THESIS

FOR THE DEGREE

OF M.D.

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AN EXPERIMENTAL STUDY

OF THE

"CUMULATION"

OF

STRYCHNINE.

From the Materia Medica Laboratory of the University of Edin.
— Professor Sir T.R.Fraser.

INTRODUCTION.

Clinical experience has shown that certain substances when repeatedly administered in the ordinary therapeutic doses, may suddenly produce symptoms of such a nature, as to suggest the rapid absorption of a toxic dose. Such substances are said to possess a "cumulative action" a term which is rather loosely applied and which seems to indicate that the phenomena are due to an accumulation of such substances in the tissues.

This subject of "cumulation" was first studied in connection with the digitalis glucosides, and the first pharmacological investigations were made by Fraenkel, who observed the cumulative effects of the digitalins on the cat.

It has been frequently stated that Strychnine also produces such effects on prolonged administration but/

but on referring to the literature it will be seen that the various statements concerning the subject are rather vague and conflicting. The phenomenon is an interesting one; it is also of practical importance , both from the clinical and toxicological standpoints.

The administration of strychnine as a remedy is frequently prolonged and in large doses :: Wood (I) advises it in the treatment of some forms of cardiac disease, where there is muscular weakness, "in rapidly ascending doses , the patient being kept if necessary for weeks and months on the verge of strychnine poisoning".

In the treatment of some forms of paralysis,it is sometimes desirable to continue the administration of the remedy, until incipient toxic effects are produced, as shown by the presence of muscular stiffness, heightened reflexes orother characteristic symptoms.

Therefore/

Therefore, from the therapeutic point of view, it seems necessary to have more definite information as regards the untoward effects of this so-called cumulation, in order that during its administration the dosage and the interval between the several doses, may be adjusted to rule out any possibility of such an action.

This question as to whether Strychnine does or does not possess a cumulative action also concerns the medical jurist. Dixon Mann (2) refers to the toxic symptoms which sometimes appear after the administration of the drug, and explains their occurrence as being due to idiosyncrasy on the part of the individual.

An interesting case of alleged poisoning by means of Strychnine was the occasion of a recent trial,/

trial, R. v. Saunders (Justiciary Court Edin. April 1913), the prisoner being accused of tainting various articles of food with minute quantities of the poison, with intent to kill. The question as to the possible cumulation of Strychnine arose during the trial. Dr W. C. Sillar, one of the medical witnesses for the Defence, in reply to a question as to whether Strychnine had or had not a cumulative action after the administration of successive doses, gave as his opinion, that it was not a cumulative poison. On the other hand, the opinion expressed by Professor Harvey Littlejohn was to the contrary, as evinced by his answer to a question put by the Solicitor General.

Q. "If this poisoning was continued, even the quantities being of the smallest character, would you expect in a short space of time there would be a fatal result?"/

result?.

A. "I certainly would think there was a great risk of a fatal result, because we know that to some extent Strychnine is cumulative in its action." (I3)

Taylor alludes to the toxic symptoms which may follow upon the frequent repetition of Medicinal doses of Strychnine, and he records an exceptional case of such accidental poisoning. Nux Vornica powder in doses of three grains, was prescribed for a patient, three times a day, and the administration was repeated over a period of sixteen days.

Four days later,, (after the remedy was discontinued) muscular stiffness, twitching of facial muscles, set in, and on the twelfth day spasms were evident. These recurred until death ensued twelve days after the discontinuance of the drug.

The investigations of the phenomena have been mostly clinical, and the views of the various observers are as previously stated contradictory.

T. Lander Brunton (3) makes the following statement "....Strychnine, to which an especial cumulative action is ascribed. After moderate doses .... have been taken for some time, it is found that instead of the effects they produce increasing gradually, as we would expect from a gradual accumulation in the blood, the symptoms of poisoning become suddenly developed, in somewhat the same way as if the dose had been suddenly increased" Arrest of excretion, he states, being the cause of this action and brought about by a vasoconstriction effect on the renal vessels.

Dixon (4) in a paragraph on cumulation makes the following statement".... it is stated that the susceptibility/

susceptibility of an animal to strychnine, a drug which produces convulsions , increases with its continued administration."

In the British Pharmaceutical Codex (5) a similar assertion is made by a contributor in the following statement, "Strychnine is excreted very slowly , and its action is therefore cumulative in other than small doses."

On the other hand Wood (i) from clinical observations, states that it shows no such cumulative action, and that even a certain degree of tolerance may be acquired by a patient after prolonged administration.

In the case of strychnine, as with other poisons, the question of tolerance has been the subject of numerous investigations.

Recently Montram and McWilliam (6) made experimental observations with strychnine , and dealing with/

with the hypothetical question of habit pathways, the question which they attempted to answer being the following:- would the impulses of Strychnine spasms if continued for any length of time, leave the pathways by which they travelled, in such a state as to be more easily traversed by succeeding impulses of the same kind? Frogs were used by them for the purpose of the experiments, and they found that with each succeeding injection, the time interval between the exhibition of the poison and the onset of spasms was shortened. Such results, they state "agree with those of other investigators of Strychnine action in which they find in continued experiments an increased susceptibility, not only in frogs, but in some of the higher animals, rabbit and/

and dog especially," Such results may be interpreted as ascribing to Strychnine this so-called cumulative action.

Worth Hale (7) in a series of experiments on the dog and guinea-pig, endeavoured to produce a tolerance for Strychnine which they administered subcutaneously. The first experiment on the dog showed that no tolerance was establised, and the result indicated that increased sensitiveness to the poison developed, for the animal died after a dose, which three weeks previously had only caused exaggerated reflexes. His second experiment also on the dog lasted for thirty-four weeks, and as a result he arrived at the conclusion that in dogs tolerance for Strychnine is very slowly acquired and very imperfect. His conclusions as regards the effect on the/

the guinea-pig, were still less definite but he states that there was a suggestion of tolerance. Although he thought that he had succeeded in producing a certain amount of tolerance for Strychnine in the dog, yet in one of the experiments - and he only reports on two - the animal showed an increased susceptibility to the poison. So his general conclusions do not seem to be in accordance with the his results of observations.

There is obviously some difficulty in interpreting the results of experiments of this nature where Strychnine is used. The lethal dose for many of the lower animals is found to vary within rather wide limits, and without a fairly accurate knowledge of the minimum lethal dose, one cannot say definitely whether/

whether any particular animal has acquired tolerance to the poison in so far as surviving the minimum lethal dose is concerned.

The guinea-pig is also a very unsatisfactory subject for observations on the toxicity of strychnine. Those who have made such experiments state that they show great individual variations in their susceptibility to the poison. Hare (11) making similar observations upon rabbits, failed to produce any lessening of susceptibility to the poison.

Thus so far, no success has been attained in the direction of producing tolerance, in the normal animal; experimenters have, however, apparently succeeded in increasing the resistance of animals to strychnine, after some alteration in the animal's condition. Thus Meltzer and Langman (12) in a series of experiments on guinea-pigs, after the removal of both kidneys, found the/

the single dose required to produce a fatal result, in such nephrectomised animals, was in excess of the minimum lethal dose for the normal animal. They concluded that the M.L.D. was raised in such animals, but they do not consider the question of shock which would be produced after the removal of both kidneys. In order to restore the normal excitability of the spinal and medullary centres, a certain amount of strychnine would be required; this might account for the extra amount required to produce a fatal result.

The term "cumulation" is generally regarded as synomymous with the effects of accumulation, yet it is possible that such an action may take place without the substance accumulating in the tissues. Thus it has been suggested that it may be the result of a "summation of effects."

The factors which are considered to bring about this accumulation are anomalies of either absorption or of excretion or both simultaneously. Thus a

substance/

substance may be repeatedly administered, but from various causes depending on the state of the alimentary tract, may for the time being remain unabsorbed. When, however, this period of delayed absorption passes over, several doses which may have accumulated in the intestine become absorbed at the normal rate for the substance resulting in the same accumulation in the tissues. On the other hand, with the absorption of the substance proceeding at the normal rate, but with its elimination delayed for some reason, such as might be caused by a constriction of the renal vessels, a similar accumulation in the tissues will result . Hatcher (8) as a result of observations on the cumulation of the digitalis principles on the lower animals, considers that such effects are produced by the persistence of action of a certain amount of the drug which has been absorbed/

absorbed and subsequently become firmly fixed in the tissues. The repeated administration of therapeutic doses will increase the amount fixed, which continues to exert its physiological effects and ultimately produces the toxic manifestations. He states, however, that a varying rate of absorption constitutes a more important factor in the production of such effects.

The questions of the absorption and the elimination of Strychnine have been described by various observers, the following being the main facts reported. The absorption is rapid whether administered by the month or by subcutaneous injection. Meltzer (9) made observations on the rate of absorption from different parts of the alimentary tract. He found that no Strychnine was absorbed from the stomach, and that with the pylorus closed even 60 Milligrammes produced no toxic effects, and the animal lived for nineteen hours. The pharynx he states, absorbs most

rapidly/

rapidly, then in order the small intestine, rectum and colon.

In the cat it is found that the convulsions appear about thirty minutes after the exhibition of a toxic dose by the mouth, but in a number of poisoning cases in man, the characteristic symptoms were evident in from five to fifteen minutes after the drug had been swallowed.

Thus the absorption of strychnine is rapid, but there is a discrepancy in the statements made by different observers, concerning its elimination.

Kratter (10) worked out the rate of excretion in man. The nitrate of strychnine was administered by subcutaneous injection, and the drug was detected in the urine half an hour afterwards, elimination being completed in forty-eight hours. Worth Hale (7) made similar observations after administration by the mouth,/

mouth; strychnine was detected in the urine after three hours, but the total elimination was delayed till the fifth day. The same observer quotes Ipsen, who, experimenting upon animals, found that the excretion in some cases began two minutes after subcutaneous administration, while Kunkel after similar experiments found that the excretion did now begin till the third or fourth day.

Dixon Mann mentions two cases in which strychnine was being administered medicinally. Incipient toxic effects were produced, but examination of the urine failed to produce evidence of the presence of strychnine, and he suggests that in such instances of intolerance to the poison, delayed elimination may be a cause.

DETERMINATION OF THE MINIMUM LETHAL DOSE OF STRYCHNINE BY SUBCUTANEOUS INJECTION FOR THE RAT.

The white rat was chosen for the present work, it being of a convenient size and easily handled, and a series of experiments to determine the minimum lethal dose by subcutaneous injection was first undertaken. For this purpose a number of healthy adult animals were selected, and their weights estimated, and in order to ensure accuracy of dosage the weight was in each case taken with a definite relation to the last meal, which would provide the correct body weight.

The hydrochloride of Strychnine (Merck) was used, and the salt was dissolved in normal saline solution. The injections were made under the skin of the flank and due care was taken that the cal-

calculated/

calculated dose was in each case administered. As the characteristic symptoms in strychnine poisoning large depend on external stimuli, the animals after the administration of the poison were not subjected to more than the usual amount of irritation in the form of noise.

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1. Male, weight 250 grammes.

Solution injected	= 0.45 C.C.
Strychnine Hydrochloride	= 1.0 mgm.
" " per kilogramme	= 4.0 "

Results.

Respiratory rate increased from 18 to 31 per 10 secs., reflexes greatly exaggerated, then followed two violent convulsions 15 mins. after administration and death occurred 5 mins. later.

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2. Male, weight 256 grammes

Solution injected	= 0.4C.C.
Strychnine Hydrochloride	= 0.9mgm.
" " per kilo.	= 3.5 "

Results/

Results.

Respiratory rate increased from 18 to 29 per 10 secs., muscular twitches followed by a series of severe convulsions 19 mins. after the injection and the animal died 11 mins. later.

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3. Female, weight 230 grammes

Solution injected	=	0.69 C.C.
Strychnine Hydrochloride	=	0.69 mgm.
" " per kilo.	=	3.0 "

Results.

Reflexes greatly increased, respiratory rate previously 17 now 28 per 10 secs. Convulsions 15 mins. after administration of poison and death occurred 15 mins. later.

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4. Female weighing 83 grammes

Solution injected	=	0.23 C.C.
Strychnine Hydrochloride	=	0.224 mgm.
" " per kilo.	=	2.7 "

Results.

Animal severely convulsed 15 mins. after the injection and died during the first convulsion.

5./

5. Male, weight, 204 grammes

Solution injected	=	0.53 C.C.
Strychnine Hydrochloride	=	0.53 mgm.
" " per kilo.	=	2.6 "

Results.

Reflexes greatly increased, mild convulsion 20 mins. after exhibition of poison and the animal died after a series of convulsions 60 mins. later.

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6. Female, weight 190 grammes

Solution injected	=	0.475 C.C.
Strychnine Hydrochloride	=	0.475 mgm.
" " per kilo.	=	2.5 "

Results.

After a period with marked exaggeration of reflexes, a series of convulsions commenced 20 mins. after administration, and death took place 40 mins. later.

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8. Female, weight 106 grammes

Solution injected	=	0.265 C.C.
Strychnine Hydrochloride	=	0.265 mgm.
" " per kilo.	=	2.5 "

Results/

Results.

Severe convulsions 12 mins. after the injection and death took 3 mins. later.

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9. Male, weight 198 grammes

Solution injected = 0.495 C.C.

Strychnine Hydrochloride = 0.495 mgm.

" " per kilo. = 2.5 "

Results.

Series of convulsions occurred, and the animal died 20 mins. after poison administered.

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10. Female, weight 169 grammes

Solution injected = 0.423 C.C.

Strychnine Hydrochloride = 0.423 mgm.

" " per kilo. = 2.5 "

Results.

One severe convulsion occurred 11 mins. after the injection, and death took place almost immediately.

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7. Male, weight 293 grammes

Solution/

Solution injected = 0.703 C.C.

Strychnine Hydrochloride = 0.703 mgm.

" " per kilo. = 2.4 "

Results.

Reflexes greatly exaggerated, mild convulsion 30 mins. after administration, but symptoms gradually pass off and animal recovers.

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11. Male, weight 330 grammes

Solution injected = 0.8 C.C.

Strychnine Hydrochloride = 0.8 mgm.

" " per kilo. = 2.4 "

Results.

Convulsions commenced 17 mins. after the injection, and death took place 11 mins. later.

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12. Female, weight 196 grammes

Solution injected = 0.451 C.C.

Strychnine Hydrochloride = 0.451 mgm.

" " per kilo. = 2.3 "

Results.

Respiratory rate 30 per 10 secs., convulsions occurred/

occurred 20 mins. after the injection, death following 20 mins. later.

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13. Male, weight 185 grammes

Solution injected = 0.425 C.C.

Strychnine Hydrochloride = 0.425 mgm.

" " per kilo. = 2.3 "

Results.

Marked exaggeration of reflexes but no convulsions, and the animal recovered.

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14. Male, weight 107 grammes

Solution injected = 0.235 C.C.

Strychnine Hydrochloride = 0.235 mgm

" " per kilo. = 2.2 "

Results.

Respiratory rate 28 per 10 secs., a series of severe convulsions but symptoms subside and recovery of animal.

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15. Male, weight 215 grammes

Solution/

Solution injected = 0.473 C.C.

Strychnine Hydrochloride = 0.473 mgm.

" " per kilo. = 2.2 "

Results.

Series of convulsions and death took place 16 mins. after the injection.

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16. Female, weight 157 grammes.

Solution injected = 0.385 C.C.

Strychnine Hydrochloride = 0.385 mgm.

" " per kilo. = 2.1 "

Results.

Respiratory rate increased from 17 to 29 per 10 secs., a few mild convulsions, recovery.

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17. Male, weight 187 grammes.

Solution injected = 0.374 C.C.

Strychnine Hydrochloride = 0.374 mgm.

" " per kilo. = 2.0 "

Results.

Respiratory rate 27 per 10 secs., series of convulsions but animal recovered.

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18. Male, weight 200 grammes

Solution/

Solution injected = 0.2 C.C.

Strychnine Hydrochloride = 0.4 mgm.

" " per kilo. = 2.0 "

Results.

Respiratory rate increased from 19-25 per 10 secs., muscular twitches, series of convulsions and death 25 mins. after administration.

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19. Male, weight 183 grammes

Solution injected = 0.366 C.C.

Strychnine Hydrochloride = 0.366 mgm.

" " per kilo. = 2.0 "

Results

Respiratory rate 30 per 10 secs., few spasms and animal recovered.

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20. Male, weight 225 grammes.

Solution injected = 0.45 C.C.

Strychnine Hydrochloride = 0.45 mgm.

" " per kilo. = 2.0 mgm.

Results.

Respirations 26 per 10 secs., a few convulsions, animal recovered.

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21. Female, weight 190 grammes.

Solution/

Solution injected = 0.361 C.C.

Strychnine Hydrochloride = 0.361 mgm.

" " per kilo. = 1.9 "

Results.

Reflexes very active, no convulsions and animal survived.

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22. Male, weight 230 grammes.

Solution injected = 1.0 C.C.

Strychnine Hydrochloride = 0.4 mgm.

" " per kilo. = 1.7 "

Results.

Respiratory rate increased from 18 to 23 per 10 secs. Recovery.

CONCLUSIONS.

A summary of the results obtained will be found on the following page. From this table it will be seen that 2.0 mgms. per kilogramme represents the smallest dose which produced a fatal result, and that death invariably occurred after the administration of 2.5 mgms. per kilo., and that a dose between these limits might or might not prove fatal.

SUMMARY OF RESULTS.

NO	Quantity Strych. Hyd.in mgms. per kilogramme	REMARKS
1.	4.0	death after 20 mins.
2.	3.5	" " 30 "
3	3.0	" " 30 "
4	2.7	" " 15 "
5	2.6	" " 80 "
6	2.5	" " 60 "
7	2.4	convulsions 30 mins. recovery.
8	2.5	death after 15 mins.
9	2.5	" " 20 "
10.	2.5	" " 11 "
11	2.4	" " 28 "
12	2.3	" " 40 "
13	2.3	survived, no convulsions.
14	2.2	" severe convulsions.
15	2.2	death after 16 mins.
16	2.1	survived, mild convulsions.
17	2.0	" series of convulsions.
18	2.0	death after 20 mins.
19	2.0	survived, a few spasms.
20	2.0	" a few convulsions.
21	1.9	" no convulsions.
22	1.7	" " "

THE CUMULATION OF STRYCHNINE.

Having determined the minimum lethal dose for the rat, experiments dealing with the phenomena of cumulation were then conducted. A series of such experiments were arranged, two white rats being allotted to each one of the series. A dose of Strychnine Hydrochloride was administered by subcutaneous injection to each member of a batch, an equivalent amount according to the body weight being used twice or thrice daily. The dosage was similar for each member of a series but varied for the several batches, as shown in the following table.

Series	No. of Experiment	Weight.	Strych. Hyd. in mgms. per kilo.	No. of injections each day.
1	1	Male, 145 gm.	1.0	3
	2	Male,160 gms.	1.0	3
2	3	Male,176 gms.	1.5	2
	4	Male,202 gms.	1.5	2
3	5	Male,250 gms.	2.0	2
	6	Female,217 gms.	2.0	2
4	7	Male,198 gms.	2.0	3
	8	Female,140 gms.	2.0	3

Healthy adult white rats were used, and their weights determined each day in order that the dose could be correspondingly varied according to the body weight.

By this means of repeated administration with observations on the effects produced from day to day, any cumulative effects would become evident. Thus notes were taken of the more apparent objective symptoms such as changes in the respiratory rate and the general state of the reflexes and the presence or absence of convulsions. These observations were in each case made about twenty minutes after the injection the state of the reflexes being compared with the normal activity, and in the following notes taken such changes are understood to be of temporary duration, the symptoms having passed off before the succeeding dose was given.

FIRST SERIES OF EXPERIMENTS.

Two rats were used and each had an injection containing Strychnine Hydrochloride 1.0 mgm. per kilo. thrice daily. Such a dose was equal to one-half of the least possible lethal dose for the rat, and an equivalent dose for a man would be about 0.06 grammes or twnety times the maximum Pharmacopoeial dose. The administration of the drug was continued for six weeks, and the results of the treatment in one of the two cases is given below and a summary of the results in the other case follows.

Experiment 1.

Male, weight 145 grammes

Strychnine Hydrochloride = 0.145 mgm.

" " per kilo. = 1.0 mgm.

The result of the experiment is tabulated as follows. The state of the reflexes was ascertained by the response to external stimuli in the forms sound, touch.

Date.	No. of Injection	Objective Symptoms.	
		Resp. rate per 10 secs.	State of Reflexes.
Oct.30	1	17	Very mild exaggeration.
	2	19	No evident change.
	3	18	Very slight increase.
31	1	19	Very little change.
	2	20	No increase in activity.
	3	18	Mild increase.
Nov. 1	i	20	Less marked degree increase.
	2	20	Very slight exaggeration.
	3	19	No increase in activity.
Nov. 2	i	21	Slight degree increase.
	2	20	" " "
	3	20	" " "
Nov. 3	ii	20	Very little increase.
	2	19	No change evident.
	3	20	" " "
Nov. 4	i	21	Slight degree exaggeration.
	2	20	Reflexes remain normal.
	3	21	Very slight exaggeration.
Nov. 5	ii	18	No change evident.
	2	21	Reflexes slightly increased.
	3	20	Very little exaggeration.

Nov. 6	1	18	Activity slightly increased.
	2	19	Normal state.
	3	19	Slight exaggeration.
Nov. 7	1	17	No change evident.
	2	20	Slightly augmented.
	3	19	" "
Nov. 8	1	19	Mild degree exaggeration.
	2	19	" " "
	3	20	" " "
Nov. 9	1	21	Increase more evident.
	2	20	Very slight exaggeration.
	3	20	" " "
Nov.10	1	18	No alteration.
	2	20	" "
	3	20	Activity slightly increased.
Nov.11	1	21	Very slight exaggeration.
	2	21	" " "
	3	19	Remain normal.
Nov.12	1	18	Normal activity.
	2	20	Very slight increase.
	3	19	" " "

Nov.13	1	19	Reflex activity normal.
	2	18	" " "
	3	20	" " "
Nov.14	1	17	Reflexes remain normal.
	2	18	Slight degree increase.
	3	19	" " "
Nov.15	1	18	Slightly augmented.
	2	20	" "
	3	20	" "
Nov.16	1	20	Very little alteration.
	2	19	Normal activity.
	3	18	" "
Nov.17	1	18	Remain normal.
	2	18	Mild degree exaggeration.
	3	17	Remain normal.
Nov.18	1	20	Slightly augmented.
	2	20	" "
	3	19	" "
Nov.19	1	20	Remain of normal activity.
	2	20	" " " "
	3	18	Very mild exaggeration.

Nov.20	1	18	Remain normal state.
	2	18	" " "
	3	19	Small degree exaggeration.
Nov.21	1	21	Mildly augmented.
	2	18	" "
	3	20	" "
Nov.22	1	18	Remain normal state.
	2	19	" " "
	3	20	Mild degree exaggeration.
Nov.23	1	20	Exaggeration well marked.
	2	20	" " "
	3	19	Slight degree increase.
Nov.24	1	20	Moderately increased.
	2	20	Very slightly increased.
	3	18	Remain normal.
Nov.25	1	19	Normal state.
	2	19	" "
	3	20	" "
Nov.26	1	18	Remain normal state.
	2	20	" " "
	3	20	Slightly augmented.

Nov.27	1	22	Well marked increase.
	2	19	Slight increase evident.
	3	20	" " "
Nov.28	1	20	Slightly increased.
	2	20	" "
	3	21	" "
Nov.29	1	22	Mildly augmented.
	2	21	Remain normal state.
	3	22	" " "
Nov.30	1	18	No increase evident.
	2	20	Slightly exaggerated.
	3	20	" "
Dec. 1	1	19	Remain normal state.
	2	20	" " "
	3	18	" " "
Dec. 2	1	18	No increase evident.
	2	18	" " "
	3	18	Slight exaggeration.
Dec. 3	1	18	Remain normal state.
	2	19	" " "
	3	19	Moderately exaggerated.

Dec. 4	1	18	Remain normal state.
	2	19	" " "
	3	19	" " "
Dec. 5	1	17	Remain normal state.
	2	19	" " "
	3	19	" " "
Dec. 6	1	18	Slight exaggeration.
	2	18	" "
	3	20	" "
Dec. 7	1	20	Slight degree increase.
	2	20	" " "
	3	19	Of normal activity.
Dec. 8	1	21	Exaggeration remarked.
	2	20	Slight degree exaggeration.
	3	20	" " "
Dec. 9	1	19	Very little increase.
	2	18	Activity normal.
	3	19	" "
Dec.10	1	20	No evident change.
	2	19	" " "
	3	20	Slight increase activity.

Experiment 2.

Male rat, weight 160 grammes.

Strychnine Hydrochloride = 1.0 mgm. per kilo.

Both experiments one and two were carried out simultaneously, and the results obtained from No. 2 differed in no respect from the results of the previous experiment. The symptoms produced at the end of the six weeks of the repeated administration were consistent with those shown at the beginning of the treatment, though varying from day to day. Thus the reflex activity showed no greater exaggeration after successive doses, neither were there any convulsions produced.

CONCLUSIONS.

From the results of these two experiments, one may draw the following conclusion. That the white rat shows no apparent increase in susceptibility to the effects of Strychnine, when doses of this substance equal to about 40% of the minimum lethal dose, or 50% of the least possible fatal dose, are administered thrice daily over a period of six weeks.

SECOND SERIES.

These experiments were carried out in the same manner as the previous ones, but the dose was changed, 1.5 mgms. of Strychnine Hydrochloride per kilogramme being administered twice daily. This was equal to 60% of the minimum lethal dose for the rat.

Experiment 43.

Male rat, weight 176 grammes.

Strychnine Hydrochloride = 0.264 mgm.

= 1.5 per kilo.

Date.	No. of Injection	Objective Symptoms.	
		Resp. rate per 10 secs.	State of Reflexes.
Nov.6	1	18	Moderate increase activity twitches jaw muscles.
	2	20	Slight exaggeration, slight spasmodic movements.
Nov.7	1	19	Very little exaggeration.
	2	18	No change evident.
Nov.8	1	23	Reflex activity greatly increased, very sensitive stimuli, spasmodic jerks.
	2	23	Much exaggeration, slight jerk fore portion of body and neck.

Nov. 9	1	24	Activity greatly increased, very excitable, slight spasm lasting few seconds.
	2	24	Moderate increase activity, muscular twitches.
Nov.10	1	24	Activity moderately exaggerated, facial muscles quivering.
	2	24	Slight increase reflex activity, not very excitable.
Nov.11	1	22	Slight increase activity.
	2	23	" " "
Nov.12	1	23	Slight increase activity.
	2	24	Moderate increase activity, sudden spasmodic movements
Nov.13	1	24	Mild exaggeration.
	2	24	" "
Nov.14	1	24	Activity greatly increased, spasmodic contraction facial muscles.
	2	24	Activity greatly increased, slight spasmodic movements.
Nov.15	1	22	Very mildly exaggerated.
	2	23	Moderate degree increase, facial muscles quivering.

Nov.16	1	23	No apparent increase in activity.
	2	24	Slight degree exaggeration.
Nov.17	1	24	Reflexes moderately exaggerated.
	2	24	" " "
Nov.18	1	25	Moderate increase reflex activity.
	2	26	Greatly increased, jerky movements, slight spasm lasting few seconds.
Nov.19	1	24	Slight degree exaggeration
	2	24	Moderate increase.spasmodic movements.
Nov.20	1	24	Activity moderately increased, twitches facial muscles.
	2	23	Activity only slightly increased.
Nov.21	1	23	Very mild exaggeration.
	2	22	" " "
Nov.22	1	23	Very slight increase in activity.
	2	24	" " " "

Nov.22	1	23	Very slight increase in activity.
	2	24	" " " "
Nov.23	1	23	Very slight increase in activity.
	2	22	Activity moderately increased, facial muscles quiver.
Nov.24	1	24	Activity moderately increased.
	2	24	Moderate increase, slight spasmodic movements.
Nov.25	1	24	Very slight increase.
	2	25	Activity moderately increased, slight spasm lasting about 3 seconds.
Nov.26	1	21	No change evident.
	2	23	Slight increase in activity.
Nov.27	1	22	Very mild exaggeration.
	2	22	No evident change.
Nov.28	1	22	Activity moderately increased, quivering of facial muscle.
	2	23	Very mild exaggeration.

Nov.29	1	25	Moderately increased, sudden jerky movements.
	2	23	Moderately increased, twitches facial muscles.
Nov.30	1	20	Very slightly increased.
	2	24	Moderately increased.
Dec. 1	1	24	Mild increase.
	2	25	Moderately increased, twitches muscles of face.
Dec. 2	1	18	No change evident.
	2	20	Very slightly increased in activity.
Dec. 3	1	17	Very slight increase.
	2	19	" " "
Dec. 4	1	19	No evident change.
	2	19	Activity very slightly increased.
Dec. 5	1	19	Activity very slightly increased.
	2	21	No evident change.

Dec. 6	1	16	Activity slightly increased.
	2	18	Very slight increase.
Dec. 7	1	19	Reflex activity normal.
	2	22	" " "
Dec. 8	1	23	Mild increase, facial muscles twitch.
	2	20	Mild increase.
Dec. 9	1	20	Very slight degree exaggeration.
	2	19	No alteration.
Dec.10	1	15	Moderate increase, sudden spasmodic movements.
	2	18	No apparent change.
Dec.11	1	20	Very slight exaggeration.
	2	19	" " "
Dec.12	1	19	Very slight exaggeration.
	2	22	" " "

Dec.13	1	14	Very slightly exaggerated.
	2	20	" " "
Dec.14	1	19	Very slightly exaggerated.
	2	19	No evident change.
Dec.15	1	22	Appeared normal.
	2	23	" "
Dec.16	1	20	No evident change.
	2	20	Very slight exaggeration.
Dec.17	1	21	Normal activity.
	2	20	" "
Dec.18	1	18	Normal activity.
	2	20	Very slight exaggeration.

Experiment 4.

Male, weight 202 grammes.

Strychnine Hydrochloride = 0.303 mgms.

= 1.5 mgms. per kilo.

An injection was administered twice daily as in the previous experiment. The symptoms presented at the end of the sixth week were practically identical with those shown at the beginning of the experiment, though varying from day to day as in Experiment three.

SUMMARY.

In Experiment 3, the symptoms produced towards the end of the experiment were of a milder character than those of the earliest period. Convulsions did not occur at any time. Thus there was no apparent increase in sensitiveness produced as a result of the administration twice daily, over a period of six weeks of doses equal to about 60% of the minimum lethal dose for the rat.

THIRD SERIES.

Experiment 5.

Male rat, weight 250 grammes.

Strychnine Hydrochloride = 0.5 mgrms.

= 2.0 " per kilo.

, Administered twice daily over a period of eight weeks.

Date.	No. of Injection	Objective Symptoms.	
		Resp. rate per 10 secs	Condition of Reflexes.
Jan. 9	1	30	Greatly increased reflex irritability, twitches jaw muscles, no convulsion.
	2	31	Reflexes greatly exaggerated, no convulsions.
Jan.10	1	30	Reflex irritability much increased, no convulsion.
	2	32	" " "
Jan.11	1	30	Reflexes greatly exaggerated, no convulsions.
	2	29	Moderate degree exaggeration, no convulsions.
Jan.12	1	28	Greatly increased excitability, no convulsions.
	2	31	Reflexes greatly exaggerated, twitches jaw muscles, slight spasm.

Jan.13	1	32	Greatly exaggerated, convulsion 20 mins. after the administration.
	2	31	Reflexes greatly increased, spasm lasting few seconds.
Jan.14	1	32	Reflexes greatly exaggerated, convulsion 20 mins. after administration.
	2	30	Moderate degree exaggeration, no convulsion.
Jan.15	1	28	Moderate degree, no convulsion.
	2	32	Greatly exaggerated and a severe convulsion occurred 15 mins. later.
Jan.16	1	35	Moderate degree exaggeration, no convulsion.
	2	35	" " "
Jan.17	1	35	Reflexes greatly exaggerated, no convulsions.
	2	37	Greatly exaggerated reflexes, convulsion 17mins. after the administration.
Jan.18	1	37	Reflex excitability greatly increased, two severe convulsions 17 mins. later.
	2	36	Greatly exaggerated, one convulsion 16 mins. after administration.
Jan.19	1	30	Moderately exaggerated, convulsion 25 mins. after the administration.
	2	35	Greatly exaggerated, convulsion 15 mins. after the administration.

Jan.20	1	35	Greatly exaggerated, no convulsions.
	2	36	Greatly exaggerated, convulsion 16 mins. after the administration.
Jan.21	1	30	Moderate exaggeration, no convulsions.
	2	34	" " "
Jan.22	1	29	Mild degree exaggeration, no convulsions.
	2	35	Reflexes greatly exaggerated, no convulsions.
Jan.23	1	28	Mild degree exaggeration.
	2	39	Greatly increased reflex excitability.
Jan.24	1	30	Moderate degree exaggeration, spasmodic movements
	2	39	Reflexes greatly exaggerated, two convulsions 17 mins. after administration.
Jan.25	1	37	Reflexes greatly exaggerated, twitches jaw muscles.
	2	38	Moderate degree exaggeration.
Jan.26	1	39	Reflexes greatly exaggerated.
	2	39	Great exaggeration, one convulsion 15 mins. after the administration.

Jan.27	1	39	Reflexes greatly exaggerated.
	2	39	Greatly exaggerated, convulsion 15 mins. after the administration.
Jan.28	1	37	Reflexes greatly exaggerated, twitches jaw muscles, spasmodic movements.
	2	36	Greatly exaggerated, slight spasms.
Jan.29	1	38	Greatly exaggerated, few slight spasms.
	2	35	Moderate degree exaggeration.
Jan.30	1	37	Great exaggeration, slight jerks fore portion of body.
	2	39	Great exaggeration, slight spasmodic movements.
Jan.31	1	30	Moderate degree exaggeration.
	2	31	" " "
Feb. 1	1	38	Moderate degree increase reflex excitability.
	2	40	Reflexes greatly exaggerated, few slight spasms.
Feb. 2	1	29	Mild degree increase in excitability.
	2	29	" " " "

Feb. 3	1	30	Moderate degree increase, slight spasmodic movements.
	2	31	Moderate increase excitability, jerky movements fore portion of body.
Feb. 4	1	30	Moderate degree exaggeration, slight spasms.
	2	31	Reflexes mildly increased.
Feb. 5	1	35	Reflexes greatly exaggerated, severe convulsion 15 mins. after administration.
	2	33	Greatly exaggerated, but no convulsion.
Feb. 6	1	30	Greatly exaggerated, twitches jaw muscles, slight spasmodic movements.
	2	30	Moderate degree increase in excitability.
Feb. 7	1	29	Reflexes mildly increased.
	2	31	Greatly exaggerated, slight spasmodic movements.
Feb. 8	1	33	Greatly exaggerated, convulsion 20 mins. after the administration.
	2	30	Greatly exaggerated reflex excitability, twitches jaw muscle.
Feb. 9	1	32	Moderate degree increase in excitability.
	2	31	Moderately increased, slight spasmodic movements.

Feb.10	1	31	Reflex excitability moderately increased.
	2	29	Moderate increase.
Feb.11	1	32	Excitability greatly increased, twitches jaw muscles.
	2	31	Moderate increase.
Feb.12	1	32	Moderate degree exaggeration.
	2	32	" " "
Feb.13	1	32	Moderate degree exaggeration.
	2	32	" " "
Feb.14	1	30	Reflex irritability much increased, one convulsion 15mins.after administration.
	2	29	Moderate degree increase.
Feb.15	1	38	Reflexes greatly exaggerated.
	2	30	Moderate degree exaggeration.
Feb.16	1	36	Moderately increased.
	2	30	" "

Feb.17	1	40	Greatly exaggerated, few slight spasms.
	2	36	Moderate degree exaggeration.
Feb.18	1	41	Moderate degree exaggeration.
	2	40	Reflexes greatly increased, few spasms, slight spasmodic movements.
Feb.19	1	36	Moderately increased.
	2	38	" "
Feb.20	1	30	Moderately increased, slight spasmodic movements.
	2	29	Moderate degree increase.
Feb.21	1	33	Reflexes greatly exaggerated, convulsion 14 mins. after the administration.
	2	31	Greatly exaggerated, few spasms, twitches jaw muscle.
Feb.22	1	29	Moderately increased.
	2	31	" "
Feb.23	1	31	Moderate degree exaggeration.
	2	30	" " " slight spasms.

Feb.24	1	32	Reflexes greatly exaggerated, slight spasmodic movements.
	2	32	Moderate degree exaggeration.
Feb.25	1	36	Greatly exaggerated, slight spasms.
	2	30	Moderate degree exaggeration.
Feb.26	1	32	Moderate degree exaggeration.
	2	33	" " "
Feb.27	1	30	Moderate degree exaggeration.
	2	29	Mild exaggeration.
Feb.28	1	30	Moderate degree exaggeration.
	2	33	" " "
Mar. 1	1	33	Moderate degree exaggeration, few slight spasms.
	2	32	Greatly exaggerated, slight spasms.
Mar. 2	1	30	Moderate degree exaggeration.
	2	31	" " "

Mar. 3	1	32	Moderate degree exaggeration.
	2	32	Reflexes greatly exaggefated, slight spasms.
Mar. 4	1	29	Mild degree exaggeration.
	2	30	Moderately exaggerated, twitches jaw muscles.
Mar. 5	1	30	Moderate degree exaggeration.
	2	33	" " " few slight spasms.
Mar. 6	1	30	Moderate degree exaggeration.
	2	34	" " " jerky movements.
Mar. 7	1	30	Moderate degree exaggeration.
	2	32	" " "

SUMMARY.

In this experiment a dose of Strychnine Hydrochloride equivalent to about 80% of the minimum lethal dose for the rat, was administered by subcutaneous injection twice daily over a period of six weeks. The

symptoms/

symptoms produced varied greatly, but the animal showed no increase in susceptibility after the six weeks of repeated administration. On the other hand the symptoms towards the end of the period were distinctly milder than those at the beginning as will be evident from the following table. From this it will be seen that convulsions occurred with greater frequency during the second week than at any other period, and that during the last week they were entirely absent.

Day	Presence or absence of convulsions.	Interval between the administration & onset of spasms.
1	Absent	
2	"	
3	"	
4	"	
5	Convulsion	20 minutes.
6	"	20 "
7	"	15 "
8	Absent	
9	Convulsion	17 "
10	"	17 "
	"	16 "
11	"	25 "
	"	15 "
12	"	16 "
13	Absent	
14	"	
15	"	
16	Convulsion	17 "
17	Absent	
18	Convulsion	15 "

Day	Presence or absence of convulsions.	Interval between the administration & onset of spasms.
19	Convulsion	15 minutes
20	Absent	
21	"	
22	"	
23	"	
24	"	
25	"	
26	"	
27	"	
28	Convulsion	15 "
29	Absent	
30	"	
31	Convulsion	20 "
32	Absent	
33	"	
34	"	
35	"	
36	"	
37	Convulsion	15 "
38	Absent	
39	"	
40	"	
41	"	
42	"	
43	"	
44	Convulsion	14 "
45	Absent	
46	"	
47	"	
48	"	
49	"	
50	"	
51	"	
52	"	
53	"	
54	"	
55	"	
56	"	

1st	Week	convulsions	occurred	after	3 administrations.
2nd	"	"	"	6	"
3rd	"	"	"	3	"
4th	"	"	"	1	administration.
5th	"	"	"	1	"
6th	"	"	"	1	"
7th	"	"	"	1	"
8th	"	"	did not occur.		

From the table it will be seen that the time which in each case elapsed between the exhibition of the drug and the onset of the convulsion varied from 25 mins. to 14 mins. The longer interval occurred during the first week or so, but this was diminished towards the later period. Such a gradual shortening in the time required for the spasms to appear, confirms in a sense the conclusions of Montram and McWilliam (6) who observed on the frog, that the time required for the spasms to appear, after a definite and constant dose of Strychnine, was reduced with each succeeding injection. Thus the earlier onset of the convulsions does not necessarily imply increased sensitiveness, but may be accounted for by the presence of the so-called "habit pathways." But after all the reduction in time was not very evident, and was rather irregular.

Experiment 6.

Female, weight 217 grammes.

Strychnine Hydrochloride = 2.0 mgrms. per kilo.

Two injections administered daily.

Date	No. of injection	Objective Symptoms.	
		Resp. rate per 10 secs.	State of Reflexes.
Jan. 9	1	25	Moderate degree exaggeration.
	2	30	Reflexes greatly increased, convulsion 15 mins. after the administration.
Jan.10	1	30	Greatly increased, two convulsions 23 mins.after the administration.
	2	31	Greatly increased excitability, few spasms.
Jan.11	1	26	Reflexes greatly exaggerated, convulsion 13 mins.after administration.
	2	30	Moderate degree exaggeration, convulsion 16mins. after the administration.
Jan.12	1	25	Convulsion 14 mins. after the administration.
	2	30	Moderate degree exaggeration.
Jan.13	1	28	Greatly exaggerated, two convulsions 24 mins. after administration.
	2	20	Moderate degree exaggeration, few slight spasms.

Jan.14	1	25	Greatly exaggerated, two severe convulsions 20mins after the administration.
	2	29	Moderate degree increase in excitability.
Jan.15	1	35	Reflexes greatly increased
	2	35	" " " few spasms.
Jan.16	1	30	A series of severe convulsions 10 mins. after the administration.
	2	32	Reflexes greatly increased, one convulsion 10 mins. after the administration.
Jan.17	1	31	Great exaggeration, convulsion 15 mins: after the administration.
	2	30	Moderate degree exaggeration.
Jan.18	1	29	Moderate degree exaggeration, two severe convulsions 17 mins. later.
	2	32	Moderate degree exaggeration, convulsion 15mins. after administration.
Jan.19	1	32	Greatly exaggerated, three convulsions 14 mins. after the administration.
	2	28	Moderate degree exaggeration.
Jan.20	1	30	Greatly exaggerated, convulsion 15 mins. after the administration.
	2	29	Greatly exaggerated, two convulsions 13 mins. after the administration.

Jan.21	1	28	Moderate degree exaggeration.
	2	34	" " "
Jan.22	1	28	Moderate degree exaggeration.
	2	31	Greatly exaggerated, convulsion 18 mins. after the administration.
Jan.23	1	30	Moderate degree exaggeration.
	2	30	" " "
Jan.24	1	29	Slight degree exaggeration.
	2	30	Moderate degree exaggeration.
Jan.25	1	31	Moderate degree exaggeration.
	2	35	Greatly exaggerated, two severe convulsions 14 min. after the administration.
Jan.26	1	30	Moderate degree increase.
	2	25	Reflexes greatly exaggerated, severe convulsion 18mins.after administration.
Jan.27	1	30	Moderate degree increase, few slight spasms.
	2	33	Moderate degree exaggeration.

Jan.28	1	31	Moderate degree exaggeration.
	2	29	" " " twitches jaw muscles.
Jan.29	1	35	Greatly exaggerated, convulsion 15 mins. after the administration.
	2	32	Greatly exaggerated, slight spasms.
Jan.30	1	32	Moderate degree exaggeration.
	2	33	" " "
Jan.31	1	30	Moderate degree exaggeration.
	2	30	" " "
Feb. 1	1	31	Moderate degree exaggeration, slight spasmodic movements.
	2	34	Reflexes greatly exaggerated, convulsion 17 mins. after administration.
Feb. 2	1	34	Greatly exaggerated, slight spasms.
	2	35	Reflexes greatly exaggerated.
Feb. 3	1	30	Moderate degree exaggeration.
	2	31	" " convulsion 14 mins. " followed by death.

SUMMARY.

The dosage was similar to that of the previous experiment, but an analysis of the symptoms produced, shows that the animal was distinctly more susceptible to the effects of Strychnine, for convulsions were of frequent occurrence, and death took place on the 26th day of the treatment. But this dose of 2.0 mgms. per kilo was found to be a possible lethal dose for rats (page 27), so that this does not necessary point to any increase in sensitiveness to the effects of the poison. On the other hand there was an apparent diminution in susceptibility during the later period, for convulsions were of less frequent occurrence as will be seen from the following table.

Day	Presence or absence of convulsions.	Interval between injection and onset of convulsion.
1	Convulsion	15 minutes.
2	"	23 "
3	"	13 "
	"	16 "
4	"	14 "
5	"	24 "
6	" (2)	20 "
7	Absent	
8	Convulsion	10 "
	"	10 "
9	"	15 "
10	"	17 "
	"	15 "
11	"	14 "
12	"	15 "
	"	13 "
13	Absent	
14	Convulsion	18 "
15	Absent	
16	"	
17	Convulsion	14 "
18	"	18 "
19	Absent	
20	"	
21	Convulsion	15 "
22	Absent	
23	"	
24	Convulsion	17 "
25	Absent	
26	Convulsion followed by death	14 "

1st	Week	Convulsions	were	produced	after	7	administrations.
2nd	"	"	"	"	"	9	"
3rd	"	"	"	"	"	3	"
4th	"	"	"	"	"	2	"

FOURTH SERIES.

Experiment 7.

Male rat, weight 198 grammes.

Strychnine Hydrochloride = 2.0 mgrms per kilo.

One injection administered subcutaneously three times a day.

Date	No. of Injection	Objective Symptoms.	
		Resp. rate per 10 secs.	State of Reflexes.
Mar. 2	1	31	Reflexes greatly exaggerated, severe convulsion 25 mins.after administration.
	2	22	Moderate degree increase in activity.
	3	36	Reflexes greatly exaggerated, slight spasms lasting few seconds.
Mar. 3	1	30	Reflex activity greatly increased.
	2	30	Activity greatly exaggerated, few slight spasms.
	3	31	" " "
Mar. 4	1	30	Activity greatly increased slight spasms, convulsion 34mins.after administration.
	2	30	Activity greatly increased, slight spasms.
	3	29	Moderate degree exaggeration.

Mar. 5	1	26	Moderate degree exaggeration.
	2	29	" " "
	3	34	Activity greatly increased, convulsion 25 mins.after the administration.
Mar. 6	1	31	Activity greatly increased, spasmodic movements.
	2	28	Moderate degree increase.
	3	33	Moderate degree increase, slight spasms.
Mar. 7	1	29	Activity greatly increased, slight spasms.
	2	30	" " "
	3	31	" " "
Mar. 8	1	29	Activity much increased.
	2	29	" " "
	3	33	Activity greatly exaggerated, slight spasms.

Mar.9	1	27	Moderate degree exaggeration.
	2	32	Activity greatly increased, convulsion 15 mins.after the administration.
	3	38	Greatly exaggerated, slight spasms.
Mar.10	1	30	Moderate degree exaggeration.
	2	29	" " "
	3	30	" " " few slight spasms.
Mar.11	1	29	Moderate degree increase.
	2	29	Activity greatly increased, slight spasms.
	3	31	Moderate degree exaggeration.
Mar.12	1	32	Moderate degree increase.
	2	30	" " "
	3	30	" " "

Mar.13	1	27	Moderate degree increase.
	2	29	" " " slight spasms.
	3	28	Moderate degree increase.
Mar.14	1	26	Moderate degree increase, slight spasms.
	2	30	Moderate degree increase.
	3	28	Moderate degree increase, slight spasms.
Mar.15	1	28	Moderate degree increase, slight spasms.
	2	29	Moderate degree increase.
	3	30	Activity greatly exaggerated.
Mar.16	1	28	Moderate degree increase, slight spasms.
	2	29	Moderate degree increase, slight spasms.
	3	35	Activity greatly exaggerated, slight spasms.

Mar.17	1	30	Moderate degree increase.
	2	39	Reflex activity greatly exaggerated, slight spasms, one severe convulsion 12 mins. after the administration followed by death.

SUMMARY.

One injection containing Strychnine Hydrochloride equal to 2.0 mgrms. per kilo. of body weight, was administered subcutaneously three times a day. The animal died after a convulsion on the 16th day. Throughout the experiment the symptoms produced after the several injections were fairly uniform, and there was no apparent increase in sensitiveness. Convulsions were of more frequent occurrence during the first few days, as in most of the previous experiments, the interval between the exhibition of the drug and the onset of a convulsion was gradually diminished as time went on, which facts will be seen from the table on the following page.

Day	Presence or absence of convulsions.	Interval between the administration & onset of convulsion
1	Convulsion	25 minutes.
2	Absent	
3	Convulsion	34 "
4	"	25 "
5	Absent	
6	"	
7	"	
8	Convulsion	15 "
9	Absent	
10	"	
11	"	
12	"	
13	"	
14	"	
15	"	
16	Convulsion & death.	12 "

Experiment 8.

Female, weight 140 grammes.

Strychnine Hydrochloride = 2.0 mgrms. per kilo.

One injection administered subcutaneously three times a day.

Date	No. of Injection	Resp. rate per 10 secs.	State of Reflexes.
Mar. 2	1	30	Activity greatly increased, slight spasms lasting few seconds.
	2	24	Activity greatly increased, severe convulsion 15 mins. after the administration.
	3	31	Activity greatly increased.

Mar. 3	1	28	Moderate degree exaggeration.
	2	30	" " "
	3	33	Reflexes greatly exaggerated, mild convulsion 18 mins. after the administration.
Mar. 4	1	30	Moderate degree increase.
	2	30	" " "
	3	35	Activity greatly exaggerated, slight spasms.
Mar. 5	1	32	Moderate degree increase.
	2	32	Activity greatly increased, convulsion 14 mins. after the administration.
	3	35	Activity greatly increased, series of convulsions 12 mins. after the administration.
Mar. 6	1	30	Greatly exaggerated, slight spasmodic movements.
	2	27	" " "
	3	31	Greatly exaggerated, convulsion 14 mins. after the administration.

Mar. 7	1	27	Mild degree exaggeration.
	2	30	Moderate degree exaggeration.
	3	33	" " "
Mar. 8	1	30	Moderate degree exaggeration.
	2	35	Greatly exaggerated, few slight spasms.
	3	32	Activity greatly exaggerated.
Mar. 9	1	32	Moderate degree exaggeration.
	2	33	" " " slight spasms.
	3	36	Moderate degree exaggeration.
Mar.10	1	29	Activity moderately exaggerated.
	2	38	Great exaggeration, slight spasms.
	3	40	Greatly exaggerated, series of severe convulsions 10 mins. after administration and animal died.

SUMMARY.

One injection containing strychnine hydrochloride equal to 2.0 mgrms. per kilo. was administered subeutaneously threeitimesya day for nine days. The animal died after a series of convulsions on the 9th day. Previous to this there was no suggestion of any increase in susceptibility; convulsions were of more frequent occurrence in the earlier period of the experiment.

Day	Presence or absence of convulsions.	Interval between injection & onset of convulsion.
1	Convulsion	15 minutes.
2	"	18 "
3	Absent	
4	Convulsion	14 "
	"	12 "
5	Convulsion	14 "
6	Absent	
7 2/3	"	
8	"	
9	Convulsions and death.	10 "

RATE OF ELIMINATION OF STRYCHNINE AFTER SUBCUTANEOUS INJECTION IN THE RAT.

With a view of determining some points concerning the elimination of strychnine in rats , the following experiment was conducted. the time required for the complete elimination of a single dose, has a greater bearing upon the subject of accumulation, than ; that required for the initial stage of the process: conseqently, as the quantity of strychnine which could be administered was small, and owing to the diffuculty of collecting the urine, observations were confined to the time which elapsed before the completion of the process.

What is meant?

Experiment.

Four rats were selected and their weights taken: strychnine hydrochloride 2.0 mgrms. per kilogramme of body-weight, was administered to each one subcutaneously. All four were afterwards kept in the same cage for the next sixty hours; the urine being collected during each period of twelve hours and subjected to examination for strychnine, The following process was

was used to separate the alkaloid from the urine:

To the urine which measured about 50 c.c., was added 5 c.c. of dilute sulphuric acid and the mixture evaporated to dryness over the water bath . The residue was treated with 40 c.c. of absolute alcohol which was then boiled , allowed to coola and afterwards filtered. The filtrate was evaporated to a syrupy consistence. The bulk of the extraneous matter was removed by a repition of this process. The residue obtained after the evaporation of the alcohol was then taken up with distilled water and transferred to a separator. The solution was alkalised with ammonia , shaken up with chloroform and the solvent allowed to separate. Trouble was encountered at this stage through a partial emulsif- of the chloroform; this was afterwards avoided by doing the shaking very carefully and taking a longer time over the process. After the chloroform was removed the process was repeated several times and the combined chloroform extracts evaporatedto dryness over the water bath. The residue left after the evaporation was treated with a few drops of concentrated sulphuric acid and afterwards taken up with distilled water: this was again transferred to the separator and shaken up with ammonia and chloroform. This process was repeated several times and the residue obtained after the evaporation of the final chloroformic extract was subjected to one of the color tests for strychnine, the reagent employed being sulphuric acid containing one two-thousandth part of

potassium/

potassium permanganate.The results obtained were as follows:

First	period	of	twelve	hours	Positive
Second	"	"	"	"	"
Third	"	"	"	"	"
Fourth	"	"	"	"	Negative
Fifth	"	"	"	"	"

Thus after a single administration of a toxic dose, the elimination of strychnine was completed within thirty six hours.

GENERAL SUMMARY.

The main facts elicited from the foregoing experiments may be summarised under three headings.

1. MINIMUM LETHAL DOSE.

The minimumlethal dose of strychnine hydrochloride administered subcutaneously, for the white rat, was found to be 2.5 mgrms. per kilogramme. This figure approximates that given by Wynter Blyth for the mouse which he states is 2.36 mgrms. per kilogramme. The smallest dose which produced a fatal result was 2.0 mgrms. per kilogramme.

2. THE RATE OF ELIMINATION.

After the administration of a single dose of strychnine hydrochloride, by subcutaneous injection, the elimination was completed within thirty-six hours.

3. THE CUMULATION OF STRYCHNINE.

Eight experiments were conducted, with dosage

Exp.	Dose in mgm.per kilo.	Injections each day	Period.	Results.
1	1.0	3	42 days	Survived.
2	1.0	3	42 "	"
3	1.5	2	42 "	"
4	1.5	2	42 "	"
5	2.0	2	56 "	"
6	2.0	2	26 "	Died.
7	2.0	3	16 "	"
8	2.0	3	9 "	"

Experiment 1.& 2

No increase in sensitiveness produced.

Experiment 3.

Acquired a very small degree of tolerance.

Experiment 4.

No increase in susceptibility produced.

Experiment 5.

A small degree of tolerance established.

Experiment 6, 7, 8.

No increase in susceptibility; animal died after a possible lethal dose.

C O N C L U S I O N S.

One may conclude ,as a result of these experiments that strychnine is not "cumulative"in its action in the lower animals.

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