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## Morphine Tolerance Acquisition as an Associative Process

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The results of several experiments supported the proposal that morphine analgesic tolerance is a manifestation of an association between the drug administration ritual and the systemic effects of the drug: (a) Presenting environmental cues previously associated with morphine, but without the drug, attenuated established tolerance (i.e., morphine tolerance can be extinguished), (b) repeated presentations of the morphine administration procedure, prior to its pairing with the opiate, retarded the acquisition of tolerance (i.e., morphine tolerance is subject to "latent inhibition"), and (c) placebo sessions interspersed between morphine sessions deleteriously affected the development of tolerance (i.e., morphine tolerance is subject to the decremental effects of partial reinforcement). These findings appear inexplicable by most traditional theories of tolerance, which do not emphasize the role of drug-associated environmental cues in the development of tolerance. Additionally, it is suggested that the conditioning analysis of tolerance is congenial with a current view of habituation, and there may be a similar associative basis for the response decrement to both endogenous and exogenous iterative stimulation.

Tolerance refers to the decreased responsiveness to a drug over the course of successive administrations; for example, although morphine has a pronounced analgesic effect the first time it is administered, the level of analgesia decreases with subsequent experi-

ence with the opiate. Many interpretations of opiate analgesic tolerance have been proposed, and most postulate some physiological change within the organism as a result of the initial drug stimulation which either prevents the drug from gaining access to opiate receptors in the brain (e.g., Cochin, 1971; Mulé & Woods, 1969) or functionally decreases the sensitivity or population of central receptors for the drug (e.g., Collier, 1965; Snyder & Matthysse, 1975).

An alternative approach to tolerance has viewed the modification of a drug's effects as a function of successive experiences with the drug as an associative process. Cohen, Keats, Krivoy, and Ungar (1965) suggested that morphine tolerance may be a form of learning, since metabolic inhibitors impair the acquisition of tolerance, much as

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they interfere with the acquisition of certain learned responses. I have recently elaborated a conditioning model of opiate tolerance that emphasizes the suggestion of Pavlov (1927, pp. 35ff) that the administration of a drug almost always constitutes a classical conditioning trial, the conditional stimulus (CS) consisting of those administration procedures or rituals reliably signaling the effects of the drug, with the unconditional stimulus (UCS) consisting of the actual chemical stimulation (Siegel, 1975b). The development of the association between environmental cues present at the time of drug administration and the systemic effects of that drug is typically revealed on a test trial by presenting the usual drug administration cues but actually administering a placebo (for a review of pharmacological conditioning, see Siegel, in press). However, as suggested by Bykov (1959, pp. 82-83), conditional drug responses evidenced in anticipation of the actual pharmacological assault should be expected to interact with the drug-induced unconditional response (UCR), and thus pharmacological learning may be evidenced by the modulation of the unconditional effects of the drug over the course of successive administrations.

A frequent finding is that pharmacological conditioned responses (CRs) are opposite in direction to the UCRs of the drugs upon which they are based. Thus, if blood sugar level is repeatedly increased by administrations of epinephrine or glucose, the administration procedure not followed by the hyperglycemic agent leads to a decrease in blood sugar (Deutsch, 1974; Mityushov, 1954; Russek & Piña, 1962); on the other hand, if blood sugar level is repeatedly decreased by injections of insulin, injection of a placebo leads to a hyperglycemic response<sup>1</sup> (Siegel, 1972a, 1975a). In subjects with a history of histamine administration, with its ensuing hypothermia, administration of a placebo leads to a hyperthermic response (Obál, Vicsay, & Madarász, 1965); conversely, if body temperature is repeatedly elevated by injections of dinitrophenol, injection of a placebo causes hypothermia (Obál, 1966). Other examples of

such compensatory pharmacological CRs are the bradycardia evidenced by dogs in anticipation of epinephrine with its tachycardiac effects (Subkov & Zilov, 1937), the hypersalivation displayed by animals with a history of administration of a variety of antisialagogues (Korol, Sletten, & Brown, 1966; Lang, Brown, Gershon, & Korol, 1966; Mulinos & Lieb, 1929; Wikler, 1948), and the decreased oxygen consumption seen in response to a placebo in subjects previously injected with either dinitrophenol or amphetamine, both of which unconditionally increase oxygen consumption (Obál, 1966).

Of special relevance to the role of drug CRs in morphine analgesic tolerance is the finding that rats with a history of morphine administration, each administration having less and less of an analgesic effect, display heightened sensitivity to nociceptive stimulation when confronted with the usual drug administration ritual but actually injected with a placebo (Siegel, 1975b, Experiments 2A and 2B). Thus, in anticipation of morphine and its analgesic consequences, rats become hyperalgesic, and, according to the conditioning model of tolerance, it is this compensatory CR summing with the opiate's UCR of analgesia that is responsible for the net decrease in the analgesic effect of morphine over the course of successive administrations.

A unique prediction of this conditioning account of opiate analgesic tolerance is that tolerance should be subject to the decremental effects of extinction. That is, if morphine tolerance occurs because environmental cues signaling the central effects of the drug elicit a compensatory CR, acting to cancel the effect of the drug, presenting these environmental procedures unaccompanied by the central effects of the narcotic to the tolerant organism should extinguish these learned responses and morphine tolerance. This prediction of the conditioning analysis

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<sup>1</sup> Although the CR to physiological doses of insulin appears to be a compensatory hyperglycemic response, conflicting findings have been reported when the UCS consists of very large doses of the hormone (see Siegel, 1975a, Note 1).

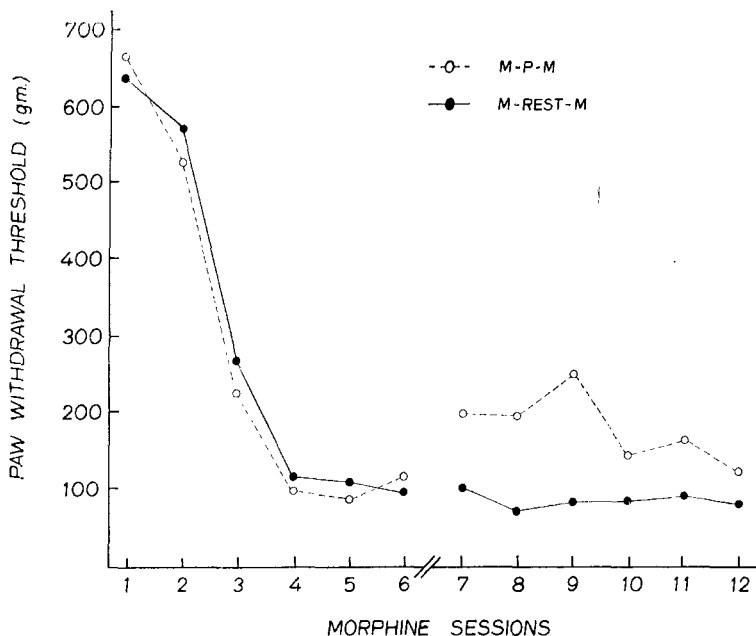


Figure 1. Mean analgesiometer paw-withdrawal thresholds after each of 12 daily morphine injections for groups receiving either 12 placebo sessions (Group M-P-M) or a 12-day rest interval (M-REST-M) interpolated between Morphine Session 6 and Morphine Session 7 (Experiment 1).

of tolerance was recently confirmed (Siegel, 1975b, Experiment 3): Using the standard "hot plate" analgesia-assessment situation (Fennessy & Lee, 1975), in which pain sensitivity in the rat is determined by observing its latency to lick a paw placed on a warm surface, I found that placebo sessions attenuated established tolerance.

### Experiment 1

Inasmuch as no nonassociative interpretation of tolerance would predict that tolerance should be subject to extinction, it was thought desirable to assess the reliability of the earlier confirmation of this prediction of the conditioning model of morphine analgesic tolerance with a different analgesia-assessment situation.

### Method

*Subjects and apparatus.* The subjects, 23 experimentally naive male 90-110-day-old, Wistar-derived rats (obtained from Canadian Breeding Farms, St. Constant, Quebec, Canada), were

housed in individual cages with food and water freely available.

Analgesia level was assessed with a commercially available version of the paw-pressure analgesiometer described by Randall and Selitto (1957), manufactured by Ugo Basile Apparatus and available from the Stoelting Company, Chicago, Illinois. The analgesiometer is designed to automatically increase, at a constant rate, the pressure applied to a rat's paw, with the rat free to withdraw its paw from the source of pressure at any time. The amount of pressure applied before the withdrawal response occurs provides a measure of that subject's pain sensitivity.

I had previously determined that placing a hood over a rat's head immediately prior to analgesia assessment minimized excess activity and decreased variability in response to paw-pressure application; therefore, just before each withdrawal determination, a cotton glove was loosely fitted over the rat's head and shoulders.<sup>2</sup> The subject was then manually held in a vertical position with its left hind paw placed between a blunt Teflon stylus and platform, with the apparatus counterbalanced such that no pressure was applied to the paw. Pressure on the stylus was then automatically increased, initially at a rate of 16 g/sec, until either

<sup>2</sup> I am grateful to Michael Leon who suggested this procedure.

the rat withdrew its paw (with the amount of pressure applied at the time of withdrawal constituting that subject's threshold for that session) or a maximum of 250 g of pressure was reached. In those cases in which the rat did not respond to the 250-g maximum pressure, the gain of the apparatus was doubled and the determination was repeated for that subject (i.e., the pressure was increased at a rate of 32 g/sec, again starting at 0 g but reaching a potential maximum of 500 g). If necessary, this procedure was repeated with gain settings increased by factors of 3 and 4 until a maximum of 1,000 g was applied to the rat's paw. If the withdrawal response did not occur to 1,000 g of pressure, a threshold value of 1,000 g was assigned to that subject for that session. Although a minority of subjects did not respond prior to the application of this highest level of pressure during the first one or two assessments while they were narcotized, they all responded well within the measurement limits of the analgesiometer by the third session.

*Procedure.* Two groups of rats received equivalent morphine injections followed by analgesia assessment for 12 sessions. For each session, subjects were transported in their home cages from the colony room to a different room (in which a constant background white noise at 60 dB [SPL] was maintained), subcutaneously injected with a 5 mg/kg dose of morphine sulfate (5 mg/ml solution), and .5 hr. later, analgesia level was assessed. Sessions were conducted daily with the exception of the protracted interval between Morphine Sessions 6 and 7, which was 12 days. The groups differed only with respect to their treatment during this 12-day period. Subjects in one group were simply left undisturbed in their home cages (Group M-REST-M). Subjects in the second group received daily placebo test sessions, that is, they were treated in the same manner as on morphine sessions except the injected substance was 1 ml/kg physiological saline rather than the opiate (Group M-P-M). Initially, 12 rats were assigned to each group, but one subject in Group M-REST-M died during the course of the experiment and its data are excluded.

## Results

The mean paw-withdrawal thresholds of both groups on each occasion that they received morphine are shown in Figure 1. As is apparent in Figure 1 (confirmed by a mixed-design analysis of variance), the two groups did not differ over the course of the first six morphine sessions, both groups displaying analgesic tolerance, that is, decreasing paw-withdrawal thresholds as a function of repeated morphine injections.<sup>3</sup> As can also be seen in Figure 1, the interpolated

treatment affected the analgesic property of the drug during the second series of morphine injections. Although Group M-REST-M rats continued to evidence the relatively low paw-withdrawal threshold responses indicative of analgesic tolerance, Group M-P-M rats evidenced relatively high withdrawal thresholds. Statistical analysis of Morphine Sessions 7-12 indicated that the difference between the two groups was significant,  $F(1, 21) = 12.8, p < .002$ .

## Discussion

During the first six morphine sessions, the rats in both groups were treated identically and evidenced equivalent analgesic tolerance acquisition functions. Thus, prior to the second series of morphine injections, both groups suffered the systemic effects of the drug equally as often, at the same intervals, and with the same analgesic effect. According to the systemic theories of tolerance, both groups should display equal tolerance when again injected with the drug. However, merely by presenting the morphine administration ritual unaccompanied by the central effects of the opiate to Group M-P-M, tolerance subsequently observed in this group was substantially attenuated. Such attenuation of tolerance was not due simply to the 12-day delay before the second morphine series, since this delay did not

<sup>3</sup> Analgesic tolerance is inferred from a trend of decreasing paw-withdrawal thresholds as a function of repeated morphine administrations. Such a trend may be subject to an alternative interpretation: The successively decreasing paw-withdrawal thresholds could be attributable to the subjects' increasing proficiency in performing the possibly pain-ameliorating paw-withdrawal response while drugged, rather than to any functional decrease in the analgesic property of the narcotic. However, it was previously demonstrated that practice in making this response is irrelevant to the display of morphine tolerance with the paw-pressure analgesiometer; that is, rats evidence similar, low-threshold responses indicative of tolerance following a series of morphine administrations and encounters with the analgesiometer whether or not the apparatus is functional (i.e., pressure is actually applied to the paw) prior to the last injection in the series (Siegel, 1976).

affect the tolerance of Group M-REST-M, which did not experience the administration ritual during this interval (in agreement with other reports that, with assessment techniques other than the paw-pressure analgesiometer, morphine tolerance dissipates little with the passage of time; see Cochin & Kornetsky, 1964; Kayan & Mitchell, 1972).

This demonstration of the extinguishability of morphine tolerance, as assessed with the paw-pressure analgesiometer, confirms the previous report in which analgesia was assessed with the hot plate technique (Siegel, 1975b, Experiment 3). These findings are in agreement with the conditioning interpretation of tolerance and not readily interpretable by most other theories of tolerance, which emphasize only the effects of the chemical stimulation and ignore the importance of cues that are present at the time of such stimulation.

### Experiment 2

The previous experiment, like the earlier demonstration of the extinguishability of morphine analgesic tolerance (Siegel, 1975b, Experiment 3), indicated that presentations of the morphine administration procedure to morphine-tolerant rats deleteriously affect the display of tolerance. In both experiments an effort was made to make the placebo-initiated extinction sessions as similar as possible to the drug administration sessions, including the application of nociceptive stimulation. Thus, only the group subjected to extinction (Group M-P-M) had any pressure stimulation and experience in making the paw-withdrawal response while not drugged. The purpose of Experiment 2 was to assess whether extinction is an effective procedure for attenuating established tolerance even if subjects do not practice the paw-withdrawal response during the extinction sessions.

Inasmuch as only a single experience with morphine is sufficient to substantially reduce the analgesic effect of a second administration (Ferguson, Adams, & Mitchell, 1969; Kornetsky & Bain, 1968), the present experiment investigated the effects of

extinction on such single-dose tolerance. In addition, in Experiment 1 the analgesic effect of each administration of the opiate was assessed on only a single occasion, .5 hr. after injection. In the present experiment the time course of the opiate-induced analgesia was investigated.

### Method

Each of 24 experimentally naive rats (of the same age, sex, and strain as those used in the previous experiment) was transported to the room containing the analgesia-assessment apparatus and subcutaneously injected with 5 mg/kg morphine; pressure sensitivity was determined with the paw-pressure analgesiometer in the manner described in Experiment 1. In contrast with the previous experiment, analgesia level was determined for all subjects on five occasions: 15, 30, 45, 60, and 90 min. subsequent to the morphine injection. All subjects received a second such morphine-analgesia-assessment session 5 days later. Half the rats were left undisturbed in their home cages during the intervening 4-day period (Group M-REST-M), and half received four daily placebo sessions but without analgesia measurement (Group M-P-M). On these placebo sessions, Group M-P-M subjects were positioned in the analgesiometer for 16 sec after each of the five intervals following injection of physiological saline, with the analgesiometer motor operated so as to make the same noise as it did during threshold determination, but an assembly was disengaged such that no pressure was applied to the paw. Thus, prior to the second morphine session both groups had but a single experience with opiate stimulation and paw-pressure threshold determination.

### Results and Discussion

The mean paw-withdrawal thresholds for both groups at each of the postinjection assessment intervals for both morphine days are shown in Figure 2. As would be expected, when both groups first received the drug, prior to any differential treatment, their time-response curves were similar. Statistical analyses confirmed that the two groups did not differ significantly at any of the five postinjection intervals on this first day. However, when they received their second injection of morphine, Group M-P-M subjects, which had interpolated experience with the administration ritual (but no additional nociceptive stimulation), evidenced a pattern of analgesia different from that of

Group M-rest-M subjects. A mixed-design analysis of variance of the Morphine Day 2 time-response functions indicated a significant Groups  $\times$  Time Since Injection interaction,  $F(4, 88) = 2.52$ ,  $p < .05$ . Subsequent pair-wise comparisons indicated that 45 min. after this second morphine administration, Group M-p-M was significantly less sensitive to the paw-pressure stimulation than was Group M-rest-M,  $t(22) = 3.77$ ,  $p < .02$ , two-tailed. The differences between the two groups were not statistically significant at any other postinjection assessment interval on Morphine Day 2.

In general, drug tolerance is evidenced not only by a decreased responsivity to a drug but also by a movement in the peak effect of the drug closer to the time of administration (e.g., Gunne, 1960). As can be seen in Figure 2, when receiving the drug for the second time, Group M-rest-M rats not only responded less than Group M-p-M rats but their peak analgesic response occurred sooner. For the purpose of substantiating the earlier peak responsiveness of Group M-rest-M rats following the

second morphine administration, the post-injection time in which each subject evidenced its maximum level of analgesia was noted. All 24 subjects evidenced their maximum analgesic response during one of the first four 15-min. intervals. Nine of the 12 Group M-rest-M animals evidenced their maximum analgesia within the first two intervals (i.e., 15 or 30 min. after the injection), but only 4 of the 12 Group M-p-M subjects evidenced their maximum analgesia during this time. The difference in frequency of attainment of maximum analgesia in the two groups in each of the two successive half-hour periods after this second morphine injection was statistically significant ( $p < .05$ , Fisher exact probability test).

When rats are injected with morphine on a single occasion, subsequent presentations of the drug administration procedure in the absence of pharmacological stimulation decrease the magnitude of tolerance obtained when the drug is administered on a second occasion. Thus, Experiment 2, like Experiment 1, provides a demonstration that morphine tolerance is subject to extinction, sup-

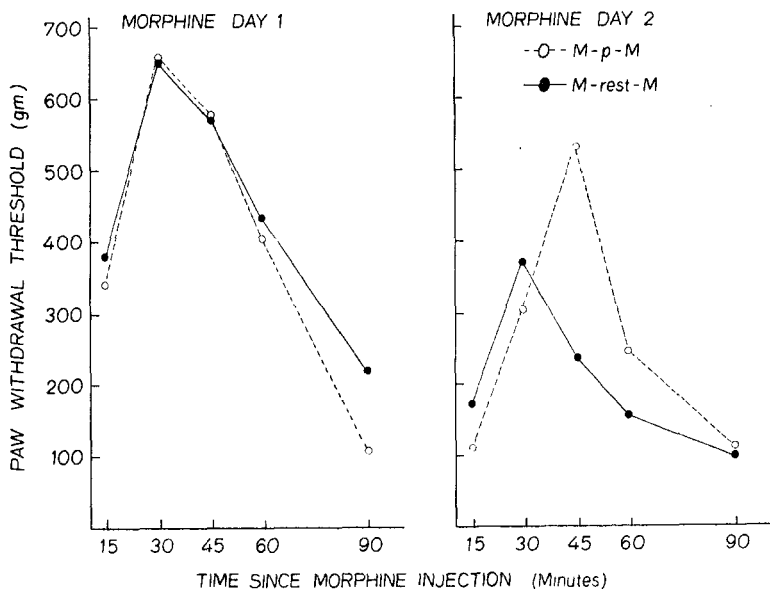


Figure 2. Time course of the mean paw-withdrawal threshold modification on each of two morphine days for groups receiving either a 4-day rest interval (Group M-rest-M) or four placebo sessions with a nonfunctional analgesiometer (Group M-p-M) interpolated between the morphine days (Experiment 2).

porting the conditioning analysis of tolerance. Additionally, the results of Experiment 2 indicate that such extinction of morphine tolerance is not attributable to any additional practice that extinguished subjects have in responding to the aversive stimulation used to evaluate the effect of the drug, since such additional practice did not occur in the present experiment.

### Experiment 3

The results of Experiments 1 and 2 demonstrated that one procedure that is effective in decrementally affecting established CRs, extinction, is also effective in attenuating established analgesic tolerance, thus supporting the conditioning analysis of tolerance. If tolerance is a manifestation of a conditioning process, it would be further expected that manipulations of the putative CS (i.e., environmental cues present at the time of drug administration) known to be effective in retarding CR acquisition would similarly retard the acquisition of morphine analgesic tolerance. One such procedure that is effective in retarding the acquisition of CRs is preconditioning exposure to the CS.

It has been reported that in many conditioning preparations, with both human and a variety of infrahuman subjects, presentations of the CS prior to the start of acquisition serve to decrease the effectiveness of that CS when it is subsequently paired with a UCS during conditioning. The deleterious effect of CS preexposure has been termed *latent inhibition* (Lubow & Moore, 1959), and reviews of the extensive literature on latent inhibition can be found elsewhere (Cantor, 1969; Lubow, 1973; Siegel, 1972b; Weiss & Brown, 1974). Although there is some controversy concerning the mechanism of latent inhibition (e.g., see Reiss & Wagner, 1972), the theoretical interpretation of the phenomenon is irrelevant for its exploitation as a technique to assess the conditioning theory of morphine tolerance. According to this theory, inasmuch as tolerance reflects an association between the predrug environmental CS and the pharmacological UCS, the course of tolerance

acquisition should be affected by the relative novelty of environmental cues present at the time of drug administration. Thus, animals with extensive experience with the administration ritual before its actual pairing with morphine should be relatively retarded in the acquisition of tolerance, compared with animals with minimal prior experience with these environmental cues, despite the fact that both groups suffer the systemic effects of the same dose of the opiate, given the same number of times and at the same intervals.

### Method

*Subjects and apparatus.* The subjects were 24 experimentally naive male rats of the same strain, sex, and age as those used in the previous experiments. In the present experiment, responsivity to pain was assessed with the hot plate technique (Fennessy & Lee, 1975). Briefly, a copper plate (30 × 16 × .6 cm) was completely submerged in a constant-temperature water bath (Narco Model 210) maintained at 54.2° C. A 12.5-cm-inner diameter, upright, clear Plexiglas cylinder was affixed with a watertight seal in the center of the copper plate, isolating a dry circular surface on the plate on which to confine the rat and assess its responsivity to heat. Thermistors in the water bath and imbedded in the plate were used to constantly monitor the temperature of the bath and copper plate.

Pain sensitivity was assessed by placing the rat on the testing surface for 30 sec and noting the number of seconds that elapsed before the rat responded. As is usual with this procedure, two types of heat-elicited responses were recorded—jumping and paw licking, with the latency of the first of these two responses constituting that subject's response latency for that session (e.g., Adams, Yeh, Woods, & Mitchell, 1969). In fact, about 88% of the 396 hot plate responses recorded in this experiment were paw licks.

Each rat remained on the testing surface for the full 30 sec, regardless of its response latency. If a subject did not respond to the heat stimulation prior to the end of this test interval, the test was nevertheless terminated (to avoid tissue damage), and that subject was assigned a response latency of 30 sec for that session. In fact, 8 of the 24 subjects in this experiment (equally distributed between groups) did not respond within the maximum interval during their first responsivity assessment after morphine administration, but all subjects evidenced response latencies shorter than 30 sec on all other sessions.

*Procedure.* The experiment consisted of 25 daily .5-hr. sessions. The first 18 sessions constituted the

preexposure phase, and the 7 remaining sessions constituted the tolerance acquisition phase. One group received 18 preexposures to the cues that would subsequently signal the effects of the drug (Group 18P). For each preexposure session, subjects in this group were transported to the same distinctive room used for testing in Experiments 1 and 2, subcutaneously injected with 1 ml/kg physiological saline and, .5 hr. later, placed on the hot plate apparatus. The second group received only one preexposure (Group 1P). Subjects in this group were left undisturbed in their home cages for the first 17 days, and they received their single preexposure on the same day the subjects in Group 18P received their last preexposure.

All subjects were treated in the same manner during the tolerance acquisition sessions (Days 19-25), which were conducted like the preexposure sessions except 5 mg/kg morphine sulfate, rather than physiological saline, was injected.

The experiment was conducted in two identical replications, with six subjects in each group being run in each replication.

### Results and Discussion

*Preexposure phase.* Figure 3 presents the mean response latency on the hot plate following each physiological saline injection during the preexposure phase for Group 18P and the single preexposure response la-3, the response latency of Group 18P tended to decrease over the course of preexposure sessions, this trend being most clearly substantiated by the significant difference between the first and the last preexposure session latencies of subjects in this group,  $F(1, 10) = 8.77, p < .02$ . Indeed, only 1 of the 12 subjects in Group 18P responded more slowly on the last preexposure session than on the first session ( $p < .002$ , sign test, excluding data from two subjects with identical scores on the first and last preexposure sessions).

Comparison of Groups 18P and 1P performances during preexposure provides additional evidence that experience in responding on the hot plate leads to shorter response latencies. The mean latency of the group receiving only a single preexposure session, although not differing significantly from the mean latency of Group 18P in the first preexposure session, was significantly longer than the last preexposure session latency displayed by the extensively preexposed group,  $F(1, 20) = 7.54, p < .02$ . It seems

clear that extensive practice with the hot plate situation leads to decreasing latencies in making the indicant response.

It should be noted that the conditioning theory of tolerance suggests that the group with the greater experience with cues that will signal morphine prior to the pairing of these cues with the drug should be slower in the acquisition of tolerance (i.e., over the course of morphine sessions, Group 18P should be more retarded than Group 1P in the development of the short-latency responding indicative of analgesic tolerance). Thus, greater proficiency in hot plate responding acquired during preexposure by Group 18P would, during subsequent morphine sessions, act in a manner contrary to the effect predicted by the conditioning analysis of morphine analgesic tolerance.

*Tolerance acquisition phase.* The mean response latency on the hot plate for both groups after morphine injection is shown in Figure 4. Examination of Figure 4 reveals that both groups evidenced similar, high response latencies following the first administration of the drug. Response latencies rapidly decreased on subsequent drug sessions, with the decrease being greater for Group 1P than for Group 18P. The high response latency of Morphine Session 1 is a manifestation of the initial analgesic effect of the narcotic. Every subject evidenced a longer response latency on this session than it did after the placebo injection on the immediately preceding preexposure session. The similarity between the two groups in responsivity to the heat stimulation in Morphine Session 1 is not readily attributable to a ceiling effect; disregarding the four subjects in each group that did not respond within the 30-sec limit of the test, the means for Groups 18P and 1P are 17.1 and 16.1 sec, respectively (this difference does not approach statistical significance).

The more rapid decrease in the response latency of Group 1P than that of Group 18P was confirmed by a mixed-design analysis of variance, which indicated that the response latency of both groups decreased across tolerance acquisition sessions,  $F(6, 120) = 24.3, p < .001$ , with the difference



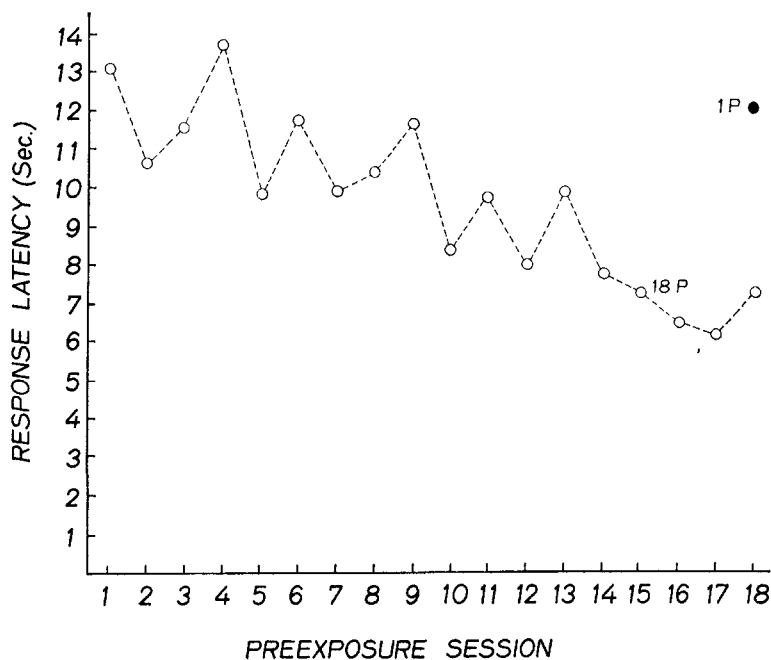


Figure 3. Mean response latency on the hot plate during preexposure following each of the 18 saline injections for Group 18P and the single preexposure injection for Group 1P (Experiment 3).

between the two preexposure conditions being statistically significant,  $F(1, 20) = 6.25$ ,  $p = .02$ .

Virtually all the tolerance observed in this experiment occurred following the first morphine injection (Figure 4). Such profound single-dose tolerance has previously been observed with the hot plate procedure and the parameters used in this experiment (a 5 mg/kg dose of morphine, with an inter-injection interval of 24 hr. and an injection-assessment interval of 30 min.), both in my laboratory (Siegel, 1975b, Experiment 1A) and elsewhere (Kayam & Mitchell, 1972, Experiment 2).

On the basis of any of the systemic theories of tolerance, it might be expected that Groups 1P and 18P should become equally tolerant to the analgesic effect of morphine. The two groups displayed equivalent levels of analgesia the first time they received the drug, and both groups had equivalent experience with the systemic effects of the drug. Indeed, it might be expected that Group 18P subjects should acquire the

short-latency hot plate responding indicative of analgesic tolerance more quickly than Group 1P subjects, since the more extensively preexposed subjects had more practice in making this response and, prior to the start of drug sessions, performed it more rapidly than did Group 1P subjects. Nevertheless, tolerance was more marked in Group 1P than in Group 18P. This finding that predrug experience with the administration procedure retards the acquisition of tolerance (i.e., that tolerance is subject to latent inhibition) supports a unique prediction of the conditioning model of tolerance, and it is not explicable by other theories of tolerance which do not emphasize the role of drug-associated environmental cues in the development of tolerance.

#### Experiment 4

The results of Experiment 3 indicated that one procedure (CS preexposure) that is effective in retarding CR acquisition is also effective in retarding the development

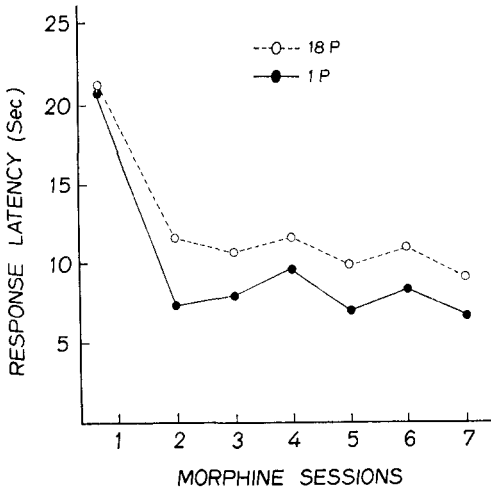


Figure 4. Mean response latency on the hot plate following each of seven morphine injections for groups receiving either 18 preexposures (18P) or 1 preexposure (1P) to the drug administration procedure prior to morphine administration (Experiment 3).

of morphine tolerance. The present experiment was designed to assess the effectiveness of a second procedure that has a deleterious effect on CR formation in retarding tolerance acquisition—partial reinforcement. If the UCS is paired with the CS on less than 100% of the trials, CR acquisition is generally poor, relative to a condition in which every CS is paired with the UCS (e.g., Beecroft, 1966, pp. 126–129; Wagner, Siegel, Thomas, & Ellison, 1964). Although most studies of partial reinforcement effects in classical conditioning have compared 100% to 50% reinforcement schedules, there is evidence that acquisition rate declines as the percentage of reinforced CSs decreases, even when the number of reinforced trials is equated in the various reinforcement schedule conditions (i.e., all reinforcement schedule groups receive the same number of CS–UCS pairings, with partially reinforced groups receiving the appropriate number of additional CS-alone trials; Hartman & Grant, 1960).

The implication of this partial reinforcement literature for the conditioning approach to morphine tolerance is clear: A partial reinforcement group (receiving many

presentations of the drug administration procedure, not followed by the systemic effects of the drug, interpolated between regular drug administrations) should display slower tolerance acquisition than a continuous reinforcement group (receiving the drug in conjunction with all presentations of the predrug cues), even when the two groups are equated with respect to all pharmacological parameters.

#### Method

Two groups, each containing six experimentally naive rats of the same strain, sex, and age as those used in the previous experiments, were each given a total of six morphine-analgesia-assessment sessions on the hot plate. The administration and assessment procedures were the same as those used in Experiment 3 except that rather than a daily drug administration, the six morphine sessions were spread over a period of 24 days. The durations of the five intervals interpolated between these six morphine sessions were 3, 4, 4, 3, and 4 days, respectively. One group of rats was continuously reinforced (Group CRF); on the days when these rats did not receive the drug, they were left undisturbed in their home cages. The second group was partially reinforced on a 25% schedule (Group PRF). Subjects in Group PRF received the drug on the same days as Group CRF subjects, but on each of the 18 days between drug administrations, they received placebo sessions; that is, they were treated in the same manner as on morphine sessions except that the substance injected was physiological saline rather than morphine.

#### Results and Discussion

The mean response latency of each group for each morphine session is shown in Figure 5. As was the case with the previous experiment, the group with more practice with the analgesia-assessment situation (Group PRF), which might be expected to have acquired greater proficiency in making the analgesia-indicant response, was nevertheless slower to respond to the thermal stimulation over the course of morphine sessions than was the group that had less practice with the assessment situation (Group CRF) but never had experience with administration cues not presented in conjunction with the systemic effects of the drug. A mixed-design analysis of variance of the

data summarized in Figure 5 indicated that the analgesic effect of morphine became less and less pronounced with successive experiences with the drug,  $F(5, 50) = 43.1$ ,  $p < .001$ , but this tolerance was greater in Group CRF than in Group PRF,  $F(1, 10) = 7.25$ ,  $p < .03$ .

As in the previous experiments, groups with equivalent experience with the systemic effects of morphine were not equivalent in their acquisition of tolerance to the analgesic effects of the opiate. Partial reinforcement retarded the development of morphine tolerance, as it does in the more traditional types of conditioning. Again, the results are expected on the basis of the conditioning theory of tolerance but not of the alternative formulations.

### General Discussion

With few exceptions (e.g., Adams et al., 1969; Cohen et al., 1965; Kayan, Woods, & Mitchell, 1969), decreased responsivity to a drug as a function of successive experiences with the drug has been considered a wholly pharmacological process. However, the experiments reported here, together with previous research from this laboratory (Siegel, 1975b, 1976), demonstrate the utility of an approach to tolerance which emphasizes the associative features of the usual drug administration procedure. If tolerance depended merely on systemic modifications elicited by repeated pharmacological stimulation, it would not be expected that non-pharmacological manipulations, such as those involved in extinction, latent inhibition, or partial reinforcement, should affect tolerance. That these manipulations are effective in modifying tolerance, in a manner expected on the basis of a conditioning analysis of the phenomenon, suggests that an understanding of drug effects requires an appreciation of the principles of learning as well as of pharmacology.

Pharmacological CRs are often compensatory in nature, and the conditioning analysis of morphine tolerance that I have proposed (Siegel, 1975b) emphasizes that subjects with experience of morphine ad-

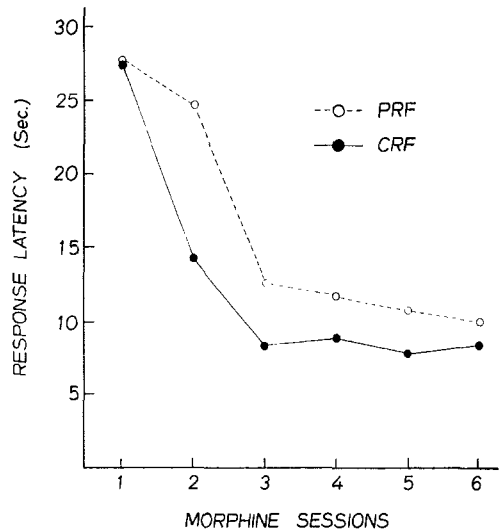


Figure 5. Mean response latency on the hot plate for each of six morphine sessions for groups in which either all presentations of the drug administration procedure were accompanied by morphine (CRF) or only 25% of the presentations were accompanied by morphine (PRF; Experiment 4).

ministration and its analgesic consequences display a compensatory hyperalgesic CR when confronted with the usual administration procedure but without the drug. Thus, when the drug is presented with the usual administration procedure, this compensatory hyperalgesic CR would be expected to attenuate the analgesic UCR, thereby decreasing the observed response to the drug.

It should be noted that there is an alternative framework with which to conceptualize the role of conditioning in drug tolerance. Using the language of information processing models of memory, Wagner (1976) recently described a conditioning analysis of habituation. This theory can readily be applied to drug tolerance, with the integrative proposal that the associative basis for the decrement in responsivity to iterative peripheral stimuli (i.e., habituation) is the same as that responsible for the decrement in responsivity to iterative pharmacological stimuli (i.e., tolerance).

The relevant aspects of Wagner's model of habituation may be briefly summarized as follows: (a) Situational cues become associated with the habituating stimulus, (b)

these situational cues then serve to pre-represent ("prime") the habituating stimulus in short-term memory, and (c) primed (or expected) stimuli are less effectively processed than unprimed (or surprising) stimuli, causing the habituating stimulus to become progressively less effective in evoking a UCR as it becomes increasingly less surprising (i.e., it is repeatedly presented in the context of the same situational cues). The model may be readily applied to the drug administration situation: When environmental cues reliably predict a drug, these cues become associated with the drug and prime the pharmacological stimulation in short-term memory, causing the drug to become less effective in eliciting responding than it would if its effects were unheralded.

The design of some experimental work supporting Wagner's memory model of habituation is remarkably parallel to that assembled in support of Siegel's associative model of tolerance. Wagner (1976) suggested that "if the long term response decrement in habituation is dependent upon the retrieval action of situational cues, we should clearly expect that it should be *context specific*" (p. 120), and he cites data supporting the situation-specificity of habituation. With respect to drug tolerance, it has been demonstrated that "the display of tolerance is specific to the environment in which the drug has been administered, and 'morphine tolerance' rats, when assessed for the effects of the narcotic in an environment other than that in which they became tolerant, evidence a relatively nontolerant response" (Siegel, 1976, p. 324). Similarly, Wagner's memory model of habituation, like my compensatory CR model of tolerance, predicts that extinction should attenuate the decremental effects of repeated stimulation. In an experiment with a design analogous to those used to demonstrate the extinguishability of morphine tolerance (Siegel, 1975b, Experiment 3; Experiments 1 and 2 of the present report), Wagner, Whitlow, and Pfautz (cited in Wagner, 1976) demonstrated that exposure to the environment in which vasomotor habituation to an audi-

tory stimulus has been previously conducted promoted recovery of the habitual response.

These similarities in habituation to peripheral stimulation and in tolerance to pharmacological stimulation are intriguing. Further research can assess the utility of an integrative theoretical approach to these two heretofore unrelated processes.

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