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Monoiodoacetic Acid Poisoning in Albino Rats: Symptoms, Minimum Lethal Dose.

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The finding of Lundsgaard[1] that monoiodoacetic acid injection into frogs inhibited the production of lactic acid by skeletal muscles on stimulation, without abolishing contraction, has revolutionized theories of the chemical mechanism of muscular contraction. Accordingly, it seemed valuable to prepare for the extension of this work to mammals by determination of the dosage required for the various symptoms, and for death.

Solutions of monoiodoacetic acid, brought to pH 7.2 by addition of sodium hydroxide, were injected intraperitoneally into unanesthetized female albino rats of 130 to 250 gm. weight, the dosage range being from 30 to 400 mg. per kg. body weight. A group of 5 animals received each dose. The rats had been starved for a period of 48 hours previous to injection.

In all animals receiving 120 or more mg. per kg. death occurred within 20 minutes. The time of onset of symptoms varied from 2 minutes with the largest dose to 8 minutes with 120 mg. per kg. The first alteration of behavior was the appearance of marked general hypoactivity, interrupted by sudden attacks of hyperactivity—running, climbing or biting, in which the movements soon became definitely ataxic. Circus movements appeared in a number of cases. Distinct hyperpnea next appeared, which often progressed to a definite inspiratory dyspnea. The hind legs became paralyzed, being dragged in an abducted posture. The animal soon became prostrate, lying on the side and making no righting movements if placed on the back. Occasionally tremors or mild clonic convulsions occurred. During various of the above stages the animals squeaked loudly, if touched or convulsed, in a manner suggesting hypersensitivity. Finally there appeared a violent tonic convulsion involving the whole body, lasting only about 10 seconds, but leaving the animal in extreme rigor in the posture given to it by the convulsion; mouth open, marked opisthotonus, elbows and wrists flexed; digits of fore feet flexed and adducted; hip, knee and ankle extended; digits of hind feet extended and abducted. The rigor was especially marked in the thoracic wall. Respiration ceased, with the

[1] Lundsgaard, E., *Biochem. S.*, 1930, **217**, 162; **227**, 51.

occasional exception of some gasping movements in the head. The heart often continued to beat slowly for as much as a minute after the rigor had set in. The above course was presented by all the 25 animals, with the exception of 2, in which the terminal convulsions were weak and in which rigor did not appear until some minutes after death and was not extreme.

All the animals receiving doses between 110 and 70 mg. per kg. died. A certain number (those dying within 30 minutes) presented the course described above for higher doses. However, with decreasing dose, an increasing number presented a much more prolonged survival, the earliest death in this second group being at 106 minutes after injection. Briefly their clinical course was: alternating periods of hypoactivity and hyperactivity with ataxia; prostration slowly developing, the animal losing righting responses and lying on the side; hyperpnea, passing into inspiratory dyspnea, each inspiration being accompanied in certain cases by general trunk and leg movements; hypersensitivity, passing into loss of sensitivity; attacks of clonic convulsions of variable duration and intensity, occasionally taking the form of rolling movements; fall of body temperature; slowing of respiration with development of irregularity; and finally death without terminal convulsions. Rigor never appeared before 15 minutes after death. All deaths occurring at times exceeding 100 minutes were preceded by the above course.

We believe that 2 fairly distinct clinical courses in the fatal poisoning may be distinguished: first, rapid sudden death, with terminal convulsions passing directly into rigor; second, slowly developing prostration with late death, rigor appearing after a definite interval.

All animals receiving 30 or 50 mg. per kg. survived at least 24 hours. These presented marked hypoactivity and moderate degrees of prostration, which reached its height in about 4 hours and per-

TABLE I.

Survival Times of Albino Rats Receiving Monoiodoacetic Acid.

Dose, mg. per kg.	Times of death min. after injection					50% Survival, Time
400	6	6	7	8	13	7.5
200	8	9	9	12	13	9.0
150	8	11	11	11	14	10.5
130	8	8	9	10	15	9.0
120	14	15	18	18	20	16.5
110	12	14	21	23	112	17.0
90	12	24	27	115	121	25.0
70	24	106	200	242	337	150.0
50	All over 24 hours					—
30	”	”	”	”		—

sisted unchanged for about 24 hours. No convulsions were observed.

In Table I there are tabulated for each dose, the time of death of each animal, and the time at which 50% of the animals remained alive. This last figure was obtained by plotting against time in minutes a curve representing the percentage of animals remaining alive at each minute; and then locating on the time axis the point where the smoothed curve crossed the 50% line. For doses of 90 mg. per kg. or greater, this value is determined solely by the animals presenting the first type clinical course; below 70 mg. per kg. solely by those presenting the second type.

The data indicate that the minimum dose killing any animal was 70 mg. per kg.; the maximum dose survived by any animal was 50 mg. per kg. The minimum lethal dose thus lies between 30 and 50 mg. per kg. Experimenters will be more interested in the doses producing the poisoning. The second type of clinical course (prolonged prostration, death without immediate rigor) was obtained in doses ranging from 70 to 110 mg. per kg., the minimum producing it in 50% of cases being 70 mg. per kg. The first type (convulsions with immedate rigor) was obtained with doses of 70 mg. and greater, the minimum producing death in this manner in 50% of cases being 90 mg. per kg.; and the minimum for 100% being 120 mg. per kg.

While this study has not included any analysis of the mechanisms involved, the impression is given that the earliest action on the intact animal is on the central nervous system, including particularly a stimulation of the respiratory center. Provided that the dose be high enough, and that the central nervous system action has produced vigorous convulsions, the rigor producing action on muscles, seen by Lundsgaard in frogs, is evident.

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Ultrasonic Radiation and Yeast Cells.

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A system capable of producing a series of high frequency waves in fluid may be constructed by placing a piezo-electric crystal of