

THE EFFECT OF ALTITUDE ON THE ACTION OF DRUGS. I. STRYCHNINE.*

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Medical and veterinary practice has long known that differences in altitude have made necessary the modification of doses in the use of many potent drugs. The purpose of these investigations is to make quantitative studies of the variation in lethal doses as well as of the speed of action of the drugs involved when all variables, except altitude, are held as constant as possible. Strychnine, as the sulphate, is the drug studied in the present communication.

Two distinct experiments were conducted. In the first series tame rats were used, in the second series, Columbian ground squirrels. One hundred tame rats

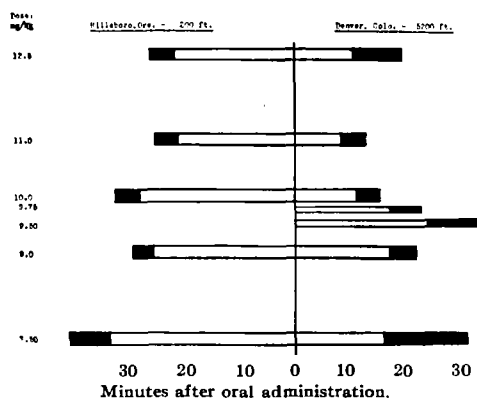


Fig. 1.—Reaction time of rats to strychnine; periods until symptoms, duration of convulsions, and death.

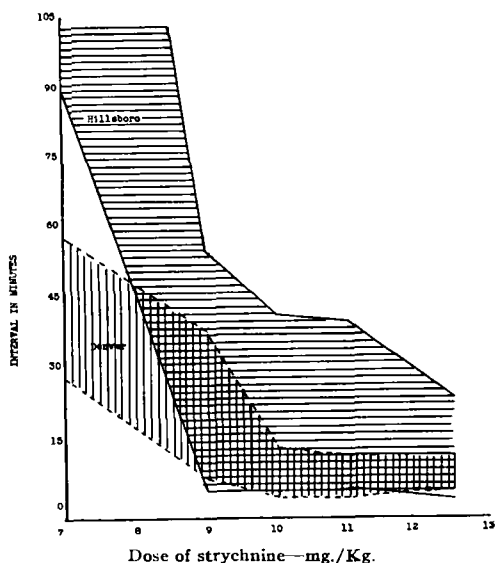


Fig. 2.—Interval between administration and tetany or death; zone indicates duration of convulsions.

of uniform size, 8 to 10 weeks old, were purchased from a Denver, Colo., breeder who raises large and healthy stock. Half of these were forwarded to Hillsboro, Ore., and the others retained at Denver. Feed for both groups was purchased at Denver and divided so the ration was identical at both stations. The animals were held for 3 months to insure complete acclimatization.

Just a few days before the tests were to be conducted, the poison solution to be used was prepared at Denver and also divided. Half of it was carefully sealed and sent to Hillsboro, and the other half retained at Denver. The same technique of administering the poison orally was employed at both elevations.

On the day of the tests, the room temperature, barometric pressure, relative humidity, and character of the weather were all recorded. There was fortunately

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a gratifying check of conditions, so the difference in barometric pressure due to the variation in altitude was the principal factor to explain the observed changes in rate and degree of strychnine action.

Table I gives the climatological comparisons at the two stations during the period of the tests.

The poison used in this test was strychnine, as sulphate, in a concentration of 2¹/₂ mg./cc. in distilled water.

Table II gives the detailed experimental results of the altitude experiments with tame rats. Fig. 1 shows the same data graphically.

In Table III the correlations were made on the basis of the probable errors (PE) of the averages and are so listed. It appears from Tables II and III that the LD₁₀₀ per cent (lethal dose for 100 per cent of the animals tested) was 12.50 mg./Kg. at Hillsboro and 10.00 mg./Kg. at Denver. Also 10/10 animals at Hillsboro died in 25 minutes after 4.1 minutes of intermittent tetany, while at Denver the figures were 15.0 and 4.0 minutes, respectively.

TABLE I.

	Hillsboro, Oregon.	Denver, Colorado.
Altitude	200 feet	5280 feet
Barometric pressure	757, 765, 768, 760 mm.	625 mm.
Temperature	20° C., 21.1° C.	22.2° C.
Relative humidity	44%, 67%, 56%, 87%	12%

TABLE II.

Dose Mg./Kg.	Ratio.	Hillsboro, Oregon.			Ratio.	Denver, Colorado.		
		*T/S Minutes.	+T/T Minutes.	φT/D Minutes.		T/S Minutes.	T/T Minutes.	T/D Minutes.
12.50	10/10	21.1	4.1	25.2	6/6	10.2	8.8	19.0
11.00	6/10	20.7	4.0	24.7	6/6	8.3	4.0	12.3
10.00	6/8	27.2	4.1	31.3	6/6	11.0	4.0	15.0
9.75	3/6	15.3	6.7	22.0
9.50	4/6	23.0	9.0	32.0
9.00	5/10	16.4	3.4	28.6	3/6	25.2	4.3	20.7
7.50	1/10	33.0	7.0	40.0	3/6	15.3	14.7	30.0

* Time to onset of spasm. + Period of intermittent tetany. φ Time to death.

TABLE III.—STATISTICAL CORRELATIONS.

Dose Mg./Kg.	T/T.		T/D.	
	Hillsboro.	Denver.	Hillsboro.	Denver.
12.50	4.1 ± 2.49	5.6 ± 2.30	25.2 ± 11.18	12.8 ± 2.58
11.00	4.0 ± 1.41	4.0 ± 3.10	24.7 ± 9.15	12.3 ± 5.25
10.00	4.1 ± 2.39	4.0 ± 1.69	31.3 ± 5.08	15.0 ± 5.08
9.00	3.4 ± 1.42	4.3 ± 1.89	28.6 ± 5.15	20.7 ± 1.50
7.50	14.7 ± 6.40	30.0 ± 8.45

In Table IV an attempt was made to evaluate the survivals in relation to the effectiveness of the dose. The averages for each dose were divided by the unit percentage of the animals that died in the series represented by the average involved. For example, at Hillsboro 100 per cent of the animals given 12.50 mg./Kg. died in 25.2 minutes; accordingly 25.2/1.00 = 25.2. However, at 9.00 mg./Kg. only 50 per cent of the animals died in 28.6 minutes, and 28.6/0.5 = 57.2. This then becomes the new average, when the survivals have been evaluated in this way. Fig. 2 shows graphically how well this system of correlation actually causes the data obtained to approach the ideal curves. In the case of the "time to death" T/D lines, at Hillsboro the curve approaches a straight line at 12.50 and again at 7.50 mg./Kg., indicating all animals would die at 12.50 or above and all animals would live below 7.50. Between those figures the curve approaches the ideal configuration. At Denver, however, the experiment is not sufficiently complete at the lower doses to draw such definite conclusions. It does, however, show that above 10.00 mg./Kg. a

straight line is approached, and that below 7.50 the tendency would be a sharp break upward, indicating a high percentage of survivals.

To determine whether the averages included in the above tables were significant, the PE of the differences between them were computed. Table V gives these data for the doses 9.00–12.50 mg./Kg. These figures were obtained from the averages of the animals that actually died, and consequently do not show the range that would have been indicated had the evaluated survivals been included. The table shows no significance for any of the figures on the period of intermittent tetany (T/T), but it does show PE of 2.9–5.56 for the T/D figures. From tables of probabilities (1) these figures mean that the chances of recurrence range from 1 in 20 to 1 in 5000. These ranges are not highly significant, but do indicate a definite effect from altitude differences on strychnine susceptibility.

Similar studies on Columbian ground squirrels were undertaken with much less detail in the field by the senior author.

The original plan was to conduct dosage trials so as to have the plant development stage similar at all elevations. This was done at the first two points studied,

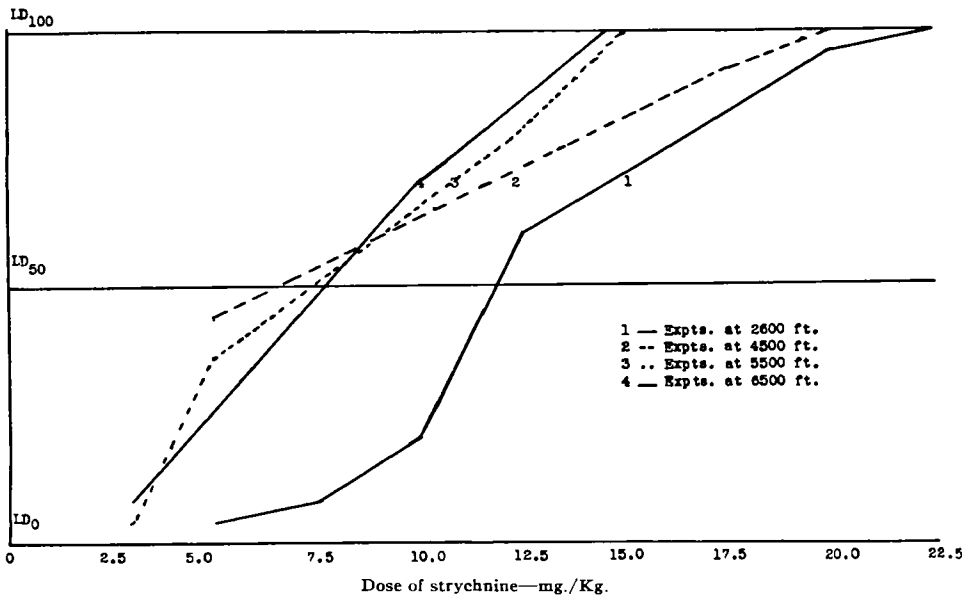


Fig. 3.—Toxicity of strychnine orally to Columbian ground squirrels.

but the third and fourth locations were reached when plant growth was approximately a week younger than that at the first two.

Elevations used were obtained from Geological Survey maps, and are accurate to 100 feet.

Table VI shows a gradual decline in the LD₁₀₀ per cent as elevation increases. Fig. 3 gives the data graphically. The animals used were obtained from areas where no trapping and poisoning had previously been done.

Table VI reveals two points of major interest:

(1) The LD₁₀₀ per cent varies inversely with the altitude. Plotting LD₁₀₀ per cent against altitude an equation can be developed: $y = 14,300 - 520x$ (where y is the LD and x the altitude). This equation suggests a decrease in LD₁₀₀ of about 2.0 mg./Kg. for each 1000 ft. increase in elevation, when Columbian ground squirrels are poisoned with strychnine. The LD₅₀ per cent doses show a similar relationship.

(2) The T/D varies directly with the altitude. This conclusion is reached, however, from correlations in which average times for entire series were taken, and exactly comparable doses are not available.

TABLE IV.—AVERAGES WITH SURVIVAL EVALUATIONS INCLUDED.

Dose. Mg./Kg.	T/T.		T/D.	
	Hillsboro.	Denver.	Hillsboro.	Denver.
12.50	4.1	5.6	25.2	12.8
11.00	6.7	4.0	41.2	12.3
10.00	5.5	4.0	42.6	15.6
9.00	6.8	8.6	57.2	41.4
7.50	70.0	29.4	400.0	60.0

TABLE V.—SIGNIFICANCE CORRELATIONS.

Dose.	T/T.		T/D.		Probable Errors of the Differences T/D.	Probability of Recurrence.
	Hillsboro.	Denver.	Hillsboro.	Denver.		
12.50 mg./Kg.						
Average time	4.1	5.6	25.2	12.8
PE _{mean}	0.79	1.03	3.54	1.15	3.33	1:40
11.00 mg./Kg.						
Average time	4.0	4.0	24.7	12.3
PE _{mean}	0.57	1.27	3.72	2.14	2.88	1:20
10.00 mg./Kg.						
Average time	4.1	4.0	31.3	15.0
PE _{mean}	0.97	0.69	2.06	2.08	5.56	1:5000
9.00 mg./Kg.						
Average time	3.4	4.3	28.6	20.7
PE _{mean}	0.63	1.09	2.30	0.87	3.21	1:35

TABLE VI.—EXPERIMENTAL RESULTS—STRYCHNINE ALTITUDE STUDIES, COLUMBIAN GROUND SQUIRRELS—ORAL ADMINISTRATION.

Altitude.	Doses. Mg./Kg.	Ratio.	Average.	
			T/T Minutes.	T/D Minutes.
2600 ft.	5.0	1/26		
	7.5	1/12		
	10.0	2/10		
	12.5	6/10		
	20.0	24/25		
	22.5	25/25	7.0	21.0
4500 ft.	5.0	11/25		
	17.5	23/25		
	20.0	25/25	11.5	35.0
5500 ft.	3.0	1/25		
	5.0	9/25		
	12.5	20/25		
	15.0	25/25	8.5	34.5
6500 ft.	3.0	2/25		
	10.0	7/10		
	12.5	22/25		
	15.0	25/25	17.8	44.4

CONCLUSIONS.

(1) A change in elevation of 5000 feet caused a 20 per cent reduction in LD₁₀₀ per cent and a 40 per cent decrease in the T/D (time to death), following oral administration of strychnine as the sulphate to tame rats.

(2) Statistical analysis shows the effects observed are not highly significant, ranging from 1-20 to 1-5000.

(3) Inclusion of survivals, by a percentage system of evaluation, causes the curves to approach the ideal.

(4) Successive increases of elevation of 1000 feet produced a definite and fairly constant reduction in LD₁₀₀ per cent of strychnine administered orally to Columbian ground squirrels.

(5) Ground squirrels appeared to be more susceptible than rats to changes in elevation.

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REFERENCE.

- (1) Munch, James C., "Application of Statistical Methods to Pharmaceutical Research. I. Measures of Accuracy," *JOUR. A. PH. A.*, 20, 126 (1931).



PORTLAND'S A. P. H. A. CONVENTION COMMITTEE.

Members of committee in charge of arrangements for convention in Portland scheduled for August 5-10, 1935. Seated: Left, A. O. Mickelsen, Local Secretary; Mrs. Ralph A. Watson, in Charge of Women's Activities, and L. G. Haack, General Chairman. Standing: Left to Right: E. A. Stipe, Transportation; Earl Gunther, Scientific Display; F. C. Felter, Publicity; Peyton Hawes, Entertainment; Fred Geue, Treasurer; Frank Nau, Vice-Chairman; and Frederick Grill, Secretary, Local Committee. Dean A. O. Ziefle, Chairman, Reception Committee, not present when picture was taken.