mimic) after 46 days. In another test, eggs of the confused flour beetle (20 per cup) were placed in ⅝-ounce (18.5 ml) jelly cups each containing 5 g of 80-mesh bleached flour. With as little as 0.1 ppm of JH-25 in the flour, no adults were observed; with 0.02 ppm, two adults were noted after 47 days, but they produced no eggs. In similar tests with pupae and adults, 50 ppm of JH-25 did not prevent reproduction. Thus, the chemical will be most effective when administered before the insects reach the pupal stage.

We speculate that the high activity of JH-25 may stem from the inability of the insect to destroy the JH mimic at the appropriate stage of its development; the insect is thus prevented from maturing normally.

The compounds were prepared by alkoxymercuration of the phenyl terpenoid ether in the appropriate alcohol, followed by demercuration with sodium borohydride (*12*). The crude product was purified by chromatography on a Florisil (*13*) column developed first with hexane and then with 2 percent ether in hexane when the desired product emerged. Each fraction from the column was analyzed by gas chromatography (*14*), and those containing the desired compound were combined. Infrared and nuclear magnetic resonance data were consistent with the structures presented (*15*). Compound JH-25 appears to be potentially inexpensive judged by the method of synthesis and the intermediates used. The configuration of the double bond in several preparations of JH-25 was 75 to 80 percent (*E*). Bioassays of the individual isomers prepared by other routes (*16*) showed the (*E*) isomer to be ten times more active than its (*Z*) analog.

The stability of JH-25 was compared with that of its 6,7-epoxy analog (*9*) by exposing 40 mg of each compound coated on glass plates (5 by 20 cm, two per treatment) to sunlight for 8 hours; the chemicals were rinsed off the plates with acetone, and the amounts remaining were determined by gas chromatography (*14*). Losses from treatment were less than 1 percent for JH-25 and 13 percent for the epoxide. Another set of plates coated with JH-25 was left in water for 24 hours; 88 percent of the chemical was recovered, indicating good stability of JH-25 to water.

The exceptionally high activity of JH-25 and some of its analogs, the likelihood that their cost will be low, and the good stability they demonstrate make these JH mimics especially promising as selective pest control agents.

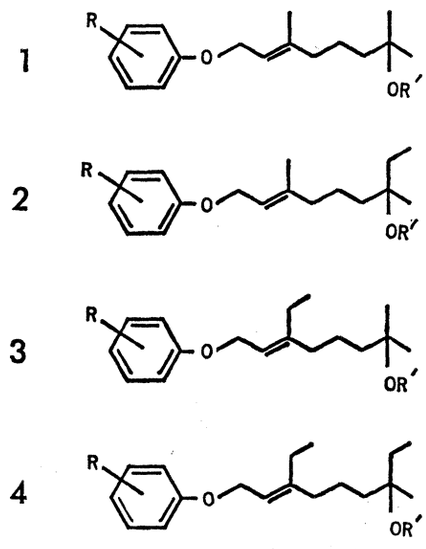

Fig. 1. Structures of aromatic terpenoid ethers.

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7. A methoxy group in place of an epoxide was reported in a promising JH compound in *Chem. Eng. News* **49** (No. 49), 33 (1971). A similar substitution in methyl juvenate decreased JH activity. [See (*2*, p. 257); the methoxy group in the fourth compound should be in position 11].
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9. This is compound IV in (*3*). When tested concurrently, JH-25 was at least 100 times more active than compound IV.
10. See R. W. Bagley and J. C. Bauerfeind (*2*, pp. 113–151) and F. M. Pallos and J. J. Menn (*2*, pp. 303–316).
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13. Mention of a proprietary product does not constitute an endorsement of this product by the U.S. Department of Agriculture.
14. A stainless steel column (180 cm long, 0.32 cm in outer diameter) containing 3 percent HI-EFF-8BP (cyclohexanedimethanol succinate) on 100/120 mesh Gas-Chrom Q (Applied Science Laboratory, State College, Pennsylvania) was used with a column temperature of 185°C and a nitrogen flow rate of 30 ml/min. Retention times were 10.2 and 12.2 minutes for the (*Z*) and (*E*) isomers, respectively.
15. For example, the nuclear magnetic resonance data on JH-25 were CCl_4, δ): 6.88 (4H, two doublets, aromatic H); 5.48 (H, triplet, $J \sim 7$ hertz, $C{=}C\underline{H}CH_2$); 4.47 (2H, doublet, $J \sim 6$ hertz, $C{=}C\underline{H}CH_2O$); 3.30 (2H, quartet, $J \sim 7$ hertz, $O{-}CH_2\underline{C}H_3$); 2.58 (2H, quartet, $J \sim 8$ hertz, $\phi C\underline{H}_2CH_3$; 208 (2H, multiplet, $C\underline{H}_2{-}C{=}C$); 1.7 (3H, singlet, $C\underline{H}_3C{=}C$); 1.2 (16H, multiplets of CH_2 and CH_3 on saturated carbon atoms). (The numbers of protons assigned were rounded to the nearest whole numbers.)
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Retrograde Amnesia Gradients: Effects of Direct Cortical Stimulation

Abstract. *Electrical stimulation was delivered bilaterally to either the anterior or posterior cortex in rats from 0.1 second to 4 hours after a single training trial on an inhibitory avoidance task. As indicated by a retention test given 24 hours later, the length of the retrograde amnesia gradients ranged from 5 seconds to 240 minutes, depending on the brain region stimulated and the intensity of the stimulating current. The stimulation intensity that was threshold for amnesia varied directly with the length of the interval between training and treatment.*

Electroconvulsive shock (ECS) administered shortly after a training experience produces a retention deficit, usually taken as evidence for retrograde amnesia (RA). As the interval between training and ECS increases, the degree of amnesia decreases. This phenomenon is termed a RA gradient (*1*). It has generally been assumed that the RA gradient directly reflects the time course of memory consolidation. Estimates of the memory consolidation period have ranged from 10 seconds to several hours (*2*, *3*). Although the fact of the RA gradient has been widely demonstrated, variations in the length of the RA gradients found in different studies have made it difficult to draw

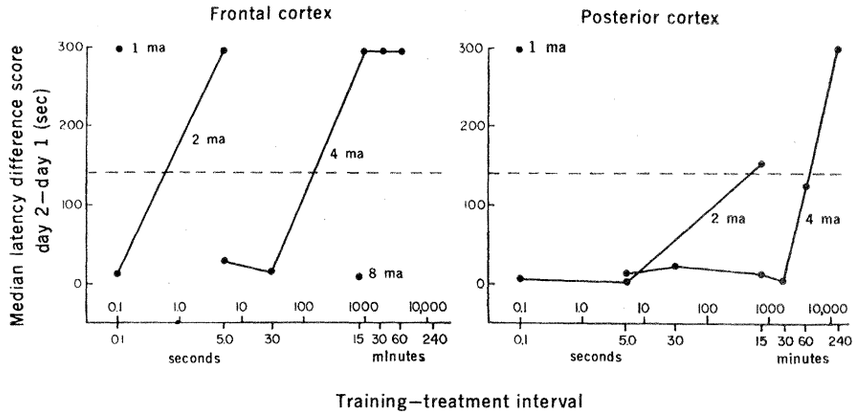

Fig. 1. Median latency difference score (day 2 minus day 1) for crossing into shock compartment. All median latencies less than 140 seconds (dotted line) are significantly lower than latencies for animals receiving foot shock only (median = 300 seconds) ($P < .05$, two-tailed Mann-Whitney U test).

any firm conclusions concerning the "true" time course of memory consolidation. In large part the difficulty is due to a misstatement of the empirical findings. The effective interval between training and treatment is not necessarily a direct reflection of memory consolidation processes. The RA gradient is only a direct demonstration of changes in the susceptibility of memory processes to disruption (*4*).

In previous examinations of RA gradients, ECS was generally administered through earclip or corneal electrodes. Direct brain stimulation—used in the present study—allows the assessment of differentiation of function of brain structures. The study reported here demonstrates that different amnesia gradients are produced by equal-intensity stimulation of frontal and posterior cortex, and that for both cortical regions the length of the amnesia gradient varies directly with the stimulation intensity.

Male Sprague-Dawley rats (Simonsen Laboratories), 55 to 65 days old at the time of training, were used. While animals were anesthetized with Nembutal, skull screw electrodes were implanted bilaterally in 200 rats over frontal and posterior cortex (2 mm anterior and 7 mm posterior to bregma, 2 mm lateral to the midline). These electrodes were attached to Amphenol miniature connector strips and cemented to the skull. The animals were allowed to recover for 7 to 10 days before training. Ten animals were unoperated controls.

Inhibitory (passive) avoidance training was conducted in a rectangular apparatus with a white safe compartment (24 by 14 by 12 cm) separated by a sliding door from a black foot-shock (FS) compartment (37 by 14 by 12 cm) (*5*). On day 1, each animal was placed in the white compartment and the sliding door was opened. When the animal crossed into the black compartment, it received a 2-ma, 2-second FS. At various intervals after the FS (Fig. 1), constant-current stimulation (1, 2, 4, or 8 ma; 0.5 second; 60 hertz) was delivered bilaterally to either frontal or posterior cortex through the skull screw electrodes. Immediately after the brain stimulation, the electrode leads were switched to a four-channel Grass model 7 polygraph which recorded frontal-frontal, posterior-posterior, and unilateral frontal-posterior cortical activity (3 to 75 hertz) for 2 minutes. Twenty animals (ten with implanted electrodes and ten without them) received FS without subsequent brain stimulation.

A one-trial retention test was administered 24 hours later. On the test trial, the animals were placed in the apparatus as before, and the door was opened. Step-through latencies were used as the measure of retention. The step-through latency is the time between the opening of the door and the moment that all four paws cross into the black compartment. The latency on day 2 minus that on day 1 was determined, and 300 seconds was used as the maximum cutoff for latency difference scores.

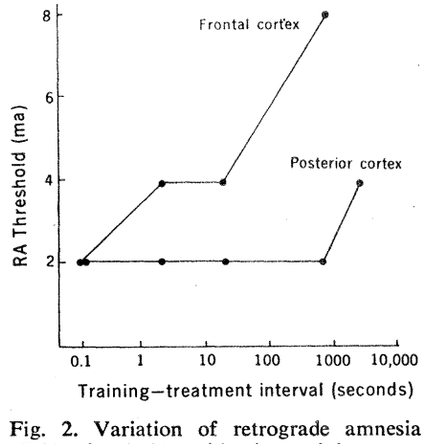

Fig. 2. Variation of retrograde amnesia (RA) thresholds with the training-treatment interval (semilogarithmic graph). The relations between threshold intensity and the training-treatment interval are different for frontal and posterior cortex.

Eighty percent of the FS-control animals had 300-second retention scores. The retention deficits varied with the training-treatment interval, the brain region stimulated, and the intensity of the stimulation (Fig. 1). For any one stimulation intensity, the maximum training-treatment interval for which significant retention deficits could be produced was longer for stimulation of posterior cortex than for the same intensity administered to frontal cortex. However, this difference could be reduced or even reversed by changing the stimulation intensities.

No retention deficit was observed in the groups that received 1-ma stimulation of either the frontal or posterior cortex immediately after the training FS. Animals that received 2-ma frontal cortex stimulation showed a retention deficit only if the treatment was administered within 5 seconds of the training; 4-ma frontal cortex stimulation was effective for those intervals less than 15 minutes; 8-ma frontal cortex stimulation was effective at 15 minutes. In contrast, animals that received 2-ma posterior cortex stimulation had a retention deficit if the treatment was administered within 15 minutes of training; animals that received 4-ma stimulation of the posterior cortex showed retention deficits if the treatment was administered at intervals up to 60 minutes.

Thus, RA gradients in this experiment ranged from 5 seconds to 240 minutes, depending on site and intensity of the stimulation. These results are consistent with evidence that RA gradients are influenced by the severity of the amnesic treatment (*2*, *6*, *7*). The length of the gradient appears to reflect a time-dependent change in the minimal amount of disruption sufficient to produce RA (Fig. 2). In this interpretation, a particular RA gradient represents the period of time during which a disruptive treatment is suprathreshold for producing RA. Weak treatments will consequently be effective for rela-

tively short periods of time after training, but more intense amnesic treatments will be effective for longer periods of time after training. We do not know the asymptote of the effective training-treatment interval, nor do we know whether there is an asymptote. Is it possible—at least in theory—to disrupt memory at any time after training if a treatment of sufficient amnesic intensity is administered? Such thinking raises the possibility of continuity between ECS-produced RA gradients (up to several hours) and some drug treatments that may be disruptive if administered a day or more after training (*7*).

The electrocorticographic recordings made after the stimulation revealed that whereas no animals had brain seizures following 1-ma stimulation of either frontal or posterior cortex, all animals that received 2-ma or more stimulation of either brain site had brain seizures. The precise brain seizure pattern varied with intensity and locus of stimulation; however, the seizure patterns for any one type of stimulation did not vary significantly at different training-treatment intervals.

Thus, although the brain seizure thresholds and patterns did not vary significantly with different training-treatment intervals, the RA threshold increased with time after training. Under the conditions of the present experiment, brain seizures represent a necessary but not always sufficient condition for RA (*8*).

Experimental results have suggested several biological correlates for RA produced by ECS and brain stimulation; among these correlates are brain seizures, postictal depression, long-term changes in brain electrical activity, neurochemical changes, and behavioral convulsions (*6, 9, 10*). It now seems clear that there will indeed be many correlates of RA as a direct consequence of the increase in the RA threshold with time after training. Since both RA thresholds and RA gradients are influenced by a host of factors—including prior experience, the measure of retention, many task variables, and the method of ECS administration (*2, 3, 10*)—reports of many different neural correlates of memory disruption can be anticipated.

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Directionality of Rewarding Impulses within the Medial Forebrain Bundle Self-Stimulation System of the Rat

Abstract. *Self-stimulation performance of rats was tested with conditioning pulses to the anterior preoptic area of the medial forebrain bundle followed at various intervals by test pulses to the contralateral posterior hypothalamic area of this bundle. Alternatively, conditioning pulses were delivered through the posterior electrode and test pulses were sent through the anterior electrode. The animals' performance in these two test sequences was indicative of (i) synaptic facilitation and (ii) a posterior convergence site of "self-stimulation impulses" in the medial forebrain bundle.*

Facilitation of synaptic effects can be demonstrated by applying conditioning (C) and test (T) stimuli to different presynaptic neurons and recording the electrophysiological response from the postsynaptic neurons onto which they converge. To study this phenomenon in heteronymous synergistic motoneurons, for example, Lloyd (*1*) stimulated two afferent branches of the biceps femoris muscle in the cat. The C pulse to one nerve was insufficient to elicit a motoneuronal discharge, while the T pulse to the other nerve did produce a motoneuronal discharge. Stimulating both nerves simultaneously produced a maximal motoneuronal response that was considerably greater in magnitude than that produced by the T pulse alone. As the interval between C and T stimuli (C-T interval) was increased, the magnitude of the response decreased until there was no facilitation with an interval of 14 msec.

In an analogous fashion, Ungerleider and Coons (*2*) demonstrated facilitation of the rewarding effects produced by bilateral stimulation of the medial forebrain bundle (MFB). Rats were taught to press a lever for a train of C-T pulse pairs (*3*) delivered to the MFB. The C pulses were sent through one MFB electrode, and T pulses were sent through the contralateral homologous MFB electrode. The self-stimulation behavior of rats was maximal for pulse pairs with a 0.1-msec C-T interval and was considerably greater in magnitude than for C pulses alone. As the C-T interval was increased, the self-stimulation performance decreased. Thus, these behavioral data suggest that impulses from opposite sides of the brain converge upon a common neuronal system whose output mediates the rewarding effects of MFB electrical self-stimulation. The MFB pathways are represented bilaterally in the brain, contain both ascending and descending fibers, and converge in a number of areas (*4, 5*). For example, some ascending fibers converge in the forebrain (for instance, septal area) and some descending fibers converge in the midbrain (for instance, ventral tegmental area). Because electrodes in the above study (*2*) were bilaterally placed in homologous MFB sites and self-stimulation performance increased as the length of the C-T interval was decreased, the site of convergence seemed to be equidistant from the two stimulating electrodes.