Reports from the Research Laboratories

of the

Department of Psychiatry

University of Minnesota

Susceptibility to Readdiction As a Function of the Addiction and Withdrawal Environment

by

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Report Number PR-64-2

August 27, 1964

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1. This research was supported in part by research grants MH-08670 and MH-8565 from U.S.P.H.S. to the University of Minnesota and by a General Research Support grant from the Medical Graduate Group Committee of the University of Minnesota to Dr. Thompson.

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Organisms which have become physically dependent upon opiate drugs can be returned to a relatively drug-free state by forced abstinence from the drug (Himmelsbach, 1942; Krueger, Eddy and Sumwalt, 1942-43; Seevers and Woods, 1953). Despite the disappearance of the physical symptoms which occur during the withdrawal period, the tendency to consume the drug is not equally diminished. This "psychic dependence"[2] upon drugs is thought by some writers to be responsible for the high rate of readdiction in human "post-addicts." While the factors controlling such behavioral dependence are unknown, experienced clinical investigators have suggested the importance of the environment in which the patient experiences withdrawal and the properties of the environment to which the "post-addict" returns (Wikler, 1953; Nyswander, 1956).

2. The term "psychic or psychogenic dependence," widely used in the clinical literature, is an unfortunate choice. Historically "psychic" phenomena have been unobservable, inscrutable and refractory to objective analysis. Despite this questionable status as a subject matter for scientific discourse, one must assume that the "psyche" is an extremely potent factor controlling drug dependence. The resulting dilemma can only be resolved by returning to the data itself--to the behavior of the dependent organism. To look to the elusive "psyche" for an answer which is clearly available in the behavior of the organism is the most damaging consequence of accepting the concept of "psychic dependence." A corollary of the notion of "psychic dependence" is the neglect of the analysis of the actual variables determining drug self-administration. Since the present analysis is focused at the level of the observable behavior of organisms and the dependence under consideration resides in the behavior of the experimental animals, it will henceforth be referred to as behavioral dependence.

Evidence accumulated over the past decade clearly indicates that infrahuman drug dependence created by self-administration comes about through a conditioning process comparable to the acquisition of behavior leading to food reinforcement or shock avoidance (Deneau, Yanagita and Seevers, personal communication; Nichols, Headlee and Coppock, 1956; Thompson and Schuster, 1964; Weeks, 1962; Wikler, Green, Smith and Pescor, 1960). The degree of similarity of drug-reinforced behavior to the more commonly studied appetitively and aversively maintained responses remains to be demonstrated. The present study analyzes the problem of readdiction as a special case of reacquisition, much as the re-conditioning of a food reinforced response has been explored.

Of the factors known to affect the rate of reacquisition of previously learned behavior, the similarity of the original learning situation to the reacquisition environment is extremely important. Perhaps equally important is the degree of similarity of the extinction environment to the environment in which reacquisition occurs[3]. It is known, for example, that behavior acquired in one environment is reacquired relatively slowly in a new environment as compared with reacquisition in the original environment. Conversely, behavior extinguished in the environment in which reacquisition occurs is relearned more slowly than behavior extinguished in a different environment. It would be predicted then, that animals which become addicted in a "home" environment and are readdicted in a different environment would readdict more slowly than those readdicted in their "home" environment. Further, animals readdicted in the same environment in which they were withdrawn will readdict slowly as compared with those readdicted in a different environment.

3. The addiction environment is considered to be the original acquisition environment, the withdrawal environment the extinction environment and the readdiction environment the reacquistion environment.

Subjects:

Forty male albino rats (mean weight 334 grams), 90-110 days old at the beginning of the experiment were subjects.

Method:

Apparatus: During the initial addiction period all of the rats were housed in the same general environment. The living cages were 9-1/2 by 7 by 7 inches (inside dimensions), with a hardware cloth floor and front wall and the side walls of galvanized steel. The rack of cages was centered in a small room with an independent temperature control maintaining room temperature at 70° F. and with a 100 watt incandescent bulb, approximately three feet overhead. The overhead light was present 24 hours per day, throughout the entire course of the experiment. All fluids were available in standard 250 ml rubber stoppered bottles equipped with stainless steel drinking tubes.

A second rack of cages was placed in an adjacent room for use in the withdrawal and readdiction phases of the experiment. These cages were of the same type as those described previously, however, the inside dimensions were 16-1/4 by 9-3/4 by 7 inches. The room temperature was maintained at 60° F. rather than 70° F. and white noise was continually present in the room. In addition, overhead illumination conditions alternated from 200 watts to 40 watts during successive five second periods. The same type of watering system was used as in the addiction phase of the experiment and feed was available at all times.

A 0.5 to 1.0 mg/cc morphine solution was used instead of standard drinking water in the addiction phase of the experiment, on the basis of findings of Nichols and co-workers (1956). The solution was prepared from morphine sulphate powder, U.S.P. by Merck and Co., and tap water.

Procedure: All rats went through a sixty-day addiction period in which the only drinking water available to them was the morphine solution (0.5 mg/cc for the first twelve days, then 1.0 mg/cc for the following 48 days). Prior to the first day on this schedule, the animals had been deprived of water for 24 hours. Of the original 48 animals started on this procedure, the eight animals ingesting the smallest volume of morphine solution at the end of the first week were dropped from the study, leaving the remaining 40 animals that were used throughout the remainder of the experiment.

During the addiction phase, bottles containing the morphine solution were placed on the cages at approximately the same time daily and measures of the volume consumed in the preceding 24 hour period were made using a 100 cc graduate cylinder (to the nearest cc).

During the second phase of the experiment, half of the animals experienced withdrawal in the same environment (S) in which addiction took place and half were transferred to the different environment (D). Assignment to the two environmental conditions was by rank ordering animals according to mean volume of morphine solution consumed on the last five days of addiction and randomly assigning one from each successive pair to the S or D withdrawal group. During withdrawal, the same bottles were placed on the cages, however, they contained tap water instead of morphine solution. The withdrawal procedure was continued for 30 days.

Following the 30 day period of abstinence the S and D groups were subdivided for readdiction. Assignment to groups was on the basis of mean volume of water consumed over the last five days, with one of each successive pair being assigned to a same (S) or different group (D). Thus, during the readdiction phase of the experiment, animals were subdivided into four groups on the basis of where

withdrawal and readdiction occurred, as follows: S-S-S, S-S-D, S-D-S, S-D-D. The following schedule was used during readdiction: five days of continual access to 1.0 mg/cc morphine solution, one day of tap water, one day of complete fluid deprivation, followed by a preference test. After the preference test the entire procedure was repeated. The primary measures used to assess the rate at which readdiction occurred were (1) the daily volume of morphine consumed during readdiction and (2) the preference test scores over the first three weeks. The preference test was based on a method developed by Headlee, Coppock and Nichols (1955) in which animals were deprived of morphine for 48 hours, then given an opportunity to consume morphine and/or tap water during a four hour test period. Animals that had become physically dependent consumed relatively larger quantities of morphine solution than animals that were not dependent. The relative tendency for the four groups to accept the bitter morphine solution was used as the second measure of susceptibility to readdiction.

Results:

The initial consumption of the morphine solution is presented in Figure 1, expressed in terms of mean daily intake in milligrams of morphine. The dosage was seen to rise gradually, reaching a peak at thirty days, followed by a slight decrease in intake. A stable level of consumption was maintained throughout the remainder of the addiction period.

Water consumption during the withdrawal period is presented in Figure 2. For both the S and D groups, volume of water consumed increased sharply for nine days, reaching a peak well above baseline level of water consumption prior to addiction (40.5 cc) or of morphine solution consumption (32.5 cc). It can also be seen that animals withdrawn in the same room in which addiction occurred, ingested larger volumes of water than those withdrawn in a different room. After

24 days, this difference appears to disappear.

During the readdiction period, two principal dependent variables were examined. The total daily intake of morphine in milligrams, and the relative preference for morphine during the four hour preference tests, were taken to be measures of susceptibility to readdiction. Figure 3 presents these data for the four groups (SSS, SSD, SDS and SDD). It can be seen that not only did the total volume of morphine consumed increase over the three week readdiction period, but the relative pre-preference for morphine as opposed to tap water increased as well. In comparing the four treatment groups, it is apparent that animals readdicted in the same environments that original addiction had taken place, readdicted significantly more rapidly than those readdicted in new environments. A further comparison of the four groups expressed in terms of a ratio of(water consumption - morphine consumed) ÷ (water consumption + morphine consumed) is presented in Figure 4. High positive ratios indicate preference for water, and negative or low positive ratios indicate relatively greater preference for the morphine solution. The null hypothesis that the initial preference scores were from the same population was rejected ($X^2 = 7.95$, $p < .05$). Animals experiencing readdiction in the same environments in which withdrawal occurred, tended to drink relatively smaller volumes of morphine solution than those withdrawn in a different environment.

Discussion:

The initial addiction data presented in Figure 1 suggests that oral addiction in the rat occurs in approximately 30 days, after which time a daily "maintenance" dose is established. This thirty-day addiction period is consistent with other data on rats (Beach, 1957; Nichols, 1960) and monkeys (Seevers, 1936). The stability of intake during the following 30 days suggests that little behavioral tolerance developed beyond the maintenace dose (approximately 100 mg/kg).

The increased water consumption during withdrawal can probably be attributed to at least two factors. Fluid loss during morphine withdrawal (e.g.,associated with diarrhea) is usually accompanied by increased fluid intake. In addition, the only way in which the withdrawal symptoms had been alleviated in the past was by ingestion of fluid available in the drinking tube. Hence, abstinence from the drug set the occasion for drinking. It was interesting that the environmental conditions in which withdrawal occurred also seemed to affect this tendency to ingest fluids. The fact that the Same (S) environment animals ingested more water than the Different (D) environment group should have been expected. The tendency to emit the learned drinking response in a different environment was diminished, as was anticipated in the introduction.

The readdiction data were consistent with the expectation that environmental similarities during addiction, withdrawal and readdiction were all of significance in determining the rate of readdiction. Two variables were examined: (1) a measure of relative "preference" or willingness to accept the rather bitter morphine solution and (2) the total intake of morphine in milligrams. It was noted that animals that had gone through withdrawal in a different environment from that in which they were being readdicted drank more morphine water than animals withdrawn and readdicted in the same environment.

Subsequent preference data revealed that animals readdicted in the same environment in which they were originally addicted had a greater "preference" for morphine water than were animals readdicted in a new environment. Both the data on total volume of morphine consumed and the relative consumption of morphine on preference days clearly indicate the significance of both the relationship of the withdrawal environment to the readdiction environment, and the original addiction environment to the readdiction environment. Hence, readdiction is more probable if the opportunity for readdiction is presented in a "home"

environment than a new environment and readdiction isalso more likely if withdrawal has taken place in unfamiliar surroundings with respect to the readdiction environment.

Conclusion:

These data are revealing in two respects. 1) They indicate that drug self-administration is subject to the control of the same environmental variables as other learned behavior. Positive transfer of training from the original learning situation (during addiction) maximizes the probability of readdiction, as would be expected. In addition, behavior weakened by extinction in one environment was less likely to recur in that same environment. 2) Moreover, these finding concur with the clinical observations that sending the "post-addict" home after withdrawal away from home is associated with a high recidivism rate. The parallel between the readdiction propensities of human and rat addicts is made all the more striking by the fact that comparable basic mechanisms seem to be operating in both cases. While such comparisons can be dangerously misleading, it is difficult to overlook the obvious similarities.

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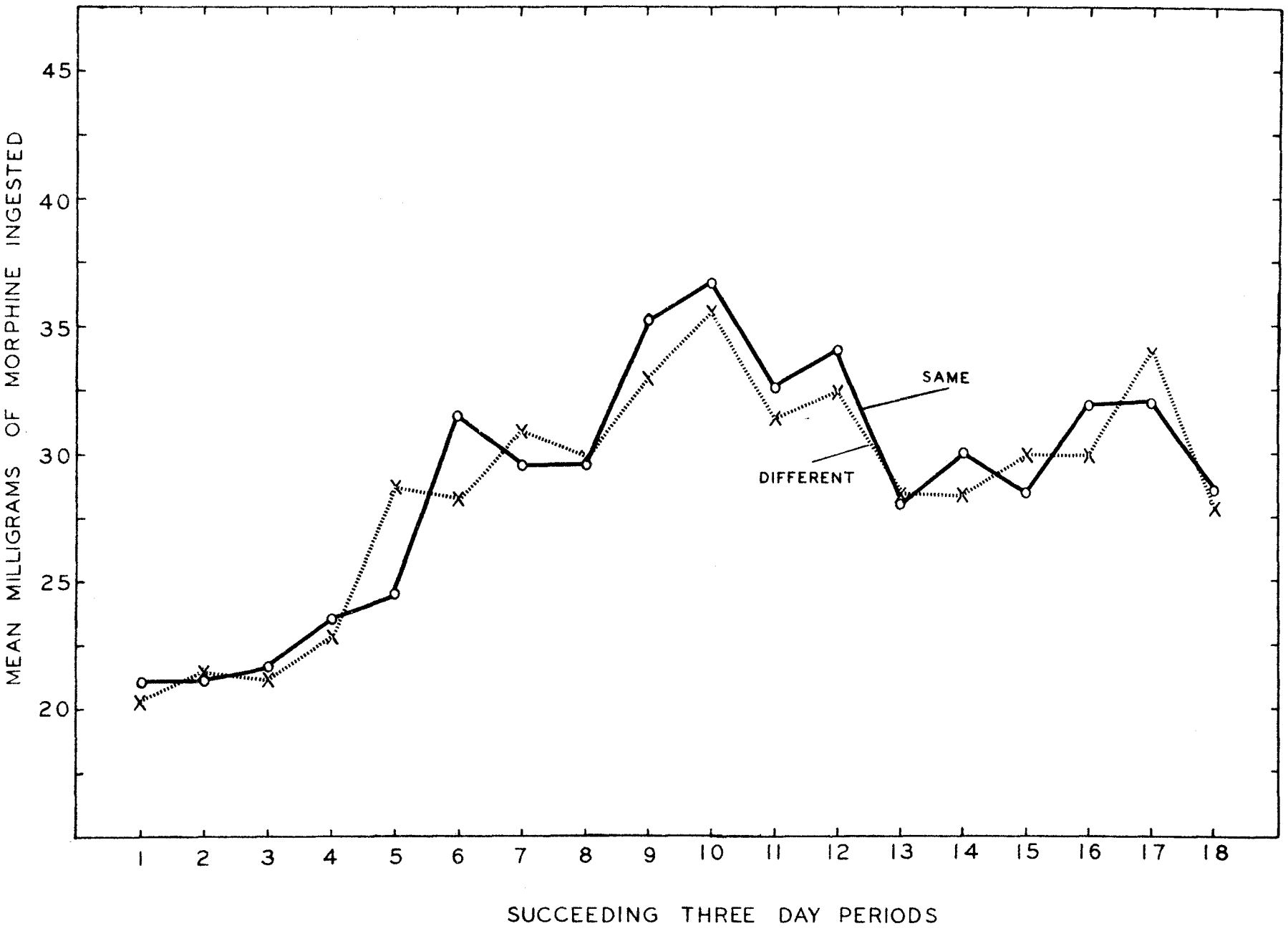
MEAN MILLIGRAMS OF MORPHINE INGESTED
45
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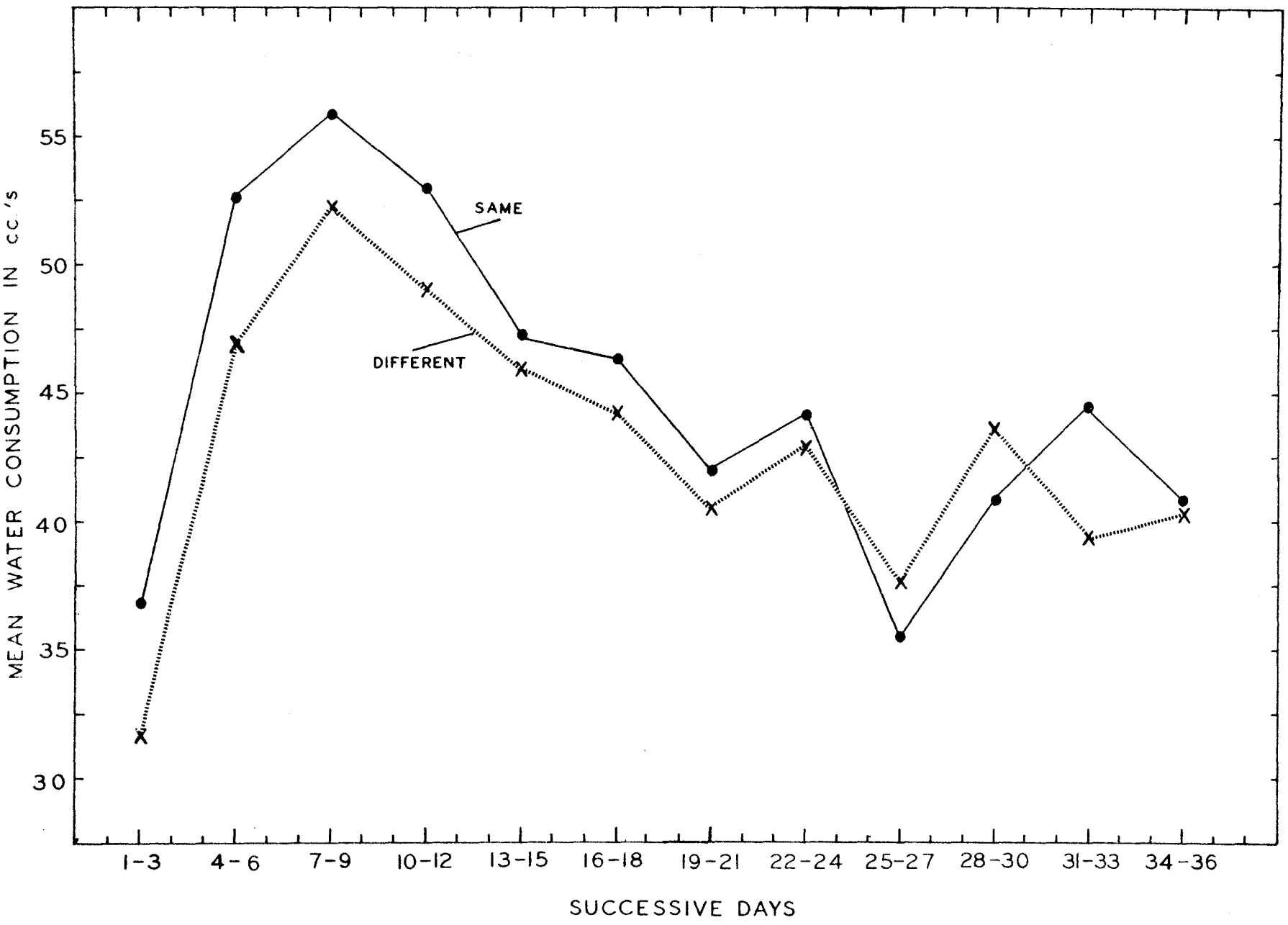
SUCCEEDING THREE DAY PERIODS


MEAN WATER CONSUMPTION IN cc's
55
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SAME
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1-3
4-6
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13-15
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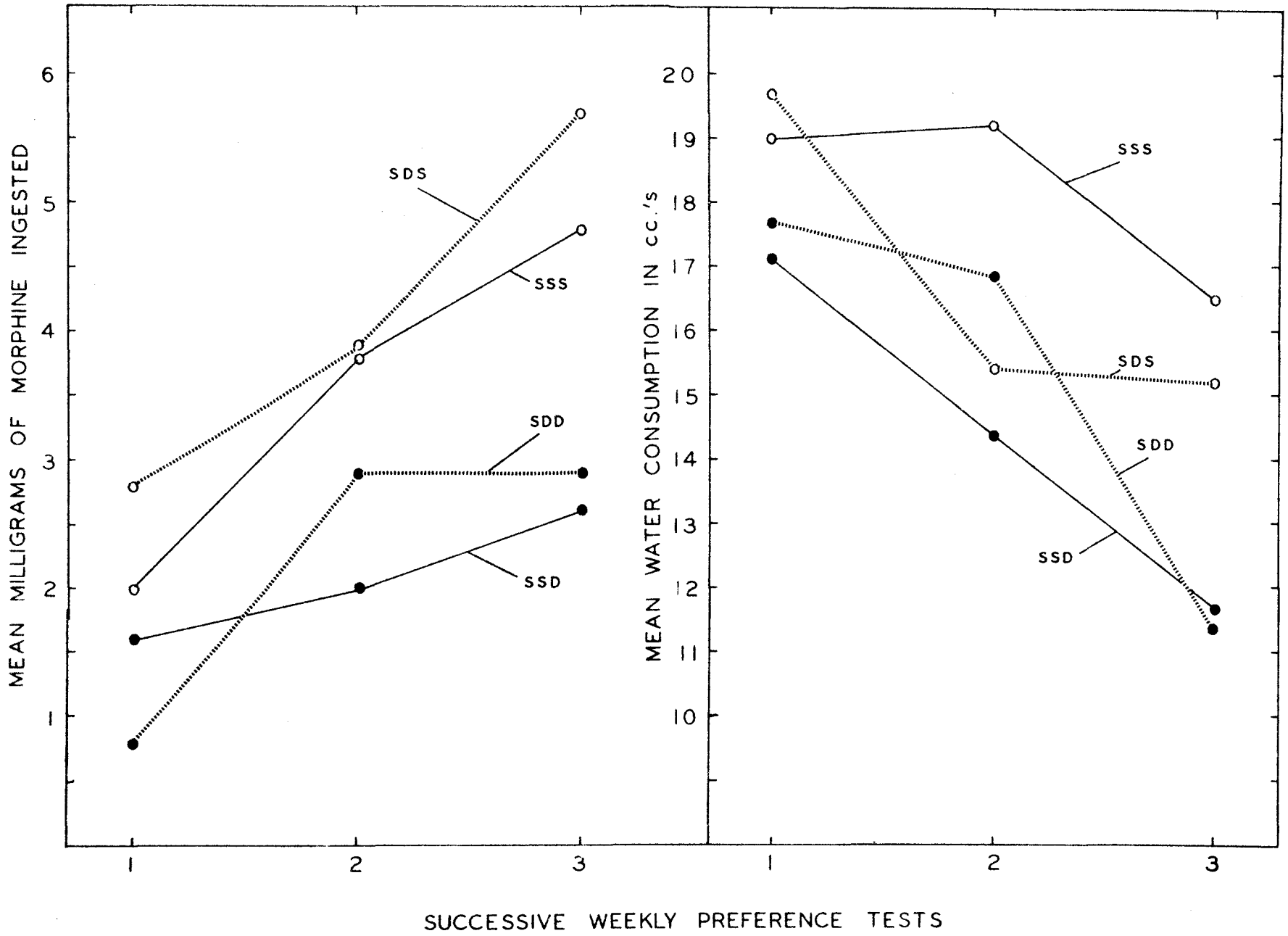
34-36
SUCCESSIVE DAYS


MEAN MILLIGRAMS OF MORPHINE INGESTED
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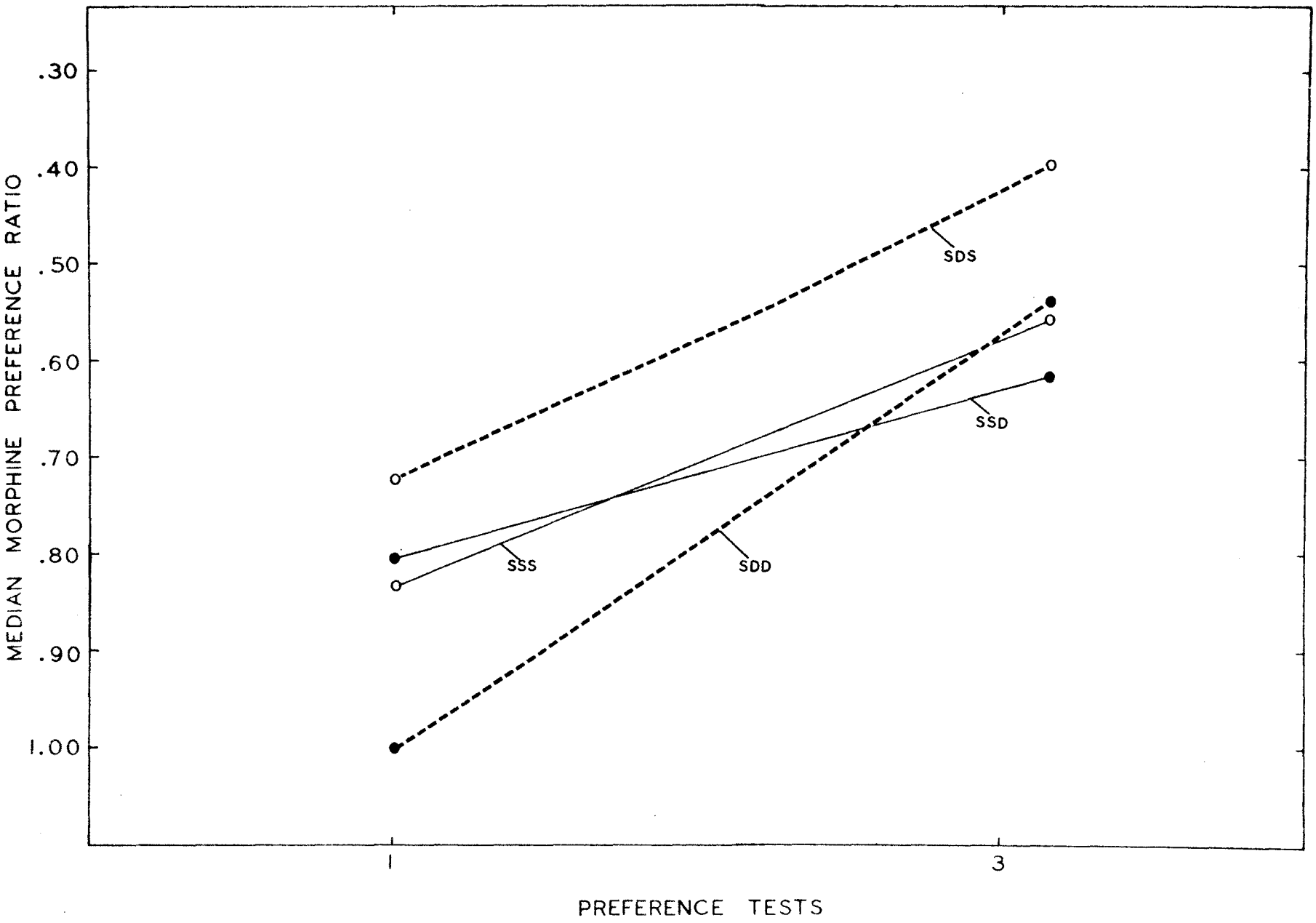
SUCCESSIVE WEEKLY PREFERENCE TESTS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MEDIAN MORPHINE PREFERENCE RATIO
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1
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PREFERENCE TESTS