John Tweedy Esqre
with the Authors kind regards

(14)

OBSERVATIONS

ON

BOX (BUXUS SEMPERVIRENS),

WITH ESPECIAL REFERENCE TO THE TRUE NATURE OF

TETANUS.

BY

SYDNEY RINGER, M.D.,
PROFESSOR OF THERAPEUTICS AT UNIVERSITY COLLEGE;

AND

WILLIAM MURRELL, L.R.C.P.,
DEMONSTRATOR OF PHYSIOLOGY AT UNIVERSITY COLLEGE.

Read May 23rd, 1876.

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(Received May 9th—Read May 23rd, 1876.)

Introductory and Experimental.

We were induced to commence an investigation of the physiological action of box from the reputation it has acquired in the treatment of hydrophobia, and the frequency with which it enters into the composition of nostrums having obtained a reputation for the cure of this disease.

The curious, and at first sight contradictory, phenomena observed in frogs which had been injected with box led us to deviate from our original plan, and to make the experiments here detailed in the hope of throwing some light on the true nature of tetanus.

As yet we have had but little experience of the use of box clinically, and it is not our intention in the present communication to offer any observations as to its employment in the treatment of disease, or its value as a therapeutical agent.

All the experiments recorded in this paper were made on frogs. We used two extracts of box; one dilute, containing in each minim the active principle of one grain of the dried leaf, and a concentrated extract three times this strength. The drug was introduced under the skin in the neighbourhood of the posterior lymph hearts by means of a hypodermic syringe. In all cases where the animal survived for some hours care was taken to keep it moist, and when not actually under observation it was placed on a glass plate in a flat covered dish containing a little water.

The extract was prepared for us by Mr. Gerrard, teacher of pharmacy at University College.

We will first describe a typical case. Two minutes after the injection the frog became dull and its movements slow, and this condition increasing, in five minutes it could not turn over when laid on its back. In twenty minutes slight tetanus occurred, at first provoked only by strong stimulation, a weaker one exciting only coördinated reflex action. At first, too, though for a very short time, the tetanus was limited to the irritated limb. Soon, however, normal reflex action was entirely replaced by tetanic convulsions, and the tetanus rapidly increased, becoming severe thirty-eight minutes from the commencement of the experiment, and remained at its height for six minutes, and then rapidly declined. (So rapid indeed is the declension sometimes, that on one occasion where the paroxysm lasted three quarters of a minute, afterwards, when re-excited, the paroxysm lasted only a quarter of a minute, and after another five minutes interval only two seconds.) The tetanus continued very weak for an hour, during which time stimulation excited only a feeble tetanic paroxysm, speedily subsiding, and tetanus could not be again produced till the animal had rested awhile. As the tetanus declined stronger irritation and a longer rest were necessary to the production of a paroxysm, whilst the attacks grew gradually feebler and feebler, till they diminished to a mere quiver of the muscles. It was evident that tetanus and paralysis were progressing together, the paralysis gradually increasing, overpowering the tetanus, and finally abolishing it.

In this case first loss of power occurred, which appeared to us more like loss of voluntary than reflex power; next, rather severe tetanus accompanied by paralysis. We had, in fact—

1. Tetanus with increased action—or strong tetanus.
2. Tetanus with depressed action—or weak tetanus.
3. Complete paralysis.

The foregoing account represents a typical experimental case, yet we met with many exceptions, the symptoms running a somewhat different course. Thus in certain cases, due as we shall show to the degree of concentration of the extract, the tetanus was very slight, so slight, indeed, that in each tetanic convulsion we think the discharge of nervous force in the cord must have been less than in a vigorous normal (coördinated) reflex act. In other instances the tetanus was still slighter, so that the nervous discharge must have been less than that in a coördinated reflex act. Here then we had simply: 1. Tetanus with depressed action. 2. Complete paralysis.

In all the cases, even when the tetanus was severe, a stage was reached when becoming no stronger than a normal reflex act, the tetanus ultimately became even weaker than a normal reflex act.

In other cases no tetanus occurred, but simply progressive paralysis, which at last became complete. These varying results were produced by the same dose of the poison in frogs of the same weight, an apparent discrepancy which our further investigations clear up. Thus a very concentrated solution of the extract excites strong tetanus, whilst the same dose diluted excites either no tetanus, or very little, as the accompanying tables exemplify. The frogs included in the first table were injected under the skin of the back in various doses with a solution the strength of three grains of the dried leaf in one minim of water, and with two exceptions this preparation produced strong tetanus. In the *first* column we give the date; in the *second* the weight of the frog; in the *third* the dose of the extract, giving the quantities in grains of the leaf; in the *fourth* the degree of tetanus induced; in the *fifth* the time of commencement of the tetanus; in the *sixth*, the time from its commencement when the tetanus begun to decline; and in the seventh the duration of the tetanus. The table is divided into two parts, in the first part the frogs were merely poisoned, in those in the second part the cord was divided opposite the occipito-atlantal membrane, and then a peg was passed upwards into the skull, thus destroying the medulla and brain (brainless frogs).

TABLE I.—*Unmutilated frogs.*

Part 1.

Date.	Weight in grammes of frog.	Dose of leaf in form of extract.	Degree of tetanus.	Tetanus first occurred in	Tetanus began to decline from its commencement.	Duration of tetanus.
April 7	...	30 grains	Strong	13 minutes		
„ 7	...	12 „	„	19 „		
„ 11	38	9 „	„	22 „	35 minutes	2 h. 25 m.
„ 12	...	12 „	„	27 „	16 „	
„ 12	...	27 „	„	18 „	15 „	1 h. 8 m.
„ 13	30	30 „	„	10 „	19 „	1 h. 8 m.
„ 20	25	9 „	„	16 „	18 „	2 h. 35 m.
„ 20	32	15 „	„	18 „	16 „	1 h. 20 m.
„ 20	24	6 „	„	29 „	11 „	2 h.
„ 20	26	9 „	„	19 „	16 „	1 h. 43 m.
„ 20	19	9 „	„	16 „	17 „	1 h. 53 m.
„ 20	23	9 „	„	18 „	20 „	1 h. 36 m.
Average	27*	12* grains		19 minutes	18 minutes	1 h. 45 m.

* These averages are calculated only where both weight and dose are given.

TABLE I (*continued*).—*Brainless frogs.*

Part 2.

Date.	Weight of frog in grms.	Dose of leaf in form of extract.	Degree of tetanus.	Tetanus first observed in	Tetanus began to decline from its commencement	Duration of tetanus.	Loss of reflex power preceding tetanus.
April 7	28	27 grains	Strong	16 min.	...	1 h. 37 m.	
„ 7	28	27 „	„	30 „	...	1 h. 10 m.	
„ 11	25	24 „	„	32 „	...	2 h. 39 m.	
„ 12	...	27 „	„	24 „	...	...	5 min.
„ 12	25	24 „	„	32 „	...	1 h.	
„ 21	27	9 „	„	47 „	53 min.	1 h.	
„ 21	29	12 „	„	33 „	27 „	1 h. 30 m.	5 „
„ 21	28	12 „	„	36 „	56 „	1 h.	
„ 21	27	12 „	„	40 „			
„ 22	22	9 „	„	26 „	29 „	1 h. 50 m.	10 „
„ 22	28	9 „	„	31 „	41 „	50 m.	5 „
„ 24	20	9 „	„	21 „	37 „	1 h. 25 m.	5 „
„ 24	31	9 „	„	34 „	24 „	1 h. 21 m.	8 „
„ 24	30	9 „	„	25 „	32 „	...	21 „
„ 24	21	9 „	„	24 „	28 „	1 h. 10 m.	5 „
May 1	22	9 „	„	21 „	28 „	1 h. 43 m.	10 „
„ 1	...	9 „	Very weak	14 „	...	...	5 „
„ 1	19	9 „	Very strong	20 „	43 „	3 h.	10 „
„ 1	19	9 „	Slight	25 „	...	1 h. 20 m.	10 „
„ 2	27	9 „	Strong	19 „	44 „	1 h. 40 m.	8 „
Average	25	14 grains		27 min.	37 min.	1 h. 31 m.	8 min.*

* Excluding the 21 minutes, average 7 minutes.

TABLE II.—*Exemplifying the effect of the dilute extract, each minim containing the extract from one grain of the dried leaf.*

Date.	Weight of frog in grammes.	Dose equivalent to dried leaf.	Amount of tetanus.	Tetanus first appeared.	Duration of tetanus.
April 13	31	5 grains	Moderate	1 h. 15 m.	50 m.
„ 13	35·5	10 „	None		
„ 13	38	15 „	„		
„ 13	29	20 „	Slight	52 m.	1 h. 11 m.
„ 19	30	5 „	None		
„ 19	32	10 „	Slight	1 h. 33 m.	20 m.
„ 19	29	15 „	Moderate	56 m.	1 h. 35 m.
„ 19	29	20 „	None		
„ 19	30	10 „	Moderate	39 m.	1 h. 50 m.
„ 19	34	10 „	None		
„ 19	30	13 „	„		
„ 20	26	9 „	Very slight	1 h. 26 m.	10 m.
„ 20	21	15 „	None		
„ 20	24	6 „	„		
„ 20	30	9 „	Very slight	57 m.	1 h. 5 m.
Average	29	11 grains		1 h. 16 m.	1 h.

In the fifteen cases in the last table, in eight no tetanus occurred, moderate tetanus in three, and very slight tetanus in four. The dilute solution produced generally very slight tetanus, each paroxysm being, so far as we could estimate, weaker than a normal (coördinated) reflex act, and in several cases much weaker.

In the second table in every instance almost complete loss of voluntary and reflex power preceded the onset of the tetanus; indeed in two cases the paralysis was complete before the tetanus set in.

We suggest that the difference in the effect produced by the two solutions is owing to the quicker absorption of the concentrated solution. Its specific gravity being greater, it will pass by the law of diffusion more quickly into the blood.

The preceding tables show that the tetanus when well marked begun on an average in 19 minutes, continued strong 18 minutes, and then rapidly declined, lasting on an average 105 minutes. With the dilute solution, the tetanus being much slighter, it begun on an average, in 27 minutes and lasted 91 minutes, (see Tables I and II for further particulars, p. 5 and 6).

As we have just said, a diluted solution induces weak or only moderately strong tetanus, which sets in much later than when fully developed by the stronger solution; moreover, great or even complete loss of voluntary and reflex power always preceded the tetanus; that in fact we get a combination of paralysis and tetanus. We offer the following explanation of these facts. In a subsequent part of this paper we shall attempt to show that in tetanus there is always diminished resistance to impressions, in the cord, and that this diminished resistance may be associated with a normal or depressed condition of the cord. In poisoning with a dilute solution absorption goes on slowly and paralysis sets in and becomes almost complete before enough of the drug has been absorbed to lessen the resistance of the cord. In other words, it requires a larger dose to diminish the resistance of the cord than to produce paralysis; hence paralysis precedes and accompanies tetanic spasms.

Does Box produce its effect through the brain, spinal cord, nerves or muscles? We shall consider these points seriatim.

Very soon after poisoning, loss of power sets in. We carefully examined in sixteen cases for the earliest evidence of loss of power and find that it varies from one to five minutes, giving an average of two minutes and a half. The quantities of the extract employed varied from five to twenty grains of the dried leaf, the average being 10·8 grains.

TABLE III.—*Showing time of onset of loss of power in frogs produced by box.*

Number of frog.	Weight of frog in grammes.	Dose of leaf in form of extract.	Strength of preparation.	Loss of power begun in
1	30	5 grains	Dilute	5 minutes
2	32	10 „	„	5 „
3	29	15 „	„	3 „
4	29	20 „	„	3 „
5	30	10 „	„	2 „
6	34	10 „	„	2 „
7	30	13 „	„	2 „
8	25	9 „	Concentrated	3 „
9	32	15 „	„	1 „
10	26	9 „	„	3 „
11	26	9 „	Dilute	1½ „
12	21	15 „	„	2 „
13	24	6 „	„	2 „
14	30	9 „	„	2 „
15	19	9 „	Concentrated	1 „
16	23	9 „	„	3½ „
Average	27·5	10·8 grains		2½ minutes

To ascertain if all or part of this loss of power is due to the action of the box on the brain or the medulla, we divided the spinal cord, opposite the occipito-atlantal membrane in fifteen frogs, and then passed a wooden peg into the skull, destroying the medulla and brain (brainless frogs). When the effects of shock had passed off, we injected under the skin of the back the concentrated solution of the extract each minim containing the extract from three grains of leaf. Tetanus first appeared in from 14 to 47 minutes, giving an average in the twenty cases of 27 minutes (see tables on pp. 5 and 6). Shortly before the onset of the tetanus, we noticed slight but distinct diminution of reflex power, so that we could fortel the occurrence of the tetanus; the loss of reflex power generally preceding the tetanus, about five minutes, though in one case there was an interval of twenty-one minutes; the average being eight minutes, or excluding the case of twenty-one minutes, the average was seven minutes. We have shown that in unmutilated frogs, loss of power occurs in two and a half minutes; tetanus occurs on an average in nineteen minutes. Where the influence on the cord and medulla is prevented, in pegged (brainless) frogs the tetanus is preceded by loss of reflex power for seven minutes; therefore the loss of power occurring during the twelve first minutes must be due to the influence of the poison on either the brain or the medulla.

To determine whether the loss of reflex action shortly preceding the tetanus in pithed frogs is a natural decline or is due to the action of the drug, we performed some comparative experiments by poisoning each alternate frog, and watching the reflex action as the poisoned and unpoisoned frogs lay side by side. We find that in unpoisoned frogs, if the animals are kept moist, reflex action continues undiminished for thirty hours, indeed sometimes for fifty hours, and persists from fifty to a hundred hours. For further details concerning the duration of reflex action we refer our readers to the section on tetanus p. 26.

We may draw attention here to one fact connected with the duration of reflex action in brainless frogs, which explains we think the variable effects of box and gelseminum on the cord. Thus, in some instances reflex action had ceased in 23 hours, whilst in others it lasted for 90 to 100 hours. There must be therefore naturally considerable differences in the condition of the cord, and hence the cord in one frog will be quickly and easily paralysed, whilst another may require a larger dose and a longer time.

In brainless frogs we found that box produced tetanus, preceded for a short time, as we have said, by diminution of reflex power, which further diminishing at last becomes complete. This loss of reflex power and tetanus must depend on the effect of the drug, either on the cord, nerves, or muscles. It will be convenient to treat separately of tetanus and paralysis.

Tetanus is certainly due to the action of the drug on the spinal cord for—1. There is no example of the induction of tetanus through the nerves or muscles. 2. If before poisoning, the abdominal aorta or one iliac is tied, thus protecting from the action of the poison the part below the ligature, yet these parts become tetanised as strongly as those subjected to the direct action of the poison. We proved this by eleven experiments; four times we tied the abdominal aorta, and seven times one iliac artery, verifying by post-mortem examination the efficiency of the ligatures. 3. If the sciatic nerve is divided, the other structures being left intact, the muscles of the extremity with the divided nerve are not tetanised. We verified this statement by three experiments, two on frogs, one on a toad. In each animal we divided the sciatic nerve of the left leg, and then injected under the skin of the back four minims of the stronger extract of box. In about fifteen to seventeen minutes, tetanus set in, which did not involve the muscles of the leg and foot of the left extremity, though some of the thigh muscles were affected. Irritation of the left leg failed to excite a paroxysm of tetanus.

Box likewise paralyses the reflex function of the cord. To prove this we experimented on four frogs, by tying the abdominal aorta and then poisoning the animal by injecting under the skin of the back three minims of the concentrated solution (equal to nine grains of leaf). The lower extremities were thus, of course, effectually protected from the action of the poison, and yet paralysis progressed just as in frogs, unprotected by a ligatured aorta. The following table shows the result of these experiments.

Date.	Weight of frog in grammes.	Dose.	Paralysis.	Tetanus.	First appeared.	Tetanus lasted
April 10	30	6 grains	Complete	Strong	33 min.	48 min.
May 1	25	9 „	„	„	16 „	87 „
„ 1	20	9 „	„	Very slight		
„ 1	19	9 „	„	None		
Average	23	8 grains			24 min.	67 min.

That both tetanus and paralysis are produced by the action of the drug on the cord is proved in our experiments regarding the influence of box on the motor nerves. In these experiments, seven in number, we tied one iliac artery, and then poisoned the animal, and in every instance save one, paralysis as complete, and tetanus as strong, seized the ligatured and protected as well as the unligatured and unprotected leg. As the muscles and motor nerves were protected by ligature, it is evident that the paralysis was not due to the action of the drug on these structures.

It is well known that some drugs as calabar bean, which paralyse through their action on the spinal cord, do likewise to a slight extent paralyse the motor nerves. Box we conclude does not affect either the motor nerves or the muscles ; for did it in any degree paralyse these structures, then on tying one iliac artery before poisoning, and thus protecting the nerves and muscles of one limb from the poisoned blood, tetanus should be more marked in the protected, and paralysis should progress more rapidly in the unprotected limb. For the poison depressing the motor nerve of the unligatured limb would diminish its conducting power, and hence lessen the tetanic contractions of its muscles. This is well exemplified by slightly pressing or stretching the nerves of one leg, when the muscles of that leg are less powerfully contracted during the tetanic spasm. Moreover, if box affects either the motor nerves or muscles the paralysis in the unprotected would progress more rapidly than in the protected leg. Again, if box affects either the nerves or muscles before the spinal cord, then loss of reflex action should occur earlier in the unprotected than in the protected limb. Now, we find as the result of seven observations given in the subjoined table, in which one iliac artery was tied, that with only one readily explicable exception, tetanus was equally well marked, that paralysis progressed equally, and was complete at the same time in both legs; moreover, the loss of reflex action begun simultaneously in both legs.

Table showing comparative amount of tetanus and paralysis in the legs produced by box after ligature of the iliac arteries.

Experiment	Date.	Weight of frog.	Dose of extract.	Proportion of dose to weight of frog.	Vessels tied.	Result.
	1876.	Grms.	Grains.			
XXXIV	April 25	76	30	...	Lt. iliac	Tetanus less in left leg than in right
XXXV	,, 25	65	27	...	Rt. iliac	Tetanus slightly less in left leg than in right
XXXVI	,, 26	25	9	...	,,	Tetanus equal
LV	May 2	24	12	...	,,	Tetanus equal; loss of reflex action equal
LVI	,, 2	25	12	...	,,	Tetanus equal; reflex action slightly greater in right leg
LVII	,, 2	22	12	...	,,	Tetanus equal; reflex action slightly greater in right leg before injection; subsequently no difference could be detected
LVIII	,, 2	19	9	...	,,	Tetanus equal; reflex action equal in both legs
Average		38	14	...		

In the last column we compare the amount of tetanus and paralysis in the protected and unprotected limbs.

This table shows that in seven frogs operated on successfully, one only exhibited any excess of tetanus, though slight, in the protected limb.

It appears then, as we have already stated, that box exerts no influence on the motor nerves or muscles. In the exceptional case just mentioned, it happened in the course of the operation, that a slight injury was inflicted on one of the abdominal nerves, thus impairing its conductivity and readily accounting for the predominance of tetanus in the limb with its uninjured nerve.

In all our operations on the abdominal vessels, we took every care to avoid stretching or even touching the adjacent nerves, but occasionally they lay in such close contact with the artery that it was extremely difficult to avoid injuring them.

With the view, however, of setting this question beyond the possibility of doubt we performed eight additional experiments, in which we resorted to a somewhat different mode of procedure. We will give the details of one of the most conclusive of these observations. We tied the right iliac artery of a large male German frog weighing sixty-five grammes. Fortunately very little blood was lost, and the animal seemed but little affected by the operation, jumping about actively on being released. An injection of extract of box equivalent to twenty-seven grains of the dried leaf was then administered in the neighbourhood of the posterior lymph hearts, care being taken that none of the fluid escaped through the incision made for the operation. Tetanus and paralysis were produced in due course, but into the details of these phenomena we need not now enter. Fifty minutes after the administration of the drug, when the paralysis was complete, and the tetanus had entirely ceased, the thighs were opened and the sciatic nerves exposed. A piece of very thin flat glass was then passed under each nerve so as to completely isolate; they were stimulated with a pair of electrodes in connection with a Du Bois Reymond's induction coil, and a one-celled Daniell's battery, every care being taken to apply the excitor to each nerve in exactly the same manner and under identically the same conditions. We occasionally used a powerful shock, but as a rule we worked with the current of minimum intensity just adequate to produce the slightest perceptible quiver in the muscles to which the nerves were distributed.

It would be wearying and unprofitable to give the actual details of each single observation. We compared the condition of the nerves as regards excitability twenty-five times during a period of a little over four hours, and were unable in any instance to detect the slightest difference in their excitability.

This case alone would, we venture to think, prove conclusively that box exerts absolutely no influence on the motor nerves. There are in addition six other cases in which we successfully tied one iliac artery, and in these the most careful observation failed to detect the existence of even the slightest or most transitory difference in the condition of the nerves.

An examination of the accompanying table will show at a glance the results obtained in this series of experiments. In the first and second cases we made a considerable number of comparative observations, so as thoroughly to satisfy ourselves as to the correctness of our conclusions, but the actual number was not noted.

Table showing condition of sciatic nerves in frogs poisoned by box after ligature of one of the iliacs.

No. of experiment.	Date.	Weight of frog.	Vessels tied.	Grns. injected	Relation of dose to weight of animal.	Time of observation after injection.	No. of comparative observations.	Result.
	1876.	Grms.						
I	Ap. 12	34	R. iliac	9	...	1 h. 41 m	?	No difference
II	,, 12	30	,,	5	...	1½ h.	?	,,
III	,, 25	65	,,	27	...	1 h.	2	,,
						1 h. 5 m.	2	,,
						1 h. 10 m.	3	,,
						1 h. 15 m.	1	,,
						1 h. 20 m.	3	,,
						1 h. 30 m.	1	,,
						1 h. 45 m.	3	,,
						2 h.	1	,,
						2 h. 30 m.	3	,,
						2 h. 45 m.	1	,,
						3 h. 10 m.	2	,,
						3 h. 30 m.	1	,,
						4 h.	1	,,
						4 h. 10 m.	1	,,
IV	,, 26	25	,,	9	...	9 h. 40 m.	13	,,
V	May 2	24	,,	12	...	4 h.	Many	The right sciatic nerve conducts better than the left, although the difference is slight
						5 h.	7	The right nerve still acts better than the left
VI	,, 2	25	,,	12	...	6 h.	6	No difference
VII	,, 2	22	,,	12	...	2 h.	10	,,
VIII	,, 2	19	,,	9	...	1 h.	8	,,

In one instance there was a decided difference in the excitability of the two sciatics, the nerve of the protected limb acting distinctly more energetically than that of the other. What value are we to attach to this exceptional result? In answer to this question we cannot do better than detail another experiment in which the operation for ligature of the iliac artery was performed. The box was given as usual, and immediately after the decline of the tetanus and the occurrence of complete paralysis the two sciatic nerves were exposed and an investigation was made of their power of conducting electrical stimuli as measured by the contractions of the muscles of the limb. The excitability exhibited by the nerve of the left leg was clearly greater than that of the right. The observation was made several times with varying strengths of current, and the result was in every case the same. At the post-mortem examination it was found that neither iliac artery had been tied!

This experiment demonstrates the fact that occasionally a difference normally exists in the relative activity of the two sciatic nerves. It may, we think, be fairly concluded that our exceptional case belongs to this category, and that the difference in the condition of the two nerves would have been equally apparent had we resorted to no operative procedure and had left the arteries intact.

Does box in any degree affect the muscles? In the experiments just detailed we tested the muscles of the opposite legs, the muscles of one extremity being protected from the action of the poisoned blood by ligature of its artery. The apparatus used to stimulate the muscles was that employed in the investigation of the motor nerves. The electrodes, however, were placed in actual contact with the muscular tissue. The general mode of procedure was in both investigations identical. In no instance were we able to discriminate the slightest difference either in the strength or the rapidity of contraction of the corresponding muscles of the two limbs. We conclude therefore that box exerts no direct influence on the muscular tissue.

We next proceeded to ascertain whether box poisons the afferent nerves, for if this drug had induced depression of these nerves, before the cord became tetanised, this condition would throw light on the paralysis preceding tetanus, for the depressed afferent nerves would convey to the cord a weaker impression, and the reflex acts would consequently be weaker. We find that the afferent nerves are not paralysed by box, and we base this conclusion on the following experiment. After tying the iliac artery of one leg and then poisoning the animal by injecting the drug under the skin of the back, we tested reflex action in both posterior extremities by holding the animal by its toes, and we found always that reflex function remained equally good in both legs. Now, if the drug poisons the afferent nerves the impressions conveyed along the poisoned limb should then be less active than those passing through the unpoisoned limb, and reflex action in place of remaining unaffected should be less perfect when the animal is suspended by the poisoned extremity. The foregoing experiment, however, being insufficiently delicate to settle this important question, we sought more convincing evidence, and four times we repeated the following experiments. We divided the cord just below the medulla, and then destroyed the medulla and brain by passing a wooden peg into the cavity of the skull. We then tied one iliac artery carefully, closing the wound with ligatures. We next determined the weakest induction currents capable of exciting reflex action in either hind leg, and then injected under the skin of the back four mimims of the concentrated extract of box. Every three or five minutes we tested the weakest currents adequate to excite reflex action in the posterior legs. As the reflex function declined, the same strength of currents would still excite in each limb an equal amount of reflex action in the poisoned as in the unpoisoned limb, till the abolition of all reflex action. We conclude, therefore, that box exerts no influence on the afferent nerves.

Having thus shown that box tetanises and paralyses by its effects on the cord, and that the afferent and motor nerves and muscles are unaffected, we wish to draw particular attention to a fact several times referred to in this investigation—that in pegged frogs, when the drug cannot of course act on the brain, after the injection of the concentrated solution of the extract, tetanus is preceded for about six minutes by loss of reflex power in the cord, and that this loss is manifested even where the subsequent tetanic convulsions are severe, and the nervous discharge in the cord is much greater than occurs in a normal (coördinated) reflex act; hence, according to the prevailing notion, the cord is said to be excited by the medicine. Very soon after the onset of the tetanus and even before it becomes severe the coördinated reflex power of the cord rapidly declines. Thus we have first marked loss of reflex power and then strong tetanus. This apparent contradiction—this loss of coördinated reflex power preceding tetanic convulsious and persisting in the intervals of the paroxysms—might be due, we thought, to the depressing influence of the drug on the motor or afferent nerves or muscles before the excitation of tetanus in the cord; but having shown that box does not affect these structures, it is clear that the drug must first lessen reflex action in the cord and then produce tetanus, the coördinated reflex power itself meanwhile diminishing. This apparent contradiction we have attempted to reconcile in the section on tetanus.

In twelve observations with unmutilated frogs, as we have already shown, energetic tetanus lasts only a short while, beginning to decline on an average in eighteen minutes, and in ten brainless frogs on an average in thirty-nine minutes, then it grows rapidly weaker and so continuing for an hour to an hour and a half; it then ceases and all reflex action is abolished. Is this due to the natural cessation of the functions of the cord, or to exhaustion from the tetanus, or to the medicine? It is not due to the natural death of the cord, for after dividing the cord opposite the occipito-atlantal membrane we found that reflex action continues unimpaired for thirty or forty hours. (For further remarks on the persistence of reflex action after death, see the section on tetanus.)

Nor is it due to exhaustion from the tetanic convulsions, since strychina induces far intenser tetanus, lasting several days, whilst the tetanus from box is much less severe and lasts only an hour or two and then ends in complete paralysis. The paralysis of the cord is therefore due to the direct action of the box.

Box, then, paralyses and tetanises the spinal cord. Are these results due to the action of the drug on Setschenow's reflex inhibitory centre; in other words, is the paralysis due to stimulation or the tetanus to paralysis of this centre? Clearly not, for both paralysis and tetanus occurred after section of the spinal cord below this centre.

The following is a summary of our conclusions:

1. Box produces loss of power by its effects either on centres of volition or on the motor centres of the brain.

2. It next depresses the reflex function of the cord.

3. It excites tetanus, the paralysis of coördinated reflex function of the cord progressing at the same time.

4. At last, by its influence on the cord, it produces complete paralysis.

5. It produces no effect on the motor and afferent nerves and the muscles.

Remarks and Observations on Tetanus.

The foregoing observations, coupled with those we published in the 'Lancet' for 1876 on gelseminum, suggest to us the following views regarding the true nature of tetanus. Tetanus is generally said to be due to stimulation of the cord, or the cord is said to be excited; but these expressions, we venture to think, are both erroneous and misleading.

We shall first consider strychnia tetanus. Here a slight irritation will develope rigid contraction of every muscle of the body, and this paroxysm can be excited in rapid recurrence for several days. Here no doubt an excessive discharge of nervous force does take place in the cord, and hence perhaps it may be deemed correct to say—though presently we shall have occasion to question this view—that the cord is stimulated or excited. But the effects produced by strychnia are not due to mere stimulation, for in that case the normal co-ordinated reflex movements should be retained and be more vigorously performed; this, however, does not happen, for on irritating a frog's posterior limb, or indeed any other part, instead of inducing the usual co-ordinated movement, all the muscles of the body become rigidly contracted, and owing to the strength of the extensor muscles prevailing over that of the flexors, the hind legs, in place of being drawn up, are powerfully extended. Here then it is evident that the impression, instead of being limited to certain parts of the cord, diffuses itself through the greater part or the whole of the cord and motor tract in the brain. As every part of the cord is excited, all coördinated action is abolished and every muscle is contracted. Thus in the case of strychnia tetanus, with increased nervous discharge, we have lessened resistance or greater diffusibility in the spinal cord.

We venture to suggest, and we trust our subsequent remarks will prove, that in the tetanus produced by poisons, this lessened resistance is the actual cause of the tetanus, and that there is in fact no excited condition of the cord; that, if the poison merely lessens resistance, then an irritation produces excessive evolution of force throughout the cord, and consequently strong tetanus; if the poison depresses the reflex function as well as the resistance, then an irritation induces slight evolution of nervous force throughout the cord, and consequently produces only weak tetanus; there is no excited condition of the cord. The correctness of this view is well shown in the tetanus excited by box, gelseminum, and jaborandi.

We shall speak first and chiefly of box. Using a concentrated solution, we find that in almost every case box excites strong tetanus, with a far greater discharge of nervous force in the cord than takes place in a normal (coördinated) reflex act; hence it is said that the cord is excited or stimulated; but the facts we are about to adduce will, we think, show that this augmented evolution of force depends merely on lessened resistance.

After division of the cord just below the medulla through the occipito-atlantal membrane and the destruction of the medulla and brain, so as to obtain simple uncomplicated effects of box on the cord, we have shown that loss of coördinating reflex power (cord paralysis) always preceded the tetanus by six or seven minutes. The tetanus sets in at first so slightly that only strong irritation excites it, weaker producing simply normal reflex acts; then, as the tetanus continues and grows stronger, and becomes more easily excited, co-ordinated reflex action quickly diminishes, to be at last entirely replaced by tetanic contraction; tetanus quickly grows weaker, and soon becomes very slight, so continuing often an hour or longer, and then ends in complete abolition of reflex action.

Thus we have diminution of reflex action *followed* by tetanus, the diminution becoming more evident as the tetanus increases, the tetanus being generally for a short time severe, and each paroxysm greatly in excess of a normal (coördinated) reflex act. Were tetanus due to stimulation of the cord, we should then have this singular and we think impossible combination, namely, first depression and then stimulation of the reflex function of the cord, this stimulation continuing concurrently with a rapid depression of co-ordinated reflex action.

Since box first weakens the reflex function before producing tetanus even when the tetanus is strong, it is probable that a larger dose is required to lessen resistance than to lessen the reflex function of the cord; hence, diminution of reflex function precedes tetanus. As soon as the quantity absorbed is sufficient to lessen resistance tetanus sets in, increasing in severity and in facility of reproductlon as the resistance in the cord grows less.

In gelseminum poisoning always, and in many cases of box poisoning generally, when the extract is much diluted, tetanic convulsions are either not more marked than ordinary (coördinated) reflex acts, or are much weaker; that is to say, the irritation exciting tetanic spasms causes a discharge of force in the spinal cord, either no greater, and in many instances much less than is expended in a co-ordinated reflex act, estimating the amount of nervous discharge by the amount of consequent muscular contraction. In all cases of poisoning by box, even when the tetanus is strong, the paroxysms grow weaker and weaker, and at last they fade away to a mere quivering of the muscles. In some cases indeed, even at its height, the tetanus is manifested in little more than a quivering of the muscles. If where the tetanus is strong it is deemed necessary to assume that in addition to lessened resistance there must be stimulation of the cord, we maintain that, in the instances now advanced, there can be no stimulation or heightened action of the cord, but the very opposite condition, the reflex function in many cases being much depressed. Here the stimulus evokes reflex action in a depressed cord, but through want of resistance in the cord the impression diffuses itself, and the reflex act itself, though weak, is tetanic in character; and when it is borne in mind that this weak tetanus is preceded always by some, often by great and sometimes by almost complete depression of coördinated reflex power, the foregoing view is rendered yet more probable.

Moreover, we would urge that if tetanus is due to an excited condition of the spinal cord, the course of the symptoms from box poisoning should be different from that we find it to be. In strong box tetanus, when according to the ordinary view, the cord is stimulated and excited, then as this condition subsides the tetanic movements should gradually decline and at last cease, normal reflex (coördinated) action returning; but we actually find that the tetanic movements continue, grow weaker and weaker, till at last all movement ceases and general paralysis ensues. It may be said that the tetanus exhausts the cord, and hence the convulsions grow weaker and weaker, as the cord becomes exhausted; but this objection is certainly without foundation; for the tetanus induced by box or gelseminum lasts little more than an hour, and is much less intense than strychnia tetanus, which endures several days without exhausting the cord.

The rapid abolition of reflex action is therefore due to the paralysing influence of box on the cord. It may be said that on the occurrence of paralysis the tetanus gradually declines; but were the tetanus due simply to heightened activity of the cord, it is evident that immediately the drug begins to depress the cord tetanus should cease; for that the same substance should simultaneously stimulate and depress the same organ is inconceivable.

In these cases, where during the tetanic paroxysm the muscular contraction is not greater than occurs in a coördinated reflex act—certainly where the contraction is weaker—we must admit that the tetanus cannot depend on an excited condition of the cord, but solely on its lessened resistance, enabling an impression to diffuse itself through the greater part or the whole of the motor tract of the cord; hence all the muscles being stimulated we get tetanus.

The order in which the symptoms occur favours the view here suggested. After poisoning by box we noticed that whilst a strong irritation excited tetanus, a weak irritation produced a weakened but natural (coördinated) reflex act. The resistive power of the cord at this stage is, we submit, only slightly weakened, so that a strong impression can diffuse itself, whilst a weaker one is confined to that part of the cord naturally associated with the irritated nerve. At first, too, the tetanus is limited to the irritated limb because the resistive power being only a little weakened, the diffusion of the impression through the cord is correspondingly limited. Then as poisoning progresses, the resistive power of the cord grows weaker and weaker, and impressions diffuse themselves more easily and more widely, till at last the whole or the greater part of the body becomes tetanised.

In making certain observations to ascertain how long in frogs reflex action continues after section of the cord, we obtained some curious and unexpected results, which strikingly confirm the view we have ventured to advance. After dividing the cord and destroying the brain by passing a wooden peg through the occipital foramen into the cavity of the skull, we allowed time for the animal to recover from the shock, and then tested the reflex irritability. This was always natural (coördinated), and unless the blows over the back were too frequently repeated, never in any case tetanic. We afterwards tested reflex action always thrice daily, morning, noon, and at night.

Soon after coördinated reflex action began to decline, we noticed that these frogs when allowed to fall the height of an inch or two on to the glass plate became slightly tetanic. The tetanic movements were still more manifestly induced by striking the animal with the handle of the forceps over the spine between the forelegs. In the ratio of the loss of natural (coördinated) reflex action these tetanic spasms became more marked, and were more easily produced; then as coördinated reflex action further declined, so did the tetanus; but even then, after all co-ordinated reflex action had ceased, a sharp blow over the spine or on one of the extremities would elicit slight tetanic extension of the legs, with much quivering of the abdominal muscles. We made careful observations on twenty-eight frogs, and with one exception these became tetanic.

We will now describe in detail one of our ordinary cases of tetanus, taking for the purpose the first on the list. The animal was a common English frog weighing eighteen grammes. The experiment was commenced on Friday the 28th of April, the weather at the time being warm and showery.

The head of the animal having been depressed with the forefinger of the left hand, the nail readily detected the depression at the base of the skull. The point of a clean, sharp knife was then introduced so as to cut through the occipito-atlantal membrane and the subjacent medulla. The extremity of a sharpened match was then thrust into the skull through the foramen magnum so as to destroy the brain with as little loss of blood as possible. The spigot of wood was retained in position, and no hæmorrhage was visible externally. The animal suffered but slightly from the shock, and in a minute or two reflex action was found to be perfect, the whole body being drawn up when lifted by one leg. Twenty-one hours after, on striking the back in the cervical region with a pair of forceps, the legs were suddenly shot out straight, in a manner which was clearly tetanic in nature. On placing side by side with this animal a frog which had just been operated on, the contrast was very great, the legs in the latter remaining perfectly motionless when the back was struck. By the evening of the second day (thirty hours after the operation) there was a little diminution of reflex action. At first, on striking the back no tetanus was observed, but on repeating the blow the legs were shot out as in the morning, but rather more strongly. On Sunday morning (forty-five and a half hours after the operation) a still further decline in the amount of coördinated reflex action was noticeable, although it was still fairly strong. The tetanus had increased in severity and was very readily excited. Lifting the animal ever so slightly from the table and then dropping it would at once induce a paroxysm, the legs being shot out and the web of the foot widely distended. On Monday both reflex action and tetanus gradually declined; and on Tuesday (the fifth day) had entirely ceased.

We will now describe an experiment in which the tetanus may we venture to think, be fairly denominated "very strong." There is no occasion to describe the mode of preparation, as it was identical with that already detailed. It was thought possible that the rapidity of decomposition in the warm laboratory might interfere with the development or duration of tetanus, and this animal was consequently kept during the time it was under observation in what we may call a miniature icehouse, the temperature of which ranged from 12° to 15° C. Four hours after the operation coördinated reflex action was good, and there was slight tetanus. During the remainder of this and on the following day the tetanus gradually increased in intensity, and in thirty-one hours after the operation was very powerful. The slightest touch on the back induced a violent tetanic spasm, in which the legs were forcibly extended. The paroxysm lasted more than a minute, and the animal was taken up by the legs and held out horizontally, so great was the rigidity. The individual muscles of the limbs stood out most prominently, and as the paroxysm declined could be seen rapidly alternately contracting and relaxing. This observation was at six in the evening, and at half past seven on the following morning both tetanus and coördinated reflex action had entirely ceased.

We introduce the results of our observations in the following table. In the first column we give the number of frog; in the second the date; in the third the degree of tetanus; in the fourth the time the tetanus began on merely striking the back once or twice (more frequent and more powerful irritation would always, as we have subsequently shown, depress the cord and produce tetaniform movements); in the fifth the time the tetanus ceased; in the sixth the time it lasted; in the seventh the time normal (coördinated) reflex action ceased.

Table comparing reflex action and tetanus in frogs which had been pegged.

No. of frog.	Date.	Tetanus, degree of.	Tetanus began.	Tetanus ceased.	Tetanus lasted.	Reflex action ceased.
	1876.		Hours	Hours	Hours	Hours
I	April 28	Moderate	30	78	48	98
II	,,	Slight	20	45	25	19
III	,,	,,	30	78	48	52
IV	,,	,,	20	46	26	30
V	,,	Moderate	20	98	78	78
VI	,,	Strong	20	69	49	52
VII	April 29	Slight	10	49	39	57
VIII	May 3	Strong	7	79	72	79
IX	,,	,,	3	75	72	75
X	,,	Very strong	3	55	52	55
XI	May 6	Slight	20	75	55	95
XII	,,	,,	20	51	31	92
XIII	,,	,,	20	28	8	28
XIV	,,	Moderate	20	71	51	68
XV	,,	,,	20	71	51	68
XVI	,,	,,	3	68	65	68
XVII	May 10	Strong	28	51	23	51
XVIII	,,	Slight	48	81	33	81
XIX	,,	Very strong	28	96	68	72
XX	,,	Moderate	23	106	83	96
XXI	,,	None	...	...	...	23
XXII	,,	Very strong	4	47	43	47
XXIII	May 15	,,	4	81	77	77
XXIV	,,	Strong	4	57	53	48
XXV	,,	Slight	4	72	68	72
XXVI	,,	Moderate	4	59	55	28
XXVII	,,	Strong	4	48	44	48
XXVIII	,,	Moderate	4	52	48	48

This table shows that in four frogs the tetanus was very strong; in six strong; in eight moderate; in nine slight; and in one it was absent.

The degree of tetanus varied much, generally it consisted of the posterior legs being strongly shot out, to be immediately relaxed, but with several frogs the paroxysms when at their height, lasted from a quarter of a minute to a minute, the legs being rigidly extended, so as to raise the animal off the table, and we could hold it out horizontally by the hind legs.

We may repeat, that directly after recovery from the shock after division of the cord, even strong irritation, unless often repeated, failed to excite tetanus, but soon after, sometimes before, normal reflex action had declined, strong irritation induced tetanus, whilst weaker irritation provoked only a coördinated reflex act. As paralysis progressed, shown in the increased weakness of the coördinated reflex acts, tetanus was more readily induced and became more marked, though even at its height the paroxysms could not be induced in rapid succession, an interval of rest being required. It will be observed that in these frogs the tetanus generally closely corresponded to the latter stages of tetanus induced by box and the whole tetanic stage of gelseminum. In some cases, however, the tetanus was strongly marked, each paroxysm lasting half a minute or even longer. These cases are comparable with the whole stage of box poisoning; for in each strong paroxysm a far greater discharge of nervous force took place in the cord than occurs in a normal (coördinated) vigorous reflex act; and therefore, according to the current views, the cord would be said to be excited. But we have pointed out that tetanus was at its height simultaneously with much weakened, coördinated reflex action, and shortly before all reflex action ceased, so that when tetanus became marked we could foretel that the cord was rapidly losing power, and that soon both coördinated and tetanic reflex action would be abolished. The duration of the tetanus varied in different frogs, corresponding to the time of continuance of normal reflex action, for though after its extinction a strong slap on the back would induce slight tetanic extension of the legs, yet this soon afterwards ceased.

It may be urged that the term tetanus is not applicable to these movements excited in brainless frogs. These movements are, however, certainly tetanic; they exhibit the character of tetanic movements, though less severe than those due to many poisons. On some occasions we obtained even strong tetanus, though never approaching in severity the powerful paroxysms induced by strychnia. With the hind limbs rigidly and tonically extended the animal could be held out horizontally. After the paroxysm declined the contraction in each muscle became clonic, and thus produced jerking extension of the legs. The paroxysm sometimes continued from half a minute to a minute; the tetanus, it is true, in these cases was unusually well marked, whilst in most of our observations the attacks were much milder, though in character still clearly tetanic, and like the declining tetanus in box and the tetanus of gelseminum. If it be objected that where the paroxysms are not severe it is not true tetanus, which we get after poisoning by box, we answer, that the weaker succeed powerful and undoubted tetanic paroxysms, these gradually growing less and less, pass insensibly into a weaker and weaker form. If, then, the weaker paroxysms after box are certainly tetanic, we are clearly justified in classing as tetanic the movements just described in brainless frogs.

This tetanus, like other forms of tetanus, depends on the spinal cord. This we proved by the following experiment:—On the occurrence of tetanus we divided the sciatic nerve of one leg, and then found that whilst in the intact leg we could readily induce tetanus, we failed to excite it in the leg with the severed nerve, though some movement occurred in the thigh muscles which receive branches above the point of division of the sciatic.

It cannot be maintained, we think, that this tetanus is due to an exalted or excited condition of the spinal cord. The tetanus is preceded by loss of reflex action; it increases in strength as the coördinated reflex action grows less; it is most marked a short time before all coördinated reflex action ceases. Like the lessened coördinated reflex action it must be due, we believe, to depression of the cord. We explain the tetanus in these brainless frogs as we explained it when occurring in the experiments with box and gelseminum. Thus, soon after death, the cord becomes depressed, and consequently reflex action becomes weaker; but with depression of reflex action we get also diminution of the resistive power of the cord, whereby impressions cease to be restricted to their proper portion of the cord, but spreading widely cause tetanic movements. At first, before much weakening of the resistance of the cord sets in, it requires a strong irritation to overcome the remaining resistance, weaker irritation still inducing coördinated reflex action. As depression of the cord progresses, the resistive power grows weaker, and the tetanic movements are more readily induced and are more marked. As, however, the cord is much depressed they are rarely severe, and an interval is required to permit the cord to recover from the effects of the previous discharge. The depression of reflex action and resistive power progress at the same time, and consequently the total loss of power of the cord both coördinated (natural) and tetanic contraction can be induced, the coördinated by slight, the tetanic by stronger irritation.

The following facts also tend to show that tetanus depends on a depressed condition of the spinal cord. In these brainless frogs, at a time when a strong irritation was required to excite even slight tetanus by a repetition of the strong irritation, as for instance giving sharp blows in quick succession over the upper part of the spine, the tetanus soon became much more marked, and it was observed that, after such strong irritation, normal reflex actions were induced with more difficulty. The correct interpretation of these facts, we think, is that the shock of a succession of blows depresses the cord's resistive power whereby the irritation diffusing itself more widely causes more marked tetanic movements, and at the same time weakens normal (coördinated) reflex action. If the irritation is pushed still further, the depression becomes so great as temporarily to abolish both coördinated and tetanic reflex action, and a short time is required for the cord to recover itself.

The following observation tends to show the validity of this explanation. On striking repeatedly a living vigorous frog strongly on the back between the shoulders, we excite at first simply coördinated reflex acts, but in a short time after each blow the posterior legs are shot out in a tetanic manner, though far less energetically than when the same phenomenon occurs in brainless frogs on the decline of reflex action. The tetaniform movement occurs only when the shock of the blows has so depressed the cord that all voluntary and normal reflex action is for the time abolished. After rest the normal (coördinated) reflex action returns, and these phenomena can be re-elicited.

It appears that some agents, like strychnia, depress only the resistive power, whilst leaving unimpaired the reflex function of the cord. Hence, with the removal of the restraining influence, slight impressions diffuse themselves throughout the cord, and produce not only a general, but likewise an excessive evolution of nervous force. Other agents depress both the resistive as well as the reflex power of the cord; hence we get tetanus, though weak in character. In some cases the effects are developed more on the reflex function than on the resistive power, and here, as with gelseminum, we get considerable paralysis with slight tetanus. This happens also with regard to strong blows on the back, which depress both functions very considerably. Other agents depress the resistive power early and markedly; and in a less degree the reflex function, with box for example, we get strong tetanus with slight paralysis. These views too, we think, will throw light upon the effect of slight chemical modifications of a drug on physiological action. Nerves in their constitution must differ from one another and from the cerebral nervous system, since a given poison may affect one part only of the nervous system; for instance, the motor nerves leaving the cord unaffected. Strychnia excites powerful tetanus, and when given in very large doses simultaneously depresses the motor nerves. If converted into an ethyl compound by substituting the radicle ethyl in place of a molecule of hydrogen, strychnia no longer tetanises, but powerfully paralyses the ends of the motor nerves. We submit that the physiological action is not entirely reversed. As strychnia it paralyses the constraining or resistive power of the cord; when converted into ethyl-strychnia, its chemical affinities being somewhat modified, it affects the motor nerves, but still it paralyses. It is not converted from a stimulant of the cord to a depressant of the motor nerves, but its chemical affinities being changed it affects the motor nerves; instead of paralysing the resistance of the cord, it paralyses the motor nerves. Its conversion into ethyl-strychnia heightens its affinities for the nerves, but lessens or destroys its affinity for that portion of the cord which restrains and localises reflex action.