Evidence from Rats That Morphine Tolerance
Is a Learned Response

Shepard Siegel
McMaster University, Hamilton, Ontario, Canada

It is proposed that the direct analgesic effect of morphine becomes attenuated over the course of successive administrations of the narcotic by a conditioned, compensatory, hyperalgesic response elicited by the administration procedure, the net result being analgesic tolerance. Using the "hot plate" analgesia assessment situation with rats, this conditioning view of tolerance is supported by several findings: (a) It is necessary to have reliable environmental cues predicting the systemic effects of morphine if tolerance is to be observed, (b) a hyperalgesic conditioned response may be observed in morphine-tolerant subjects when drug administration cues are followed by a placebo, and (c) merely by repeatedly presenting environmental cues previously associated with morphine (but now presented with a placebo), morphine tolerance can be extinguished.

Tolerance is said to have developed when, after repeated administrations, the effect of a given dose of a drug is less than it was originally. Tolerance to many of the effects of narcotics (especially opiates), such as analgesia, develops rapidly and reliably, and numerous hypotheses have been presented to account for the phenomenon. In summary, (a) the relevant effect of early experience with the drug may be to alter the organism's metabolism such that the drug is subsequently more efficiently metabolized (Mulé & Woods, 1969); (b) after the drug molecules exert their action on central receptor sites, they may continue to occupy these sites thereby decreasing the population of receptor sites that can be stimulated by the same drug on a later occasion (Schmidt & Livingston, 1933); (c) the initial drug administrations may induce the formation of "silent receptors," which functionally reduce the effects of later drug administrations by serving as "dead spot" receptors for drug molecules that would

otherwise stimulate active "pharmacological receptors" (Collier, 1965); or (d) narcotics may be conceived of as antigens, with tolerance reflecting an immunitylike process (Cochin & Kornetsky, 1968). All these theories of tolerance, hereinafter grouped together as *physiological theories* (for a review, see Cochin, 1970), postulate some systemic change within the organism as a result of the initial drug experience that decreases receptor sensitivity to the drug, allows the drug to be metabolized more quickly, or serves to bind the drug before it can exert its action.

An alternative approach, proposed here, might be termed a *conditioning theory* of tolerance. According to this view, narcotic tolerance is the result of the learning of an association between the systemic effects of the drug and those environmental cues that reliably precede these systemic effects. Pavlov (1927, pp. 35ff) suggested that the administration of a drug could be viewed as a conditioning trial, with the actual pharmacological assault constituting the unconditioned stimulus (UCS) and the immediately antecedent environmental cues serving as the conditioned stimulus (CS). The development of the association between these stimuli may be revealed if the subject after a history of administration of the drug is presented with the drug administration procedure *not* followed by the systemic ef-

...ts of the drug—rather, for such a con-
...tioned response (CR) test session, a
placebo is administered.

There has been a considerable amount of
interest in the theoretical and practical im-
portance of conditioned pharmacological
responses (Gantt, 1957; Loucks, 1937; Sie-
gel & Nettleton, 1970). Although many
forms of drug CRs can be conceptualized
and have been reported, conditioned drug
responses are commonly opposite in direction
to the unconditioned effects of the drug.
Thus, it has been reported that in animals
with a history of administration of an anti-
cholinergic drug, such as atropine or Ditran,
which induces antisialosis, the administra-
tion procedure without the drug leads to
excessive salivation (Lang, Brown, Ger-
shon, & Korol, 1966; Wikler, 1948); in ani-
mals in which tachycardia has been repeat-
edly induced by injections of epinephrine,
the injection procedure alone causes a de-
crease in heart rate (Subkov & Zilov, 1937);
subjects repeatedly made to evidence allergic
reactions by allergen injections evidence
immune reactions when confronted with the
injection procedure (for a review, see Hull,
1934, pp. 413–416); in animals with a history
of administration of a hyperglycemic agent,
such as glucose or epinephrine, the adminis-
tration procedure alone leads to a decrease
in blood sugar (Deutsch, 1974; Mityushov,
1954; Russek & Piña, 1962); in organisms
repeatedly experiencing the hypoglycemic
effects of injected insulin, the injection pro-
cedure alone leads to an elevation in blood
sugar (Lichko, 1959; Siegel, 1972, 1975).[1]
These anticipatory responses, being com-
pensatory in nature, should serve to at-
tenuate the drug-induced unconditioned
response (UCR), therefore the net effect of
the drug should decrease over successive
drug administrations. Such a decreased
response to a drug as a function of successive
experiences with the drug defines tolerance.

According to the present conditioning
theory, tolerance to the analgesic effects of

morphine results because environmental
cues regularly paired with the administra-
tion of the drug come to elicit a compensa-
tory CR, hyperalgesia, which algebraically
summates with the stable, unconditioned
analgesic effects of the narcotic. Thus, en-
vironmental cues consistently predicting
the systemic effects of the drug should be
crucial to the development of tolerance since
they enable the subject to make timely com-
pensatory CRs in anticipation of the anal-
gesic UCR. Several experiments by Mitchell
and his colleagues (Adams, Yeh, Woods, &
Mitchell, 1969; Kayan, Woods, & Mitchell,
1969) indicate that the rate of development
of analgesic tolerance to morphine is highly
dependent upon the availability of environ-
mental cues uniquely present at the time of
drug administration. Using the standard
"hot plate" assessment situation (Jóhan-
nesson & Woods, 1964), in which pain sensi-
tivity in the rat is assessed by observing its
latency to lick a paw when placed on a warm
surface, these investigators reported that
analgesic tolerance to morphine developed
much more rapidly when subjects were con-
fronted with the distinctive analgesia as-
sessment environment on each of the five
occasions that the drug was administered
(even if the nociceptive stimulation was not
applied until the fifth occasion) than if they
were introduced into this environment for
the first time on the fifth occasion that the
drug was administered. Experiments 1A
and 1B were designed to assess the reliability
of these reports of the importance of drug-
associated environmental cues in the acqui-
sition of tolerance.

EXPERIMENT 1A

Method

Subjects and apparatus. The subjects, 29 experi-
mentally naive, male, 90–110 day-old, Wistar-de-
rived rats (obtained from Quebec Breeding Farms,
St. Constant, Quebec, Canada), were housed in
individual cages with food and water freely avail-
able. Responsivity to pain was assessed using re-
cent modifications of the hot plate technique
(Eddy & Leimbach, 1953). Briefly, a 1,200-ml
mixture consisting of equal parts by volume of
acetone and ethyl formate was boiled in a rec-
tangular copper container (19 × 19 × 15 cm). The
container was completely enclosed with the ex-

---

[1] Although the CR to physiological doses of
insulin appears to be a compensatory hyperglyce-
mic response, conflicting findings have been re-
ported when the UCS consists of very large doses
of the hormone (see Siegel, 1975).

ception of provision for a condenser coil to liquify the vapor and return it to the vessel. The temperature of the vapor and the top surface of the vessel were constantly monitored and remained at $54.2°$ C ($\pm.2°$ C). Pain sensitivity was assessed by placing the rat on the surface of the container for 1 min and noting the number of seconds that elapsed until it first licked a paw (hereinafter referred to as the paw-lick latency). Thus, analgesic responses are indicated by relatively long paw-lick latencies and hyperalgesic responses by relatively short paw-lick latencies.

Procedure. Three groups of rats received equivalent morphine injections on four occasions, the interval between injections being 48 hr. The fourth occasion was the test session, during which the pain sensitivity of all the rats was assessed on the hot plate in the test environment subsequent to the drug injection. The groups differed only with respect to the cues associated with the morphine administrations on the three prior sessions.

One morphine group was used to demonstrate the initial analgesic UCR of the drug and the development of tolerance over the successive drug administrations. This group was treated identically on Sessions 1-3 and Session 4, i.e., morphine-induced analgesia was assessed on the hot plate apparatus in the test environment each time the drug was administered (Group M-HP, i.e., morphine-hot plate; $n = 8$). For each session, rats in this group were transported in their home cages from the colony room to a different room, which contained the hot plate apparatus, subcutaneously injected with a 5 mg/kg dose (of a 5 mg/cc solution) of morphine sulfate, and .5 hr later, placed on the hot plate apparatus.

A second morphine group was included to assess whether any apparent drug tolerance observed in Group M-HP, as revealed by decreasing paw-lick latencies across sessions, may be attributable to merely increasing practice in making the possibly pain-ameliorating, paw-licking response while drugged rather than to any functional decrease in the narcotic's analgesic properties. This group was treated like Group M-HP except that the hot plate apparatus was not turned on until the fourth test session; for Sessions 1-3, these rats were placed on the surface of the vessel when it was at room temperature ($21.2°–22.2°$ C). For this second morphine group (Group M-CP, i.e., morphine-cold plate; $n = 7$), the environmental cues preceding the morphine effects and analgesia assessment were the same on Sessions 1-3 as on Session 4. However, these rats never practiced the paw-licking response on the hot surface until the test session; thus, relatively rapid reactions on Session 4 by Group M-CP rats would be attributable to drug tolerance rather than to acquired proficiency in paw-licking while narcotized.

A third group of rats suffered the same systemic effects of the morphine equally as often and at the same intervals as rats in Groups M-HP and M-CP except that a different set of cues was associated with the systemic effects of the drug on the

first three sessions than on the fourth, hot plate session. For this group, for Sessions 1-3, the morphine was administered in the colony room simply by removing the rat from its cage, injecting the drug, and returning the rat to its cage. Thus, this group (Group M-CAGE; $n = 8$), like Group M-CP, had its first morphine-induced analgesia assessment on Session 4, and differed from Group M-CP only because the environmental cues surrounding the morphine administration were different on the three prior occasions that the drug was administered.

Finally, a fourth group also received four hot plate analgesia-assessment sessions in the test environment, but all the injections were physiological saline rather than morphine. This group (Group S, i.e., saline; $n = 6$) provided an undrugged baseline, indicating the effects of the repeated injections and hot plate experiences per se.

Results and Discussion

The mean paw-lick latency for each group on each session is shown in Figure 1 (for Groups M-CP and M-CAGE, of course, the response was assessed only on the last session). As indicated in Figure 1, the characteristic analgesic effect of morphine was observed on the first session—rats receiving the narcotic for the first time (Group M-HP) had significantly longer paw-lick latencies than rats receiving saline ($U = 7.5$, $p < .02$). As was also expected, the analgesic effects of morphine became less and less pronounced on the successive sessions in which the drug was administered; a Wilcoxon matched-pairs signed-rank test indicated that Group M-HP rats had significantly shorter paw-lick latencies on Session 4 than Session 1 ($T = 0$, $p = .01$). As is also apparent in Figure 1, on Session 4 Group M-CP rats responded to the hot plate as did Group M-HP rats, the small difference between the two groups not approaching statistical significance, that is, Group M-CP rats evidenced the short-latency paw-licking response indicative of morphine tolerance on the fourth occasion that they received the drug despite the fact that they never experienced the heat stimulation and did not practice the response on Sessions 1-3, indicating that such practice (cf. Kayan et al., 1969) or repeated experience with the morphine while nociceptively stressed (cf. Adams et al., 1969) is irrelevant to the demonstration of analgesia tolerance in this test situation.

Both groups of m M-HP and M-CP, paw-lick latencies not from that of Group S that Groups M-HP ceiving morphine an logical saline prior to

As is obvious in CAGE, in marked co HP and M-CP, was analgesic effects of n ences between Group of Groups M-HP an tically significant (U $U = 12$, $p < .04$, resp Session 4 response la CAGE was not signifi that which would be e time rats receive the assessment (i.e., the Se HP rats). Thus, these earlier reports of the in sociated environmental ment of tolerance (A Kayan et al., 1969).

Prior to the test se phine groups suffered induced systemic effe and at the same interv groups should have be same metabolic, cellula modifications presumed tolerance (see Cochin, expected, according to logical theories of toler groups should be equ analgesic effects of the n M-CAGE, the group th in a distinctly different pretest sessions, does no cation of tolerance to n session suggests that rel with the drug administr in affecting the developr

EXPERIME

Method

Subsequent to the tes CAGE rats continued to be i the same 5 mg/kg dose was assessed for three ad interval between sessions r that the course of the dev

n on the fourth, hot plate
, for Sessions 1–3, the mor-
in the colony room simply
om its cage, injecting the
rat to its cage. Thus, this
2; $n = 8$), like Group M-
iine-induced analgesia as-
and differed from Group
environmental cues sur-
administration were dif-
r occasions that the drug

ip also received four hot
ent sessions in the test
e injections were physio-
in morphine. This group
$i = 6$) provided an un-
ing the effects of the re-
plate experiences per se.

atency for each group
iwn in Figure 1 (for
I–CAGE, of course,
ssed only on the last
n Figure 1, the char-
ect of morphine was
ission—rats receiving
rst time (Group M-
longer paw-lick la-
ing saline ($U = 7.5$,
pected, the analgesic
:came less and less
ccessive sessions in
dministered; a Wil-
gned-rank test indi-
IP rats had signifi-
latencies on Session
$p = .01$). As is also
in Session 4 Group
to the hot plate as
the small difference
is not approaching
hat is, Group M-
short-latency paw-
tive of morphine
occasion that they
the fact that they
at stimulation and
iponse on Sessions
practice (cf. Kayan
d experience with
iceptively stressed
s irrelevant to the
esia tolerance in

Both groups of morphine-tolerant rats, M–HP and M–CP, evidenced Session 4 paw-lick latencies not significantly different from that of Group S rats, despite the fact that Groups M–HP and M–CP were receiving morphine and Group S physiological saline prior to analgesia assessment.

As is obvious in Figure 1, Group M–CAGE, in marked contrast to Groups M–HP and M–CP, was not tolerant to the analgesic effects of morphine. The differences between Group M–CAGE and each of Groups M–HP and M–CP were statistically significant ($U = 5.5$, $p < .002$ and $U = 12$, $p < .04$, respectively). Indeed, the Session 4 response latency of Group M–CAGE was not significantly different from that which would be expected the very first time rats receive the drug and analgesia assessment (i.e., the Session 1 value for M–HP rats). Thus, these results confirm the earlier reports of the importance of drug-associated environmental cues in the development of tolerance (Adams et al., 1969; Kayan et al., 1969).

Prior to the test session, all three morphine groups suffered the same morphine-induced systemic effects equally as often and at the same intervals. The rats in these groups should have been subjected to the same metabolic, cellular, or immunifacient modifications presumed to be responsible for tolerance (see Cochin, 1970). It would be expected, according to any of the physiological theories of tolerance, that the three groups should be equally tolerant to the analgesic effects of the narcotic. That Group M–CAGE, the group that received the drug in a distinctly different environment for the pretest sessions, does not evidence any indication of tolerance to morphine on the test session suggests that reliable cues associated with the drug administration are important in affecting the development of tolerance.

EXPERIMENT 1B

Method

Subsequent to the test session, Group M–CAGE rats continued to be injected with morphine at the same 5 mg/kg dose and pain sensitivity was assessed for three additional sessions (the interval between sessions remaining at 48 hr) so that the course of the development of tolerance
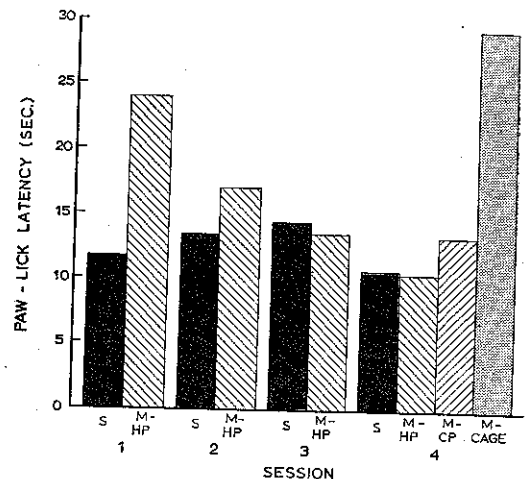

FIGURE 1. Mean paw-lick latency on hot plate for four sessions for groups in Experiment 1A, (Abbreviations used in group names: S = saline; M = morphine; HP = hot plate; CP = cold plate.)

over four drug administrations in these animals could be compared with that previously displayed by Group M–HP rats.

Results and Discussion

The mean paw-lick latencies for the four sessions for Group M–CAGE rats (subsequent to the three sessions in which they received the narcotic in their home cages) and the mean latencies previously demonstrated by Group M–HP rats on four sessions are shown in Figure 2. As is clear in Figure 2, the development of tolerance in M–CAGE rats was not at all facilitated by their earlier experiences with morphine in their home cages, i.e., the previous experience with the drug did not lead to any "savings" in the acquisition of tolerance. Tolerance acquisition appears to depend upon a number of pairings of a distinct drug administration/assessment ritual with the direct effects of that drug rather than upon merely the frequency of drug insults. Such pairings, according to a conditioning theory of drug tolerance, are necessary for the organism to associate predrug cues with the physiological effects of the drug and to make the compensatory CR that functionally attenuates the drug UCR.

EXPERIMENT 2A

As can be seen in Figure 1, by comparing the Groups M–HP and S reaction times over
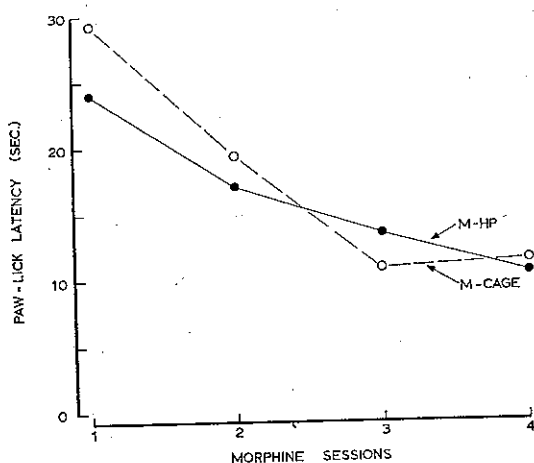
FIGURE 2. Comparison of the acquisition of morphine–analgesia tolerance (decrease in mean paw-lick latency after successive administrations of the drug) for Groups M–HP and M–CAGE of Experiment 1B. (Abbreviations: M = morphine; HP = hot plate.)

the four sessions, morphine-injected rats tend to respond increasingly like saline-injected control rats as they have more and more experience with the drug. Indeed, Group M–HP rats rapidly became so tolerant to the analgesic effects of the drug that they responded on the hot plate as rapidly as saline-injected animals. According to a conditioning theory of morphine tolerance, the morphine-tolerant, short-latency response of Group M–HP rats results from a preparatory hyperalgesic CR summating with the narcotic's analgesic UCR, and it should be possible to observe this conditioned increased pain sensitivity in response to those cues that have been predictors of systemic morphine. Experiment 2A was designed to demonstrate this hyperalgesic CR directly.

Method

Following the usual 48-hr intersession interval, the morphine-tolerant Group M–HP rats of Experiment 1A received a fifth session which was conducted like the previous four sessions except the substance injected was physiological saline rather than morphine.

The Group M–HP placebo-elicited hot plate response was compared with the placebo-elicited responses of two control groups. One was provided by Group S, which simply received a further placebo session. Thus, on Session 5, Group S rats

had the same amount of experience with the injection procedure and assessment situation as Group M–HP rats, but never received morphine. A second control group was included to assess whether any unusual placebo-elicited hot plate sensitivity of Group M–HP could be attributed to residual systemic effects of previously injected morphine or to withdrawal from dependence upon the drug (see Tilson, Rech, & Stolman, 1973). This group received four morphine injections prior to the placebo test, of the same dose and at the same time as Group M–HP, but always in the colony room. Thus, this second control group, hereinafter called Group M–CAGE:4 ($n = 8$), was treated in the same manner as Group M–CAGE of the earlier experiment, but received four, rather than three morphine injections in the colony room. Group M–CAGE:4 received its first experience with the hot plate environment and analgesia-assessment situation when it received a placebo on Session 5.

Results and Discussion

The mean Session 5 paw-lick latencies, after the placebo, for Groups S, M–CAGE:4, and M–HP were, respectively, 10.3 sec, 9.1 sec, and 4.4 sec. The reaction latency was significantly shorter for Group M–HP than for Groups S or M–CAGE:4 (both $Us = 2.5$, both $ps < .002$), and these latter two control groups did not differ significantly from each other. Thus, in response to a ritual that had been associated with morphine administration but now not followed by the central effects of the drug, morphine-tolerant Group M–HP rats displayed hyperalgesia. Rats with equivalent experience with the ritual without association with the narcotic (Group S) or with the narcotic without association with the ritual (Group M–CAGE:4) did not evidence such hypersensitivity to pain.

EXPERIMENT 2B

A further experiment was conducted in an attempt to demonstrate in a within-subject rather than between-subject design that hyperalgesia follows morphine administration cues in morphine-tolerant rats.

Method

A hot plate response-latency baseline was established for each of the six Group S rats by calculating their mean response latency for a total of seven consecutive sessions in which they received physiological saline prior to pain sensitivity assessment. Longer-than-baseline response late

would be evidence of anal
-baseline latencies eviden
the four sessions following
ion, these rats were inject
g/kg) rather than saline
te placement. By comparing
ncies following each morph
r baseline, the initial analg
development of tolerance c
ese now-morphine-tolerant
urbed in their home cages fc
in received four physiologic
ions. With the exception o
ween the last morphine ses
cebo test session, the interse
hr.

Results and Discussion

As would be expected fro
g., Cochin & Kornetsky,
k latency did not vary
urse of the initial baseline
bjects all received physi
ior to analgesia assessmen
ean baseline paw-lick lat
c; it was 11.7 sec on the fir
on and 14.5 sec on the last b
ere being no significant tre
e sessions.

Figure 3 presents the mean
paw-lick latency from
lowing each of the four m
ons and, two wk later, fou
line injections. As can be s
the analgesic effect of the i
morphine is clear; paw-lic
ost doubled from baseline l
eased by 100 %. Reaction ti
lowing subsequent morphi
ntil by the fourth injection o
ese rats were responding on
ith about the same latency
rug baseline levels. When test
late 2 wk later (after any resi
ffects of the drug had dissi
t al., 1973) after a placebo, the
olerant animals were clearly h
o the heat. Their reaction ti
ost 40 % below their baseline
ificantly shorter response laten
atched-pairs signed-rank tes
< .025). As is also clear in
ese subjects were successive
ith the placebo test sessions th
f the hyperalgesic response te

RE

lifference that did no[...]
ificance (.10 > p >
y measured in still
would reveal no dif-
ups during the first
xposure to the shock
ce would further sup-
that cues associated
ims & Calhoun, 1972)
iment in general can
retrieval and organi-
3e or, suppression re-

data from the retest
tention test confirms
ent 2— that there is a
from ECS for those
that behaved amnes-
. As in Experiment 2,
a difference in step-
ween FS-ECSop and
> .05), whereas this
ignificant at Test 1;
encies between FS-
ip was now significant
nereas there had been
for these two groups.
that on a retest trial
ie total time spent in
ore appropriate index
through latency. Ani-
ing memory on this
om shock chamber to
vior not usually ob-
xed animals (see also
. Therefore, Mann-

.E 3

N Shock Compartment
IMENT 3

tep ugh	Horizontal	Vertical
)0	26*	10.2
)0	26	8.8
'5	14*	7.2
31	7.5	7.8

for identification of
otshock; ECS = electro
open door; cl = closed

t, significantly different

---

ies would be evidence of analgesia, and shorter-
than-baseline latencies evidence of hyperalgesia.
For the four sessions following baseline determi-
nation, these rats were injected with morphine
(5 mg/kg) rather than saline prior to each hot
plate placement. By comparing the rats' paw-lick
latencies following each morphine injection with
their baseline, the initial analgesic response and
the development of tolerance could be evaluated.
These now-morphine-tolerant rats were left un-
disturbed in their home cages for 2 wk, when they
again received four physiological saline–hot plate
sessions. With the exception of this 2-wk delay
between the last morphine session and the first
placebo test session, the intersession interval was
48 hr.

Results and Discussion

As would be expected from earlier work
(e.g., Cochin & Kornetsky, 1964), the paw-
lick latency did not vary much over the
course of the initial baseline sessions (when
subjects all received physiological saline
prior to analgesia assessment). The overall
mean baseline paw-lick latency was 12.9
sec; it was 11.7 sec on the first baseline ses-
sion and 14.5 sec on the last baseline session,
there being no significant trend across base-
line sessions.

Figure 3 presents the mean percent change
in paw-lick latency from baseline levels
following each of the four morphine injec-
tions and, two wk later, four physiological
saline injections. As can be seen in Figure
3, the analgesic effect of the initial injection
of morphine is clear; paw-lick latency al-
most doubled from baseline levels, i.e., in-
creased by 100%. Reaction time decreased
following subsequent morphine injections
until by the fourth injection of the narcotic
these rats were responding on the hot plate
with about the same latency as their pre-
drug baseline levels. When tested on the hot
plate 2 wk later (after any residual systemic
effects of the drug had dissipated; Tilson
et al., 1973) after a placebo, these morphine-
tolerant animals were clearly hypersensitive
to the heat. Their reaction times were al-
most 40% below their baseline levels, a sig-
nificantly shorter response latency (Wilcoxon
matched-pairs signed-rank test, $T = 1.0$,
$p < .025$). As is also clear in Figure 3, as
these subjects were successively presented
with the placebo test sessions the magnitude
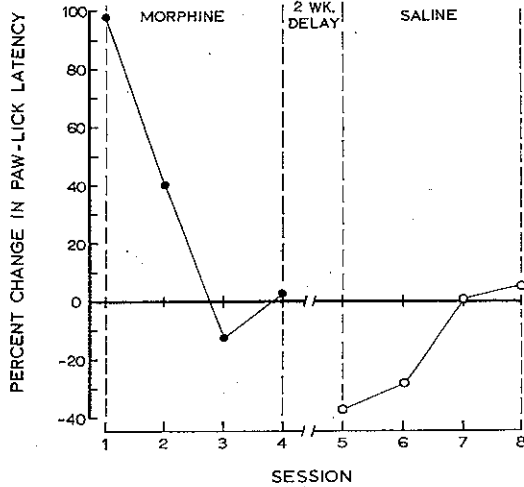of the hyperalgesic response tended to de-

---

Figure 3. Percent change from baseline paw-
lick latency after each of four morphine injections
and, 2 wk later, after four physiological saline in-
jections (Experiment 2B).

crease, i.e., their response latency returned
to baseline levels. It appears that as the drug
administration procedure is successively
presented *without* the systemic effects of the
drug, the hyperalgesic response in morphine
tolerant rats is subject to extinction, sug-
gesting that it is indeed a CR. Inasmuch as
it is proposed that it is this hyperalgesic CR
that is responsible for observed analgesia
tolerance, extinction should be an effective
procedure for eliminating tolerance.

Experiment 3

If in the morphine-tolerant animal those
environmental procedures associated with
the central effects of the drug elicit a com-
pensatory CR, presenting these environ-
mental procedures unaccompanied by the
central effects of the narcotic should serve
to extinguish these learned responses and
morphine tolerance. In other words, placebo
test sessions should constitute an effective
procedure for attenuating established toler-
ance. This prediction of a conditioning
theory of tolerance was assessed in this ex-
periment.

Method

Two groups, each containing six experimentally
naive rats of the same sex, strain, and age as those
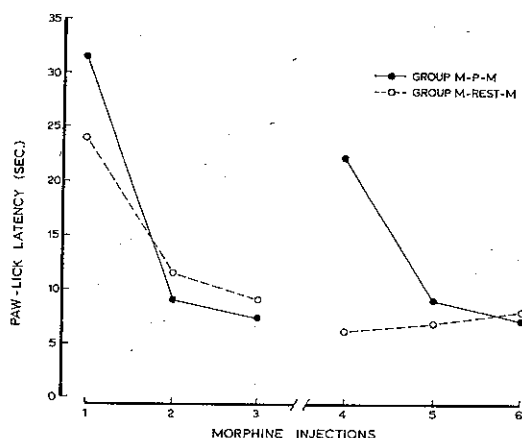used in the previous experiments, were each given

FIGURE 4. Mean paw-lick latencies after each of six daily morphine injections for groups receiving either nine placebo sessions (Group M-P-M) or a 9-day rest interval (Group M-REST-M) interpolated between morphine Sessions 3 and 4 (Experiment 3).

a total of six morphine-analgesia assessment sessions, using the same procedures as described earlier. The interval between sessions was 24 hr with the exception of the protracted interval between Sessions 3 and 4, which was 9 days. The two groups differed only with respect to their treatment between these third and fourth sessions. One group was simply left undisturbed in its home cage (Group M-REST-M). The second group received daily placebo test sessions, i.e., they were treated in the same manner as on morphine sessions except the substance injected was physiological saline rather than morphine (Group M-P-M).

Results and Discussion

The mean paw-lick latencies of both groups on each occasion that they received morphine are shown in Figure 4. Both groups evidenced tolerance to the analgesic effects of morphine over the course of the three initial administrations of the drug. Group M-REST-M continued to evidence morphine-tolerant, short-latency responses when again tested with the narcotic after the delay interval, as would be expected from previous work demonstrating that morphine tolerance dissipates little simply with the passage of time (Cochin & Kornetsky, 1964). However, when tested with morphine after the same delay interval, Group M-P-M evidenced a nontolerant, long-latency response. There was no overlap in the Ses-

sion 4 paw-lick latencies of Groups M-REST-M and M-P-M ($U = 0$, $p = .001$). As can be seen in Figure 4, Group M-P-M rats had to be "retolerated" to morphine, despite the fact that they had suffered the systemic effects of the narcotic equally as often as Group M-REST-M rats.

The finding that mere repeated presentations of a drug administration procedure, unaccompanied by the central effects of the drug effectively obliterated morphine-analgesia tolerance is a unique prediction of a conditioning theory of tolerance, and is not explicable by theories of tolerance that do not emphasize the role of drug-associated environmental cues in the development of tolerance.

GENERAL DISCUSSION

It has been previously suggested that learning can influence responsivity to drugs (see Thompson & Pickins, 1971) and that "... a drug-test interaction occurs with morphine and can play a role in the development of tolerance to the analgesic effect of this drug" (Adams et al., 1969, p. 251). The present experiments were designed to assess a specific Pavlovian conditioning interpretation of the phenomenon of morphine tolerance. Based on earlier reports that the CR to a variety of pharmacological agents is compensatory in nature, it seems reasonable that the direct, unconditioned analgesic effect of morphine is normally modulated by a morphine-anticipatory hyperalgesic CR, the net result being reflected by the development of morphine tolerance. This conditioning analysis of morphine tolerance is supported by several findings: (a) It is necessary to have a consistent set of environmental cues reliably predicting the systemic effects of morphine if rapid tolerance is to be observed (Adams et al., 1969; Kayan et al., 1969; Experiment 1A of the present report); (b) experience with morphine in one environment does not facilitate the acquisition of morphine tolerance in another environment (Experiment 1B); (c) the compensatory hyperalgesic CR may be directly observed in morphine-tolerant animals when they are confronted by the drug administration ritual not followed by
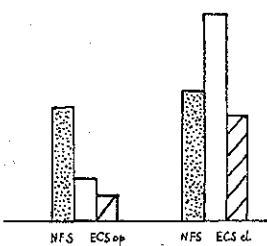
st 24 hr later (white bars),
;op failed to avoid on Test
:h tests. Abbreviations for
e shock; op = open door;

ificant, $t(17)$ = 3.480,
·ence between vertical
ite significant, $t(17)$ =
·re were no differences
;op and NFS-ECSop
:CScl and NFS-ECScl,
tivity difference found
nd NFS-ECSop groups
influence of the "mem-
·en though this memory
adaptive passive avoid-

-through latencies for
can be seen in Figure
·ssible latency at retest
· there were no medians
, all maximum median
in Figure 1 as 60+ in
ae presentation of the
:e behavior of Group
·ver to the door-open
ning that the avoidance
due to an activation of
tshock and the organi-
iate response during the
.oor-closed period. This
avoidance behavior on
in Group FS-ECSop,

the central effects of the drug (Experiments
2A and 2B), this hyperalgesic CR being
subject to experimental extinction (Experi-
ment 2B); and (d) mere presentation of
those environmental cues previously as-
sociated with the narcotic, when presented
in conjunction with a placebo, is an effective
procedure for extinguishing established mor-
phine tolerance (Experiment 3). The con-
clusions concerning the mechanism of mor-
phine tolerance in the rat are, of course,
limited to the relatively small dose of the
drug (5 mg/kg) and to the analgesia-evalua-
tion situation used in these experiments
(although the hot plate procedure is per-
haps the most commonly used of the simple
assessment techniques for pharmacologically
induced analgesia; see Evans, 1964).

The present findings concerning the im-
portance of the interaction between condi-
tioned and unconditioned responses in
contributing to the observed effect of a drug
parallel Pavlov's (1910) discussion of the
significance of his original "psychic secre-
tion" observations, i.e., that digestive re-
sponses in anticipation of feeding make a
significant contribution to normally ob-
served patterns of digestive functioning.
Subsequent research has demonstrated the
importance of conditional responses in the
normal and pathological functioning of a
variety of physiological systems in many
species including humans (e.g., Ádám, 1967;
Bykov, 1959). This work on the interaction
of learning and physiological processes,
conducted mostly by Eastern European and
Soviet physiologists, is the foundation of a
"synthetic physiology", ". . . a science of
the course of vital processes in an integral
organism *during its various natural relations
with the surrounding medium*" (Bykov, 1960,
p. 25; emphasis added). It would appear
that inasmuch as drug administration is
almost invariably predicted by a set of cues
(the administration procedure, or ritual), the
response of an "integral organism" to a drug
can be best understood as a combination of
the direct reflexive effects of the drug as it
acts on central receptor sites and the effects
conditioned to the drug administration pro-
cedure.

REFERENCES

Ádám, G. *Interoception and behaviour*. Budapest: Publishing House of the Hungarian Academy of Sciences, 1967.

Adams, W. H., Yeh, S. Y., Woods, L. A., & Mitchell, C. L. Drug-test interaction as a factor in the development of tolerance to the analgesic effect of morphine. *Journal of Pharmacology and Experimental Therapeutics*, 1969, *168*, 251–257.

Bykov, K. M. *The cerebral cortex and the internal organs*. Moscow: Foreign Languages Publishing House, 1959.

Bykov, K. M. (Ed.), *Text-book of physiology*. Moscow: Foreign Languages Publishing House, 1960.

Cochin, J. Possible mechanisms in development of tolerance. *Federation Proceedings*, 1970, *29*, 19–27.

Cochin, J., & Kornetsky, C. Development and loss of tolerance to morphine in the rat after single and multiple injections. *Journal of Pharmacology and Experimental Therapeutics*, 1964, *145*, 1–10.

Cochin, J., & Kornetsky, C. Factors in blood of morphine-tolerant animals that attenuate or enhance effects of morphine in nontolerant animals. *Proceedings of the Association for Research in Nervous and Mental Disease*, 1968, *46*, 268–279.

Collier, H. O. J. A general theory of the genesis of drug dependence by induction of receptors. *Nature*, 1965, *205*, 181–182.

Deutsch, R. Conditioned hypoglycemia: A mechanism for saccharin-induced sensitivity to insulin in the rat. *Journal of Comparative and Physiological Psychology*, 1974, *86*, 350–358.

Eddy, N. B., & Leimbach, D. Synthetic analgesics: II. dithienylbutenyl- and dithienylbutyl-amines. *Journal of Pharmacology and Experimental Therapeutics*, 1953, *107*, 385–393.

Evans, W. O. A critical review of some new methods in animal analgesiometry. *Journal of Clinical Pharmacology and New Drugs*, 1964, *4*, 179–187.

Gantt, W. H. Pharmacological agents in study of higher nervous activity. *Diseases of the Nervous System*, 1957, *18*, 339–341.

Hull, C. L. Learning: II. The factor of the conditioned reflex. In C. Murchinson (Ed.), *A handbook of general experimental psychology*. Worcester, Mass.: Clark University Press, 1934.

Jóhannesson, T., & Woods, L. A. Analgesic action and brain and plasma levels of morphine and codeine in morphine tolerant, codeine tolerant and non-tolerant rats. *Acta Pharmacologica et Toxicologica*, 1964, *21*, 381–396.

Kayan, S., Woods, L. A., & Mitchell, C. L. Experience as a factor in the development of tolerance to the analgesic effect of morphine. *European Journal of Pharmacology*, 1969, *6*, 333–339.

Lang, W. J., Brown, M. L., Gershon, S., & Korol, B. Classical and physiologic adaptive conditioned responses to anticholinergic drugs in

conscious dogs. *International Journal of Neuro-pharmacology*, 1966, *5*, 311–315.

Lichko, A. E. Conditioned reflex hypoglycaemia in man. *Pavlov Journal of Higher Nervous Activity*, 1959, *9*, 731–737.

Loucks, R. B. Humoral conditioning in mammals. *Journal of Psychology*, 1937, *4*, 295–307.

Mityushov, M. I. Uslovnorleflektornaya inkret-siya insulina (The conditional-reflex incretion of insulin). *Zhurnal Vysshei Nervnoi Deiatel (Journal of Higher Nervous Activity)*, 1954, *4*, 206–212. (Read in translation prepared by L. J. Shein, Department of Russian, McMaster Univ.)

Mulé, S. J., & Woods, L. A. Distribution of N-C^{14}-methyl labeled morphine: I. In central nervous system of nontolerant and tolerant dogs. *Journal of Pharmacology and Experimental Therapeutics*, 1969, *168*, 251–257.

Pavlov, I. P. *The work of the digestive glands* (W. H. Thompson, trans.). Charles Griffin and Company: London, 1910.

Pavlov, I. P. *Conditioned reflexes* (G. V. Anrep, trans.). London: Oxford University Press, 1927.

Russek, M., & Piña, S. Conditioning of adrenalin anorexia. *Nature*, 1962, *193*, 1296–1297.

Schmidt, C. F., & Livingston, A. E. The relation of dosage to the development of tolerance to morphine in dogs. *Journal of Pharmacology and Experimental Therapeutics*, 1933, *47*, 443–471.

Siegel, S. Conditioning of insulin-induced glycemia. *Journal of Comparative and Physiological Psychology*, 1972, *78*, 233–241.

Siegel, S. Conditioning insulin effects. *Journal of Comparative and Physiological Psychology*, 1975, *89*, 189–199.

Siegel, S., & Nettleton, N. Conditioning of insulin-induced hyperphagia. *Journal of Comparative and Physiological Psychology*, 1970, *72*, 390–393.

Subkov, A. A., & Zilov, G. N. The role of conditioned reflex adaptation in the origin of hyperergic reactions. *Bulletin de Biologie et de Médecine Expérimentale*, 1937, *4*, 294–296.

Thompson, T., & Pickens, R. (Eds.). *Stimulus properties of drugs*. New York: Appleton-Century-Crofts, 1971.

Tilson, H. A., Rech, R. H., & Stolman, S. Hyperalgesia during withdrawal as a means of measuring the degree of dependence in morphine dependent rats. *Psychopharmacologia*, 1973, *28*, 287–300.

Wikler, A. Recent progress in research on the neurophysiologic basis of morphine addiction. *American Journal of Psychiatry*, 1948, *105*, 329–338.