 5 per cent of curarin

A frog (tibia) was now prepared by tying the heart, abdominal aorta & one aorta V.C. at the heart as described in the experiments on curarin

Jany. 89. Experiment by injection into an artery.

11. 35 am. About 1/180 th of filtrate = 0·0008 gramme curarin made up to ·5 cc with water injected into the untied aorta.

11·40 Occasionally a slight spasmodic movement, otherwise quite quiet.

11·43 Injection of about the 1/50 th of filtrate = 0·003 grm. curarin made up to ·5 cc with water

11·45 Marked spasmodic movements of all the unparalysed parts - especially the legs

11·50 Unmistakeable tetanus the lower extremities being absolutely rigid. When a general spasm of the unparalysed muscles is not present, individual

muscles & groups of muscles are attacked by frequent spasms. Reflex tetanus easily induced.

These & other experiments were 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 crystallinic salt to form & the chemical examination, so far as the small substance available would allow, shewed the active principle to be identical with curarin. Boehm's confirmation made this certain.

Mr. im Thurn M.A. Oxon., author of 'Among the Indians of British Guiana', states that Strychnos toxifera 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 curare 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 cord of the active principles of plants other than certain species of Strychnos may be dismissed for a single strychnos bark (Toxifera) is sufficient to yield large quantities of a curarin which is chemically & pharmacologically identical with the pure curarin separated from curare by Boehm. 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 strychnine combined with some organic body in the form of an ammonium salt.

Valentin[62] (p352) believes that curare ~~curare~~ contains strychnine, because, in the first place, it is derived from Strychnos plants (Schomburgk) & in the second place, because it gives reactions which show that it contains that alkaloid (Wittstein. Koch). The first reason we have seen to be quite insufficient, & the second is only partly acceptable, - some of the reactions are similar to strychnine 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 strychnine 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 clonic spasms "wechselkrämpfe" which are always weak, soon disappear & 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) strychnine & yet, that its administration does not produce tetanus, it is suggested that the strychnine is combined with some organic body after the manner of methyl or ethyl strychnium but that curare is not actually methyl or ethyl strychnium, since the muscle curves and symptoms after poisoning with these substances do not quite correspond with those obtained after the administration of curare.

Gubler[85] (p392) makes a statement somewhat similar in kind. He suggests that the reason why curare, a substance certainly derived from the

Strychnos family of plants in South America, acts as a paralysing and not as a tetanising poison, is that methyl or ethyl strychnium is formed, & that these as shewn by the experiments of Crum-Brown & Fraser & Jolyet & Cahours are paralysing but not tetanising poisons.

p682 " dans les remarquables résultats
" obtenus en France et en Angleterre à l'aide
" des dérivés de la strychnine résultats dont
" personne, à notre connaissance, n'a eu
" 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-strychnine offrent une singulière
" analogie avec celles du curare. Elle nous
" apparait dans les expériences de Crum-
" Brown et de Thomas Fraser aussi bien que
" dans celles d'André Cahours et de Jolyet "

Bartholow[63] (p558.) practically expresses the same idea (1884) " that a remedy
" obtained from members of the strychnos
" family of plants and a paralyser in action
" should antagonise Strychnine is a remarkable
" fact. In the process of preparation
" employed by the Indians it is in a high
" degree probable that Methyl Strychnine is formed,
" & this substance, as was originally shewn by
" Crum-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 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 of Strychninn body ?

There are Six accounts by eye witnesses of the native preparation of Curare.

1. Condamine.[19] Mem. de l'Acad. des Sc. t XII 1745 p 391.
2. Bancroft.[20] Essay on Natural History of Guiana. London. 1769 p 288.
3. Castelnau.[23] Relation d'une exped. dans les part. centr. de l'Amériq: du Sud. 1843-7 pp 14. 17. 20
4. Humboldt et Bonpland.[21] Travels to the Equat. Regions of the New Continent 1799-1804 London 1877 vol v p 518
5. Schomburgk[24] Reisen in Brit. Guiana. Leipzig 1847. vol 1 p 450.
6. Im Thurn.*[61] Among the Indians of (British) Guiana. London. 1883 p 311.

These accounts agree in describing the process "

* Thurn's remarks p 344 that "the effect of curali is gradually to diminish & finally to stop the action of the heart of any animal into the blood of which it enters" Mr. I. has perhaps heard this from natives or others but of course it is quite erroneous.

as the concentration of an infusion or decoction made from a number of barks. Humboldt[21] & Schomburgk[24] give very complete details. The essential bark was pounded, packed in a leafy funnel, & cold water allowed to percolate slowly through the mass. The yellow coloured 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 darts. The addition of this glutinous matter changed the colour of the fluid to black. Further concentration was obtained by exposure to the heat of the sun (Schomburgk loc. cit.)

The accounts of some of the early writers are evidently absurd. Foreign matter - serpents' teeth &c. - has been found in some curares & 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 <u>decomposed</u> more or

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 strychnium, & 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 nerve ends, which is not the primary action of strychnine. The basis does not therefore exist from which the methyl & strychnium 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 & strychnium, — the curarin being a yellow amorphous substance, not forming crystalline salts & giving with strong sulphuric acid in the cold a red violet colour, (Boehm' p190) whereas the methyl strychnium differs entirely on these points (Stahlschmidt [64] p 522)

But what is equally conclusive is the physiological test. The minimum

paralysing dose of the sulphate of methyl Strychnium (a very soluble salt & much more active than the Iodide - (Crum Brown & Fraser[65] p 160)) was found to be 0·0008 gramme for a frog weighing 34 grammes (Buchheim & Loos[66] p 206.) That is to say 0·000024 gramme per gramme weight of frog. But the same quantity of pure curarin produces tetanus and ~~100~~ 85 times less has an equal paralysing 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 & brought forward have therefore been shewn 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 paralysing action on motor nerve ends does not act as a tetanising agent on the cord & vice versa. This is very well shewn by Testuts conclusions on akagga (M'boundou) bark, which was found to cause tetanus in small doses & paralysis with large. It was held therefore (Vulpian cited by 18 p 621) that 2 principles were present, one causing tetanus & the other paralysis. Heckel & Schlagendauffer Vulpian. loc. cit. shewed 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 67 (p 331) gives most of the bibliography.

If a perfectly pure strychnine salt causes tetanus in small doses & paralysis of motor nerve ends in large, (the protected part being in violent tetanus) there can be no objection to the alkaloid of

another species of Strychnos causing paralysis in small doses & tetanus in large doses (the unprotected parts being paralysed)

Kolliker[3] (p339) 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

Bernard[2] (p312) & Pelikan[6] (p405) speak of strychnine & curare acting in an opposite manner, but, obviously, they only speak of the prominent actions of the poisons in ordinary doses & give no proof to shew that strychnine does not in large doses paralyse the motor nerves.

Walton[68] (p315), 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 weakens the conclusion. Walton therefore concludes that there is no similarity between the actions of curare & strychnine - an altogether erroneous conclusion.

As none of these authors state that they have tried large doses their conclusions have really no value on this question.

Now, the proofs on the opposite side are absolutely conclusive, & as the matter is very important in connection with any comparison with curarine, 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 curare; or at least that large doses paralyse.

1. Müller[69]. Handb. der Physiol. Coblenz. 1844 i. 549.
2. Matteucci[70] Traité des Phénom. électro phys. Paris. 1844. p243
3. Moreau[71]. Compt. Rend. 1855. p143.
4. Ambrosoli[72] Gaz. Médic. 1857 p525.
5. Vittich[73]. Bericht über der Fortsch. der Anat. 1857 p434.
6. Martin-Magron & Buisson[5]. Journal de Physiol (Brown-Séquard) 1860 t iii p342. (they give above citations)
7. Richet[74] Compt. Rend. July 1880. 91. p131
8. Vulpian[75] Compt. Rend. Feb. 1882. 94. p555

& Leçons sur les Subst. toxic et médic[18].

10. Rongers[77] Arch. f. Anat. u Physiol. 1884 p334
9. Heckel & Schlagendauffer[76]. Journ. de l'Anat et Phys. 1881 ii 153 (cited by Vulpian p621)

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

(1) Tie the sciatic artery and vein in one extremity of a frog, and, - that the paralysing action may be very clearly seen - inject sub-cutaneously 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 freely on direct stimulation.

(2) Tie one sciatic artery & vein and cut both sciatic nerves & poison as before. Convulsions 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 paralysed.

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 tetanus, 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 gm. per kilo in the dog) into a vein (Richet[74] loc. cit. Fulpian[75]). The convulsions quickly disappear, & artificial respiration requires to be maintained to prevent death, just as in curare poisoning. The heart & circulation continue good for hours. When artificial respiration is stopped, the heart continues to beat for several minutes & asphyxia causes no convulsions. On exposing the Sciatic nerves & vagi not the least effect is produced by strong electrical stimulation but the muscles readily contract on direct stimulation. (Fulpian[78] p. 88) 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 & confirmed by Wood 6th p330)

Wood remarks " such doses probably kill
" the nerve centres just as large doses of a
" cardiac stimulant overwhelm & paralyze the vagus".

The experiment referred to however gives us no information as to the condition of the nerve centres. Vulpian & Richets' experiments shew that the heart & circulation continue good after the motor nerve ends are completely paralysed. The experiments on protected frogs shew, further, that the protected part continues in active tetanus long after the unprotected parts are paralysed. 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, &, 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-Magron & Buisson - have

on the other hand, been made to shew that their 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 0·00001 gramme produce tetanus in small frogs without any paralysing action on the ends of moter nerves, while 0·00001 gramme of Curarin produces complete paralysis of the ends of moter nerves without any tetanising action on the cord. On the other hand, in protected frogs, 0·001 gramme of Curarin (& less) causes immediate paralysis of the unprotected parts, & when fallacies are avoided, violent tetanus of the protected parts, while 0·005 gramme of Strychnine causes violent tetanus of the protected parts, & complete paralysis of the moter 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 analagous 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 curarin 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 &c. 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 & Fraser[65] shewed to be so general. For example, tetra-methyl-ammonium in a dose of g. 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 inhibetory 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 ⅛ 0·02 gramme 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 curarin is administered.

In some of the modified alkaloids, where it is unnecessary to carefully consider the changes introduced by the <u>increased paralysing power</u>, the protection of parts, alterations in the time of appearance, order & strength of symptoms, <u>the fatal dose</u> &c it is easy to determine that there are <u>characteristic actions</u> – for example Methyl Atropium dilates the pupil, just as Atropine does. (Crum. Brown & Fraser [65] f. 404.)

It is necessary therefore to examine carefully <u>the nature & completeness</u> 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 <u>wide</u> conclusion is not quite warranted, and there is ground therefore for testing its correctness.

Stahlschmidt[64] prepard & experimented with the methyl strychnium salts in 1859. He found (p 523) that doses which were very large, when compared with active doses of strychnine, (0.11 gram. gramme in a rabbit in 24 hours) were without poisonous activity and concluded therefore that the new body was inert.

Schroff[78] experimented in 1866 with the nitrate of Methyl Strychnium. He found that it caused symptoms of paralysis of a curare like kind. Reflex tetanus sometimes occurred at recovery, (De Bry- Imang. Dissert) and Schroff sought to explain this, by the supposition that strychnine was liberated in the body by the decomposition of the methyl strychnium salt.?

I have not been able to get the paper by Schroff for further reference.

Crum Brown & Fraser[65] 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 paralysing 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 cord, 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. When, – as in the case of curarin, – 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. strychninum salts & the cause of death. Crum. Brown & Fraser's 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 34 experiments recorded, set aside the 28 on warm blooded animals. These consisted in the administration of the methyl strychninum, by the stomach & subcutaneously, to rabbits &c; & terminated in the more or less speedy death of the animal, when the

minimum dose which paralysed 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, & 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 strychnium salts depends entirely on the different details of dosage, duration of observations &c & 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-strychnium
" 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 & on stimulating it with a weak
" interrupted galvanic current, movements occurred in
" the tied limb only; not the slightest effect occurred
" in any part to which the poison had access. At
" the same time the muscles were everywhere active, and
" freely contracted when directly stimulated. The
" sciatic nerve was then exposed in the tied limb
" above the points of ligature, & on stimulating it
" energetic movements occurred below the knee of
" that limb, & there only. The heart was at this
" time acting at the rate of 50 per minute

" This experiment was repeated with one
" grain of Iodide of Methyl-Strychnium & 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,
" excepting that its origin & insertion, & the nerve
" fibres entering it were untouched that all its
" bloodvessels were ligatured. One-tenth of a grain
" of sulphate of methyl strychnium 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
" & 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 4 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, & after the necessary stimulations the experiment was as described concluded. In the last 2 experiments, one muscle was protected, & 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 53·1 grammes, received therefore about 5 times the minimum paralysing dose. In the second experiment the frog weighed 39·8 grammes, received about 4 times the minimum paralysing dose of the sulphate.

Crum Brown & Fraser have demonstrated very clearly, by these experiments, the great change which the addition of Iodide of Methyl has produced in the symptoms - paralysis 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 Strychnium 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, & 20 minutes or so where one muscle is protected. A tetanising 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 was tried, & this, as we have seen in the case of one body acting on motor nerve ends, (curarin), is not free from fallacy.

Jolyet & Cahours (p 904.) experimented in 1868 with Methyl Strychnium salts. They found that pure preparations could be obtained as Iodide of Methyl acted readily & strongly (p1108) on Strychnine. Small doses caused paralysis in unprotected frogs in 15 to 20 minutes. Larger doses produced (p905) tetanic symptoms in the protected part "quelque temps après que les nerfs moteurs ont "perdu leur excitabilité'" These tetanic symptoms were weaker, & of much shorter duration than those produced by Strychnine.

Crum Brown & Fraser [50] (p560), in criticising this conclusion, suggest that the convulsive movements could readily be explained by the presence of Strychnine, as an impurity, in the methyl Strychnium 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 convulsant symptoms were removed.

No doubt, if a methyl Strychnium salt causes tetanic symptoms soon after an ordinary dose has been administered subcutaneously, it is impure.

Crum Brown & Fraser do not mention any new experimental evidence, & apparently therefore,

refer to what they have already shewn in the experiments 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 Jolyet & Cahours' methyl strychnium was impure, it is yet to be ascertained how a pure specimen does act, at later stages of the poisoning.

Buchheim & Leo's[66] (p205) experimented in 1840 with a large number of substances which acted as paralysing agents on motor nerve ends. Among these were Methyl & 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 undertaken 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 paralysing dose for a frog weighing 34 grammes was 0·0008 gramme, and that when 0·01 gramme 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 shew 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 ligature 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 & Loos 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 tetanic

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[62] experimented in 1873 with an Iodide of methyl strychnium obtained from Flückiger, & a sulphate of methyl-strychnium obtained from Fraser.

He found, before recording the muscle curves, that the Iodide (p229) in small doses, in unprotected frogs, caused feeble strychnine like spasms. Larger doses caused paralysis.

The sulphate (p234), in a dose of 4 mgm., caused complete paralysis in 3 or 4 minutes, without any appearance of spasm. When the poison acted more slowly or feebler (1·5 mgm.) it produced symptoms resembling the Iodide, the frog shewing, 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 curarized 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 strychninum. Attention is chiefly directed to the action on the vagus N., & the spinal cord is not specially referred to.

Before making experiments on the fatal action of methyl strychnium very care was taken to ensure that the preparations used were pure

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

An Iodide of methyl-strychnium was obtained after the method described by Stahlschmidt[64] (p 514). As Iodide of Methyl acts very strongly upon Strychnine, (Jolyet & Cahours[19] 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·grm) was mixed with recently precip- chloride of silver (4 grm.) & water (100 grm.) & 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 any unacted upon by the Iodide of Methyl might be expected to be got rid off.

The residue was then crystallized from absolute alcohol in which Strychnine is almost insoluble (Fresenius p 356)

The crystals shewed under the microscope as fine glistening 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.

Wm. Dott, for Messrs Duncan Flockhart & Co. Edinburgh, made an Iodide of Methyl Strychnium 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 Strychnine being formed. I do not know (private) if finely powdered Strychnine was treated with the Iodide of Methyl, as in Stahlschmidt's process, or whether the Strychnine was dissolved in chloroform, & then the Iodide of Methyl added.

When a saturated watery 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 Strychnium.

As the Iodide is not freely 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 Strychnium

sulphate was extracted with absolute alcohol. & obtained on evaporation in the form of tufts of fine needle shaped crystals.

On dissolving .5 gramme in 10 c.c. distilled water (5% sol^{n}), & rendering the solution alkaline with Sodium carbonate, no precipitate formed, but, on the second day, a violet red colour began to appear (the hydrate Stahlschmidt p 519 or oxidation products). The greatest quantity of strychnine which 10 cc. water (cold) would dissolve is about 0.0017 gm. therefore, assuming that this was present, means were taken to get rid of it, by repeatedly shaking up the solution (.5 gramme in 10 cc) 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 cc 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 & extracted with a small quantity of absolute alcohol. Filtered. Tufts of fine needle shaped crystals were obtained, with a fine powder where evaporation was rapid. This product weighed 0.259 gramme.

I can see no possibility of the least trace of strychnine being present. or if so, since the active dose of Methyl strychninium sulphate is 0.001 to 0.005 gramme, its 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 (sulphate ?) employed by Cunn Brown & Fraser.[65]

Experiment. IV Frog 37 grammes. Temp^{re} 22° C.

Imi. after administration 0 Minutes. Injection of 0.003 gramme in .3 cc water into ant. thoracic sac of frog weighing 37 grammes. The post. extremities protected as usual.

8. Head rests on the table & respiration feeble.

10. Respiration ceased. Corneal reflex absent. Heart 46 per minute - strong. When laid on back the legs keep extended without movement.

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

20. Reflex in protected part good.

30. Reflexes can hardly be obtained. About 40 pinches, both light & severe, all over the protected & nonprotected parts caused no movement, just as often occurs with curare, & then when it seemed as if the animal was paralysed a vigorous reflex movement occurred.

50 During the last 20 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 3 pinches " " "

57 6 " " " "

58 34 " so that the "reflexes are" rather depressed, or easily exhausted.

Time after administration in minutes

75 Reflexes much more acute now. Every stimulation, especially if sudden tho' slight, acts no matter where applied. The reflexes are in the form of sudden jerks, not complete extensions, 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 tetanus lasting 3 or 4 seconds.

105. Several spontaneous jerks & twitches of legs & toes

110. Distinct tetanus of lower extremities on tapping the head with the forceps. 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 gramme to a frog weighing 43 grammes - a larger relative dose than that employed by Crum Brown

& Fraser - motor paralysis followed in about 3 minutes in the unprotected parts. Up to 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 & 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 & a half after, & signs of weakness soon appeared.

While in some experiments the tetanus was quite unmistakeable, in others it was feeble, & 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, more or less, to those bodies which paralyse the ends of motor, & probably vasomotor 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 22 per minute, the energy was good & the heart was of considerable size during diastole, being well filled with blood. On injecting 0·005 gramme Methyl strychnium sulphate dissolved in ·2 cc water into the thigh (subcutaneously) the heart, after a few minutes, began to shew some diminution in size. After 15 minutes the heart was much smaller & its 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, & resembled the heart of a frog which had been bled to death, or where complete vasomotor paralysis had been caused by the destruction of the spinal cord. After a little more than an hour the reflexes in the protected 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 flexed. The reflexes were then tested, & found to be quite simple. On applying ·1 cc solution, containing 0·002 gramme of the sulphate, to the cord no effect followed for nearly 7 minutes & then sharp tetanus set in. During the next 30 minutes

the faintest touch to any part renewed the spasms

At the same time, in a third frog, a solution (·25 cc), containing two or three milligrammes of the sulphate, was injected directly into the aorta, after the preparation described in the experiments with curarin, & marked tetanus immediately followed & 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 ½ minutes & 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 curare, to an impairment of the circulation, & consequent imperfect diffusion of the poison & 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 & strychnium salts, because (1) attention has been chiefly directed to the action on motor nerves & experiments have been terminated before the convulsant action could manifest itself; (2) a spinal action has not been anticipated, & has not therefore been specially looked for (3) the impaired absorption & diffusion has been overlooked.

These results show clearly that pure methyl strychnium 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 & removed.

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~~ alters the order & intensity of ~~symptoms~~ the actions, & thereby the symptoms, dosage mode of death &c. In methyl strychnium, the tetanising action of strychnine on the cord is delayed & diminished, & the paralysing action on motor nerves hastened & increased.

By artificially giving to strychnine the constitution of an ammonium base its characteristic actions are not destroyed, but the order & 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 analagous results to those which in this instance follow the process of chemical addition occur when the process of substetution is employed, as when the H in morphine ($C_{17}H_{18}NO_2-OH$) is replaced by an alcohol-radical ($C_{17}H_{18}NO_2-OC_2H_5$) = codethyline (Grimaux)

Here is a marked <u>decrease</u> of the narcotic action, & an <u>increase</u> of the tetanising action in <u>Codeine</u> ($C_{17}H_{18}NO_2-OCH_3$) or methyl-morphine. The ethyl sub-stitution bodies derived from morphine give tetanus with small doses, but paralysis with large doses (Bochefontaine cited by <u>Schroeder</u> 82 p117)

In addition to the chemical change having modified the narcotic & tetanising actions the action on moter nerve ends is also affected. This action with very large doses of morphine is <u>just</u> perceptible, but with a large dose of codeine in a frog (0·01 grm.) 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 shewing tetanic symptoms

It is hardly necessary, before concluding this part of the examination, to refer to the bygone statement by Bernard[2] (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 misinterpretation of experimental facts, where, 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 motor paralysis of the bloodvessels of that limb, which will generally therefore (Vulpian[18] p 493) receive a greater share of curarine containing blood than the limb with the intact nerve, where, as has been shown, the circulation is slowed & the arteries narrowed at the beginning of poisoning with small doses (Kolliker[13] p 44) (Ellis

As the total quantity of curarine necessary to produce paralysis of the whole body is only about 0·00007 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 Curarin, & long after the spinal cord was paralysed, 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, & where 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 nerve on the undivided side is only apparent, & is due (Martin Magnus & Burnison[5] p361 Exp 8th) 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 unwearied muscles of the other side. (Kolliker[3] p303) (Peiper[6] p173)

Vulpian[8] (p193) in addition suggests that the violent muscular contractions may favour the paralysing action of Strychnine on the endings of the nerves in some way. But this action is trifling with small doses of Strychnine & the condition is sufficiently explained by the muscular exhaustion.

This is not a true difference therefore between Curarin & 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 & depression of the reflexes & often closely resembling paralysis of the cord or sensory nerves.
2. That the spinal cord is not directly paralysed by curarin, but, after the administration of large doses by subcutaneous injection an actual depression & paralysis of the cord 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 ensues, but complete uncertainty exists as to the quantity which is absorbed & reaches the cord. When this fallacy is avoided in experiments, an increase of reflex excitability & tetanus is invariably observed. This conclusion is confirmed by special experiments on warm blooded animals

4. That similarly every 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 tho' 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 of Schomburgk (British Guiana) (Benth.) 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 & African strychnos barks, & the curarin of some of the South American strychnos ~~plants~~ barks are quantitative rather than qualitative - both producing tetanus & 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 strychninum 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 shew 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 curarin, to paralysis of the circulation.

The action of Curarin on the Blood Pressure.

An experimental research on the action of pure Curarin on the circulatory apparatus should prove of some value & interest because uncontrollable disturbances & obscurities in the results of experiments do appear in the employment of crude curares 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, & it was impossible to say, 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 curares & 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 Traube[83] and von Bezold[84] on the action of the arrow poison on the circulatory organs of warm blooded animals.

Traube[83] experimented on dogs & found that with the vagus intact injections of 12 milligrammes 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[84] who experimented on rabbits summarizes his experiments as follows;- that, on cutting the vagi & sympathetics the injection of small doses of the arrow poison caused an increase of the blood pressure from 100 to 160 m.m. & 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 14 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 & quickening of the heart, & later, on increasing the dose, the opposite occurred.

Stimulation of the spinal cord after poisoning with small & medium doses still produced a considerable rise of blood pressure even altho' the vagi were already paralysed.

Long afterwards (1876 &c.) curare was specially employed in some physiological observations on the innervation of the blood vessels & 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 Latschenberger & Deahna[85] the following passage appears (p159) in the introduction to the experiments & may be rendered 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 metronome. As is known there is a curare which like Strychnine 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 to us, but if it sank then it was suitable. With the curare of the first kind one does not obtain a regular tracing & cannot tell whether the features are independent or appear as the result of influences. But in spite of

" <u>good curare</u> there are rabbits, which on the other
" hand are so sensitive that one <u>cannot obtain</u>
" <u>a regular tracing</u>; such animals cannot be
" used. These are large French rabbits, especially
" young animals

In another part of the same paper the authors directly attribute certain symptoms to a <u>strychnine containing curare</u> p 143 " The stimulation of the centres does not
" only shew itself in waves; <u>strychnine con-</u>
" <u>taining curare</u> 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 (s Fig. 22) "

<u>Gaitzner & Heidenhain</u> [86 (p 514)] in the course of experiments in the same direction in 1878, observed in many cases during the action of small & medium doses of curare in rabbits, marked & long continued rises of blood pressure in consequence of exceedingly slight stimulation of the skin (blowing of the breath &c), while strong & 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. G. & H. did not think that the

cause of this strong increase of blood pressure lay in psychical influences, because the same phenomenon 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.

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

Most authors consider that curare does not directly affect the heart, but Rezold[8] (1684) & Vulpian[18] (1868) especially draw attention to the fact that a large dose of curare may stop the heart. Vulpian cannot explain this because as a rule the heart seems unaffected. This symptom is considered in treating Curin.

The condition of the vagus nerve during curare poisoning has been investigated in detail by Boehm[87]. His experiments are exclusively on cats, & shew that, after the inhibitory function of the vagus is paralysed, further stimulation produces a quickening of the heart's action through the accelerater fibres which still remain active.

Different authors have made observations on the action of curare on vasomotor nerves.

Vulpian[78] (1895. 320 f. 326.) found that the vasomotor nerves were only slightly weakened by curare, if excessive doses were not employed, & that one could obtain all those results which could be obtained through experiment on non-poisoned animals. The vaso constricter & vaso dilater nerves continue active, & all reflex vasomotor actions can be studied after the motor nerves are paralysed. Vulpian could only destroy their action (vago sympathetic & lingual) in dogs after exceedingly large doses, doses which readily paralysed the vagus action on the heart.

Gaskell[88] (1873) 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 dilater nerves & left the constricters intact. He also mentions that v. Frey "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- "maxillary gland, yet greatly diminished that "action. He further mentions Eckhard's statement "that stimulation of various parts of the cord "produces no erection of the penis whatever, as soon as sufficient "curare has been given to just paralyze all "muscular action, but, instead, that there is "a diminution of flow from the cut surface "of the corpora cavernosa during the stimulation"

Bernstein[89], 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 Gaskell in his experiments on the muscle vessels. He also considered that no contraction of vessels occurred (p 599) + slowing of the blood stream - the immediate consequence of the nerve stimulation in the living animal - because the experiment was not under the same conditions as in life.

Vulpian[18] (p 301) states that he has made many experiments in deeply curarised animals, where, on stimulating the peripheral end of the divided sciatic nerve with a very strong faradic current, a diminution + cessation of the haemorrhage occurred from a wound in the foot, without any muscular contractions in the limb - shewing therefore a constriction of vessels. On stopping the stimulation the haemorrhage recommenced + again ceased on resuming the stimulation.

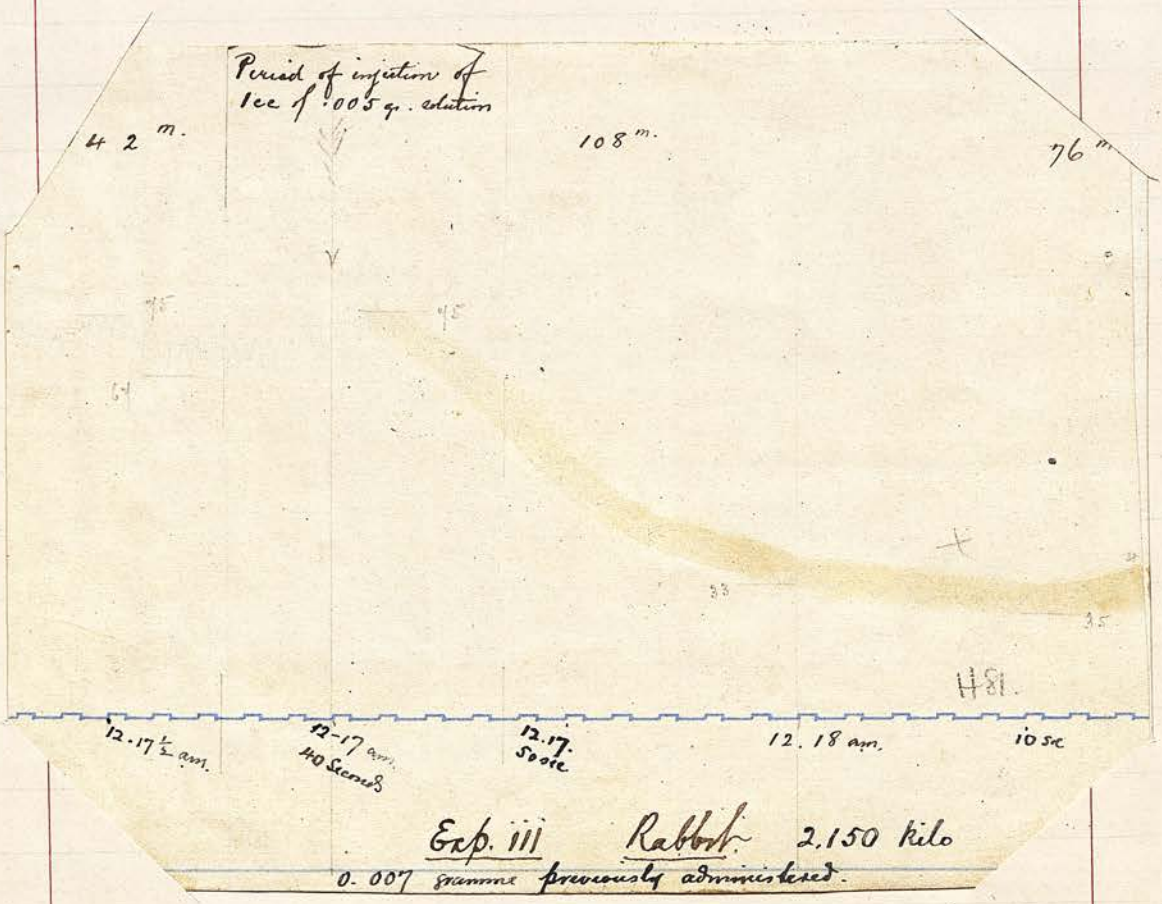
Kobert[90] (p 105) found, as in Bernstein's experiment, that the stimulation of the sciatic nerve produced, when curarised blood was circulated

through the limb of a dog an increase of the blood stream. When blood was circulated through the posterior extremity of a dog, ex through a horn of a sheep's uterus, & curare added, a strong quickening of the blood stream followed.

The experiments by Waters (p 461) 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 oesophagus, stomach intestine &.

Bowditch & Warren[41] and Ellis[41] (p 437) 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 rythmical electrical stimulation" of the nerve causing in the cat & frog dilatation of the vessels, while "shocks of a greater degree of frequency cause 'an immediate contraction'"

Couty & Lacerda[52] (p 725) state that the fall of blood pressure which occurs after large doses of curare is due to a paralysis of the unstriped muscle of the vessels.



Exp. iii Rabbit 2.150 kilo

0.007 gramme 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 vaso motor centres in rabbits is especially interesting

I The injection of watery solutions of Curarin into the bloodvessels (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.

II 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 min:

III When the dose is very large (say 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.

IV The minimum complete paralysing dose for the rabbit by intravenous injection was about 0·0002 gm per kilo of body weight. But the action of the minimum dose was very brief. After 0·0003 – 0·0005 gm. the diaphragmatic

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 gramme, in from 30 to 90 minutes & longer.

Some examples of the fall of pressure are given below.

Table I

Animal (intact)	Amount & number of Dose	Pressure at time of the injection	Lowest pressure reached	Maximum amount of fall	2mi after injection before maximum depression reached	2mi after injection before pressure recovered original level: often only for brief pe
Cat	1st 0.001	176 mm.	42 mm.	134 mm.	2¾ minutes	3 minutes.
	2nd 0.002	156 "	122 "	34 "	40 seconds	6 "
	3rd 0.003	140 "	54 "	86 "	3 minutes	Remained for 10 min: at 54 mm. & then quickly returned to 140 mm.
Cat	1st 0.0015	164 "	120 "	44 "	2 "	10 minutes
	2nd 0.0015	140 "	100 "	40 "	3 "	4 "
	3rd 0.002	140 "	78 "	62 "	80 seconds	14 "
	4th 0.01	125 "	56 "	76 "	2 minutes	9 "
Cat	1st 0.001	180 "	152 "	28 "	65 seconds	5 "
	2nd 0.0015	167 "	130 "	37 "	40 "	8 "
	3rd 0.005	155 "	87 "	68 "	120 "	not recovered
	4th 0.01	135 "	59 "	76 "	40 "	2 minutes
Dog	1st 0.001	141 "	146 "	25 "	120 "	4 "
	2nd 0.005	158 "	130 "	28 "	30 "	1⅔ "
	3rd 0.01	203 "	100 "	103 "	80 "	did not again rise beyond 164 mm.
Rabbit	1st 0.001	125 "	very irreg. tracing	146 mm. Maximum 96 " Minimum		
	2nd 0.002	121 "	no change on average pressure but maximum raised & min. lowered.			
	3rd 0.004	130 mm.	93 mm.	37 mm.	120 seconds	8 minutes.
	4th 0.005	142 "	81 "	61 "	60 "	5 "
	5th 0.004	143 "	75 "	68 "	60 "	no further rise above 130 mm.
	6th 0.005	102 "	23 "	79 "	120 "	no recovery above 66 mm.

V

In rabbits the initial fall of pressure may not be observed or be very slight when small & medium doses are injected very slowly

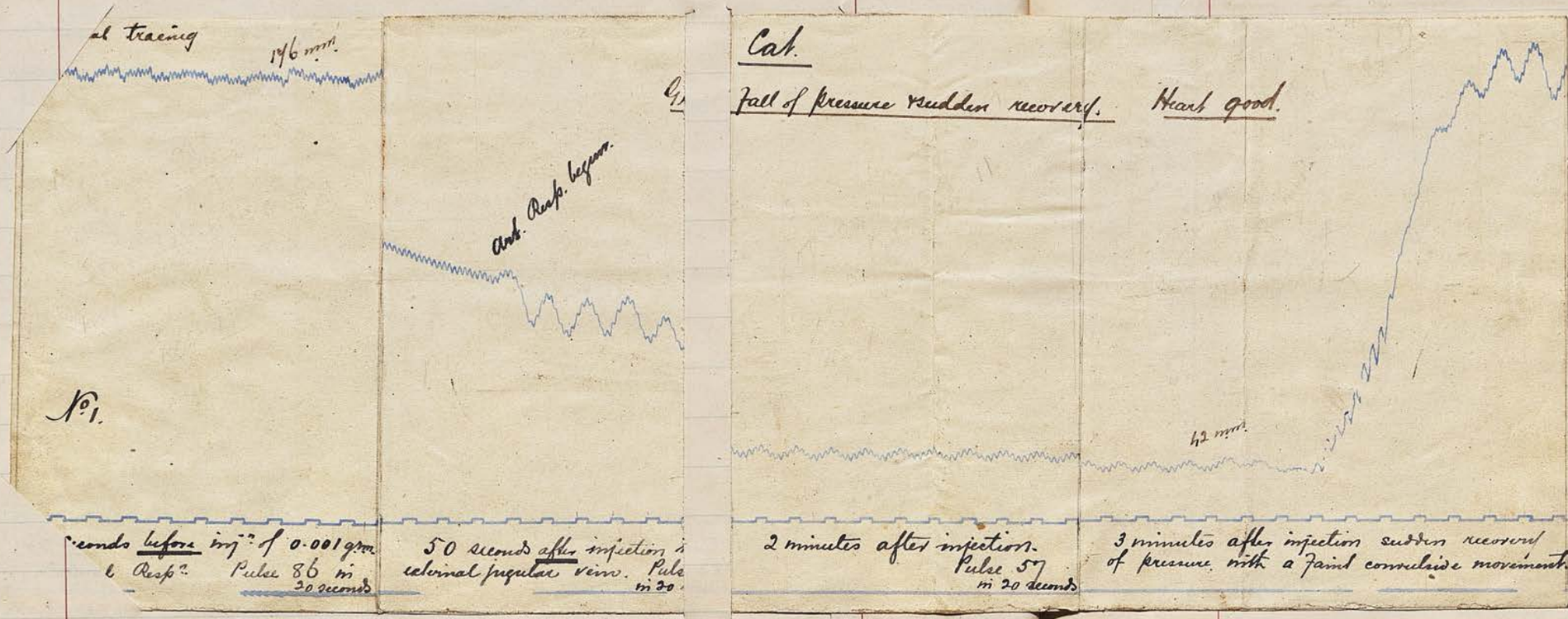
VI

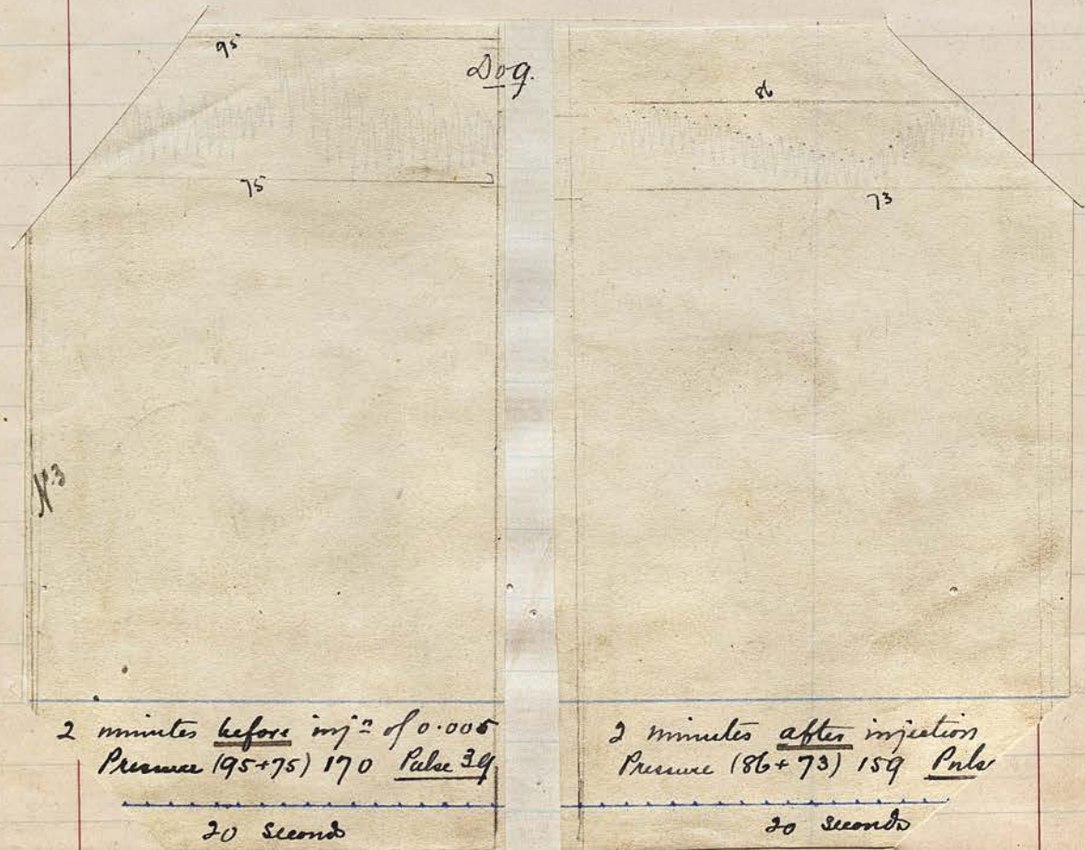
This fall of blood pressure immediately on injecting the poison appears under the following conditions

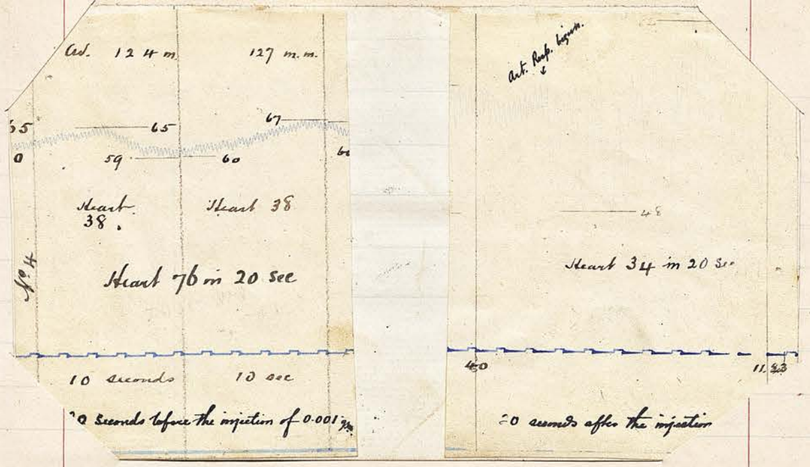
1. When the injection is made into either a vein (jugular or saphenous) or an artery (upper end of carotid). It cannot therefore be due to any local action on the heart.
2. When the inhibitory action of the vagus is excluded, by previously dividing both nerves or by administering a paralysing dose of Atropine
3. When all central influences on the heart have been removed by dividing all the nerves passing to it (depressor &)
4. When the influence of the vaso motor centres is removed by previous section of the spinal cord at the neck
5. When the central reflexes are paralysed or depressed by a sopotific eg. Methane

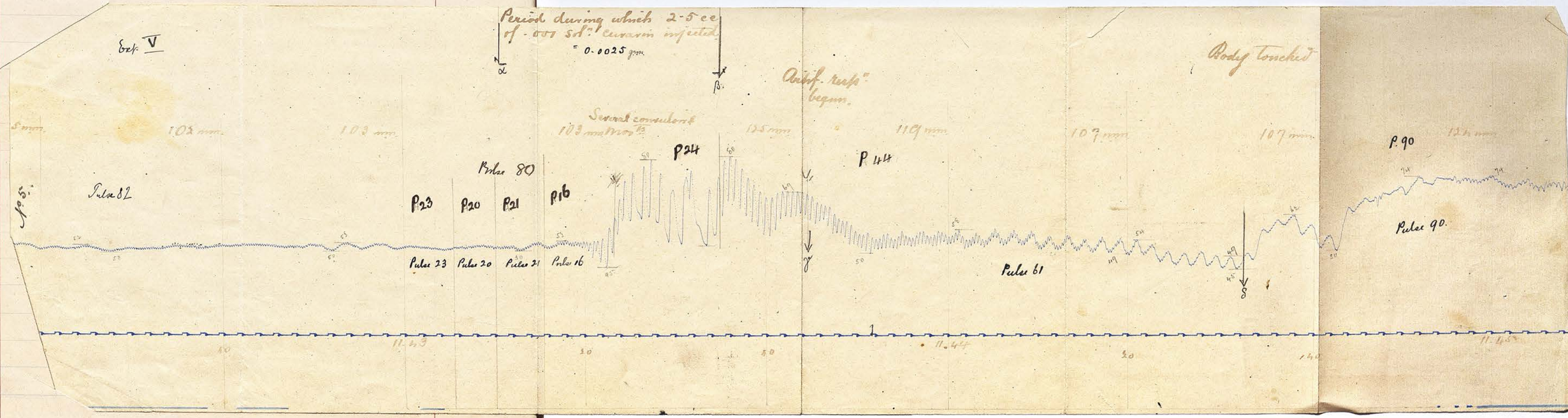
The cause of the passing fall of pressure would appear to lie therefore in the vessels themselves.

The character of the tracing during this temporary fall of pressure is shewn on the accompanying tracings on the next page.


al tracing
146 mm.
Art. Resp. began.
No 1.
Cat.
Fall of pressure sudden recovery. Heart good.
42 mm.
seconds before inj^n of 0.001 grm
& Resp^n Pulse 86 in 20 seconds
50 seconds after injection
cervical jugular vein. Pulse in 20
2 minutes after injection.
Pulse 57 in 20 seconds
3 minutes after injection sudden recovery of pressure with a faint convulsive movement.


95
Dog.
86
75
73
No 3
2 minutes before inj^n of 0.005
Pressure (95+75) 170 Pulse 39
20 seconds
2 minutes after injection
Pressure (86+73) 159 Pulse
20 seconds


Heart 76 in 20 sec
Heart 34 in 20 sec
10 seconds before the injection of 0.001
20 seconds after the injection


Period during which 2·5 cc of ·001 Sol.ⁿ curare injected
= 0·0025 gm.
Artif. respⁿ begun.
Several convulsions
Body touched
Pulse 82
Pulse 80
Pulse 23
Pulse 20
Pulse 21
Pulse 16
Pulse 61
Pulse 90.

The primary fall of blood pressure produced by small, but motor paralysing, 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 grm. 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 gramme reduced the pulse rate from 258 per minute (blood pressure average 176 mm.) to 171 per minute (blood pressure average 42 mm.) 3 minutes afterwards. 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 shewn 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 paralyse the vagus. In the dog & cat it seems to depend on the change in blood pressure as well.

VIII In rabbits slight convulsive movements occur usually 15 or 20 seconds after the administration of small doses (·001 - ·002½) of curarin. Their causation has been discussed in the early part of the paper.

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

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

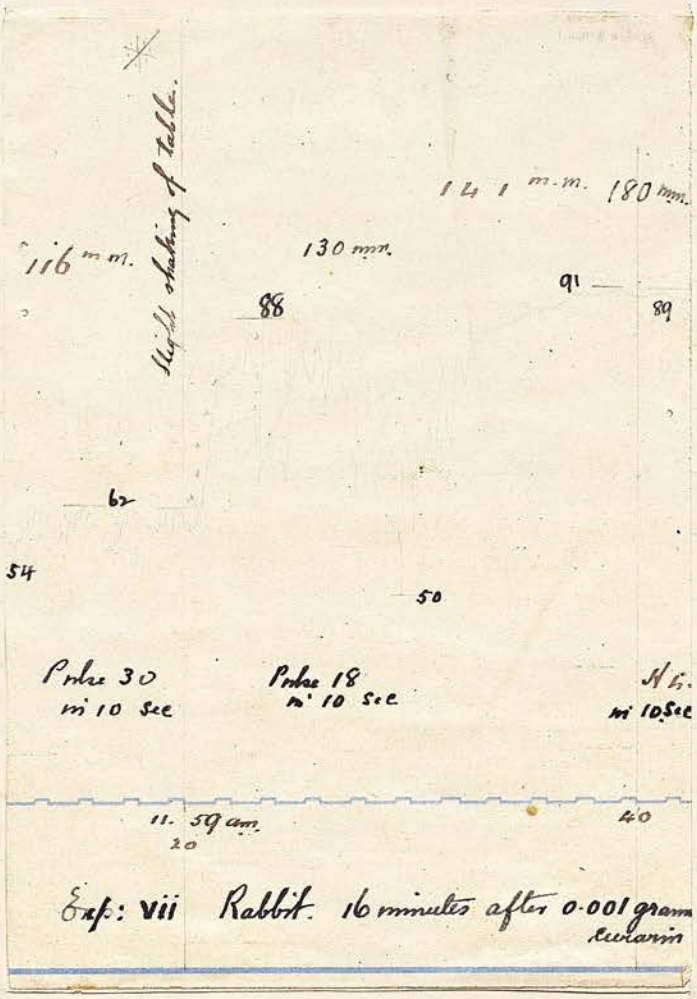
XI When somewhat large doses of curarin are administered the vagi are quickly paralysed, & the rate of the pulse varies after a time with the changes of tension produced by further doses, & with secondary causes.

XII The blood pressure tracing in dogs & cats is, after the administration of any dose of curarin, very regular & usually free from unexpected variations. In rabbits however the tracing is only regular & constant after the administration of large doses. Small moter paralysing doses of curarin cause immediately on

the injection long pointed waves (vagus pulse), accompanied by a fall or frequently enough a rise of pressure. This is well shewn in the tracings.

XIII Very soon after the injection in the Rabbit 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 curarin, a slight stimulation be applied to the paralysed animal - such as puffing the breath on the fur covering the abdomen &c - there usually occurs a almost instantaneous often 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 30 to 78 millimetres of mercury. The total pressure frequently reaches 170 & 180 mm., an exceedingly high pressure for a medium sized rabbit. When the tracing is watched for say an hour marked rises 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, pinching the rabbits 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 shews great irregularities. If the pressure is not too high

No 6



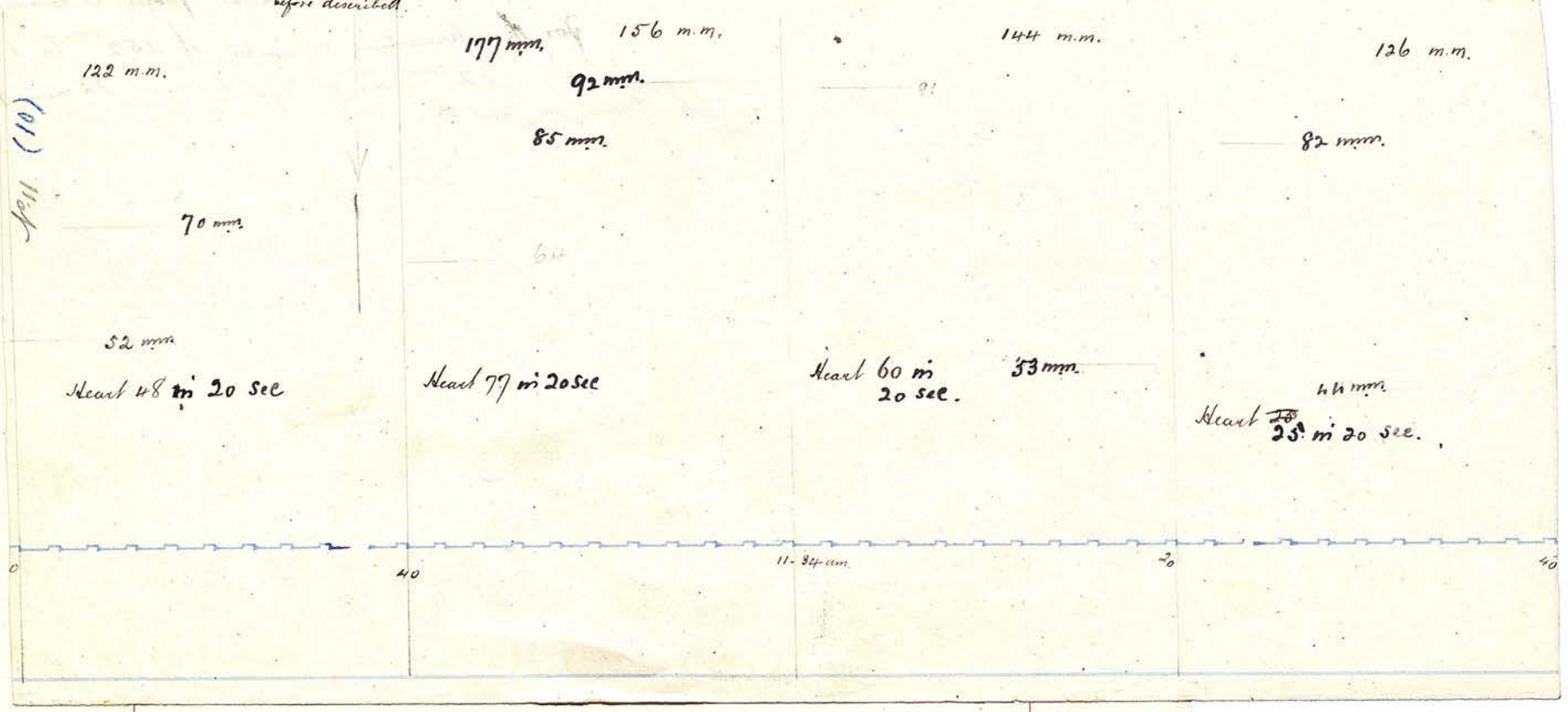
Exp: VII Rabbit. 16 minutes after 0·001 gram
Levarin

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. (62+54) & the pulse 30 in 10 seconds, but, 10 sec. afterwards, with the pressure 88+50 = 138 mm. the pulse was about 18 in 10 seconds, & showed a marked vagus type. Ten seconds later, as the pressure still rose, the regulative function of the inhibitory centre became weaker, & was finally quite set aside when the pressure reached 180 mm. (91+89), the heart beating at the rate of 45 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. & 45.

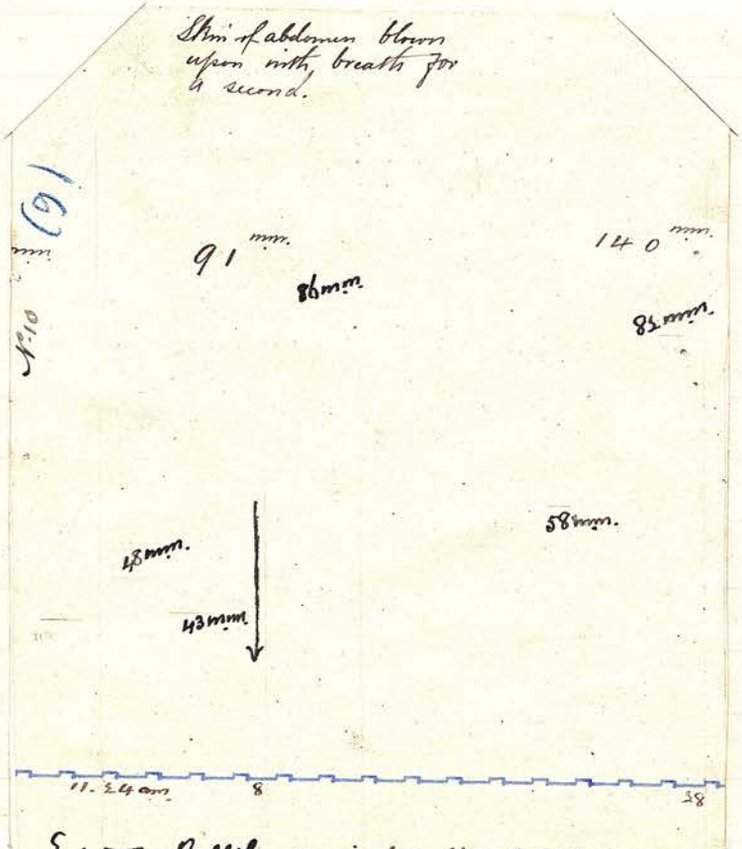
By & by, as the tension gradually falls, the tracing shows sudden descending curves as the vagus action succeeds in asserting itself for a moment. After this, when the vagus action is no longer overcome by the high tension, there may be a considerable length of tracing shewing a vagus pulse before there 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 its 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
(2.150 kilo.) rapi intact.

Skin blown upon for a moment as before described.



Skin of abdomen blown upon with breath for a second.



Exp. IV Rabbit. 4 minutes after 0.001 gramme curare
(1690 grammes)

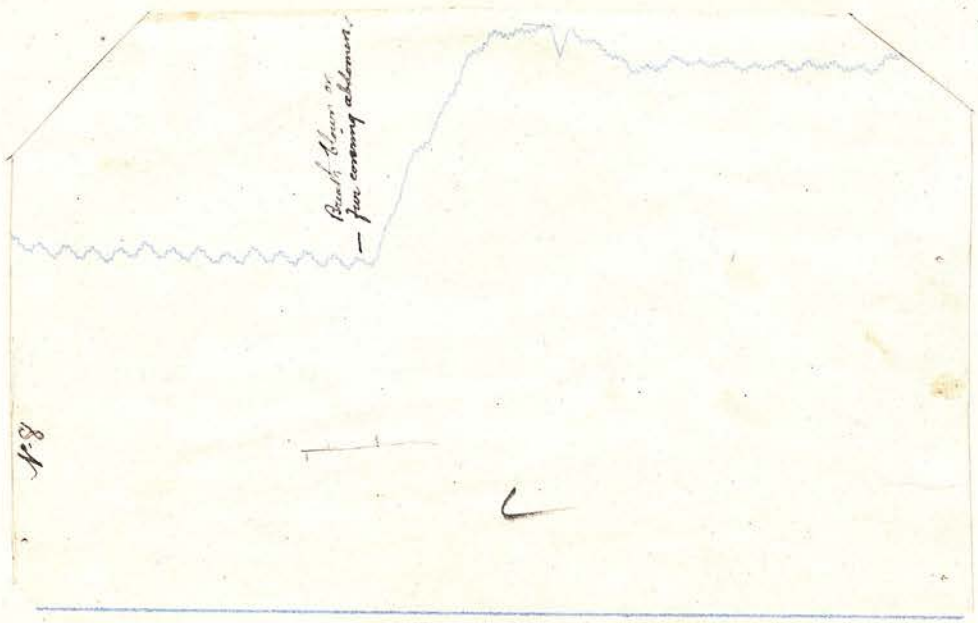
to a relatively slight extent.

Examples of action of slight stimuli in Rabbits completely paralysed by Curarin & kept alive by artificial respiration

Blood Pressure tracings

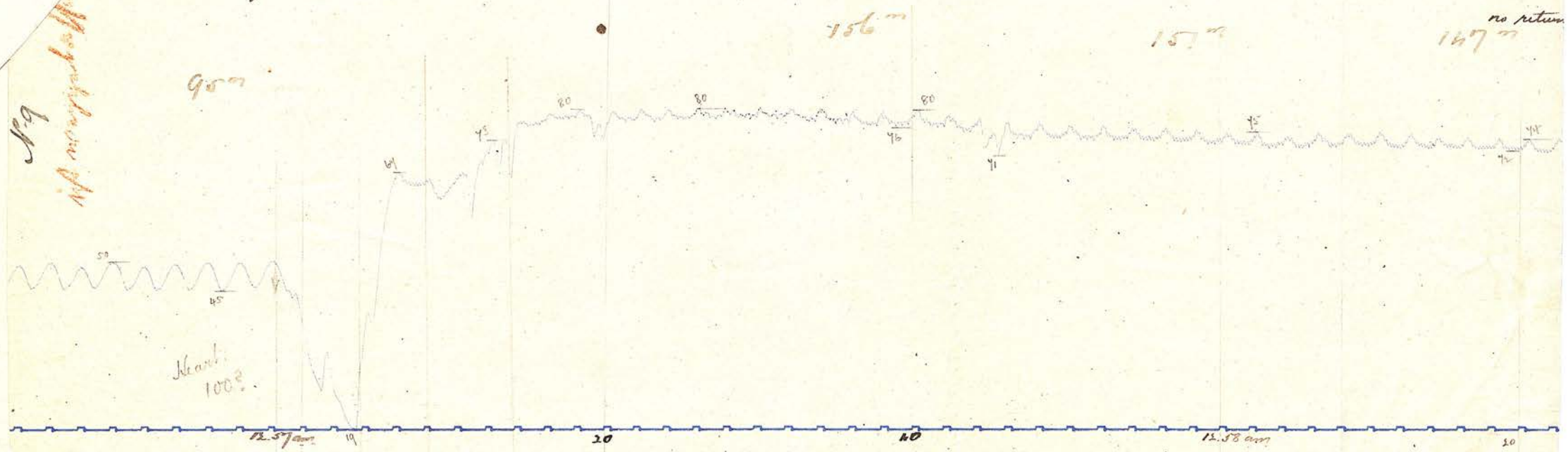
Exp.	Dose of Curarin	Max. point of pressure before stimulation (blowing on skin)	Max. point of pressure after stimulation	Max. amount of rise	Time taken before max. point reached	Time before pressure returned to previous level
III	0·001	146 m.m.	174 m.m.	28 m.m	4 seconds	4 minutes
	0·002	142 "	186 "	44 "	4 "	2 "
	0·004	132 "	174 "	42 "	10 "	Continued
	0·005	134 "	144 "	10 "	6 "	1 minute
	0·004	100 "	112 "	12 "	6 "	20 seconds
	0·005	66 "	no effect.			
IV	0·0005	96 "	172 "	76 "	3 "	10 minutes
	0·001	100 "	158 "	58 "	4 "	15 "
		108 "	130 "	22 "	3 "	20 seconds
	0·001	80 "	90 "	10 "	5 "	4 "
		78 "	126 "	48 "	4 "	3 minutes
V	0·0025	98 "	124 "	26 "	5 "	Continued
		100 "	150 "	50 "	6	10 minutes
		92 "	112 "	20 "	3 "	5 seconds
		130 "	no further rise			
	0·003	99 "	109 mm.	10 "	3 "	5 "
		88 "	no effect.			
VI	·0008	114 "	Skin thrown upon	several times during first 15 minutes without effect.		
		122 "	140 mm. spontaneous rise	48 "	4 Seconds	50 seconds
		132 "	182 "	52 "	14 "	1 minute
VII	0·0025	116 "	158 " both vagi cut	42 "	5 "	4 "
	0·0005	98 "	150 " after stimul. lower end of vagus.	52 "	20 "	5 "
		100 "	160 after stimul. lower end of vagus.	60 "	9 "	6 "
XXXI	0·005	98	158 after atropine	60 "	5 "	Continues

No 8



Rabbit. Vagi fully paralysed by Atropine. Tracing 2 minutes after administering 0.005 grammes curarin.

Stimul of right vag. lower end. for 5 Secs. Strength. 100 mm.



Rabbit Exp. VII. Vagi cut. 0.001 gm curarin

On the tracing opposite is shewn 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 shewn in the other tracings.

Also on the tracing opposite is shewn 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.

XV

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

1. Division of the spinal cord at the neck
2. The administration of a soporific substance eg. 0·5 – 1· grm. Urethane
3. The administration of a large dose of Curarine.

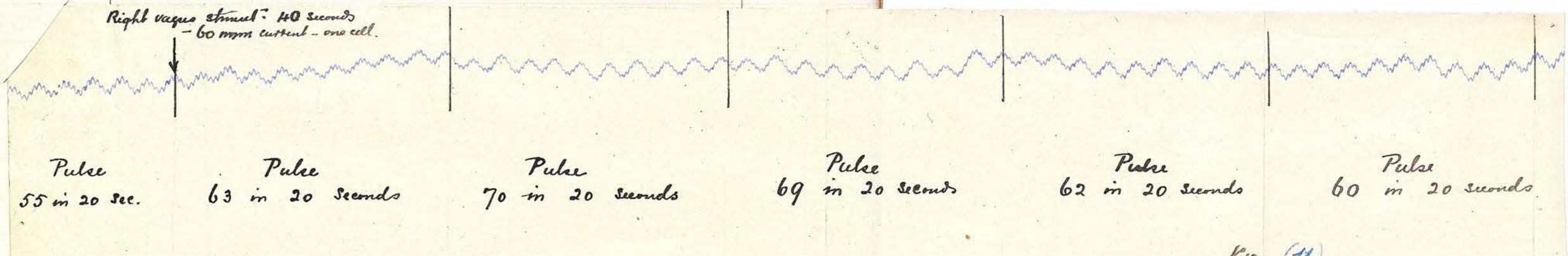
The tracings shew only negative features on blowing on the skin. In the first case the influence of the chief vaso motor centre is cut off, in the second its reflex excitability is blunted & in the third the reflex

excitability cannot manifest itself owing to the peripheral paralysis.

This increase of the reflex excitability of the vaso motor centres is a distinct feature therefore of the action of the active principle of curare. It is this which was described by Latschenberger & Deanha 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 Heidenhain & Grützner in curarised rabbits. I have only tried two sorts of curare in this direction, & both gave the same results as with curarine.

XVI 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 vaso motor centres are only stimulated with a large dose the result could not well be observed on the tracing owing to the peripheral depression.

XVII It is known that the inhibitory action of the vagus on the heart is suspended by curare. Several milligrammes of curarine (eg 0·005) usually cause this. Slight differences occur in different animals in the amount of resistance offered by the vagus to the



Pulse 55 in 20 sec.

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

No 12 (11)

Exp. iii. Cat. after 0.008 gramme curarin

paralysing action. The vagus of the rabbit seems most resistant, the cat least so & the dog intermediate.

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

1. R. Vagus stimulation for 40 seconds with current of 60 m.m. (single cell) in Cat after 0·008 grm. curarin
The pulse before stimulation was 56 in 20 seconds
The rate each 20 seconds during & 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 mm. (single Grove cell) in cat after ·0012 grm. curarin
The pulse before stimulation was 63 in 20 seconds.
The rate each 20 seconds during & 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 mm (single Grove cell) in same cat.
The pulse before stimulation was 63 in 20 seconds.
I 64 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 20 seconds following, & then a gradual return to the former rate during the next minute.

XIX In all three animals, the vagus nerve recovers its inhibitory action before the motor nerves distributed to the voluntary muscles.

XX Even after very large doses of Curarine, of 20 to 40 times the paralysing dose (0.01 – 0.02 grm.), stimulation of the sympathetic nerve in the neck causes in the rabbit dilatation of the pupil.

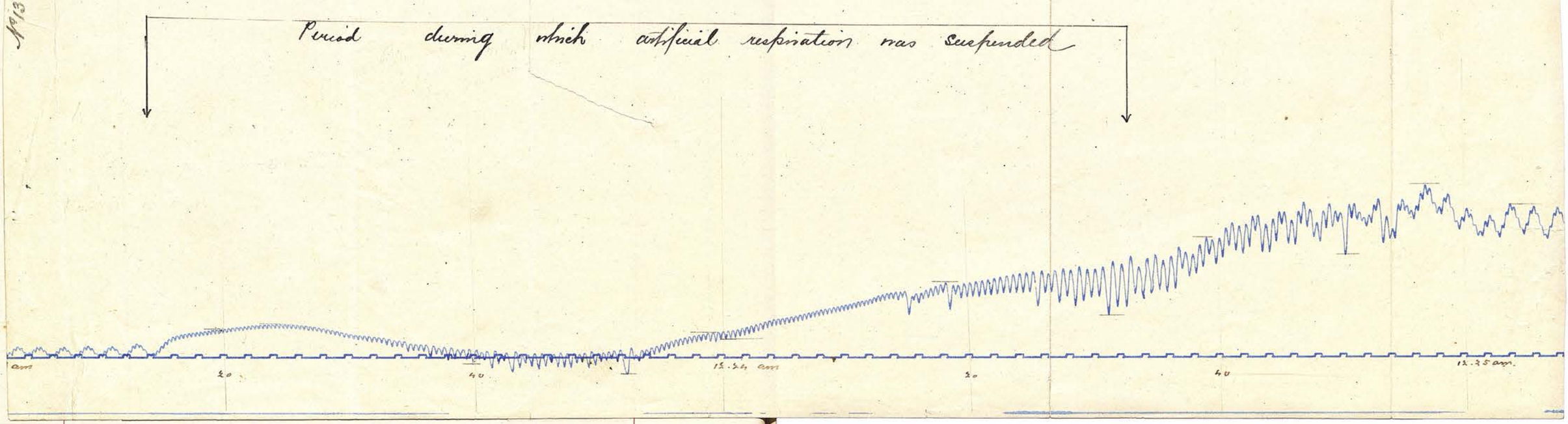
XXI After the inhibitory function of the vagus is, for the time being, paralysed in the rabbit (0.005 grm) the stimulation of the central end of the depressor nerve lowers the blood pressure distinctly, indicating the reflex activity of the vaso motor centres.

XXII 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 vaso 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 grm. & more the pressure sinks, & such stimulation no longer produces any effect.

XXIII If the spinal cord be divided in the neck in the rabbit between the 3rd & 4th cervical vertebrae, & a small or medium

Rabbit (1820 grammes) ~~1 hour~~ 59 mins. after administration of 0.001 grm. Curarin.
Cord previously divided in neck.

Period during which artificial respiration was suspended



paralysing dose be administered, direct stimulation of the spinal vaso motor centres 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 per cent - 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 worthy of note after the cord was divided. Schlesinger (cited by Wood[67] p332) found that Strychnine produced a rise of pressure after division of the cord but Klapp (cited by Wood[67] p332) in such experiments did not get any rise of pressure.

No. 14 (14)

90 mm.

78

69
147

*

90

80
140

Traube-Hering curves.

Cat. after 0.007 gramme curarin

Artificial respiration stopped.

Artificial respiration resumed.

No. 15

195 mm.

167 mm.

Traube-Hering curves.

Dog ( ) after 0.016 gramme curarin.

Artificial respiration stopped.

Artificial respiration resumed.

No. 14 (13)

11.59 am.

XXIV When the animal is ~~curar~~ completely paralysed by curarin & the artificial respiration is suspended the activity of the vaso motor centres is shwon in the Traube-Hering curves This is shwon on the two accompanying tracings.

XXV After the administration of small & medium doses stimulation of the splanchnic nerve readily raises the blood pressure. As the dose of curarin is increased up to 0·01 — 0·014 grm. stmulation has less & less effect. A still larger dose may be required before direct electrical stmulation of the cord fails to raise the pressure.

XXVI When very large doses of curarin are administered to the rabbit we obtain a perfectly regular tracing shwing a low pressure, which, as the poison is excreted, shwos a constant tendency to recover. If the large dose is adminstered at once, the pressure shwos considerable power of recovery, & may soon even exceed its original level. If an experiment is prolonged, & dose after dose be given, until, after 1 or 2 hours a large total has been reached, the lowering of pressure is very great & permanent. There 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.

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

1. Stimulation of the central end of the divided sciatic nerve, blowing on the fur &c.
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.

XXVIII Is the condition of the blood pressure after large doses of curarin 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 barium is injected, there is an immediate rise of pressure, although, previously, stopping artificial respiration & stimulating the upper end of

the divided sciatic nerve had no effect.
Now the initial fall of pressure is not due to any paralysing 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 grm. curarin into the jugular vein of a rabbit produced a steady fall of pressure from 130 m.m. to 120 mm. At this point, while the pressure was still falling & the animal was quite paralysed, the breath was sharply blown on the fur covering the abdomen for a moment, & the pressure almost instantly rose to 172 m.m. Meanwhile the injection was being steadily continued and an additional ·004 grm. had no effect in lowering the pressure.

Had no stimulation been applied, & the increased reflex excitability of the centres not 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 paralysing action of curarin on the vaso constrictor nerves as it passes along. As the poison reaches the capillaries, tissues & veins, comparatively fresh blood flows along the arteries, & they contract again under the normal

action of the centres. Unless the curarine 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, & referred to in the section on the early fall of pressure, the injection of only .001 gramme 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 grm. from 106 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) & the pressure rapidly rose to between 180–190 mm. as a maximum. When the pressure was at 160 mm. ·0085 grm. was injected rapidly & the pressure fell to 97 mm. A minute later ·015 grm. was injected & 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, & at 60 mm. (very strong current) the pressure began slowly to rise, & 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 sciatic nerve raised the pressure from 140 to 170 mm. The injection of .01 grm 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 cord 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 .02 grm curarin hardly any changed occurred in the pressure (11.22 am.) On stopping artificial respiration (11.29 am.) the pressure fell & the heart slowed. The ~~upper part~~ divided cord was then stimulated 5 times with electric currents (Sec. coil 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 minutes 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, & electrical stimulation (Sec. coil 120 mm) raised the pressure from 113 to 180 mm. On administering 0·003 grm curarin the usual reflex excitability followed but the pressure did not reach a higher level than 170 mm. After 31 minutes 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 rise of pressure to stimulation of the upper end of the sciatic nerve & stoppage of artificial respiration. On administering an additional ·005 grm. the pressure was further reduced to 50 mm. & now 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 Splanchnic nerve were tested in 4 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 secs with an electric current (sec. coil 120 mm.) caused a rather sharp rise of pressure of 20 – 30 mm. After the injection of .01 grm. the pressure quickly recovered, but after .02 grm. 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 shewing that the centres were active but could effect nothing, as in the case of electric stimulation, until the vaso constrictor nerves recovered. When stimulation of the splanchnic with this current raised the pressure about 10 – 15 mm. & stimulation of the upper end of the sciatic raised it 5 mm. the pressure was 70 mm.

Had the general pressure remained low & shown no recovery, while yet the same stimulation of the splanchnic produced an effect which shewed 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 curarine is concealed by the weakness or paralysis of the vaso 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 curarine 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 raso motor centres after large doses, but, on the contrary, the usual gradual recovery of the blood pressure within a comparatively short time from the administration, & coincident with the increasing effect of stimulation of the splanchnic nerve or spinal cord shews that the centres are in all probability acting very vigorously indeed.

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

The raso motor nerves are fully paralysed for the time at least by doses of curarin of 100 to 300 times the dose necessary to paralyse the motor nerves, & this paralysis is much more quickly recovered from than that of the vagus or motor nerves

It has already been shewn that curarin acts on the motor centres after the manner of Strychnine, & these observations on the vasomotor system in the rabbit add an additional & important proof.

One only requires to refer to the quotation taken from Latschenberger & Deahna's[85] paper

to emphasize the practical importance of this question in experimental work. Observations of the action of poisons on the heart might very well be made in curarized rabbits where the excitability of the centres was prevented by some soporific (urethane &c.) which had no special action, & where the vagus was not paralysed by a dose exceeding about 0·005 grm. curarin.

Accurate observations in curarized rabbits on the vascular nerves & centres must be extremely difficult. Although small doses cause no obscurity by paralysing the ends of vaso motor nerves, & so rendering the vascular system irresponsive 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. When large doses are given the vaso motor nerves are weakened more or less & 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 Fritzsche & Heidenhain &c have drawn attention to this action of some curares.

The conclusion that curarin stimulates vascular nerve centres just as it does motor nerve centres seems to be fully borne out by the symptoms produced in man

Encyc. d. Sc. méd. 1880 (Chauffe p 422)

Lioville & Vicsini[38] experiments shew, 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 & an increase of the secretions. Several times a marked rigor took place at the end of an hour & a half at the most, & lasted three hours at the most. The temperature in the axilla rose even to 40·4° C. The pulse from the commencement of the rigor was small & frequent, but, after the rigor, was bounding, the rate remaining the same or even increasing, the sphygmographic tracing shewing 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 36 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 dryness 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 & experiment) (Vulpian[18] p376 Vi), the polyuria & glycosuria. (Bernard[2] p342. Eckhard[92] p166 Vi. Ve.) have been frequently observed. The rise of external temperature referred to however by Vulpian[18] was associated with a fall of internal temperature & was due to the vaso motor paralysis, artificial respiration, & other secondary (p381) causes.

Röhrig & Zuntz[93] (1890) found that in curarized rabbits the regulation of warmth was reduced to a minimum, & the oxidation processes in the muscles paralysed. They took the blood pressure (p84) 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 hour of the poisoning.

Zuntz[94] (p537) observed later that when equable artificial respiration was kept up & only small doses of curare employed, the oxygen used & carbonic acid exhaled sank to one half

Jolyet[95] found that the carbonic acid exhaled was even more reduced than this, & Valentin[42] (599) observed in frogs that large doses of curare greatly diminished the quantity of oxygen absorbed & carbonic acid excreted. Observations on animal heat in animals completely paralysed are not comparable therefore to those made by Voisin & Liouville[38] on man, where the central influences were not neutralized or prevented. As the rise of temperature was not due to convulsions (muscular) 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 in part to a central action, because the curare by the motor paralysis & the chloral by paralysing the nerve centres prevents its development.

On comparing the action of strychnine & 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 ~~act~~ strongly on the vasomotor centres (·0005—·001 gramme in rabbits) without paralysing the vasomotor nerves, while small doses of curarin (·0005-·001 gramme) also stimulate the reflex excitability of the centres, but in dogs & cats 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 (·59 gramme of hydrochlorate in dog weighing 12 kilos Vulpian p 485) 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 (Vulpian loc. cit)

Small doses of Strychnine cause a marked rise of blood pressure, but it is very noticeable that this rise is followed (Demps p 319) by a fall in from 20 sec to 1 to 2 minutes below normal. Very often the tracing shewed no rise of pressure in his experiments during tetanus. When curare was administered to rabbits dogs & cats the pressure, on the contrary, shewed after Strychnine

marked & long 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 prevented. The rise of pressure in Demy's experiments on rabbits (VI & VII) from 100-156 mm. 105-160 mm. after slight stimulation could have been produced in a curarized rabbit without strychnine, as has been shewn in the tracings in the earlier part of this Section.

When very large doses of strychnine are injected into a vein the blood pressure just as in the case of curarin, immediately falls. This has been attributed by Klapp (cit. by Wood p333) to an immediate (paralysis) 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 paralysing doses of curarin.

When artificial respiration was kept up after these small doses sugar quickly appeared in the urine. When periods of vascular excitability 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 paralysing dose of curarin was administered but central stimulation & motor spasm prevented by a narcotic dose of urethan neither glycosuria or haemoglobinuria 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 sedative 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 pushed often before much benefit is got. The reputation

of other medicinal agents *per se* 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 noticing that Lactic acid has soporific properties (Medical Times ii. 1872. 205). If this supposition proves correct on trial then soporific substances generally will benefit diabetes, some which have no spinal & stimulant action may be of decided value.

The invariable 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 shews that in a perfectly healthy animal with its muscular system paralysed, a body which does not act on the blood, but which in a particular dose causes great reflex excitability of the vaso motor centres & periods of tetanus of the vascular system 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 milligrammes 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 & toes becoming white & dead, perhaps with a distinct rigor, & pain over the kidneys. In some cases the pulse seems to fall to 50 however & in others to rise to 90 or 100 (Tagge's Medicine 96 ii p588).

Nervousness is said to play a part in the disease, as it is seen particularly in persons whose fingers turn cold on excitement (Tagge's loc cit)

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 <u>vasomotor spasm</u> may cause the appearance of blood & blood pigment in the urine

If this on excluded examination should prove to be the cause of the symptoms in Paroxysmal Haemoglobinuria the treatment would obviously be to administer <u>central sedatives</u>, since these prevent the reflex excitability

Another disease which is typically one of vasomotor spasm is Agne. Here also blood not unfrequently appears in the urine, extensive deposits of blood pigment (Melanaemia) occur in different parts.

During the cold stage, when the vaso motor spasm is at its worst & the pulse is small & frequent, no treatment is usually adopted further than keeping the patient warm & 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 curarine, we might hope that the same results would follow in diseases where the symptoms indicated a similar disorder.

In this direction I observe a note in the last edition of Roberts' medicine 97 p233 "Dr. Mossmann, of Greenville U.S. informs me that "full doses of chloral, given just before the "expected paroxysm of intermittent fever, will "prevent its occurrence." This is exactly what one would expect, since chloral prevents the reflex excitability of the vasomotor centres.

It is recognized that emetics greatly assist the action of quinine in ague.

Brunton p375 remarks "indeed cases of ague
" may be sometimes cured by the use of emetics
" alone without Quinine, while Quinine without
" Emetics is not infrequently 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 weaken the heart & depress
the vasomotor centre, & if an attack of
ague can be prevented by a soporific
dose of Cheral, just as it prevents vaso
motor spasm in experiments on rabbits
with Strychnine & Curare it is a question
if ~~the~~ beneficial action of Quinine 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 medicinal use of Strychnine causes fits
in some cases resembling those of tertian
ague" (Lewin cited by Brunton p874). Brunton
suggests that these "were 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

in Ague has been observed – "a draught of cold air on the surface causing contraction of the cutaneous vessels & shivering" & "opium appears useful in such conditions probably by lessening the excitability of the vasomotor centre" (Brunton 16. p 867)

I would before this have tried the effect of sedatives to the vasomotor centres in preventing or stopping attacks of ague & made observations on the pulse in Paroxysmal 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.

Curin.

Vulpian[18] (p360-2) speaks of cases where curare paralysed the heart, the auricles beating twice as fast as the ventricle, which was finally arrested from failure of the cardio-motor 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.

Bezold[8], Paul Bert,[52] & Couty & Lacerda[52] (cit. p698) also note 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 shewed a constant quivering movement. Both were filled with blood. With doses 20, 50 & 100 times larger the heart never shewed any sign of failure, apparently because the exceedingly high & sudden changes in tension were removed.

Leaving out of account those cases of simple cardiac failure, (mechanical) the circumstance that a curare may act on the heart is amply

& satisfactorily explained by an examination of curin.

All the reagents for the alkaloids give in watery solutions of curare voluminous precipitates. Boehm (p176) 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 - Curin. Boehm found curin in a variety of curares. but especially in those which left a considerable insoluble residue when treated with water. This residue contained much curin. It is not very soluble in water, has a bitter taste, is precipitated by the reagents for alkaloids as a colourless & amorphous body, & unlike curarin, it gives no characteristic reaction with concentrated oil Sulphuric Acid (Boehm p179)

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. (·001g) causing the death of a rabbit weighing 1.6 kilo. Boehm states (p180) however that 5 to 10 milligrammes of curin itself is without action in frogs & rabbits. He seems only to have directed his attention to a possible action on motor nerve ends, (curin has not this action) & not observed therefore

the change in the heart.

As Boehm's chemical examination of Curare is not yet complete, & as it is not yet certain that the specimens obtained from different curares are quite pure & identical with one another, it is only necessary to examine it sufficiently to shew how fallacies may arise in working with crude poisons in exp: ~~work~~.

Exp. 1. Frog. 19th Oct. 1887. No 1 Curare.

p.m. 3.43	Heart exposed – regular, well filled. strong. Rate 34 per. min.	
.49	Rate 37 per min.	
.50	Injection of .004gramme in 5cc into the thigh.	
54	" 40	
4.2	Injection repeated.	
7	" 42	A part of the vent. near the aortic bulb bulges during systole.
14	" 43	The centre & left side of the ventricle contract first & become pale while the right side & apex are still red & distended.
17	" 30	Ventricle occasionally stops & its contraction is quite disorganised. Sometimes the contraction is vermicular & at other times different parts of the ventricle contract quite irregularly.
21	Auricle 44 " Ventricle 34	More regular contraction of ventricle.
23	" Aur. 42 " Vent. 21	do
30	" Aur. 44 Vent. 22	do
42	" Aur. 41 Vent. 30	Upper half of ventricle contracts while the apex is bulged out & red. During the diastole red lines appear across the ventricle.
	20th Oct.	
10 am.	Aur. 24 Vent. 12	Action of the ventricle peristaltic.

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 20th Oct, 24th Oct & 2nd Nov: similar results were obtained.

Exp V 24th Feb. 1888 Curare No 2.

6. 20 p.m. Heart exposed. Strong, well filled regular

31. Rate 20 Inj.n .01 gramme in .5cc into thigh Subcut.
35 " 22
40 " 24
50 " 28

7. Inj .007 . . .3cc " "
10 " .01 . . .5cc
25 " 30 Systole very prolonged but incomplete. The ventricle dilated with vermicular movement.
30 " 22 Pause of the ventricle for 10 seconds.
35 Stopped in diastole Occasionally the ventricle makes an abortive attempt to contract.
40 Several drops of a 1% solution of atropine caused no change. The respiration reflexes & motor power continue good.

25th Feb.

10 am. Frog dead. Ventricle small rigid.

Exp. VI 27th Feb. 1888 Curare No 2

10. am. .01 gramme in .5cc water injected subcutaneously in frog weighing 50 grammes.

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

1.10 p.m. Aur. 8 (feeble) per min.
Vent. 4 (strong).
20 " 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. Frog dead. On forcing blood into the ventricle it contracts but tends to remain contracted
On exposing the sciatic nerve & Stimulating it the muscles contracted fairly well.

Exp. VII 27 Feb. 1888. Frog. Curin N°2

Heart exposed at 4.20 pm. found acting well.

4.20	Rate 36	Inj: ·0050 in ·25 CC.
5.10	" 38	All parts of the ventricle do not relax at the same time the systole is long but less perfect than usual.
5.45	" 34	The heart is in a state of complete but feeble peristalsis. The ventricle is always contracting but yet remains large & red & never is emptied.
6.20	Vent. 10 Aur. 20	The base of the heart contracts first & the blood is driven into the apex which is bulged out.

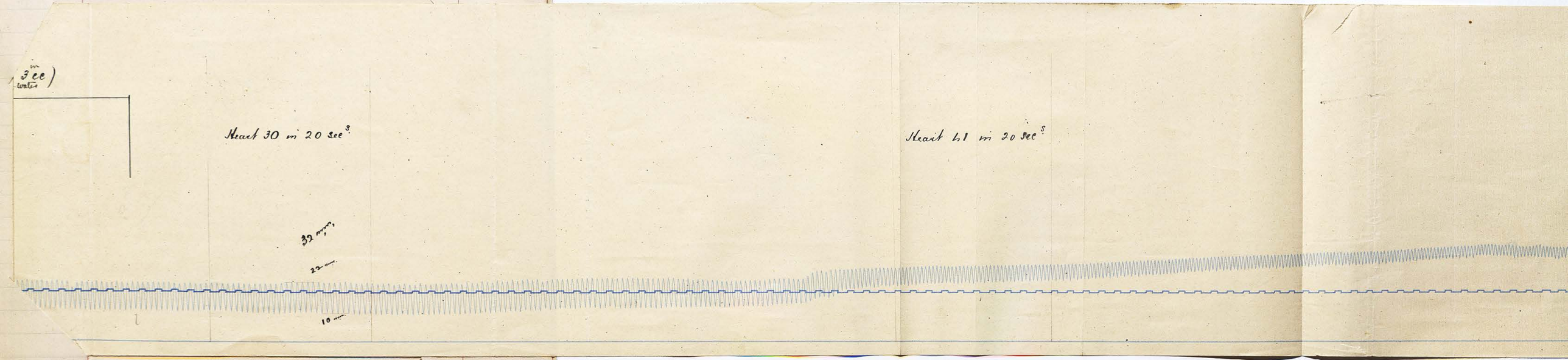
Exp. VIII 27 Feb. 1888. Frog. Curin N°2

5.30	Heart 38 per. min. Regular. Small. Injected ·005 gramme 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 & so greatly impeding the circulation.

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

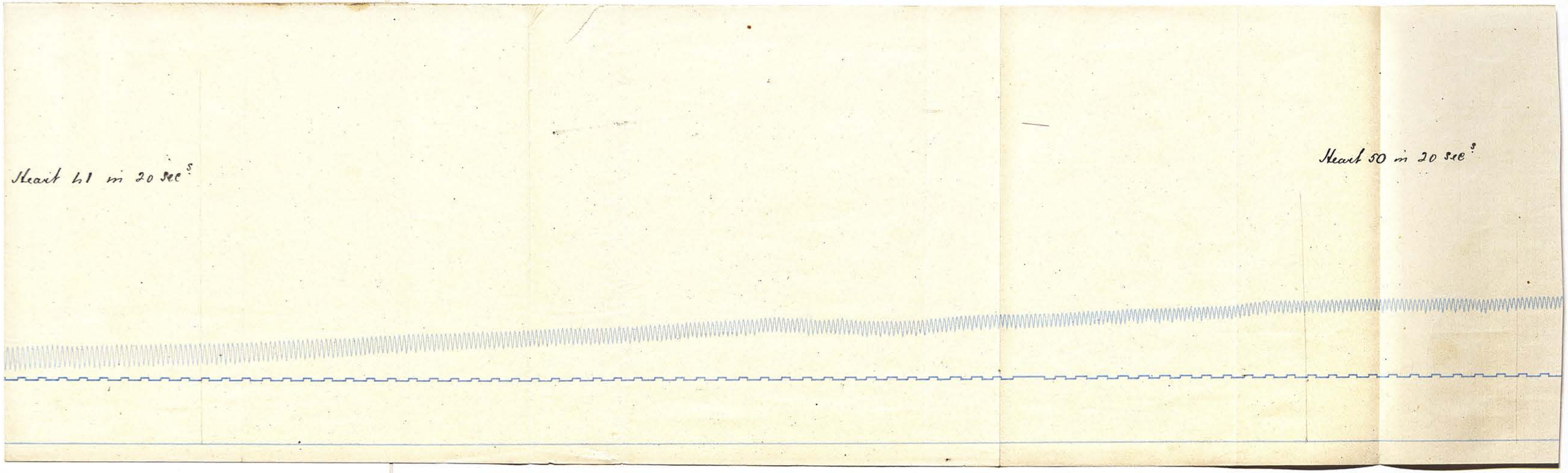
In the first experiment 0·24 gramme was injected into the jugular vein & the heart almost immediately stopped. In the second experiment ·08 gramme was injected into the saphenous vein but the pressure fell to zero & the heart continued contracting for 14 minutes in a feeble irregular way, & then stopped.

In 3rd experiment a distinct fall of


3 sec
Heart 30 in 20 secs
Heart 41 in 20 secs
32 mms
22 mms
10 mms

Heart 41 in 20 secs

Heart 50 in 20 secs



pressure & slowing 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.

Notes on Exp. III. 2nd Aug. 1887

Dose.	Average pressure before injection	Lowest level of pressure after inj.	Time taken before max. depress. reached	Period before recovery.	Pulse per ~~minute~~ 20 sec. Before inj.	Pulse per ~~minute~~ 20 sec. After inj.
1st ·020 gramme	84 mm.	67 mm.	50 seconds	3 minutes	44	67
2nd ·020	86 "	53 "	35 "	1¼ "	71	58
3rd ·04	86 "	36 "	40 "	5 "	61	37
4th ·06	85 "	32 "	60 "	8 "	55	30
5th ·08	(vagi cut) 84 "	29 "	120 "	9 "	65	30
6th ·01	49 "	48 "	120 "	6 "	53	46

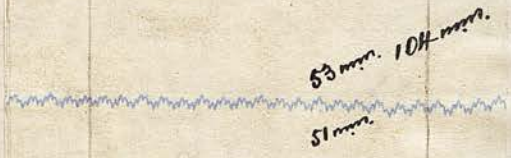
The tracing at the 4th " injection is shewn opposite. The injection of ·06 gramme reduced the pressure from 85 to 32 mm. & the rate of the pulse from 55 to 30 per ~~minute~~ 20 Seconds. The ampletude of the contractions during the slowing was marked.

Experiment IV was similar in character. In experiment V both vagi were divided & artificial respiration maintained. On injecting 3 cc (·06 grm.) slowly into the Saphenous 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~~ 20 sec. On stimulating the lower end of one divided vagus (right) the heart

1st Feb. 1888

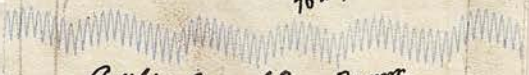
VI Rabbit 1.370 Kilo.

Curin + Atropine



2 minutes after .08
Atropine (no curine)
Heart 93 in 20 sec.
Pressure 104 mm.

10 minutes after 2nd injection of Curin.



Artificial resp.n 70 mm.

After 2nd injection of Curin - tracing at 11.5 am.
Heart 53 in 20 secs
Pressure 146 mm

1st Inj: 10.40 am .02 gramme
2nd Inj: 10.55 " .028 "

stopped for a second or two as usual. The urine contained no sugar or blood

In experiment VI a considerable dose (·08 grm.) of Atropine was first injected & the vagi fully paralysed (inhibitory action). On injecting ·02 grm. urin the pulse slowed just as before. After a second injection of ·028 grm. urin the pulse slowed from original 279 to 159 per minute & the pressure rose from 104 to 146 mm. 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 respirations after a little became powerful & very rapid. On giving a third injection of ·03 the heart stopped completely. On exposing it the auricles were found contracting & continued for 15 minutes. Occasionally an imperfect ventricular contraction of ventricles 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 &c. of curin 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 Boehm, from various circumstances, thinks it possible that curin 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, tho' 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 winter 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 we possess of Strychnos toxifera, but exactly corresponded with the description by

Planchon[53] p527) of a plant which he has named Strychnos Gubleri which was brought from Venezuela by M. Thirion, Consul General in 1864. This Strychnos is reputed to be the basis of the curare of the upper Orinoco district, but is not identical Planchon[53] thinks with the 'bejuco de Mavacoure' of Humboldt & Bonplan[21] (p519) from which certainly curare was prepared.

Although this Strychnos Gubleri doubtless enters into the composition of the curare of this district, Planchon has advanced no proof that it is the basis of the curare. Its claims only rest on native reports to the French Consul, & on the fact that it is undoubtedly a Strychnos. 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 Curin, but Professor Boehm, to whom I sent a small piece of a young stem, assured me that it did not contain Curin. Only a small quantity of the specimen could be obtained, but sufficient to shew that it could not be compared in action or poisonous activity to

Strychnos toxifera.

There seems to be no doubt that several of the Strychnos barks are cardiac poisons. MM. Conty & de Lacerda[52] (p1035) found that an extract from the bark of the Strychnos Gardneri 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 nerve ends.

These authors also record the interesting fact, that, on boiling the extract from Strychnos triplinervia & some curares the paralyzing action on nerve ends was destroyed, & replaced by a paralysing action on the heart. Other curares were not decomposed by prolonged boiling shewing apparently that the active principle is not always the same. As the natives always prepare the curare by making a decoction & 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 Curarin so 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 & Weir Mitchell[98] obtained from New Granada two arrow poisons named Corroval & Vao 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 Strychnos plant obtained from Kew 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 paralysing substances, or cardiac poisons (weak) or mixtures of these. Both seem to be derived from Strychnos plants although Lobert[99] (p647) states that the Pebas tribe (Pérou) use an arrow poison which acts on the heart, & is derived from a Menispermaceous plant (Chondrospermum). I do not know that such a plant has been identified botanically, & proved at the same time experimentally to have such an action.

I can only now repeat the hope that these last experiments on Curine have (apart from any intrinsic interest) a practical value, in so far as they indicate a possible source of error in the use of crude curare as an aid in research, & replace the suspicions which

have sometimes been entertained about different (Kulpman 18 p202)
curares by actual facts.

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