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Studies on the Elimination of Strychnine*

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The problem of the disposition of strychnine by the animal body has been the subject of several previous studies. Hale (1), using extraction with immiscible solvents and a colorimetric test, came to the conclusion that strychnine is slowly excreted and that dogs develop a slow, imperfect tolerance, while results from guinea pigs are less conclusive. Hatcher and Smith (2), using more than lethal doses in anesthetized dogs and estimating biologically in cats, found that small amounts of strychnine were excreted in the urine within a few minutes, and Hatcher and Eggleston (3) noted no tolerance in cats, dogs or guinea pigs, following chronic studies of 12 days' duration. Evidence presented in the above papers indicates that urinary excretion of strychnine accounts for only a portion of the total administered, that active diuresis increases the amount excreted but is not a life-saving measure, and that the liver plays a part in the detoxification of strychnine. In humans, Weiss and Hatcher (4) found that the liver eliminates about $^{5}/_{6}$ of the total and the kidneys excrete only that which the liver fails to eliminate. It has been reported by Mostrom and McGuigan (5) that repeated injections of strychnine nitrate shorten the onset of spasms in frogs and they conclude that a "habit" is formed by use of pathways which are not normally used. There was apparently no tolerance.

Following subcutaneous administration to white rats, Schwartze (6) found that these animals could all dispose of 33% of the lethal dose within 2 hrs., while half of them could dispose of 50% and an occasional animal could dispose of 67% during the same period. He also pointed out that all evidence of strychninization disappeared within 18 hrs. and that intermittent injections (at 2-hr. intervals) produced a discontinuous or uneven strychninization.

Taking into consideration the fact that analysis of excreta for small, tolerable amounts of strychnine is very difficult and that such values at their optimum represent only a portion of the ingested drug, the studies herein reported have been directed toward (*a*) pharmacological detection of the accumulation of strychnine, or of tolerance to it, following prolonged periods of daily administration, and (*b*) determination of the rate of essential elimination or duration of pharmacological action. The applications and limitations of essential elimination

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TABLE I.—THE EFFECT OF DAILY PARENTERAL ADMINISTRATION OF ONE-HALF THE CONVULSIVE DOSE OF STRYCHNINE ON THE SLEEPING TIME OF RATS FOLLOWING INTRAPERITONEAL INJECTION OF SODIUM PENTOBARBITAL

No. of Rats	Sex	Daily Strychnine, Days	Pentobarbital, Mg./Kg.	Sleeping Time, Min. Mean	Sleeping Time, Min. Range	Mean Weight, Gm.	Date
7	*F*	Parent	30	141	134–150	232	May 12
7	*F*	Control	30	84	71–93	138	Apr. 28
10	*F*	20	30	90	79–103	127	Apr. 29
9	*F*	Control	30	222	169–279	224	Sept. 4
7	*F*	145	30	204	183–265	211	Sept. 4
8	*M*	Parent	30	59	47–67	331	May 12
10	*M*	Control	30	45	30–62	173	Apr. 28
9	*M*	20	30	49	44–60	183	Apr. 29
9	*M*	Control	30	67	46–87	323	Sept. 6
7	*M*	147	30	68	16–102	321	Sept. 4

studies have been discussed by Dille (7) and by Hazleton and Green (8).

In order to avoid the possibility of variation in the potency of the drug such as Ward, *et al.* (9), reported, all of the drug was administered in the form of solutions of U. S. P. Strychnine Sulfate from a single lot.

EXPERIMENTAL

DAILY PARENTERAL ADMINISTRATION

Rats.—Male and female adult, albino rats on a diet of Purina dog chow checkers were used in these experiments. The use of adults only was deemed advisable in view of the observations of Schwartze (10) and of Poe, *et al.* (11), that the toxicity of strychnine decreases with the age of the rat until maturity, after which it stabilizes. The experiments consisted of two groups as follows:

1. Following the determination of the approximate convulsive dose for females as 1.25 mg./Kg.,[1] one-half this dose was given daily by intraperitoneal injection to a group of 10 animals, a comparable number of controls being kept under identical conditions. The rats were weighed and the daily dose adjusted at approximately 30-day intervals throughout the entire period of 205 days. At appropriate intervals the response of both the treated group and the controls to light anesthetic doses of sodium pentobarbital and to the convulsive dose of strychnine was determined.

The convulsive dose for males was determined as 2.0 mg. and the experimental procedure outlined above was followed for a group of 10 males and their controls. The period of daily administration for this group was 185 days. By the term "daily" is meant 6 days per week.

(*A*) The results obtained following the intraperitoneal administration of 30 mg. of sodium pentobarbital 24 hrs. after the last daily dose of strychnine are shown in Table I. Sleeping time was measured from the time of injection until the animals were able to right themselves after being gently turned onto their backs. Statistical evaluation by Fisher's table of "t" method (12) indicates that there is no significant difference between the controls and the treated animals of any experiment. While the effect of strychnine on barbiturate narcosis is debatable, it is significant that daily administration of strychnine does not alter in any way the normal response to this typical central nervous system depressant. In the female group, it was noted during the final experiment that after the tail and front quarters made definite righting movements, there was an abnormally prolonged delay before the hind quarters recovered sufficiently to permit complete righting. Since righting was taken as the end point, this phenomenon may account in part for the marked difference in sleeping time between this group after 20 days and after 145 days. A portion of the difference in sleeping time for both males and females may also be attributed to age and seasonal variation. In connection with the latter factor there are included in Table I values for males and females of the untreated parent generation which were determined in the spring of the year at a time comparable to the 20-day determination. For each sex this value falls between the 20-day value (spring) and the final value determined in the fall when the experimental groups were comparable in weight with the parent generation.

(*B*) At various intervals the animals described above were used to determine the response to the convulsive dose of strychnine 24 hrs. after the last daily dose. The results from the females are summarized in Table II; from the males, in Table III. Although there is considerable variation in both sexes it would appear that (*a*) there was no accumulation of the drug since, in spite of a low margin of safety between the convulsive and lethal doses, the deaths were infrequent and uniformly distributed, and (*b*) any tendency toward tolerance is extremely slight and does not appear in either sex until after 54 days of administration. During the interval between the 165th and the 205th day, the rats of the control group and of the treated group were mated and daily administration of strychnine was continued throughout mating and pregnancy. Approximately 10 days post partum the values for the 205th day

[1] Unless otherwise noted all doses are expressed in milligrams of drug per kilogram of animal body weight. Hereafter the words "per kilogram" may be omitted to avoid repetition.

were obtained and the series discontinued. Both the controls and treated groups appear to be slightly more susceptible to strychnine following pregnancy.

TABLE II.—THE RESPONSE OF FEMALE RATS TO INTRAPERITONEAL INJECTION OF A CONVULSIVE DOSE OF STRYCHNINE FOLLOWING VARIOUS PERIODS OF DAILY PARENTERAL ADMINISTRATION OF ONE-HALF THE CONVULSIVE DOSE. TWENTY-FOUR HOURS ELAPSED BETWEEN THE LAST DAILY DOSE AND THE CONVULSIVE DOSE

No. of Rats	Daily Strychnine, Days	Dose of Strychnine, Mg./Kg.	Convulsions Positive	Negative	Death
6	Test dose	2.0	6	0	6
4	Test dose	1.5	4	0	3
12	Test dose	1.25	7	5	0
10	Test dose	1.125	1	9	1
9	Control	1.25	5	4	0
9	30	1.25	9	0	0
9	Control	1.25	8	1	0
10	54	1.25	7	3	1
9	Control	1.25	6	3	0
7[a]	165	1.25	2	5	0
9[b]	Control	1.25	9	0	0
5	205	1.25	4	1	0

[a] Two animals were killed by error in daily dose.
[b] These are post partum values; two with litters not included.

TABLE III.—THE RESPONSE OF MALE RATS TO INTRAPERITONEAL INJECTION OF A CONVULSIVE DOSE OF STRYCHNINE FOLLOWING VARIOUS PERIODS OF DAILY PARENTERAL ADMINISTRATION OF ONE-HALF THE CONVULSIVE DOSE. TWENTY-FOUR HOURS ELAPSED BETWEEN THE LAST DAILY DOSE AND THE CONVULSIVE DOSE

No. of Rats	Daily Strychnine, Days	Dose of Strychnine, Mg./Kg.	Convulsions Positive	Negative	Deaths
12	Test dose	2.0	4	8	2
10	Control	2.0	2	8	0
10	25	2.0	3	7	1
10	Control	2.0	4	6	1
9	54	2.0	4	5	1
9	Control	2.0	4	5	1
6	167	2.0	2	4	0
8	Control	2.0	6	2	0
7	185	2.0	3	4	1

2. The convulsive dose for metrazol in female rats was determined as 35–38 mg. following intraperitoneal injection. The 38-mg. dose was adopted for the following experiments: To determine the additive effect of strychnine and metrazol, 0.1 convulsive dose of strychnine was injected intraperitoneally and 10 min. later, at about the time of maximum absorption, the convulsive dose of metrazol was given. The results in Table IV indicate that there is no additive effect from these doses, or from the combination of 0.25 convulsive dose of strychnine with the convulsive dose of metrazol under similar conditions. There is, however, a slight increase in the time of onset of convulsions, measured from the injection of the metrazol.

One-half the convulsive dose of strychnine was given daily to a group of 17 female rats for a period of 30 days, and 24 hrs. after the last daily injection, the convulsive dose of metrazol was administered. There was a slight increase in the number of convulsions and a rather marked delay in the time of onset. After 7 additional days of strychnine injections, metrazol produced a marked increase in incidence of convulsions with a decrease in time of onset, although the latter remained above the normal. Four days after the withdrawal of strychnine, the incidence of convulsions following metrazol was still high and the time of onset prolonged. Even after 25 days' withdrawal the response was about twice normal, although after this period the latent period had returned to normal. Following this period the response to the convulsive dose of strychnine was approximately normal.

The results of the experiments just described indicate that while no additive effect between single doses of strychnine and metrazol could be demonstrated, the prolonged daily administration of strychnine sensitizes or conditions the animals to the convulsive action of metrazol.

Monkey.—An adult, male rhesus monkey was used in these experiments. The diet consisted of Purina dog chow checkers supplemented by half an orange daily, water *ad lib.* and occasional greens. The convulsive dose of strychnine following sub-

TABLE IV.—THE RESPONSE OF FEMALE RATS TO THE INTRAPERITONEAL INJECTION OF A CONVULSIVE DOSE OF METRAZOL FOLLOWING SINGLE INJECTIONS OF STRYCHNINE AND FOLLOWING VARIOUS PERIODS OF DAILY ADMINISTRATION OF ONE-HALF THE CONVULSIVE DOSE OF STRYCHNINE

No. of Rats	Single Dose of Strychnine, % of C. D.	Daily Strychnine, Days	Metrazol, Mg./Kg.	Convulsions Occurrence Number	Occurrence Per Cent	Time of Onset, Min.
27	...	...	35	10	37	3.5
29	...	...	38	11	38	3.5
14	10	...	38	6	43	4.2
14	25	...	38	6	43	3.7
17	...	30	38	9	53	5.7
17	...	37	38	13	76	4.3
17	...	Withdrawn 4 days	38	15	88	4.7
17	...	Withdrawn 25 days	38	14[a]	82	3.6
15	100	Withdrawn 31 days	..	10	67	...

[a] Two deaths, the first of the series.

cutaneous injection was found to be 0.6 mg. This dose caused hyperexcitability, twitches of the limbs, incoördination and an occasional mild, spontaneous, clonic convulsion followed by recovery. At this time the body weight was 3.25 Kg., and daily subcutaneous administration of one-half the convulsive dose, or 1.0 mg. total, of strychnine was begun. This dosage was continued for 220 days (except Sundays), at the end of which period the body weight was 4.63 Kg. and daily dosage represented 36% of the convulsive dose. Twenty-four hours after the last daily dose, the convulsive dose of 0.6 mg. was repeated and the response was almost identical with the original. Daily administration was discontinued. These results are indicative of no accumulation or change in susceptibility to the action of strychnine after a prolonged period of daily administration of the drug.

After a period of 85 days during which no drug was administered, the above dose of 0.6 mg. was repeated. The response was more marked than previously, as was also the response to the same dose again 2 weeks later, each case necessitating the administration of sodium pentobarbital to insure complete safety of the animal. At intervals of two weeks, single doses of 0.5 and 0.4 mg. were given. The smaller dose caused only hyperexcitability, slight incoördination and an occasional twitch, while the dose of 0.5 mg. duplicated very closely the effects formerly produced by 0.6 mg. and was taken as the convulsive dose for later experiments on essential elimination.

ESSENTIAL ELIMINATION

Rats.—The rate of essential elimination of strychnine by male and female rats was determined by intraperitoneal injection of portions of the predetermined convulsive dose at definite intervals of time until the onset of convulsions. Details of the method and the importance of the various factors involved have been discussed elsewhere (8), and it will suffice here to say that the results shown in Table V indicate that when the rate of administration is sufficiently rapid female rats can essentially eliminate strychnine at a rate of 0.9 mg./Kg./hr., which is equal to 72% of the convulsive dose per hr. Pregnant females have a lower rate of essential elimination, the average for ten animals being 0.67 mg./Kg./hr., which is equal to 54% of the convulsive dose for nonpregnant animals per hr. This lower rate is presumably due to the abnormal *central nervous system/body weight* ratio and perhaps to some extent to the apparent increased susceptibility of pregnant animals noted in the post partum results above.

The average rate of essential elimination for male rats was 1.85 mg./Kg./hr., or 93% of the convulsive dose per hr., although some showed practically no elimination and others had a considerably higher rate. This extreme variation in the response of male rats to strychnine has been noted by other workers, notably Ward and Crabtree (13). In the table those animals which convulsed when a total of only one convulsive dose had been given are indicated as less than (<) the value for the next injection, while those that did not convulse after two or more convulsive doses are indicated as more than (>) the value for the last dose given.

Ten minutes is the shortest practical interval, since this approximates the average time of onset of convulsions following the single doses administered to the animals in Tables II and III. The rate of essential elimination was calculated according to the formula:

$$\frac{\left(\begin{matrix}\text{Total drug in}\\ \text{mg./Kg.}\end{matrix}\right) - \left(\begin{matrix}\text{Convulsive dose}\\ \text{in mg./Kg.}\end{matrix}\right)}{(\text{Time in hrs.})} = \left(\begin{matrix}\text{Essential elimination}\\ \text{in mg./Kg./hr.}\end{matrix}\right)$$

Time is measured from the time of the first injection to the time of the last injection, no allowance being made for the interval between the injection and the convulsion since this latent period should be approximately equivalent to that following the single injection of a convulsive dose.

Rabbits.—In preliminary experiments it was found that intravenous injection of 0.17 mg. caused convulsions in 4 of 6 animals, with 2 deaths, and this dose was considered to be the convulsive dose for the basis of the following experiments.

Adult male albino rabbits were used and the rate of essential elimination was determined by two methods, the first of which was by intravenous injection of portions of the convulsive dose at definite

TABLE V.—THE RATE OF ESSENTIAL ELIMINATION OF STRYCHNINE BY RATS FOLLOWING INTRAPERITONEAL INJECTION OF PORTIONS OF THE CONVULSIVE DOSE AT VARIOUS INTERVALS OF TIME. CONVULSIVE DOSE (C. D.) = 1.25 MG./KG. FOR FEMALES, 2.0 MG./KG. FOR MALES

No. of Rats	Sex	Rate of Administration C. D., %	Interval, Min.	Average Rate of Essential Elimination Mg./Kg./Hr.	C. D./Hr.	No. of Injections, Av.	Remarks
5	*F*	25	15	>0.65	>0.52	11	No convulsions
5	*F*	25	15	0.65	0.52	7.4	
10	*F*	25	10	0.67	0.54	6	Pregnant
10	*F*	25	10	0.90	0.72	7	
10	*M*	25	20	>0.94	>0.47	9	No convulsions
2	*M*	25	15	1.13	0.57	8	
7	*M*	25	15	>1.13	>0.57	10	No convulsions
4	*M*	25	10	<0.80	<0.40	4	Value of fifth
9	*M*	25	10	1.85	0.93	9	
6	*M*	25	10	>2.28	<1.14	14	No convulsions

TABLE VI.—THE RATE OF ESSENTIAL ELIMINATION OF STRYCHNINE BY RABBITS FOLLOWING INTRAVENOUS INJECTION OF PORTIONS OF THE CONVULSIVE DOSE AT VARIOUS INTERVALS OF TIME. CONVULSIVE DOSE (C. D.) = 0.17 MG./KG.

No. of Rabbits	Rate of Administration C. D., %	Interval, Min.	Average Rate of Essential Elimination Mg./Kg./Hr.	C. D./Hr.	No. of Injections, Av.	Remarks
5	10	15	> 0.012	> 0.07	12	No convulsions
4	20	15	> 0.082	> 0.48	11	No convulsions
10	20	10	0.122	0.72	12	All convulsed
3	20	8	0.146	0.86	11	All convulsed
4	20	5	0.183	1.08	8.5	All convulsed

TABLE VII.—RATE OF ESSENTIAL ELIMINATION OF STRYCHNINE IN RABBITS FOLLOWING SLOW INTRAVENOUS INFUSION OF SOLUTION CONTAINING 0.02 MG./CC. CONVULSIVE DOSE (C. D.) = 0.17 MG./KG. FIGURES IN PARENTHESES ARE CORRECTED VALUES BASED ON A 3-MIN. LATENT PERIOD

Wt. of Rabbit, Kg.	Vol. of Solution, Cc.	Total Strychnine, Mg.	Elapsed Time, Min.	Rate of Administration Cc./Min.	Mg./Kg./Hr.	Average Rate of Essential Elimination Mg./Kg./Hr.	C. D./Hr.
2.41	54.1	1.08	112	0.48	0.241	0.149	0.88
	(52.6)	(1.05)	(109)			(0.147)	(0.86)
2.60	65.5	1.31	77	0.85	0.393	0.261	1.53
	(62.9)	(1.26)	(74)			(0.255)	(1.50)
2.02	27.2	0.54	30	0.91	0.539	0.200	1.18
	(24.6)	(0.49)	(27)			(0.164)	(0.96)
2.40	55.8	1.12	60	0.93	0.465	0.295	1.74
	(53.0)	(1.06)	(57)			(0.286)	(1.68)
2.07	60.9	1.22	43	1.42	0.829	0.585	3.44
	(56.7)	(1.14)	(40)			(0.562)	(3.31)

intervals of time until convulsions occurred. Calculation of the rate was the same as that described for rats above. The results are summarized in Table VI and it will be noted that the rate of administration considerably influences the determined rate of essential elimination. Except for the first group of animals, each injection represented 0.2 convulsive dose or 0.034 mg./Kg., the final rate of administration being determined by the frequency of injection. Since intravenous administration eliminates the absorption factor, it is necessary to consider only the latent period of action to establish the minimum interval of time which will allow full development of effects before the succeeding dose is given. The latent period for strychnine sulfate following intravenous injection to rabbits was found to be 3 or 4 min. and therefore a 5-min. interval should allow for unusual variation in the response of individual animals. At this rate of administration rabbits can essentially eliminate an average of 0.183 mg./Kg./hr., or slightly over one convulsive dose per hr.

The second method of determination involved the slow intravenous infusion of a dilute solution of strychnine sulfate. The animals were tied to the operating position in a supine position and, under local anesthesia with 2% procaine hydrochloride and epinephrine, the external jugular vein was exposed and cannulated. In some of the experiments, respiratory and blood pressure tracings were made from the cannulated trachea and common carotid artery, respectively. Although these tracings aided in differentiating between the occasional struggles and the strychnine convulsions, they are not essential to the experiment.

The strychnine solution, containing 0.02 mg./cc., was administered from a burette at various manually controlled rates until definite spontaneous convulsions occurred. From the data thus obtained the rate of administration and the rate of essential elimination were calculated and are presented in Table VII. The corrected data are based on a latent period of 3 min. for the onset of convulsions following intravenous injection of strychnine. It will be noted that the rate of essential elimination increases with the rate of administration with the exception of the third animal in the table. In this case the convulsion was relatively mild and the infusion was continued for 12 min. longer before the incidence of a violent convulsion which terminated in death. At this time the rate of essential elimination was 0.253 mg./Kg./hr. The results from these experiments, unqualified, indicate that following sufficiently rapid intravenous infusion rabbits can essentially eliminate at least 0.562 mg./Kg./hr., or about three convulsive doses per hr.

Monkey.—In the experiments previously described, the latent period between subcutaneous injection of strychnine and the onset of convulsions in the monkey was 10 to 12 min. and the convulsive dose, 0.5 mg. For the determination of the rate of essential elimination by injection of portions of the convulsive dose at definite intervals, 0.2 convulsive dose was injected every 15 min. until the occurrence of convulsions after the seventh injection. The rate of essential elimination, calculated as previously described, was thus 0.127 mg./Kg./hr., or approximately 25% of the convulsive dose per hr.

Guinea Pigs.—In view of the previously mentioned inconclusive results from guinea pigs it seemed advisable to include this species in the current investigations. Attempts to establish a mean convulsive dose for strychnine, however, led to the

conclusion that methods based on such a value could yield valid results only if extremely large numbers of animals were used. Inspection of Table VIII will show that nonlethal convulsions can

TABLE VIII.—DETERMINATION OF THE CONVULSIVE DOSE OF STRYCHNINE SULFATE FOLLOWING INTRAPERITONEAL INJECTION IN GUINEA PIGS

No. of Animals	Dose of Strychnine, Mg./Kg.	Convulsions: Observed Data Positive	Convulsions: Observed Data Negative	Convulsions: Integrated Data Positive	Convulsions: Integrated Data Negative	Deaths
3	2.5	0	3	0	32	0
2	3.0	0	2	0	29	0
1	4.0	0	1	0	27	0
12	5.0	3	9	3	26	1
10	6.0	2	8	5	17	0
7	7.0	2	5	7	9	0
11	10.0	7	4	14	4	4
1	15.0	1	0	15	0	1
1	20.0	1	0	16	0	1
1	25.0	1	0	17	0	1

be obtained with doses of from 5 to 10 mg., the double integrated data (14) indicating a mean value of approximately 7 mg. As a result of the above observations, no further attempt was made to determine the rate of essential elimination in guinea pigs.

DISCUSSION

Throughout the course of these experiments there has been little evidence to indicate that the daily administration of strychnine to rats or the monkey over long periods of time has led either to accumulation or to the development of tolerance to the action of the drug. It must therefore be assumed that the total amount given has been essentially eliminated and that such prolonged administration does not interfere with the ability of the body to eliminate the drug. It is apparent, however, that pregnancy induces a relative increase in susceptibility and decrease in capacity for essential elimination and this fact may be of considerable importance if large doses of strychnine are to be given repeatedly.

If, as it appears, the daily administration of strychnine sensitizes the rat to the convulsive action of metrazol while single doses do not, it is desirable to consider the mechanism of such an action. Perhaps the observation of Mostrom and McGuigan (5) offers the best explanation until further information is available. Thus, while metrazol is not primarily a spinal drug, it does have some such action and if the synaptic resistance is gradually lowered by strychnine the spinal action of metrazol might be sensitized. Since evidence is cited to indicate that the strychnine does not accumulate and the time interval of this experiment would not include seasonal variation, it follows that the sensitization must be of physiological nature. Further support of this view is (*a*) in general, the time of onset of metrazol convulsions was decreased, (*b*) the sensitization was slow in developing and lasted for a considerable time after withdrawal of the strychnine, (*c*) the response to full doses of strychnine remains approximately normal. It is not probable that the sensitization is due to the accumulation of metrazol in view of the rapid rate of essential elimination reported by Hildebrandt and Muegge (15) and the possibility of acquired refractiveness to this drug discussed by Pollock, *et al.* (16).

The importance of maintaining a high blood concentration of drug for the study of elimination has been pointed out by Schwartze (6) for strychnine and by Haggard and Greenberg (17) for alcohol. The results herein described clearly demonstrate that a wide range of values for essential elimination may be obtained depending upon the method used and the rate of administration. In the infusion method, an apparent discrepancy exists between results indicating an essential elimination rate of 0.562 mg./Kg./hr. and the fact that administration of the drug at the rate of 0.241 mg./Kg./hr. will cause convulsions within 2 hrs. This is very largely due, however, to the influence of the rate of administration upon the rates of elimination and accumulation and is the subject of detailed consideration elsewhere (8). It is apparent that the intravenous infusion method will produce the higher results, but that extravascular repeated injection, while introducing the factor of variable absorption, will give valid and satisfactory values if the experiment is properly designed. The results from the latter method perhaps more nearly represent elimination of therapeutically administered drug than do the intravenous values.

Although Hatcher and Brody (18) discussed the significance of the latent period of action for digitalis in the estimation of its persistence of action, this factor has usually been ignored in the consideration of the elimination of other drugs. The correction for latent period of strychnine indicates that at slow rates of administration this procedure does not materially affect the results, but at more rapid rates the effect is significant and would be even more so if the latent period were relatively longer.

CONCLUSIONS

1. No definite evidence of accumulation or tolerance could be found following relatively long periods of daily parenteral administration of one-half the convulsive dose of strychnine to the rat or monkey.

2. Daily administration of the above dose of strychnine sensitizes the rat to the convulsive action of metrazol. A possible mechanism for this action is discussed.

3. Under the conditions described the following rates of essential elimination of strychnine sulfate were determined:

(*a*) Female rats, intraperitoneal, 0.9 mg./Kg./hr.

(*b*) Pregnant rats, intraperitoneal, 0.67 mg./Kg./hr.

(*c*) Male rats, intraperitoneal, 1.85 mg./Kg./hr.

(*d*) Male rabbits, repeated intravenous injection, 0.183 mg./Kg./hr.

(*e*) Male rabbits, intravenous infusion, 0.562 mg./Kg./hr.

(*f*) Male monkey, subcutaneous, 0.127 mg./Kg./hr.

(*g*) Male guinea pigs, intraperitoneal, found unsatisfactory for the methods used.

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A Study of a Strychnos Species*†

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The genus *Strychnos* occupies a rather unique position in the vegetable kingdom because its various species exhibit widely varying physiological actions. While some of the species thus far examined from a chemical and physiological standpoint are exceedingly poisonous, others are entirely harmless, and in numerous cases highly prized as foods. The poisonous action is due mainly to the alkaloids strychnine and brucine. These alkaloids have been found to exist in all the different parts of some species. In other species, however, only certain parts are poisonous, thus indicating that the alkaloids may be localized.

In 1928 a quarantined plant of the species *Strychnos spinosa* was received from the U. S. Bureau of Plant Industry to be planted in the botanical garden at the University of Florida. The growth of this plant was not successful although it was able to exist. Upon inquiry at the Sub-Tropical Experiment Station at Homestead, Florida, it was learned that this species was thriving and producing fruits. Interest was aroused as to the alkaloidal content and toxicity.

After making a careful review of the literature it was found that the only investigations of this species had been on the fruits and even then conflicting results were reported concerning the toxicity and the presence of alkaloids. Also, through the years, the true identity of this plant had become confused.

This investigation was undertaken in the light of these reports to attempt to clear up these contradictions and uncertainties and

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