large overall volume of the drug was given in a regimen that abolished the usual decreases in rate following large doses of LSD (three doses of 0.08 mg/kg), the apparent attenuation of discrimination was not present (Fig. 1, top). This is, though the rate decreased somewhat, this decrease did not alter the shape of the generalization gradient. Furthermore, when a percentage measure was used, the effect of three doses of 0.08 mg/kg of LSD was completely obliterated (Fig. 2, top). The differences between 0.16 mg/kg and control (Fig. 2, bottom) probably can be accounted for by the fact that the animal emits only very few responses after 0.16 mg/kg of LSD. In that case, a difference of only one or two responses between stimuli represents a dramatic change in the percentage measure. Therefore, in spite of apparent alterations in the animal's ability to discriminate after 0.16 mg/kg of LSD, these effects can be attributed to drug-induced changes in the animal's rate of responding; thus, the drug is not affecting sensitivity but is, rather, affecting the animal's response output.

These results are consistent with our own work with LSD on discrete trial generalization (*4*) as well as with the results of a signal detection analysis in which the effects of LSD on sensitivity are measured separately from its effects on response bias. The results are also consistent with numerous reports that the rate of occurrence of a behavior is an important determinant of drug effects (*10*). They also point out the importance of eliminating the confounding effect of changes in response output from measures of sensitivity (*11*).

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Facilitation of the Long-Term Store of Memory with Strychnine

Abstract. *Female mice (C57BL/6 strain), repeatedly administered strychnine sulfate for 10 days after exposure to a six-unit maze, showed significantly improved learning when trained again. This facilitation effect was not due to overall enhancement of learning ability and could not be attributed to retrograde facilitation of consolidation processes.*

Low dosages of analeptic compounds, such as strychnine, can facilitate memory processes (*1*). The evidence accumulated thus far indicates that facilitation of memory occurs only when the drug is injected within several hours after the daily training session (*1, 2*). It is generally accepted that such drug treatments operate on the labile phase of memory and that as the memory trace stabilizes it becomes more resistant to facilitating or impairing agents (*1, 3*). Although the period of susceptibility to enhancing treatments appears to be less than 1 hour after training, the susceptibility interval for interference has been shown to be several hours or even longer (*3*), depending on the treatment used. The facilitation and interference studies provide the strongest evidence for a time-dependent or consolidation notion of memory. Even though time-dependent aspects of memory have not been quantified, it is generally agreed that within 24 hours a memory trace has consolidated to the extent that it is part of the long-term store (*1–3*). To test whether a trace in the long-term memory store could be facilitated, we administered strychnine long after the period of susceptibility to enhancement effects.

Adult female mice (158; 60 to 95 days of age) of the C57BL/6 strain, housed six to ten to a cage and deprived of water for 48 hours, were exposed, on a single trial, to six successive brightness discriminations (*4*). The maze contained six units, in addition to a starting box and a goal box, linearly arranged (*5*). The starting box and the entryways into each discrimination unit and the goal box were painted flat gray. The goal box was painted flat white. Each of the six discrimination units was divided into two alleys, one painted flat black and the other flat white. The white side of the unit was unobstructed and considered correct. The black alley was obstructed by a transparent vinyl barrier that could not be detected by the animals at the choice point. The six units were arranged such that white appeared LRRLLR (L, left; R, right), eliminating solution of the problem with either a position or alternation preference. On entering the goal box, the subjects were allowed access to a 0.3 percent solution of saccharin in tap water for 20 seconds and were not able to reenter the maze. Initial errors (first entry into the incorrect alley of each discrimination unit) and total errors (initial and all reentries into incorrect alleys) were scored. A subject, therefore, could make no more than six initial errors on a single trial, whereas the range of total errors was not constrained. Latency to enter the goal box after introduction into the starting box was also measured. Approximately 30 minutes after the last animal finished running the maze, all animals were given access to water for 1 hour. Twenty-four hours later, each animal was given a second trial in the maze, with the above procedure. One hour after the last animal completed its training session, all animals were given free access to water.

We balanced for initial errors on the two trials and formed six nearly equivalent groups. Although there was a small, unsystematic overall reduction in error scores on the second day, analyses of variance on this trial showed no significant differences among the groups for initial errors ($F = .65$; d.f. = 5,100) or for total errors ($F = .34$; d.f. = 5,100). Beginning 24 hours after the last maze trial, each animal in the six groups received the first of a series

of ten daily intraperitoneal injections of the following: (i) a low dosage (0.2 mg/kg) of strychnine sulfate for 10 days [LD(1–10)]; (ii) a high dosage (1.0 mg/kg) of strychnine sulfate for 10 days [HD(1–10)]; (iii) 0.2 mg/kg of strychnine sulfate on the first day and the vehicle (sterilized tap water) on the other 9 days [LD(1)]; (iv) 1.0 mg/kg of strychnine sulfate on the first day and the vehicle on days 2 to 10 [HD(1)]; (v) 0.2 mg/kg of strychnine sulfate on the fifth injection day and the vehicle on the other 9 days [LD(5)]; or (vi) the vehicle on all 10 days (control). Twenty-four hours after the last injection, all animals in the six groups were again water deprived. Twenty-four hours later each animal was given a single trial in the maze, and thereafter a single trial each day until it attained the learning criterion of no more than two initial errors summed over two consecutive days (*6*, *7*).

The LD(1–10) group, which received the low dosage of strychnine for 10 days, displayed superior retention when tested again (Fig. 1 and Table 1). One-way analyses of variance of trials, initial errors, and total errors to criterion were significant (trials: $F = 2.98$, d.f. = 5,100, $P < .02$; initial errors; $F = 2.66$, d.f. = 5,100, $P < .03$; total errors: $F = 2.31$, d.f. = 5,100, $P < .05$) (*8*). For all of the analyses, each group was tested against the control group by means of Dunnett's *t*-statistic (*9*). In each case, only the LD(1–10) group differed significantly from the control group (trials: $t = 3.05$, $k = 6$, d.f. = 100, $P < .02$, two-tailed; initial errors: $t = 2.97$, $k = 6$, d.f. = 100, $P < .02$, two-tailed; total errors: $t = 2.86$, $k = 6$, d.f. = 100, $P < .04$, two-tailed). These results suggest that facilitation produced by strychnine in this situation may be dose dependent, because neither the HD(1–10) nor the HD(1) groups differed from the control group. Furthermore, it is clear that the full expression of the facilitation phenomenon observed requires repeated administrations of the drug; although the LD(1) and LD(5) groups tended to be superior, they did not differ significantly from the control group.

An obvious interpretation of these results is that low dosages of strychnine administered repeatedly enhances overall learning ability. To test this hypothesis we trained three additional groups to criterion. The naive animals in the three groups received (i) 0.2 mg/kg of strychnine sulfate (naive, LD); (ii) 1.0 mg/kg of strychnine sulfate (naive, HD); or (iii) the vehicle each day for 10 days (naive, control). Forty-eight hours after receiving the last injection, all animals were trained to criterion as previously described. One-way analyses of variance were not significant for the three measures (trials: $F = 1.43$, d.f. = 2,48; initial errors: $F = 1.56$, d.f. = 2,48; total errors: $F = 1.69$, d.f. = 2,48). Furthermore, these groups required more training and made more errors in achieving criterion than any of the six groups that received initial training (see Table 1). It is clear, therefore, that repeated administration of strychnine did not increase overall learning ability in this situation.

Table 1. Mean ± standard errors of the mean for trials, initial errors, and total errors to criterion.

Group	*N*	Trials to criterion	Initial errors to criterion	Total errors to criterion
Control	18	4.89 ± .43	9.28 ± 1.38	11.28 ± 1.96
LD(1–10)	18	3.17 ± .38	4.39 ± .97	5.22 ± 1.30
HD(1)	18	4.84 ± .63	9.11 ± 1.89	10.17 ± 2.34
LD(1)	18	4.00 ± .28	6.67 ± .82	7.33 ± .99
HD(1–10)	17	4.77 ± .36	8.24 ± .87	9.35 ± 1.13
LD(5)	17	3.94 ± .24	6.41 ± .72	7.00 ± .82
Naive, control	17	5.12 ± .40	10.24 ± 1.02	11.65 ± 1.07
Naive, LD	17	5.24 ± .51	10.59 ± 1.48	12.18 ± 1.75
Naive, HD	17	6.41 ± .85	13.94 ± 2.32	16.47 ± 3.00

Several studies with rats have reported that prior treatment with analeptics can result in the facilitation of learning (proactive facilitation). Those which employed strychnine found that the drug had to be administered in a specific period during development; moreover, the facilitating effect occurred most often as a drug-environment interaction (*10*). In a more comparable paradigm, Bauer and Duncan (*11*) reported facilitation of acquisition after repeated administration of *d*-amphetamine. It should be noted, however, that they began training 24 hours after the last injection, and for their appetitive procedure their animals were water deprived throughout the injection period. These differences in procedure, organism, and drug may very well un-

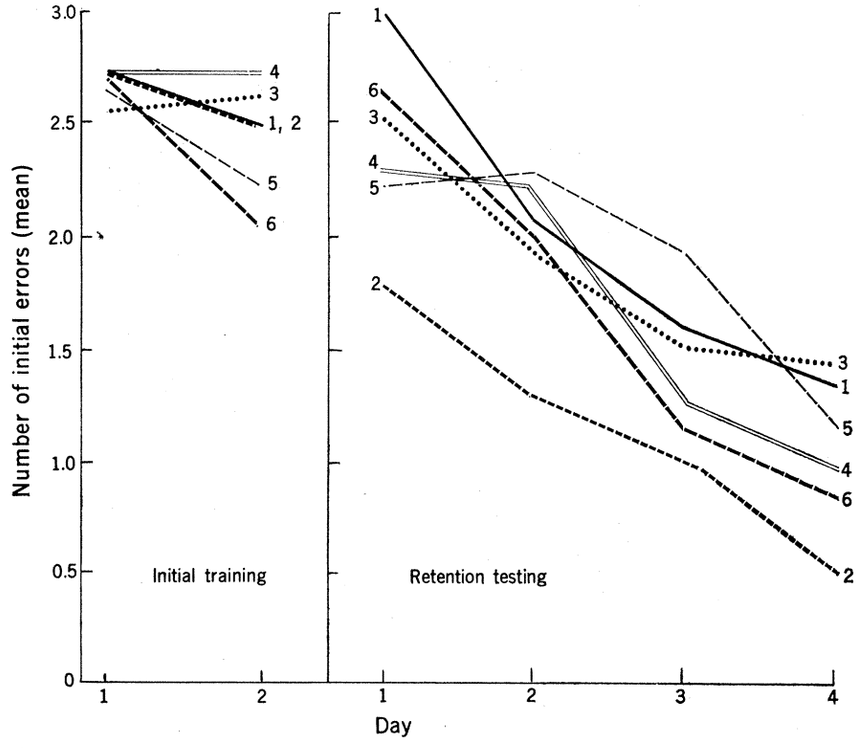

Fig. 1. Mean number of initial errors for the two initial training and the first four retention trials of groups: *1*, control; *2*, LD(1–10); *3*, HD(1); *4*, LD(1); *5*, HD(1–10); *6*, LD(5).

derlie the discrepancy concerning proactive facilitation.

It might also be argued that the drug was operating on consolidation processes. Since it is generally assumed that consolidation is a progressive stabilization of a memory trace over time, our data suggest that this labile phase of memory lasts for at least 5 days. That there was a trend toward facilitation in the LD(1) group supports this contention. The same trend, however, appeared in the LD(5) group. Thus we would have to postulate not only that the labile phase persists for at least 5 days, but also that there is equipotentiality of the memory trace throughout this time period. These assumptions are not supported by previous investigations, which found no evidence of retrograde facilitation of memory when the drug was administered at intervals beyond several hours after training (*1–3*). Furthermore, the consolidation argument can be vitiated since neither the LD(1) nor the LD(5) group differed significantly from the control group in this study.

It is conceivable that the observed facilitation could be attributable to performance factors unrelated to memory. For instance, the repeated drug administration could have increased motivational, arousal, or attentional levels. Further, activity levels as well as sensitivity to the white and dark alleys could have been altered. If, however, any of these variables were responsible for the reported enhancement, it is likely that the naive groups given strychnine would have been similarly facilitated.

Since strychnine was facilitating only to animals that had received prior exposure to the maze, the most reasonable interpretation of these results is that strychnine influenced the long-term store of memory. There are several ways in which strychnine could have produced the observed enhancement. The drug could have strengthened the informational representation of the training experience or could have retarded the decay of that representation from the long-term store (prevention of forgetting). Alternatively, strychnine may have increased the accessibility of information in the long-term memory store (enhancement of retrieval processes). At present, these alternatives cannot readily be distinguished. It should be noted that some investigations of facilitation of memory have employed repeated administrations of the analeptic compound over many days. The facilitation observed in some of these studies may be due in part, therefore, to the enhancement of the long-term store of memory. Finally, the most significant finding of this research is that the long-term store of memory is dynamic and susceptible to pharmacological manipulation.

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6. Although some animals reached criterion in less than 4 days, all were tested for at least 4 days to provide sufficient data for examining learning curves (see Fig. 1).
7. The LD_{50} of intraperitoneally injected strychnine sulfate for C57BL/6 female mice (60 to 90 days old) maintained in our animal colony is 2.5 mg/kg.
8. Latency on the first retention day varied significantly among groups ($F = 4.76$, d.f. $= 5,100$, $P < .01$). All of the groups that received strychnine displayed shorter latencies than the control group; however, latencies did not correlate with either error measure and, consequently, were not further analyzed.
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Atmospheric Circulation of DDT

In their article "DDT in the biosphere: Where does it go?" Woodwell *et al.* (*1*) present an admirable review of knowledge about the storage and transport of DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] and a mathematical model to describe its movements. They conclude that DDT is ultimately stored in the depths of the ocean after evaporation into the atmosphere, transferal from the atmosphere to the ocean primarily by rainfall, and subsequent movement downward in the ocean, until dispersed.

The model as presented necessarily requires many assumptions, and the validity of their conclusions must be questioned on the basis that measurements of atmospheric concentrations of DDT, as judged by the one reference given on the subject (*2*), are completely incompatible with the requirements of the model. In order that DDT be transported as proposed, Woodwell *et al.* calculate that a worldwide circulation of DDT components, largely as vapor, must be present at a concentration of 80 ng per cubic meter of air, with a mean residence time of 4 years. These estimates are of course approximate, and local deviations could be expected with higher concentrations in the vicinity of areas where DDT is being applied and lower values in areas where cleaning of the atmosphere is occurring. Stanley *et al.* (*2*), in a survey of atmospheric concentrations, found *maximum* values at various locations in the range of 10 to 2000 ng of total DDT components per cubic meter of air, apparently largely particulate in nature and related to local applications. The background level, however, can hardly be more than the 2 ng/m^3 observed repeatedly at one location (Dothan, Alabama) where significant agricultural applications are reported, or the 10 ng/m^3 maximum observed at the Salt Lake City site. In about 20 percent of the measurements of Stanley *et al.*, the concentration of DDT was less than the detectable limit of 0.1 ng/m^3 (*p,p'*-DDT). If there is a long-term, worldwide circulation, it must be at a level which is not more than 10 percent, perhaps much less than 1 percent, of the predicted value. Even at this level of accuracy, the results could perhaps be considered a tribute to the general analysis made by Woodwell and