THE ACTION OF ARSENIATE OF SODA AND ARSENIOUS ACID ON FROGS.

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IN the *Archiv für Anat. Physiolog.*, &c. 1866, p. 481, Sklarek records some experiments concerning the action of arsenic on frogs. He says, that in about five minutes after injecting it, the animal lies flat with extended extremities, and without breathing. Pinching or other irritation excites neither reflex action nor voluntary motion, though much voluntary power remains, for on lifting the animal, or withdrawing a leg, or turning the frog on its back, it displays active voluntary movements. In a short time, however, the animal becomes completely paralysed. Arsenic, therefore, paralyses first sensation and reflex action, and sometime afterwards voluntary power.

Now paralysis takes place in this order after mechanical arrest of the circulation by ligature, or by excision of the heart. Arsenic being a powerful paralyser of the heart, we were induced to undertake this series of investigations to ascertain whether arsenic paralyses simply by arresting the heart's action. Our experiments show that arsenic does not paralyse simply by its action on the heart, but that, like potash, it has a poisonous action on all nitrogenous tissues, and destroys their function.

We commenced our experiments in October, 1877. We first experimented with arseniate of soda, using a solution of the same strength as that employed by Sklarek, but we obtained very different results from those described by him. We then tried arsenious acid dissolved by the aid of a small quantity of soda, and with this form of the drug we obtained effects similar to those recorded by Sklarek. In this paper we shall describe, first the action of arseniate of soda, and then of arsenic, and point out in what respects they differ; then we shall adduce experiments proving that arsenious acid is a protoplasmic poison, destructive of the function of nitrogenous tissue.

The action of Arseniate of Soda on Frogs.

We employed the soda salt, since soda, unless used in very large quantities, does not paralyse frogs, whilst even a small quantity of a potash salt produces complete paralysis. We injected under the skin the quantity used by Sklarek in his experiments, but we obtained very different results. Thus paralysis set in slowly, and sensation persisted as long, or almost as long, as voluntary power. Sensation first ceased in the toe and foot, whilst in the calf and thigh it still remained good. Then in some cases sensation ceased before the loss of voluntary power, but in others continued as long as voluntary power. Table I. shows the weight of the animal, and the dose of arsenic administered.

Table I. Solution injected hypodermically under skin of back.

Arseniate of Soda, 1 in 20 solution.

Date.	Weight of animal in grammes.	Dose in grains.	
Oct. 23	$28\frac{1}{2}$	$\frac{1}{5}$	
„ 23	21	$\frac{1}{10}$	
„ 23	33	$\frac{3}{5}$	
„ 24	32	$\frac{3}{20}$	
„ 24	27	$\frac{3}{20}$	1 in 40 solution.

Though we administered large doses, from $\frac{1}{10}$th to $\frac{3}{5}$ths of a grain, still for several hours the poison produced no effect, the frogs in these experiments remaining unaffected $4\frac{1}{2}$, 11, $4\frac{1}{2}$, 7, and 7 hours respectively, and then paralysis set in.

In the first experiment, after 11 hours, only very slight reflex action remained.

In the second, after 13 hours, only slight reflex action remained, and next morning the animal was found dead.

In the third, the animal died in 11 hours.

In the fourth, voluntary movement was extinguished in 11 hours, but reflex action remained good. This frog was found dead next morning.

In the fifth, after 11 hours, slight voluntary power remained, and reflex action was unimpaired. Next morning we found the frog dead.

These experiments show that for several hours (4 to 11), after poisoning with arseniate of soda, the animal remains unaffected; that complete paralysis is not established in less than 13 hours; and that voluntary power disappears before reflex action.

The action of Arsenious Acid on Frogs.

The effects of arseniate of soda being so different from those described by Sklarek, we next experimented with arsenious acid. As arsenious acid is so little soluble in water, we were obliged to add an alkali, and chose soda, avoiding potash, this base having such a powerful action on all the tissues. Mr Gerrard prepared for us a solution containing a grain of arsenious acid to five of water, adding hydrate of soda in the proportion of 1 in 22.

This solution we injected under the skin of the back, and we give the results in Table II.

The experiments there tabulated show that in poisoning by arsenious acid, sensation and reflex action continue longer than voluntary action; for pinching the leg excited reflex action after complete loss of voluntary power, indicating that the afferent nerves still conducted impressions. In this table we have used the term "sensation" to point out that the afferent nerves are still active.

The effects therefore of arsenious acid dissolved by the aid of soda are very different from the effects of arseniate of soda. With arseniate of soda, the paralysis does not begin till four or more hours, and does not become complete for twelve or more hours, whilst after arsenious acid paralysis becomes complete in 40 minutes.

It might be just possible, we thought, that the powerful effect of the arsenious acid solution was due to the rather large quantity of soda it contained. To ascertain whether the soda played any part in the paralysis, we experimented with a solution of soda prepared for us by Mr Gerrard, containing the same proportion of soda as in the arsenious acid solution. This we injected under the skin of the back of two frogs, employing the same proportionate dose of soda to the weight of the animal, as in the previous experiments with arsenious acid. Beyond the primary shock, lasting about a minute, this injection produced no effect; therefore the paralysis following the injection of the arsenious acid solution is entirely due to the arsenic. The arsenious acid solution produced a far greater shock than the simple soda solution, and it occurred to us that this was due to the great concentration,

Table II.

Arsenious acid dissolved with aid of liquor sodæ. Solution containing 1 *grain of arsenious acid in* 5 *of the solution. Hydrate of soda* 1 *in* 22.

Date.	Dose in grains.	Weight of animal in grammes.	Proportionate dose.	Loss of sensation and reflex action begun.	Loss of sensation and reflex action complete.	Loss of voluntary power begun.	Loss of voluntary power complete.
Oct. 25	$\frac{1}{5}$	24	$\frac{1}{1852}$	6 min.	55 min.	6 min.	45 min.
„ 25	$\frac{2}{5}$	23	$\frac{1}{887}$	5 min.	33 min.	1 min.	28 min.
„ 27	$\frac{1}{10}$	23	$\frac{1}{3551}$	7 min.	56 min.	7 min.	56 min. } 1 in 10 solution
„ 27	$\frac{1}{5}$	15	$\frac{1}{1158}$	7 min.	52 min.	7 min.	47 min. } 1 in 10 solution
„ 30	$\frac{1}{20}$	10	$\frac{1}{3088}$	5 min.	23 min.	5 min.	23 min. } 1 in 20 solution
„ 30	$\frac{1}{10}$	15	$\frac{1}{2316}$	5 min.	29 min.	5 min.	29 min. } 1 in 20 solution
Nov. 5	1	21	$\frac{1}{324}$		36 min.	4 min.	41 min. 1 in 5 solution
			Average	5·8 min.	40·5 min.	5 min.	38 min.

Experiments with solution of hydrate of soda 1 *in* 22.

Oct. 26	$\frac{1}{22}$	21	No effect except the primary frightened state lasting one minute.
	$\frac{1}{11}$	21	No effect except the primary frightened state lasting one minute.

therefore in our two last experiments we diluted the solution to 1 in 10 with the effect of greatly reducing the shock.

But whilst the effects of arseniate of soda differ greatly from those of arsenious acid dissolved in soda, the difference consists in the rapidity of the occurrence of the effects, for in both cases the afferent nerves retained their conducting power as long, or even longer, than voluntary power continued.

In this respect, therefore, our observations differ from those of Dr Sklarek, who found that sensation and reflex action were abolished in about six minutes. The reconcilement of this difference is, we think, to be found in the time of year the experiments were made. We presume (for unfortunately Dr Sklarek does not give the season) that his investigations took place in the months of May, June, July, or August, whilst ours were made in October. We have found similar differences, as we have already said, in the effect of arrest of circulation, and in potash poisoning.

We had hitherto used very strong solutions of arsenious acid, 1 in 5, 1 in 10, and 1 in 20. The 1 in 5 solution appeared to have a strong topical action; and to test if this were so, we injected some of the solution under the skin of the thigh. After complete paralysis we stripped off the skin, and examined the muscles. Those the solution had reached were yellowish and quite hard, and did not in the slightest degree contract on the application of a strong galvanic current. We therefore used a much weaker solution, namely, 2 per cent., the strength employed by Sklarek. We should have used this weaker form at first; but, with so weak a solution, we could not give our frogs anything like the doses he administered.

Mr Gerrard made us a 2 per cent. solution with just sufficient liquor sodæ to dissolve the arsenic. We injected five minims of this under the back of a frog, and after the induction of complete paralysis, we examined the muscles, and they appeared unaffected; moreover, the back and thigh muscles contracted under galvanism, as well as the muscles of the rest of the body. This solution therefore has no immediate topical action. We therefore made a series of observations with this 2 per cent. solution, always injecting it under the skin of the back, close to the posterior lymph-hearts.

We first give a short account of the symptoms induced by these small doses. Soon after the injection the animal becomes quiet, but sensation, reflex action, and voluntary power, are unimpaired. In ten to twenty minutes the animal often gapes, and keeps its mouth open, and sometimes puts its paws into its mouth. It looks as if sick, and two frogs actually vomited. Then, after twenty to thirty minutes, voluntary power declines, sensation continuing apparently quite unimpaired till all movement ceases, or nearly ceases. It is difficult to tell when reflex action begins to decline, as it is often difficult to decide between a voluntary and a reflex act. A few hours after death a very strong post mortem rigidity sets in.

Table III.

Solution of arsenious acid 2 per cent. dissolved with the aid of smallest quantity possible of liquor sodæ.

Date.	Dose in grains.	Weight of animal in grammes.	Proportionate dose.	Loss of sensation begun.	Loss of sensation and reflex action complete.	Loss of voluntary power begun.	Loss of voluntary power complete.
Nov. 6	$\frac{1}{10}$	31	$\frac{1}{4786}$	4 min.	42 min.	4 min.	42 min.
„ 8	$\frac{1}{25}$	18	$\frac{1}{6948}$	32 min.	52 min.	26 min.	52 min.
„ 8	$\frac{1}{50}$	20	$\frac{1}{15440}$	38 min.	57 min.	38 min.	57 min.
„ 9	$\frac{1}{50}$	34	$\frac{1}{26248}$	70 min.?	130 min.	33 min.	130 min.
„ 9	$\frac{1}{50}$	40	$\frac{1}{30880}$	77 min.?	108 min.	28 min.	108 min.
„ 9	$\frac{1}{50}$	30	$\frac{1}{23160}$	48 min.	58 min.	26 min.	58 min.
„ 9	$\frac{1}{50}$	29	$\frac{1}{22388}$	75 min.	80 min.	30 min.	80 min.
„ 10	$\frac{1}{12}$	33	$\frac{1}{6114}$		49 min.	4 min.	49 min.
„ 10	$\frac{1}{25}$	21	$\frac{1}{8106}$		41 min.	6 min.	41 min.
„ 13	$\frac{1}{25}$	31	$\frac{1}{11966}$		60 min.	20 min.	60 min.
„ 14	$\frac{1}{8}$	43	$\frac{1}{5311}$		34 min.	5 min.	34 min.
„ 15	$\frac{1}{25}$	26	$\frac{1}{10036}$		42 min.	2 min.	42 min.
				Average	62·7 min.		62·7 min.

Table IV. shows that even small doses varying from $\frac{1}{4000}$ to $\frac{1}{30000}$ of the weight of the animal quickly paralyse, for on the average of these twelve experiments paralysis was complete in 62 minutes. We were astonished to find how very fatal arsenious acid is to frogs, for $\frac{1}{30000}$ of the weight of the animal produced complete paralysis in 108 min., and $\frac{1}{80000}$ killed the frog on the third day, and we were likewise astonished to find how far more poisonous arsenious acid is than arseniate of soda, $\frac{1}{5}$ gr. of this salt requiring 11 hours to produce almost complete paralysis.

Table IV.

Solution of arsenious acid ½ per cent. dissolved with the smallest quantity possible of liquor sodæ.

Date.	Dose in grains.	Weight of animal in grammes.	Proportionate dose.	
Nov. 10	$\frac{1}{100}$	33	$\frac{1}{50900}$	Died on second day
„ 10	$\frac{1}{100}$	21½	$\frac{1}{33100}$	Died on second day
„ 10	$\frac{1}{200}$	26	$\frac{1}{80288}$	Died on third day
„ 12	$\frac{1}{200}$	27	$\frac{1}{83376}$	Died on third day
„ 12	$\frac{1}{200}$	25	$\frac{1}{77200}$	

This general paralysis is due to the action of the poison on the central nervous system, for after complete paralysis, on the direct application of galvanism, the muscles still contract and the motor nerves still conduct.

We are now in a position to attempt to answer in part the question we put at the beginning of this paper—Does arsenic paralyse simply by arresting the heart?

We must first compare the times respectively when paralysis became complete after poisoning by arsenic, and by mechanical arrest of the circulation. In Table II. we find that after poisoning by arsenic, paralysis became complete on an average in 40 minutes, and in a subsequent set of experiments, where a smaller dose of arsenic was administered, the results of which are given in Table III., paralysis became complete on an average in 62 minutes. These experiments were made in October and the first half of November. In the month of October mechanical arrest of the circulation, as we have shown in a previous paper, produces complete paralysis in the average time of 42 minutes. With regard to these figures, it is evident that arsenic may indirectly paralyse the central nervous system by its paralysing action on the heart, for mechanical arrest will produce complete paralysis as soon, and sometimes sooner, than after poisoning by arsenic.

We next performed the following experiments to attempt to decide this question.

We poisoned three frogs by injecting a solution of arsenic under the skin of the back. Two became completely paralysed respectively in 56 and 60 minutes, and the third was greatly paralysed, though some movement continued, in 60 minutes. At the times just stated we placed the web under the microscope and found the circulation completely arrested in all three frogs, and on opening the chest the heart was found motionless and widely distended with blood. These experiments likewise tend to show that the general paralysis may be due to arrest of the heart.

In some other experiments, however, after complete paralysis we found the heart beating well, in one instance at 30 per minute. Unfortunately we omitted to examine the circulation in the web.

As after the general paralysis the motor nerves conducted impressions, and caused the muscles to contract vigorously, it is obvious that the general paralysis is due to the condition of the central nervous system, and not to the condition of the nerves and muscles; moreover, as in some instances after general paralysis, the heart still beat fairly well, we conclude that arsenic does not act through the heart, but is a direct paralyser of the central nervous system.

How are we to explain the varying effects of arsenic on the heart? We have seen that in some cases the heart is speedily arrested, whilst in others it continues to beat after complete paralysis. This difference is, we think, due to the dose. A large dose is quickly absorbed and conveyed in large quantity to the heart, arrests it at once, leaving very little to be distributed through the circulation, the general paralysis being then mainly due to this arrest of the circulation. In other cases, under a smaller dose, the heart is not so quickly stopped, but enough arsenic is distributed by the circulation to paralyse the central nervous system before the heart.

We shall next show that arsenic is both a muscle and a nerve poison, as well as a direct paralyser of the central nervous system.

In some experiments on frogs with a 2 per cent. and a still weaker solution of arsenious acid, dissolved with the aid of a small quantity of liquor sodæ, we noticed some curious effects. Even so early as six or eight hours after death strong *rigor mortis* set in, and this suggested the idea that arsenic is a muscle as well as a nerve poison, and to test the validity of this conjecture we performed the following experiments.

We poisoned two frogs with $\frac{1}{12}$ and $\frac{1}{25}$ gr. of arsenious acid, in a 2 per cent. solution, injected under the skin of the back, close to the posterior lymph-hearts. A summary of the effects is given in Table III. Nov. 10. As soon as the two animals became completely paralysed, we divided the cord of another frog, opposite the occipito-atlantal membrane, and passed the blade of the forceps into the skull, destroying the brain. The wound bled freely, and we took no steps to check the hæmorrhage. This frog we used as a standard to compare the muscular contractility of the arsenicized frogs.

Seven minutes after complete paralysis we tested the muscles through the skin, and found that the muscles of the brainless frog contracted rather better than those of the arsenicized frogs. In an hour and an half the muscles of the brainless frog contracted decidedly better than the muscles of the arsenicized frogs. In three hours and a half the muscles of the brainless frog still contracted energetically with a weak current; whilst the strongest current excited only very feeble and scarcely visible contractions in the arsenicized frogs. We noticed also in the arsenicized frogs that the weak muscular contraction was excited equally with a comparatively gentle current as by the strongest the battery could compass. Next morning, eighteen hours after complete paralysis, we found the arsenicized frogs quite stiff; whilst very good, though relatively weaker reflex action continued in the brainless frog. The strongest current failed to excite any muscular contraction in the muscles of the arsenicized frogs, whilst a weak current produced strong muscular contraction on direct application to the muscles in the brainless frog. We then stripped off all the skin from the arsenicized frogs, and during this process we noticed the curious fact, which we shall hereafter refer to, that the cuticle came off very easily, indeed it could be rubbed off. Then we again tested the muscles of the anterior and posterior extremities, and failed to produce the slightest contraction with the strongest current from a one-celled du Bois-Reymond induction coil.

This experiment seemed to render it highly probable that arsenious acid is a muscle-poison, though it must be admitted the comparative experiment with the brainless frog was hardly a satisfactory test to determine whether arsenic acts directly on the muscles or by arresting the heart; for though we allowed the animal to bleed freely from the wound when we divided the cord, we did not cut out the heart, and so though but little blood was left in the vessels, probably this little circulated and supplied the tissues with oxygen. We therefore performed some more experiments free from this possible fallacy.

Each morning we poisoned a frog by injecting the 2 per cent. solution into the connective tissue of the axilla, to avoid the direct topical action on the hind legs. When this animal became completely paralysed we cut the cord of another frog opposite the occipito-atlantal membrane, destroyed the brain, and then extirpated the heart. The two frogs were then laid side by side, and during the day we frequently tested them with the interrupted current, first through the skin, and when this failed to contract the muscles, we removed the skin, and applied the electrodes directly to the muscles. We also tested the nerves.

We give the results of our experiments in Table V.:

Table V. Duration of muscular contractility after poisoning with arsenious acid, 2 per cent. solution dissolved with a small quantity of liquor sodæ.

Date.	Weight of frog.	Dose of arsenic in grains.	Proportionate dose.	Complete paralysis.	Muscular contractility ceased in
Nov. 10	33	$\frac{1}{12}$	$\frac{1}{6114}$	49 min.	$3\frac{1}{2}$ hours*
„ 10	21	$\frac{1}{25}$	$\frac{1}{8106}$	40 min.	$3\frac{1}{2}$ hours*
„ 13	31	$\frac{1}{25}$	$\frac{1}{11966}$	60 min.	$9\frac{1}{2}$ hours
„ 14	43	$\frac{1}{8}$	$\frac{1}{5311}$	34 min.	$5\frac{1}{2}$ hours
„ 15	26	$\frac{1}{25}$	$\frac{1}{10036}$	42 min.	$5\frac{3}{4}$ hours
			Average	45 min.	5·6 hours
Duration of muscular contractility in brainless frogs with extirpated heart.					
Nov. 12					25 hours
„ 13					48 hours
„ 14					29 hours
„ 15					15 hours
				Average	29 hours

This Table (V.) shows that in frogs poisoned with arsenious acid, muscular irritability ceases in from three to nine hours, whilst the irritability persists in brainless frogs with extirpated heart, from one to two days, or an average time of 29 hours. How does arsenic arrest muscular contraction? Does it act by arresting the heart's action? The Table shows that arsenic does not paralyse the muscles by arresting the heart: for if arsenic paralyses the muscles only through its action on the heart, the muscular irritability should persist as long in the arsenicized frogs as in the frogs with extirpated heart. The loss

* Had not quite ceased, but the strongest current of a one-celled du Bois-Reymond battery excited only the slightest contraction.

of muscular irritability, therefore, is not due to arrest of the circulation, but to the direct action of the arsenic on the muscles; in other words, arsenic is a muscle-poison.

We next devised another set of experiments further to test the validity of our conclusion, that arsenious acid is a muscle-poison. We divided the cord of a frog opposite the occipito-atlantal membrane, and passed a wooden peg into the cavity of the skull, destroying the brain and preventing hæmorrhage. Now we tied a ligature tightly round the left thigh, close to its junction with the trunk, to arrest the circulation, then we injected the arsenious acid into the left axilla, and, from time to time, tested the muscular irritability of the ligatured and the non-ligatured poisoned legs, and in Table VI. we give the results.

Table VI. Table showing the duration of muscular irritability in a poisoned and unpoisoned leg of pithed and pegged frogs.

Date.	Dose of arsenious acid in grains.	Weight of frog in grammes.	Proportionate dose.	Reflex action destroyed.	Muscular irritability in poisoned leg ceased in	Muscular irritability in ligatured non-poisoned leg ceased in
Nov. 15	$\frac{1}{12}$	24	$\frac{1}{4446}$	27 min.	17 hours*	43 hours
„ 15	$\frac{1}{25}$	25	$\frac{1}{9650}$	44 min.	17 hours*	41 hours
„ 16	$\frac{1}{25}$	27	$\frac{1}{10422}$	50 min.	7 hours	16 hours
„ 16	$\frac{1}{50}$	21	$\frac{1}{17833}$	53 min.		
„ 17	$\frac{1}{12}$	37	$\frac{1}{6855}$	38 min.	9 hours	40 hours
„ 17	$\frac{1}{12}$	35	$\frac{1}{6484}$	35 min.	16 hours	31 hours
			Average	41 min.	13 hours	34 hours

Here we see that the muscles of the poisoned posterior limb lost their irritability in an average time of 13 hours, whilst in the limb tightly ligatured the muscles retained their contractility an average time of 34 hours. The results shown in this Table clearly demonstrate that arsenic is a muscle-poison.

It is worthy of notice, that after complete destruction of reflex

* An interval of eleven hours, namely from 8.30 p.m. to 7.30 a.m., elapsed between our observations; at 8.30 p.m. the muscles contracted well, next morning at 7.30 a.m. contraction had ceased; thus these figures are not very correct, and probably muscular irritability lasted a shorter time than here stated.

action, the muscular irritability continued equally manifest in both hind legs for three to six hours.

Our experiments, moreover, show that arsenious acid is also a nerve poison. In several previous experiments we noticed that the motor nerves in arsenicized frogs became paralysed many hours before the motor nerves of frogs with mechanical arrest of the circulation. We determined, however, to make some further experiments intended especially to ascertain the action of arsenious acid on motor nerves. We poisoned frogs, by injecting a 2 per cent. solution under the back, and simultaneously prepared some test-frogs, by dividing the cord opposite the occipito-atlantal membrane, and then cut out the heart to arrest circulation. Then we tested the sciatic nerve with the interrupted current through the skin, morning, noon, and night.

It may be said perhaps that we should not have tested the conductivity of the sciatic nerve through the skin, that we should have exposed it and isolated it on a piece of glass. Now this would have invalidated our experiment, for by isolating the nerve we should have separated it from the tissues and cut off the blood-supply, thus preventing the poison reaching the nerve either through the circulation or by imbibition. Arsenic, like potash, quickly paralyses the heart, so that but little of the poison reaches the tissues through the blood. Its paralysing effects are due to its diffusion by imbibition through the tissues, isolation therefore would have prevented the play of the arsenic on the nerve. Moreover, as we treated the test-frogs in the same way, our experiments are so far trustworthy, as a reference will show that on applying the electrodes over the sciatic of arsenicized frogs the nerve ceased to conduct impressions to the lower leg and foot muscles sooner than in the case of the unpoisoned test frogs.

Table VII. exhibits our results.

Although we poisoned and tested six frogs, it will be seen that only four are available in evidence. In two experiments, between the interval of our visits, the muscular irritability, on the direct application of the electrodes, had ceased, and it is obvious we could test the conductivity of the sciatic nerve so long only as the muscles could contract. In the four remaining experiments we found that the sciatic nerve ceased to conduct several hours before the muscles lost their contractility. We infer, therefore, that in these instances the sciatics were paralysed; moreover, on comparing the time it took to paralyse the sciatics of arsenicized frogs with the time it took to paralyse the sciatics of test-frogs, we found that the sciatic nerves of arsenicized frogs ceased to conduct impressions many hours before the same nerves in the test-frogs. Thus in the arsenicized frogs, the sciatics became paralysed, respectively, in 4, 4, 14, and 10 hours, giving an average of

Table VII. Action of Arsenious Acid on Motor Nerves and Muscles.

Date.	Dose in grains.	Weight of animal in grammes.	Sciatic nerve ceased to conduct.	Muscular irritability ceased in: Anterior extremities.	Muscles of back.	Thigh.	Lower leg muscles.	Place of injection.
Feb. 26	$\frac{1}{12}$	28	Left 4 hours	4 hours		8 hours	8 hours	Right axilla
			Right 8 hours	4 hours		8 hours	8 hours	
„ 26	$\frac{1}{12}$	32	Left 4 hours	4 hours		5 hours	8 hours	Left axilla
			Right 4 hours	4 hours		5 hours	8 hours	
„ 26	$\frac{1}{25}$	28	4 hours	4 hours		4 hours	4 hours	Under skin of back
„ 26	$\frac{1}{12}$	38	8 hours	8 hours		8 hours	8 hours	Under back
„ 27	$\frac{1}{50}$	31	Left 14 hours	10 hours		10 hours	R 10 hours L 19 hours	Under back
„ 27	$\frac{1}{50}$	30	10 hours	10 hours		10 hours	16 hours	Under back
			Average	6 hours		7 hours	10 hours	

Test Frogs. Cord divided and heart excised.

Date.	Dose in grains.	Weight of animal in grammes.	Sciatic nerve ceased to conduct.	Anterior extremities.	Muscles of back.	Thigh.	Lower leg muscles.	Place of injection.
Feb. 26			34 hours	38 hours	28 hours	34 hours	54 hours	
„ 26			28 hours	24 hours	28 hours	24 hours	40 hours	
		Average	31 hours	31 hours	28 hours	29 hours	47 hours	

8 hours, whilst the sciatics of the test-frogs with arrested circulation conducted for 34 and 28 hours respectively, giving an average of 31 hours. We conclude, therefore, that arsenic is a paralyser of motor nerves.

These experiments on nerve incidentally confirm our conclusion that arsenic is a muscle poison, as the following averages extracted from Table VII. shows.

Table VIII (Resumé of Table). The average duration of muscular contractility.

	Anterior limb.	Thigh.	Lower leg.
Arsenicized frogs	6 hours	7 hours	10 hours
Unpoisoned frogs	31 hours	29 hours	47 hours

On the strength of the following experiment we suggest that arsenious acid is also a poison to afferent nerves.

We immersed the left leg of a frog, for two minutes, in a two per cent. solution of arsenic, and on removing it we found sensation abolished, for pinching it neither excited voluntary nor reflex movement, whilst the animal still retained complete voluntary power over the limb. The animal continued in this condition an hour and a half. On examining it in five hours and a half, we found it completely paralysed.

The muscles became paralysed in the following order: left leg, right thigh and back in nine hours, and right lower leg muscles in 17 hours. The right sciatic became paralysed in 12 hours. It is evident that the poison did not spread by means of the circulation but passed by imbibition up the left immersed leg, poisoning next the muscles of the back and right thigh with the right sciatic nerve, and lastly some hours afterwards reaching and poisoning the right lower leg muscles. This experiment also shows that arsenious acid is a nerve poison, for the right sciatic early ceased to conduct impressions to the lower leg muscles.

As in this experiment the local application of an arsenious acid solution destroyed sensation in the immersed leg, it is, we suggest, at least feasible that when conducted to the sensory nerves, either by the circulation or by imbibition, the poison would equally destroy sensation.

The preceding experiments, we venture to think, clearly establish that arsenious acid is a protoplasmic poison, affecting first the more highly organized nervous centres, next the nerves, and last the muscles. The evidence tending to show that arsenious acid directly paralyses the central nervous system, being not so conclusive as we could wish, we were led, through a suggestion of Dr Burdon Sanderson, to perform another set of experiments. Arsenious acid, as we have said, quickly arrests the heart, so that but little arsenious acid finds its way through the circulation. We therefore injected a solution into the vessels. We first divided the cord and passed a peg through the wound into the cavity of the skull; we then opened the chest and introduced a cannula into the bulb of the aorta, and having securely tied it, we injected the solution, containing one per cent. of common salt, and a half per cent. of arsenious acid dissolved by the aid of a very small quantity of liquor sodæ.

At the same time, we performed some test-experiments to ascertain the effect of the injection of a one per cent. solution of common salt. These frogs were in all other respects treated like the arsenicized frogs. The results are shewn in Table IX.

Table IX. Solution of Arsenious Acid injected through the blood vessels.

Date.	Reflex action ceased.	Sciatic nerve paralysed.	Muscular irritability ceased in: Anterior limbs.	Thigh.	Lower leg muscles.	Strength of solution.
Mar. 6	8 min.		5 hours	5 hours	5 hours	½ p. c.
„ 7	immediately injection finished.		5 hours	5 hours	5 hours	„
„ 7	„	5 hours	5 hours	5 hours	10 hours	„
„ 9	„		5 hours	5 hours	5 hours	⅕ p. c.
Test frogs injected with solution of common salt.						
Mar. 4	48 min.	25 hours	40 hours	40 hours	42 hours	¾ p. c.
„ 7	60 min.	28 hours	28 hours	36 hours	40 hours	1 p. c.
Average	54 min.	26·5 hours	34 hours	38 hours	41 hours	

Now these experiments confirm our previous conclusions. They show that arsenious acid directly poisons the central nervous system, and does not affect it only by arresting the heart. Thus in the frogs, injected with common salt, whose circulation was of course arrested when we divided the bulb to insert the cannula, reflex action persisted for 48 and 60 minutes respectively, whilst in the case of the frogs whose vessels were injected with the arsenious acid solution, the reflex action in three cases was destroyed when we had finished the injection, and in the remaining case it lasted only eight minutes.

These, like some of the previous experiments, show that arsenious acid is a muscle-poison, for muscular irritability was lost in the arsenicized frogs in five hours, whilst it persisted in the frogs injected with common salt solution, in the anterior limbs 34 hours, in the thighs 38 hours, and in the lower leg muscles 41 hours.

Whilst our experiments show that arsenious acid is a poison to all nitrogenous tissues, they fail to prove whether it is equally poisonous to all tissues, or whether it manifests an especial action on some, as on the brain, cord, &c., or even on parts of these. Our experiments were not designed, and do not help us, to decide these points.

How does arsenious acid destroy the vitality of nitrogenous tissues? Does it kill by preventing oxidation, or by combining with the tissues? Our observations do not enable us to answer this question. One fact we noticed seems to suggest that it destroys in neither way. Thus conductivity of the motor nerves and the muscular contractility do not cease for some hours after poisoning by arsenious acid. In our early experiments, in which we administered the poison hypodermically, we thought that by arresting the heart quickly the poison did not get diffused by means of the circulation, but by imbibition through the tissues. This slow diffusion of the poison seems to explain the tardy action on the nerves and muscles; but this solution is not strictly correct, for even when the poison was injected through the vessels, yet paralysis did not for several hours set in in the nerves and muscles, though, indeed, sooner than in frogs poisoned hypodermically. We may conclude, therefore, that even when brought into immediate contact with the tissues, arsenic, unless in a very concentrated state, requires some hours to produce paralysis. Now, if arsenic acted solely by arresting oxidation, or by combining with the tissues, we should expect it to produce its effects much earlier.

We may draw attention to a curious effect of arsenious acid on the skin of frogs. We have said that in our experiments we noticed that a few hours after the hypodermic injection we could strip off the cuticle with the greatest readiness over every part of the body. We give in the following Table the results of our observations. We tied a tight ligature round one hind leg of some of the frogs to protect the tissues below from the effect of the poison.

Table X. Action of Arsenious Acid on the Cuticle.

Date.	Proportional dose.	Begun.		Begun.
Nov. 13	$\frac{1}{11966}$			9 hours
„ 14	$\frac{1}{5311}$			5½ hours
„ 15	$\frac{1}{10036}$			42 min.
		Begun in non-ligatured leg.	Begun in ligatured leg.	Begun on trunk.
„ 15	$\frac{1}{4[\text{illegible}]46}$	12 hours	None in 24 hours	3½ hours
„ 15	$\frac{1}{9650}$	12 hours	25 hours	3½ hours
„ 16	$\frac{1}{10422}$	5½ hours	None	5½ hours
„ 16	$\frac{1}{6853}$	9 hours	None	9 hours
„ 17	$\frac{1}{6484}$	5 hours	None	5½ hours
	Average	8·7 hours		5·4 hours

Table X. shows that desquamation begins on the trunk on an average in five and a half hours, in the leg on an average in eight and a half hours. That the desquamation is due to the arsenious acid is well shown by the absence of desquamation in the limb surrounded by a tight ligature. Moreover, that the desquamation depends on the arsenious acid is well shown also by the experiments recorded in Table XI. In these experiments we killed the frogs by dividing the cord and cutting out the heart, and then watched carefully for several days without detecting any desquamation.

Is this desquamation a peculiar result of arsenious acid, or does it follow the hypodermic injection of other poisons? We tested chloride of potassium, aconitia, extract of duboisia, and acetate of strychnia.

Table XI. Desquamation in dead but unpoisoned frogs.

Date.	None in
Nov. 30	72 hours
„ 30	72 hours
Dec. 1	58 hours
„ 1	58 hours
„ 3	48 hours
„ 3	48 hours
„ 8	84 hours
„ 8	84 hours

Table XII. shows the effect of chloride of potassium.

Table XII. Desquamation.

Chloride of Potassium 1 *in* 5.

Date.	Cuticle strips off at place of injection.	No general desquamation took place during	Desquamation in
Nov. 20		24 hours	
„ 21		53 hours	
„ 21		53 hours	
„ 21		48 hours	
„ 22		30 hours	48 hours
„ 23		24 hours	
„ 23	72 hours	72 hours	
„ 24	24 hours	48 hours	
„ 24	24 hours	48 hours	
„ 24	24 hours	48 hours	
„ 24	24 hours	48 hours	
„ 24	24 hours	48 hours	
„ 26	34 hours	34 hours	
„ 26	24 hours	24 hours	
„ 26		48 hours	
„ 27		24 hours	
„ 30		24 hours	
„ 30		24 hours	
„ 30		24 hours	
„ 30		24 hours	
Dec. 1		48 hours	
„ 3		48 hours	
„ 3		48 hours	

From this Table it appears that in about 24 hours desquamation occurs at the place of injection, but none elsewhere.

The other poisons produced no desquamation as Table XIII. shows.

Table XIII. Frogs poisoned with Aconitia.

Date.	No desquamation in
Dec. 8	48 hours
„ 8	48 hours
„ 8	48 hours
„ 8	48 hours
Extract of Duboisia.	
Jan. 3	40 hours
„ 9	24 hours
Acetate of Strychnia.	
Jan. 8	38 hours
„ 8	38 hours

SUMMARY.

1. Arsenious acid is a poison to all nitrogenous tissues.

2. Whether it is equally poisonous to all nitrogenous tissues, or is especially poisonous to some structures, our experiments do not decide.

3. Whilst it rapidly paralyses the central nervous system, it requires some hours to destroy the conductivity of the motor nerves and muscular irritability.

4. It causes in a few hours separation of the cuticle of the whole body.