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STRYCHNINE VI. VARIATION IN PHYSIOLOGICAL ACTION OF C.P. STRYCHNINE.*

BY JUSTUS C. WARD,[1] JAMES C. MUNCH[2] AND F. E. GARLOUGH.[1]

For many years, men using strychnine alkaloid for the control of noxious rodents and predatory animals have noticed variation in the results obtained. The earlier explanations were that variations in field and animal conditions or in the methods of placing the poison baits were responsible. It was incredible that a substance as chemically stable as strychnine would not be uniform in its toxic properties. Wide-spread complaints, traceable to the same lot of poison, have become so prevalent within the past few years, however, that we have been forced to recognize the probability that something was wrong with those lots.

Since we had, for several years, been running tests for the "free base," and the crystal size of the incoming lots of alkaloid, we made an attempt to associate the per cent of free base or the physical size of the particles with the reported troubles. There was no correlation—in fact, the alkaloid carrying the lowest free base very often proved the most efficient toxic agent, and the crystal size was entirely too variable a factor for any conclusions to be drawn. The most toxic alkaloids and the least toxic were often practically the same size—either large or small.

During the past few years, the Denver laboratory has tested biologically 27 lots of the alkaloid, originating from five wholesale distributors. Our system of tests has been by means of stomach tube to white rats. A test suspension of the alkaloid in the concentration of 1 mg. of strychnine to each cc. of suspension was made with the assistance of 1 per cent acacia. The animals to be used were weighed and divided into comparable series. The doses were computed for each animal, and the dose for the first rat measured out in a hypodermic syringe. The animal was then placed on a holding board and a wooden gag, having a $^3/_{16}$" hole in it, was placed in its mouth. A No. 8 soft rubber catheter was then passed through the hole in the gag into the animal's stomach. The syringe was shaken to insure

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* Scientific Section, A. PH. A., Portland meeting, 1935.

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uniform suspension, and the dose administered. A 1-cc. rinse was forced through the catheter, which was then removed, and the animal placed back in the cage for observation. The time at which the dose is administered, and that of the first spasm are recorded, as well as the time until the stoppage of the heart.

We use 25.00, 22.50, 20.00, 17.50, 15.00, 12.50, 10.00, 7.50 and often 6.00 mg. per Kg. body weight as our standard series of doses for preliminary trials. Two rats are desired for each dose in preliminary work, and ten for each in confirmatory tests. Certain digressions from this plan were necessary during the work herein reported, owing to lack of sufficient uniform animals.

Table I shows the differences in the physical and chemical examinations, as well as the variations in killing ability of these poisons. From this table it appears that fifteen of the twenty-seven alkaloids were tested on eleven or more animals. The other twelve samples were tested on five animals to the series, and are consequently useful largely for corroborative data. It also appears that Samples A-1 and B-1 show the greatest difference in toxicity. A careful study of these extremes was made to confirm our observations of a more general nature. Table II gives our tests with these two alkaloids in detail.

TABLE I.—CHEMICAL AND BIO-ASSAY OF STRYCHNINE ALKALOIDS.

Manufacturer.	Sample Number.	Alkaloidal Content, %.	$LD_{100\%}$ Rats, Mg./Kg.
A	1	99.31	Over 25
	2	...	Over 25
	3	...	20
	4	...	20
	5	...	17.5
	6	...	17.5
	7	...	15
	8	...	15
	9	99.70	12.5
	10	...	Below 10
B	1	98.86	7.5
	2	98.91	7.5
C	1	...	20
	2	98.68	15
	3	...	12.5
	4	...	7.5
	5	...	7.5
	6	...	7.5
D	1	...	20
	2	98.28	15
	3	99.30	15
	4	...	15
	5	...	12.5
	6	...	10
E	1	...	12.5
	2	...	10
	3	98.60	7.5

To demonstrate that this wide variation is not altogether due to possible faulty technique or to an unexpectedly wide difference in physiological responses,

TABLE II.—COMPARATIVE TOXICITY OF STRYCHNINE ALKALOIDS A-1 AND B-1; STOMACH TUBE ADMINISTRATION TO WHITE RATS.

Sample.	25.0. T/S.[1]	T/D.[2]	20.0. T/S.	T/D.	15.0. T/S.	T/D.	12.5. T/S.	T/D.	10.0. T/S.	T/D.	7.5. T/S.	T/D.
A-1— I	11.0	18.0	S[3]	S	S	S	S	S	S	S	..	..
II	4.5	6.5	..	..	6.0	9.5	..	..	..	..	7.0	10.0
	5.0	8.0			6.5	10.5					8.5	9.5
	7.5	9.0			7.0	9.0					14.0	19.0
	8.0	12.0			7.0	10.0					18.0	28.5
	8.0	16.0			12.5	20.0					26.0	31.0
	8.0	19.0			13.0	31.0					S	S
	9.0	10.5			15.0	21.0					S	S
	13.5	33.0			16.0	23.5					S	S
	16.0	32.0			24.0	32.0					S	S
	S	S			39.5	42.5					S	S
	S	S			..	..						
	S	S			..	..						
Av. II	8.8	16.2			14.7	20.9					14.7	19.6
B-1— I	8.0	13.0	9.0	15.0	12.0	15.0	9.0	13.0	10.0	15.0	..	..
II	5.0	8.5	..	..	4.0	5.0	..	..	..	..	6.5	8.5
	6.0	7.0			4.0	5.5					7.0	15.5
	6.0	7.5			5.0	14.0					9.0	13.0
	6.0	12.0			6.5	8.5					9.5	12.0
	6.0	12.0			8.0	11.0					11.5	18.0
	6.5	8.5			9.5	14.0					12.0	23.0
	7.5	12.0			12.0	17.0					12.5	15.5
	8.0	12.0			15.0	17.0					16.0	32.0
	14.0	16.0			16.0	18.5					26.0	27.5
	15.0	16.5			20.0	21.0					S	S
Av. II	8.0	11.20			10.0	13.2					12.2	18.3

FOOTNOTE: [1] T/S denotes time in minutes between administration and spasm.
[2] T/D denotes time in minutes between administration and death.
[3] S denotes survived.

TABLE III.—COMPARATIVE TOXICITIES OF A-1 AND B-1 AS THE SULPHATES; INTRAPERITONEAL INJECTIONS TO WHITE RATS.

Sample.	Dose: Mg./Kg. 10.00. T/S.	T/D.	7.5. T/S.	T/D.	5.0. T/S.	T/D.	4.0. T/S.	4.0. T/D.	3.5. T/S.	T/D.	3.25. T/S.	T/D.	3.0. T/S.	T/D.	2.75. T/S.	T/D.
A-1	2.0	5.0	1.0	7.0	3.0–4.0	9.0–8.0	4.0–4.0	5.0–6.0	7.0	21.0	4.0	7.0	8.0–14.0	20.0–16.0	10.0	13.0
B-1	3.0	5.0	3.0	4.0	3.0–2.0	15.0–3.0	5.0–2.0	12.0–4.0	3.0	5.0	9.0	15.0	10.0	12.0	S	S

Av. A-1: T/S— 5.5
T/D—10.6.

Av. B-1: T/S—4.4
T/S—9.0.

we prepared the sulphates from the two alkaloids and administered the solutions of these salts by intraperitoneal injection. Table III gives the results of this test. This tabulation shows that although the differences are smaller, they are still in the same direction.

A further test was made using laboratory-recrystallized alkaloids in comparison with the original commercial products. Six different lots of the commercial material were recrystallized in the laboratory and the twelve lots of poison thus obtained were tested. The laboratory-recrystallized product had a fairly uniform crystal size, whereas the original alkaloids were decidedly variable. The commercial alkaloid and the laboratory crystals from that alkaloid did not show any difference in toxicity.

CONCLUSIONS.

1. Commercial strychnine alkaloids of C.P. quality show definite and marked differences in toxicity.
2. These differences are of such magnitude that serious variation in results are noted in their use in economic poisons.
3. These differences have not been associated with determinable changes in chemical or physical properties.
4. Recrystallization of the various alkaloids does not alter their lethal efficiency.

THE INFLUENCE OF CERTAIN SALTS ON MORPHINE TOXICITY AND NARCOSIS IN MICE AND RATS.*

BY J. M. ORT AND W. G. CHRISTIANSEN.[1]

The study of synergism and antagonism among drugs has, admittedly, many fascinating theoretical and practical possibilities. In the field of morphine pharmacology, for instance, it is conceivable that certain drugs exist which can greatly potentiate the action of morphine in all of its manifestations, thus decreasing the dosage required. But, much more important, such a potentiator may some time be found which will affect only the narcotic action of the drug or at least will not proportionally increase its vicious habit-forming effects.

The influence of atropine on the activity of morphine is, of course, well recognized. F. Schmitz, for example, studied not only atropine in this connection but also lobelia, coramine, cardiazole, hexetone and pyramidon. (On the influence of central nervous stimulants on morphine poisoning (1).) W. Peters has reported that antipyrine is a morphine synergist. (A morphine-sparing ampul preparation (2).)

Bancroft (3) and his co-workers have made a most extensive study in this field, making use of the facts and theories of the modern science of colloid chemistry to expand the theory of anesthesia and the behavior of nervous tissues originally proposed by Claude Bernard. The essence of this theory is that anesthesia or narcosis results when the colloids of the cells of the nervous tissues are either abnormally reversibly dispersed or coagulated.

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