mal to animal and are proportional in speed and extent to the frequency of stimulation. However, a single shock or the cessation of a train of shocks in certain other cells occasionally releases a complex escape pattern comprising 30 seconds of coordinated activities. The execution of this pattern is not appreciably modified by the frequency of stimulation.

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Effects of Thiopental Sedation on Learning and Memory

Abstract. *Subjects who were administered thiopental showed a loss of memory for events discussed while they were under sedation. We tested the subjects for recognition memory of pictures and recall of associated pairs of letters and words, and found that the subsequent memory loss was correlated with the concentration of thiopental in the venous blood at the time the material was learned. Retention did not appear to be state-dependent because the subject, while under sedation, could recall material learned prior to sedation, and because recall was not facilitated by reinstatement of the sedation.*

We have observed that thiopental sedation may be accompanied by loss of memory for events discussed by patients while under the influence of the drug. In this experiment we examined the questions of whether the memory decrements produced by barbiturate sedation are caused by failure of initial fixation, by interruption of the so-called memory-consolidation process (*1*), or whether the difficulty is one of not being able to remember when the physiological state at retrieval differs from that during learning (state-dependent retrieval) (*2*).

All subjects were paid volunteers (control, $n = 2$; group 1, $n = 12$; group 2, $n = 10$). While the learning and recall procedures were essentially alike throughout, for group 2 thiopental was administered by intermittent injection (thiopental, 2.5 percent) and the subject's state of alertness was monitored through response to random digits presented by a prerecorded tape, one digit occurring every 3 seconds for 5 minutes (*3*). The subject was required to press a telegraph key every time he heard three consecutive odd numbers; an increase in errors was taken as an index of loss of vigilance owing to sedation. For group 2 the drug was continuously infused (thiopental, 0.3 percent) and an operant-response measure was used as an index of loss of vigilance (*4*). A loud high tone was presented in randon alternation with a loud tone of lower pitch. A tone occurred every 10 seconds and remained on until the subject terminated it by pressing the correct one of two buttons. The slope of the subject's cumulative response curve was taken as an index of his level of alertness. We tried to keep the subjects of both group 1 and group 2 at a level of sedation just short of unconsciousness.

Two sets of learning and memory materials were used. One consisted of ten simple line drawings of familiar objects which the subject was asked to describe when they were first presented, to insure that the pictures were adequately perceived while the subject was under sedation. In a later test the subject selected the familiar pictures from a set containing half familiar and half novel ones. The second kind of material consisted of six easily associated pairs of letters and words (for example, W-water, F-flower, C-camel). These were learned by the anticipation method to the point of one perfect recitation (*5*). In a later test for recall, the cue letters alone were presented. Both materials were so easy that two control subjects, who were always given a placebo instead of thiopental, made perfect scores throughout. Further evidence of the ease of the learning materials was obtained from the ten subjects of group 2 who learned a list of associated pairs before they were placed under sedation. Of these, eight learned in a single trial, and two learned in two trials.

Before the drug was administered, a base-line blood sample was taken and vigilance tests were given. The subjects of group 2 learned a control set (set A) of the associated pairs. In order to test for possible retrograde amnesia (or possible state-dependent recall), the subjects were tested for retention immediately after the drug took full effect. For both groups, the first set of pictures (set 1, recognition test) was now presented and the subject described each one. After the presentation of the pictures, six associated pairs (set B) were learned to one perfect recitation. After a lapse of 30 minutes (filled with incidental conversation to maintain consciousness; blood samples were also taken and vigilance tests administered), the subject was tested for recognition of the set 1 pictures and recall of the set B associated pairs. This method determined the extent of memory loss under sedation. Then, another blood sample was drawn, vigilance tested, and another set of materials learned: set 2 of recognition pictures and set C of associated pairs. After a final blood sample and vigilance test, the experiment was terminated for the day. The subject commonly slept for 2 or 3 hours, was sent home, and returned to the laboratory the following day for a 24-hour retention test.

Electroencephalograms recorded periodically throughout the session showed clear modifications, indicating that sedation was adequate.

Groups 1 and 2 represent essentially two experiments, because some of the

difficulties in the course of experimentation with group 1 led to the improvements in technique with group 2. The trend of results is similar within both groups, but the effects of sedation on behavior are more severe in group 2. That these results are due to differences in sedation, rather than to other differences in the experiment, is indicated by a comparison of the concentrations of thiopental in the venous blood in the two groups throughout the experiment (Table 1). The differences are significant ($F = 3.46$; df = 3, 27; $P < .05$). A t-test shows the means to be significantly different on the fourth blood sample ($P < .05$); this is the point at which the subject learns the material on which he is to be tested for post-sedation retention on the following day. Because different vigilance tasks were used in the two groups it is not possible to use these measures to discriminate between the groups; general observation confirmed that continuous infusion of thiopental induced a more uniform sedation. Because feedback from the vigilance test was used to monitor the amount of infusion, it is not surprising that there were no consistent relationships in the groups between the vigilance scores and the concentrations of thiopental in the venous blood.

That the amnesic effect of thiopental was not retroactive was demonstrated by the ten subjects of group 2. They had learned set A of associated pairs before they were given thiopental, and, when they were tested for recall while under sedation, their scores were nearly perfect (mean of 5.8 correct out of a possible six items, no subject missing more than one item).

When not under sedation, the subjects in group 2 learned the associated pairs in a mean of 1.2 trials, while the subjects of group 1, under sedation, required a mean of 5.75 trials (2.99, standard deviation) to learn set B and those of group 2 required a mean of 10.00 trials (2.98, standard deviation). These differences between the groups in mean trials required for learning the material are statistically significant ($P < .05$). The greater impairment of learning in group 2 gave evidence that the sedation was deeper when thiopental was continuously infused. The relationship between learning and the degree of sedation is further attested by a correlation within group 2 between the trials required for learning and the concentration of thiopental in venous blood

Table 1. Concentration of thiopental in the venous blood : mean number of micrograms of thiopental per milliliter of blood. Means and standard deviations are noted.

Sample 1	Sample 2	Sample 3	Sample 4
	Group 1 (n = *11*)*		
10.71	10.66	10.60	10.59
(2.16)	(1.39)	(1.62)	(1.17)
	Group 2 (n = *10*)		
11.18	12.12	12.19	13.39
(3.81)	(3.55)	(2.83)	(3.01)

* One subject missing because of technical difficulties.

(*6*) at the end of the session ($r = .78$, $P < .02$).

When tested while under sedation for material learned during sedation (recognition set 1, and associated pairs set B), subjects of both groups showed marked decrements after 30 minutes in both recognition and recall (Table 2). The differences between the groups are significant for recognition ($P < .01$), but not for recall. Normally alert subjects show no loss over this short period of time.

The subjects returned to the laboratory 24 hours later and were asked to recall all they could remember concerning the previous day's experiment. The spontaneous free recall varied from virtually complete amnesia to detailed recall of the session. Tests for both the recognition material and associated pairs showed deficits (Table 2), confirming the clinical observations of amnesia in subjects placed under barbiturate sedation. Again group 2, with higher sedation, appeared to show greater impairment than group 1, although neither the difference in recognition nor that in recall is statistically significant. The control subjects showed no overnight loss with these easy materials.

Table 2. Retention by subjects who learned the material while under sedation. Ten pictures and six associated pairs were presented. Means and standard deviations are given. Group 1, $n = 12$; group 2, $n = 10$.

Group	Picture recognition	Recall of associated pairs
Retention after 30 minutes under sedation		
1	7.00	4.58
	(3.79)	(1.31)
2	1.70	3.90
	(2.87)	(1.34)
Retention after 24 hours, awake		
1	6.50	2.67
	(3.26)	(1.37)
2	3.90	1.90
	(2.77)	(1.20)

There are differences in overnight effects, with possibly some increase for picture recognition in group 2 (reminiscence effect), but losses in retention of associated pairs in both groups after 24 hours (Table 2). Some subjects in group 1 showed essentially no impairment under sedation; however, for them no improvement is possible. Limiting the analysis to those who showed some impairment of recognition while under sedation (Table 2), seven of the 12 subjects of group 1 are available for study, and all ten subjects of group 2. Of these 17 subjects showing some impairment of retention while under sedation, 13 improved in their recognition scores after 24 hours when tested in the waking state, three scored the same, and only one had a reduced score after 24 hours. The consistent change of 13 of 17 subjects is statistically significant by the sign test ($P < .025$). There is a tendency for the subject to recover items learned under sedation when he is tested while awake 24 hours later; thus he recognizes more at that time than he did when tested 30 minutes after learning the items and while still under sedation. It should be noted that these are not repeated tests on the same items, but comparable tests on different items.

The situation is different for the associative learning. Selecting those subjects who showed impairment of learning while under sedation (and hence had an opportunity to improve), we find eight subjects from group 1 and all ten from group 2. For these 18 subjects, 13 show greater losses overnight than under sedation, two remain unchanged, and three cases do better in the waking state. By a sign test the loss by 13 of the 18 cases is statistically significant ($P < .05$).

Following the 24-hour retention test, four subjects of group 1 were again administered thiopental as on the preceding day in order to determine whether memory might be improved under sedation. When sedation was judged to be the same as that for the original learning state, both recognition and associative learning were tested in the usual manner. None of the subjects' scores improved, and one subject scored less well when under sedation for the second time than he had when tested while awake. These results are coherent with the loss of retention shown by those tested earlier while under sedation.

For nine of the subjects, all known

Table 3. Attempted recovery under hypnosis compared with recovery while the subject is awake. Means and standard deviations are given. Four subjects were under high sedation and five under low.

Condition	High sedation (14–30 μg/ml)	Low sedation (8–13 μg/ml)
Recognition items correctly identified (out of 10)		
Awake	1.50 (1.00)	6.20 (1.79)
Hypnosis	3.50 (1.00)	6.00 (3.16)
Associated pairs correctly recalled (out of 6)		
Awake	2.50 (1.73)	1.60 (0.55)
Hypnosis	2.75 (1.89)	2.00 (0.71)

from earlier testing to be highly susceptible to hypnosis, the 24-hour retention test was followed by an effort to recover more information through hypnosis. To avoid the effect of exposure during the earlier test while awake, these subjects were tested for only half the items while they were awake, and the other half was saved for the test for recall under hypnosis. The subjects are grouped in Table 3 by the concentration of thiopental in their venous blood during the final learning period. In the four subjects with higher concentrations of the drug in their blood (mean, 16 μg/ml) there was some slight recovery of the recognition items. All four subjects recovered something more under hypnosis, while only one of the five in the lower sedation group did. There was no evidence of recovery of the associated pairs. It appears that for those who suffer large decrements under the drug more has been registered than is recovered when they are normally conscious.

That short-term memory is interfered with is shown by the greater number of trials required to learn the easy associated pairs when the subject is under sedation. Some of the items entered into long-term storage, for they were recovered after 24 hours; compared, however, with the perfect retention by control subjects, the marked losses after 30 minutes (under sedation) and after 24 hours (tested while awake) show impairment of longer-term memory.

The alternative possibility to interference with memory storage is that retrieval is interfered with. The evidence for some recovery under hypnosis (particularly of recognition material) indicates that more may in fact be stored than is recovered. There was, in fact, some spontaneous recovery of recognition material over the 24 hours for the sedated group, not under hypnosis, a fact which supports the same conclusion. However, the observation that material learned before administration of thiopental was recovered without impairment during deep sedation indicates that the memory defect is not simply one of retrieval. That material learned while awake was readily retrieved under sedation adds to our other observations that the drug-induced memory deficits were not state-dependent.

Results do not give unequivocal support to any of the current theories of consolidation processes in memory. In general, they are coherent with the interpretation of the sedated state as one of lowered intellectual functioning, in which attentive, discriminative, and associative processes are interfered with, with the consequent impairment of both learning and retention characteristics of the poorer learner.

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Mental Retardation

Although I agree with many aspects of Zigler's "developmental" theory of retardation (*1*), several points appear to merit further discussion and clarification. A key portion of his developmental theory is given in the following: " . . . the familial retardate's cognitive development differs from that of the normal individual only in respect to its rate and the upper limit achieved. Such a view generates the expectation that, when rate of development is controlled, as is grossly the case when groups of retardates and normals are matched with respect to mental age, there should be no difference in formal cognitive processes related to I.Q." (*1*, p. 294).

In this statement, Zigler defines mental age (MA) as the rate of intellective development. In the same paragraph, however, he refers to MA as the "level" of intellective functioning. Zigler's apparent failure to distinguish rate of development from level of development leads to a questionable prediction from his theory—namely that retardates and normals of the same MA will be similar with respect to their cognitive functioning.

Mental age is a transformation of the score made in an intelligence test and is a measure of the current level of intellective functioning, not of the rate of accumulation of knowledge. If an individual's chronological age (CA) is also known, then the intelligence quotient (I.Q.) may be calculated: I.Q. $= (MA/CA) \times 100$. The I.Q. score is a rough index of the amount of information accumulated in a given number of years of life; thus it is a measure of rate.

According to Zigler, if groups of retardates and normals are matched for MA there should be no difference in formal cognitive processes related to I.Q. Figure 1 represents the growth in mental age of a hypothetical normal child, born in 1955, and progressing at the rate of one MA unit per year (I.Q. $= 100$), and of a retarded child, born in 1950, who is progressing at the rate of one-half MA unit per year (I.Q. $= 50$).

Assume that the two children were chosen for a learning experiment in 1960 because they both had MA's of 5 years. According to Zigler, if nonintellective factors are held constant, the performance of the retarded child should equal that of the normal child. But note that the two children have dif-