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Behavioral Toxicity of DDT

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BEHAVIORAL TOXICITY OF DDT

Travis Thompson and Patrick Lilja

Toxic effects of insecticides are usually described on the histological, physiological, or biochemical level, or clinical toxicologists report gross symptoms of toxicity in patients accidentally exposed to dangerous drugs. However, very few attempts have been made to explicate the behavioral effects of chronic exposure to insecticides. The few related studies that have been conducted have dealt with compounds like strychnine (Lashley, 1917; McCaugh and Thomson, 1962; Petronovich, 1963; Cooper and Krass, 1963), picrotoxin (Breen and McCaugh, 1961; Verhave, 1957), and various poisonous industrial vapors and gases (Medved, Spynu and Kagan, 1962; Horvath, Franktik, and Formanek, 1963). Information about the behavioral effects of chronic exposure to common insecticides is singularly lacking. The purpose of the present research was to evaluate the behavioral toxicity of chronically administered DDT (2:2-[p-Chlorophynyl]-1:1:1-trichlorethane).

DDT is relatively nontoxic in terms of acute lethality. The acute oral median lethal dose (LD-50) in the rat ranges from 150 to 180 mg. per kilogram of body weight. Detoxification of DDT is very slow, with only 10 per cent of the primary metabolite recoverable from the urine during the first five days following an oral dose of 2.5 mg. in rats. None of the unchanged insecticide can be recovered in the urine, and only a small fraction is found in the feces. The major part of the drug appears to be stored in fatty tissues and detoxified very slowly via little-understood metabolic pathways. Thus, the net effect of repeatedly administering low or moderate doses of DDT is accumulation of the drug until a lethal level

is reached (Williams, 1959).

Among the earliest signs of chronic DDT toxicity in humans is "buzzing" or "ringing" auditory sensations. In rats, chronic administration is associated with generalized lowering of the threshold for excitation of central neural tissue. Stimuli which were previously subthreshold initiate action potentials. If DDT administration is continued, spontaneous firing of neurons ensues, producing spontaneous sensations and tremors and, ultimately, convulsions. A period of increased auditory acuity has been reported before this degree of toxicity is reached (Hayes, 1959; Shankland, 1964). The exact nature and limits of this increased acuity is not, however, clear. The present research was designed to delineate objective changes in auditory acuity under a chronic DDT regime, using operant behavior under auditory discriminative control.

Method

Subjects

Four male albino rats, weighing 360 to 390 gm. at the beginning of the experiment, served as subjects.

Apparatus

Two standard one-lever Foringer chambers for conditioning operant behavior in rats were used for training and testing. These chambers were also connected with compatible relay-timing-and-switching-control apparatus. Foringer multiple-stimulus control panels were used as tone generators, and the standard speaker mounted in the test chamber was used to present auditory discriminative stimuli. The lower of two tone-frequency ranges was used for the discriminative stimulus. The ventilating fans on the test chambers were not used, since the noise produced by the fan

motor interfered with the auditory discrimination. The test chambers were in rooms separate from the control apparatus.

The animals were housed in standard rat cages with galvanized steel walls and hardware cloth floors and fronts. Water was continuously available in 250 cc. stoppered bottles fitted with stainless steel drinking tubes. Food used in the home cages was Purina Fox Chow, while 45 mg. Noyes pellets was used as the reinforcer in the conditioning chambers. Temperature in the animal room ranged from 66° F to 72° F, and illumination was on a 12-hour light-dark cycle.

Pure DDT was powdered in a mortar and dissolved in peanut oil (50 mg. and 150 mg. per cubic centimeter). The solution was injected subcutaneously on the animal's back, using a #22 hypodermic needle. No attempt was made to sterilize the solution.

Procedure

After two weeks' adaptation to the laboratory routine, with ad libitum food and water, a food-deprivation regimen was initiated. The animals were food deprived to 85 per cent of their free-feeding weights and maintained at that level throughout the experiment. After weights had stabilized, the animals were conditioned to press the telegraph-key lever for food reinforcement on a regular reinforcement schedule. Subsequently, a series of 30-minute sessions were run in which a tone was introduced for one-minute intervals. Lever pressing during the one-minute periods was reinforced, while responses at other times went unreinforced. After responding during nontone periods had nearly ceased, the reinforcement schedule during the tone was changed from regular reinforcement to a variable interval of one minute. The range of intervals was from five seconds to

three minutes, with a mean of one minute. Session length was decreased to 15 minutes, with eight one-minute tone (S^D) periods and seven one-minute (S^Δ) nontone periods. After two weeks of daily sessions on this schedule, responding during the two intervals stabilized, with very few responses emitted during nontone periods and a stable rate of responses emitted from session to session during tone periods. At this point, a series of sessions were run on which the volume of the S^D tone was progressively diminished. When approximately the same number of responses were being emitted during tone and nontone periods, the volume was increased slightly, and conditioning continued at that tone volume. Those subjects whose ratio of S^D/S^Δ response rates was less than 2.0 were discarded from the study. The four subjects used had mean S^D/S^Δ ratios of 2.1, 2.9, 2.2, and 2.3 for the last five base-line days. For two sessions, all four animals received subcutaneous injections of peanut oil two hours before the session began. Data from these control sessions provided base lines from which to compare subsequent performance under the influence of the insecticide. Every day, two hours before the experimental session, two of the four animals received 50 mg. per kilogram of body weight, while the other two received 150 mg. per kilogram of body weight. Insecticide administration was continued for 35 days, or until the animal died. Gross symptoms, such as tremors, were noted.

Results

Figure 1 presents response rates during S^D and S^Δ periods for rat 47 on the two control days of peanut oil administration and on the succeeding 26 days of treatment with 150 mg. DDT. The overall rate of lever pressing during both S^D and S^Δ periods increased; however, the relative rate

increase during tone periods was greater than during nontone periods. A similar phenomenon was observed for rat 57, where the relative increase during the S^D period was even more marked. After approximately five days of insecticide administration, the rates during the two periods converged.

Rat 41 received 50 mg. DDT over a 34-day period, with a progressive increase in rate during both S^D and S^Δ periods. There was no consistent trend indicating a differential effect on S^D and S^Δ responding. The record of response rates during S^D and $S\Delta$ periods for rat 52 (50 mg.) presents a slightly different picture, in that the S^D response rate progressively increased and the S^Δ response rate progressively decreased. After approximately two weeks of treatment, this trend stabilized with no further convergence.

The two animals receiving 150 mg. died after 26 days of treatment with DDT, while the two receiving 50 mg. were still functioning after 35 days of treatment. Beginning on the sixth and seventh days of DDT treatment, animals receiving 150 mg. exhibited fine tremors in the rear limbs, which grew progressively more pronounced with successive days of treatment. By the fifteenth day of DDT administration, both animals were ataxic and exhibited coarse tremors in both hind and front limbs. The two subjects receiving 50 mg. exhibited fine tremors beginning on the seventeenth and twentieth days of treatment. These symptoms were erratic and not clearly discernible on each daily examination.

Discussion

The relatively greater increase in response rate during S^D periods than in S^Δ periods from the second through the sixth day of DDT administra-

tion suggests that discrimination of tone-on from tone-off was enhanced by the toxin. After the eighth day of treatment, not only did the relative difference between S^D and S^Δ response rates lessen but the overall rate of lever pressing diminished. Thus, any improvement in auditory acuity produced by DDT was transient and quickly followed by generalized deterioration of performance. It seems unlikely that the change in discriminated behavior was due to purely generalized "excitability," since the nontone lever-pressing rate increased only slightly, while rate during the tone period exhibited a very marked increase (see Figures 1 and 2).

It may seem gratuitous to describe enhanced discriminative performance as toxic. However, changes in neural and reflex activity which would otherwise be considered within normal ranges, are considered signs of toxicity when they are the result of DDT administration (Shankland, 1964). It would seem that a change in any biological system which is produced by a known toxin and which is part of a larger syndrome of damage to the organism can appropriately be called toxicity. In this case, the changes in performance under auditory discriminative control might be thought of as behavioral toxicity, since discrimination is by definition a behavioral biological process.

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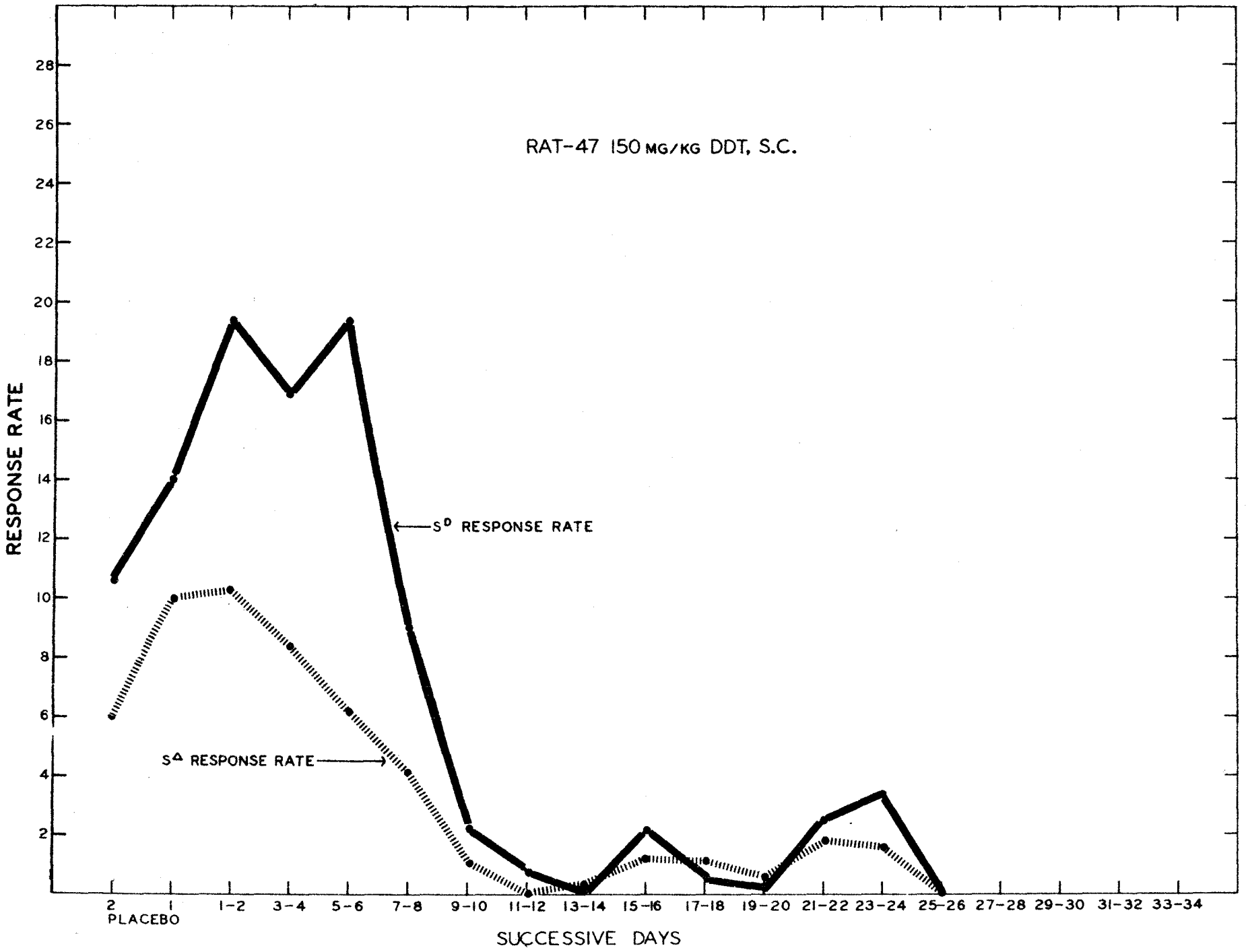
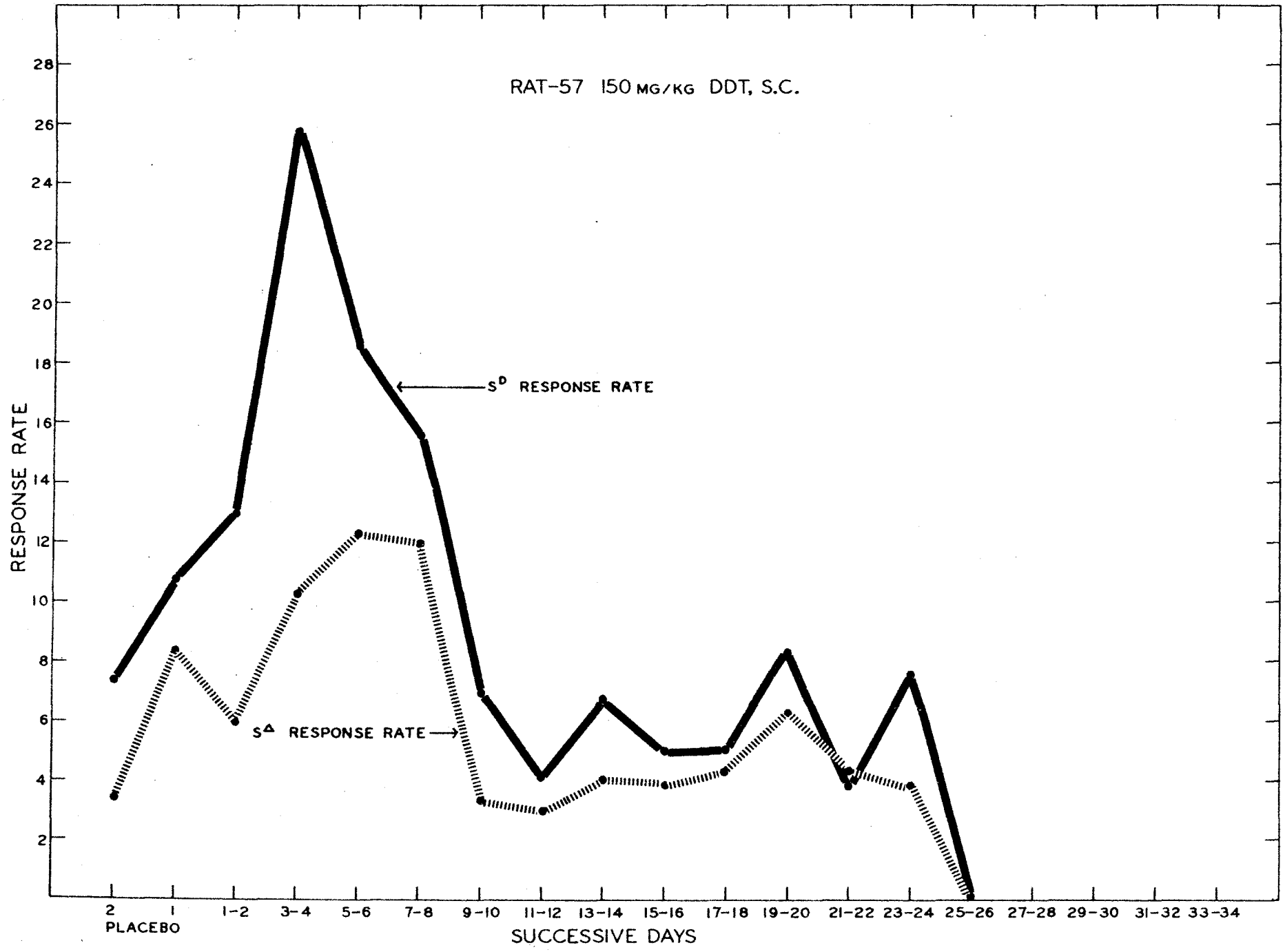
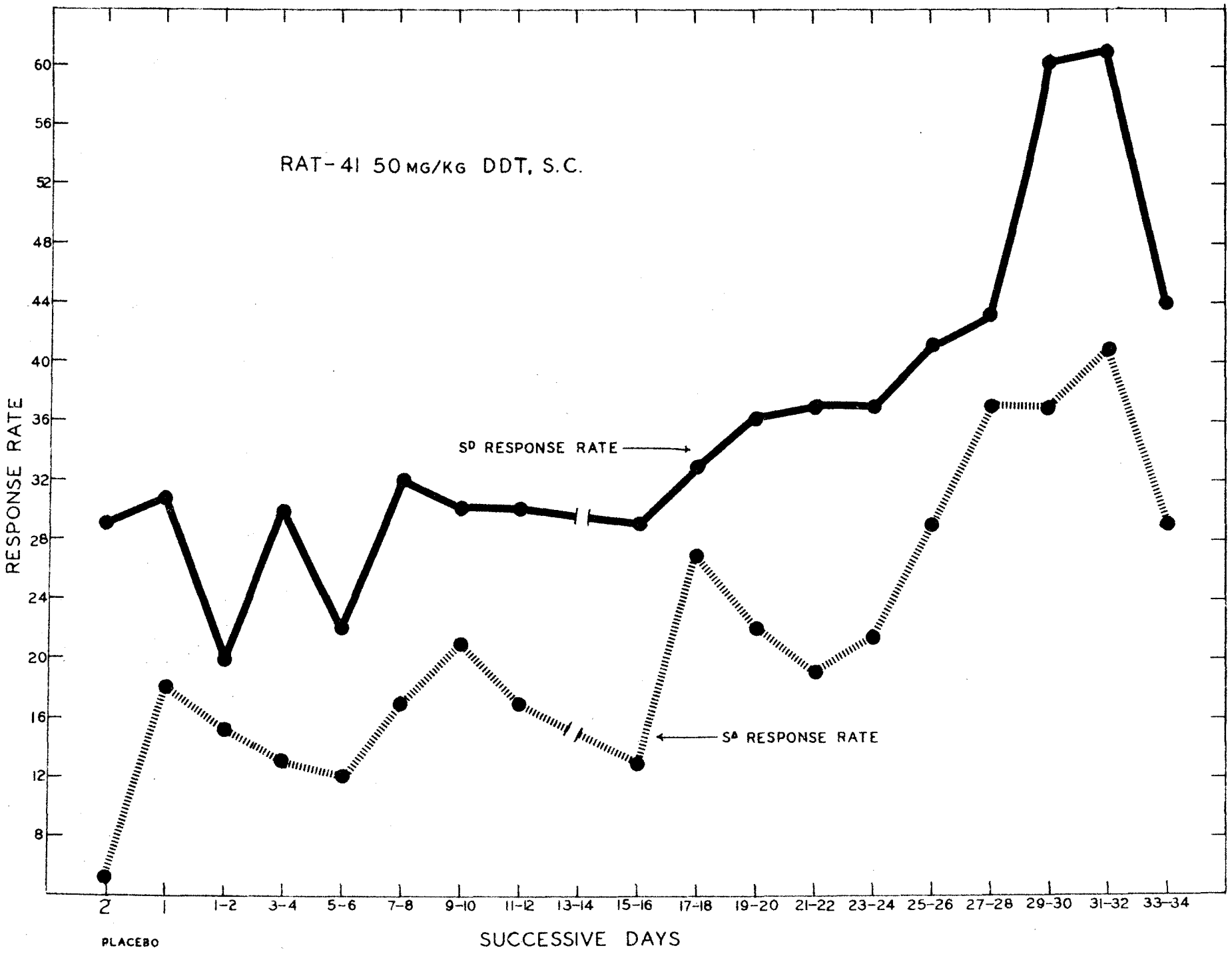
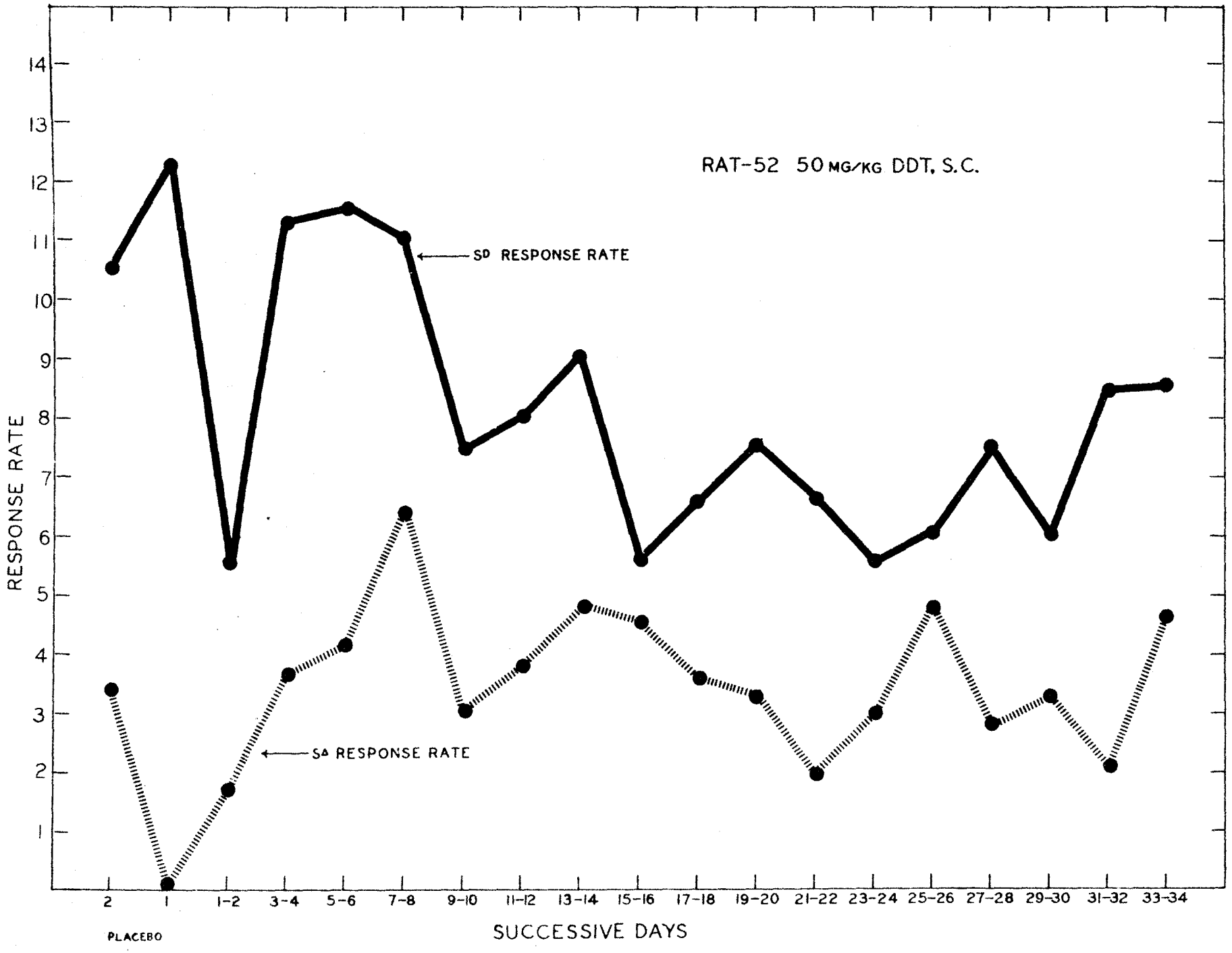

RAT-47 150 MG/KG DDT, S.C.
RESPONSE RATE
28
26
24
22
20
18
16
14
12
10
8
6
4
2
←S^D RESPONSE RATE
S^Δ RESPONSE RATE →
2 PLACEBO
1
1-2
3-4
5-6
7-8
9-10
11-12
13-14
15-16
17-18
19-20
21-22
23-24
25-26
27-28
29-30
31-32
33-34
SUCCESSIVE DAYS


RAT-57 150 MG/KG DDT, S.C.
RESPONSE RATE
28
26
24
22
20
18
16
14
12
10
8
6
4
2
S^D RESPONSE RATE
S^Δ RESPONSE RATE
2
PLACEBO
1
1-2
3-4
5-6
7-8
9-10
11-12
13-14
15-16
17-18
19-20
21-22
23-24
25-26
27-28
29-30
31-32
33-34
SUCCESSIVE DAYS


RAT-41 50 MG/KG DDT, S.C.
RESPONSE RATE
60
56
52
48
44
40
36
32
28
24
20
16
12
8
SD RESPONSE RATE
SΔ RESPONSE RATE
2
1
1-2
3-4
5-6
7-8
9-10
11-12
13-14
15-16
17-18
19-20
21-22
23-24
25-26
27-28
29-30
31-32
33-34
PLACEBO
SUCCESSIVE DAYS


RAT-52 50 MG/KG DDT, S.C.
SD RESPONSE RATE
SA RESPONSE RATE
RESPONSE RATE
14
13
12
11
10
9
8
7
6
5
4
3
2
1
2
1
1-2
3-4
5-6
7-8
9-10
11-12
13-14
15-16
17-18
19-20
21-22
23-24
25-26
27-28
29-30
31-32
33-34
PLACEBO
SUCCESSIVE DAYS