In the adult animal the secretion of adrenocorticotropin, as well as that of other tropic hormones, is moderated by the median eminence region of the hypothalamus. This area is undeveloped during the early postnatal period (*8*). Etkin (*4*) has shown that thyroxine accelerates the maturation of this region in the tadpole. We conclude that this hormone has accelerated the maturation of the central nervous system mechanism underlying this physiological adaptive response (Table 1).

Eayrs and Lishman (*9*) have shown that thyroid hormone deficiency delays the appearance of certain behavioral responses, including the "startle response," in early postnatal life. The maturation of this defensive reflex (*10*) is shown in Fig. 1. Thyroxine-treated rats develop this response several days earlier than controls. Electroencephalograms were obtained from rats 4 to 15 days of age (Fig. 2). In agreement with the results of Bradley *et al.* (*11*), only sporadic electrical deflections of small amplitude appear before 10 days of age (*12*). However, in all age groups the preponderance of high-amplitude waves in the thyroxine-treated animals was in contrast to control animals which generally exhibited waves of lower amplitude. These high amplitude waves changed to low amplitude when arousal stimuli were presented. Thyroxine-treated animals are already responding at day 12, and by day 15 there are characteristic changes in the electroencephalogram. The apparent single response of a control animal on day 12 (Fig. 2c) was not reproducible. Light elicited changes in the electroencephalogram in control animals at an age (15 days) when their eyes were not yet fully opened. At this time the eyes of thyroxine-treated animals are already opened (*2*). The accelerated development of bio-environmental interaction, as evidenced by the earlier onset of the adrenalcortical response to stress, development and response of the electroencephalogram to novel stimuli, and the "startle response," complements the additional observations that the treated animals, when 16 to 18 days of age, acquire a conditioned-avoidance response more rapidly than untreated controls (Fig. 3). The biochemical and histological events underlying accelerated maturation of the central nervous system are not yet known (*13*).

The development of the central nervous system is severely retarded when there is a neonatal thyroid deficiency. The thyroid hormone may therefore play an important role for developing neurons to establish, during certain "critical" (or plastic) periods in early postnatal life, the web of interconnections that lay the foundation for the later behavioral repertoire of the organism.

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14. Supported in part by PHS grant AM06603. We thank Dr. B. Komisaruk and Dr. P. G. McDonald for suggestions, and the Western Research Support Center, Veterans Administration Hospital, Sepulveda, for help in the statistical analysis of the behavioral data.

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Magnesium Pemoline: Effect on Avoidance Conditioning in Rats

Abstract. *Rats administered 20 milligrams of magnesium pemoline per kilogram of body weight learned to avoid shock in a jump-out apparatus in fewer trials than did controls. However, the results suggested that the principal effect of the drug was to facilitate the avoidance behavior of those animals that tended to "freeze" in response to electric grid shock. No differences in retention were observed between experimental and control animals that had achieved equal levels of learning.*

Plotnikoff (*1*) has reported that oral administration of magnesium pemoline in rats enhances acquisition and retention of a conditioned avoidance response in a jump-out apparatus. Bowman (*2*) subsequently questioned Plotnikoff's interpretation of the retention data because the drug and control groups had not achieved equal levels of learning prior to the retention test. We have assessed the generality of Plotnikoff's acquisition findings and tested the retention effect when all animals had achieved equal levels of learning.

Plotnikoff (*1*) tested rats which had been selected as "slow learners." Our data from preliminary experiments suggested that such "slow learners" are rats which adopt a freezing response in the jump-out apparatus. That is, rats which fail to exit from the chamber within the first few acquisition trials tend to adopt a motionless, rigid posture when placed in the box on subsequent trials; hence they learn the required jump-out avoidance response more slowly (*3*). We attempted to determine the extent to which the facilitative effects of magnesium pemoline upon avoidance learning is restricted to rats that freeze in response to shock.

Male Sprague-Dawley rats (230 to 250 g) were caged singly in a large colony room and had free access to food and water. Each rat was handled 1 minute each day for 3 days before selection and testing. The apparatus, essentially that described by Plotnikoff (*1*), consisted of a wooden chamber (20 by 30 by 50 cm) with a grid floor (3-mm diameter bars spaced 2 cm apart). An escape opening 20 cm square was cut into one wall 30 cm above the grid floor, and an escape platform extended outside the box. The escape platform and adjoining interior wall of the chamber were covered with wire mesh (13 mm squares) which enabled the rats to climb out of the box. The testing room was lighted by a 10-watt bulb located approximately 1 m directly above the test chamber. A white-noise

Table 1. Mean trials necessary for the rats to attain criterion in acquisition training for the drug and control groups under the different shock conditions of groups 1, 2, and 3. Number of animals in each group is given in parentheses.

Condition	Mean trials (No.)		
	Group 1	Group 2	Group 3
Drug	13.8(9)	7.4(14)	4.7(12)
Control	24.0(9)	11.6(14)	5.4(12)

level of 60 db was maintained in the room.

On the day of acquisition training each animal received a single injection directly into the stomach by means of a No. 8 French catheter. Either magnesium pemoline (20 mg/kg body weight) or 2.5 ml of the vehicle alone (0.3 percent tragacanth suspension) was injected 30 minutes before the first acquisition trial (*4*). Each rat was then placed on the grid of the chamber and 15 seconds later a tone 1000 cycle/sec and 6 db above white noise was presented. After 10 seconds of tone, the grid floor was charged by an electric shock from a Davis constant voltage source and scrambler unit through a 250,000-ohm series resistance. The tone and shock continued until the rat exited (group 3) or until 5 seconds had elapsed (groups 1 and 2). All animals were tested until they showed three consecutive avoidance responses, each within 10 seconds after being placed on the grid; this level of learning constituted the criterion. After each rat attained this criterion, it was returned to its home cage. The four retention trials presented approximately 24 hours later were identical to acquisition trials except that shock was omitted. In all phases of testing the interval between trials was 8 to 10 minutes.

Freezing behavior was manipulated by testing animals under three different procedures. The procedure for group 1 was designed to insure that freezing behavior would invariably occur. The 18 rats in group 1 were selected from a group of 30 animals according to Plotnikoff's criterion (*1*), that is, failure to leave the apparatus in a three-trial test session the day before acquisition training. During acquisition training, group 1 rats received a mild shock (80 volts) for not more than 5 seconds per trial. If the rat failed to exit within 5 seconds after the onset of shock, the shock was terminated and the animal was removed by hand.

Animals in groups 2 and 3 were not tested before acquisition training and therefore no selection was involved. Group 2 ($n = 28$) received a 110-volt shock for not longer than 5 seconds and were removed by hand if they failed to exit in that time. The procedure for group 3 ($n = 24$) was designed to minimize freezing behavior. These animals received a 140-volt shock which was terminated only when the animal left the apparatus. This procedure insured that freezing responses were never reinforced by shock termination.

Table 1 contains the mean number of trials necessary for the rats to attain the criterion. These data (*5*) indicate that the rate of acquisition of the avoidance response was affected by the drug, by the shock condition, and by the interaction of the two. Although the rate of acquisition was generally increased by magnesium pemoline, the absolute magnitude of the facilitatory effect of the drug was directly related to the amount of freezing behavior each shock condition produced. This interaction between the drug effect and the shock conditions can be considered from two viewpoints. More intense shock may have produced such rapid learning that the effect of the drug was masked; or, stated conversely, the effect of the drug became apparent only with milder, brief shocks where the learning rate was slow enough to permit facilitation. However, a second interpretation of the observed interaction is that magnesium pemoline interferes with freezing behavior, and only in this way does it appear to "facilitate learning."

Table 2 contains the mean exit latencies on the four retention trials given 24 hours after acquisition training (*6*). Although the different shock conditions produced differential retention (rats that received high and intermediate amounts of shock demonstrated more retention than the rats that were selected before acquisition training and that received low amounts of shock) the drug had no reliable effect upon retention under any shock condition (*6*). Bowman (*2*) has suggested that the retention effect which Plotnikoff reported (*1*) might be attributed to the differential performance level of Plotnikoff's experimental and control animals before the retention test. Our results support Bowman's contention. Administration of magnesium pemoline before acquisition training had no effect upon retention when the level of initial learning was controlled.

The mechanism by which magnesium pemoline enhances avoidance learning in the jump-out apparatus is unclear. One hypothesis would attribute the effect to the properties of the drug which stimulate the central nervous system (*7*). The resultant increase in general motor activity would, by decreasing freezing behavior, ostensibly facilitate avoidance learning. A second possibility is that the drug makes the rats more reactive to shock; therefore the observed facilitative effect is comparable to increasing the effective shock intensity. A third hypothesis would attribute the facilitative effect of magnesium pemoline to its action upon some general learning mechanism (*1*, *8*) by means of its action upon the biochemical systems which synthesize nucleic acids (*9*). Further behavioral testing should differentiate between these possible explanations and demonstrate whether or not the effect is related to a basic biochemical learning mechanism.

Table 2. Mean latency in seconds on four retention trials for the drug and control groups under the different shock conditions of groups 1, 2, and 3. Number of animals in each group is given in parentheses.

Condition	Mean latency		
	Group 1	Group 2	Group 3
Drug	17.2(9)	7.6(14)	8.0(12)
Control	10.4(9)	5.8(14)	8.7(12)

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3. Although "freezing" obviously competes with a jump-out avoidance response, freezing is adaptive in another sense because jumping about on an electric grid intermittently maximizes the current density at the rat's paws and thus also maximizes the noxiousness of the shock. In this sense, then, rats that learn to freeze may not necessarily be slow learners.
4. Rats were injected by W. Beatty and S. Zornetzer, and P.W.F. tested them without knowing which animals received the drug.
5. An unweighted means analysis of variance of trials to criterion (Table 1) revealed a statistically significant effect of drug ($F = 10.73$; $df = 1,64$; $P < .001$), shock conditions ($F = 27.51$; $df = 2,64$; $P < .001$) and their interaction ($F = 3.39$; $df = 2,64$; $P < .05$).
6. An unweighted means analysis of variance revealed a statistically significant effect of shock conditions ($F = 4.55$; $df = 2,64$; $P < .01$), but no significant drug ($F = 1.71$; $df = 1,64$) or interaction ($F = 1.23$; $df = 2,64$) effect.
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