ing strength (Fig. 2, G–I). An action potential was not evoked in this cell, since the resting potential was 35 mv. The field potential was recorded in the immediate vicinity of the cell after withdrawal of the microelectrode (Fig. 2J, negative up). The EPSP is not followed by the large inhibitory postsynaptic potential (IPSP) which would be recorded under similar conditions in cat Purkinje cells (*11*). Figure 2K shows a repetitive activation of a Purkinje cell by a parallel fiber activation, and in Fig. 2M a WM stimulus precedes the Loc stimulation. Both cells had a resting potential of 40 mv. As in the previous case, there is no sign of an IPSP. The field potential was recorded in the vicinity of the cell prior to penetration (Fig. 2M). The extracellular Purkinje-cell action potentials are apparent. The negative potential following Loc stimulation is the parallel-fiber field. Most cells recorded intracellularly had resting potentials ranging from 30 to 55 mv, and thus only small action potentials could be evoked.

Our findings combine to demonstrate the absence of long-lasting inhibition upon frog Purkinje cells. The field potentials initiated by parallel-fiber activation may be interpreted as produced conjointly by the parallel-fiber action currents (initial spike-like negativity) and the dipole evoked in the Purkinje cells by the synaptic depolarization of their superficial dendrites. This synaptic impingement would establish a current sink, seen as a large negativity near the surface, and a source of current from the basal dendrites and soma responsible for the production of the deep positive potentials. The negative-positive transient observed at depths of 200 to 500 μ seemingly represents compound action potentials of Purkinje cells produced by the activation of parallel fibers, its maximum amplitude corresponding roughly to the level of the Purkinje-cell layer (300 μ). In accordance with this interpretation, the reduction of the negative-positive transient at a depth of 400 to 500 μ would be understandable, since the Purkinje-cell axons turn laterally towards the cerebellar peduncles after reaching the granular layer (*3*). The reversal of the field at 100 μ implies that the superficial Purkinje-cell dendrites cannot generate action potentials but serve as current sources to the soma and thick dendrites below. A similar lack of superficial dendritic invasion has been observed in this animal during study of the antidromic fields at approximately the same depths (*12*). The fact that there is much less lateral spread of the positivity than in the cat corroborates the suggestion that in the cat the out-of-line positivity is largely due to the inhibitory action of stellate (*2*) and basket cells (*1, 2*). Reduction of the antidromic field produced at short intervals after a strong Loc stimulation can be explained as being caused by the collision of the antidromic action potentials with the action potentials being evoked orthodromically after the Loc stimulation (Fig. 2, D–F). However, the possibility of a short-term inhibitory action by the activation of axon collaterals of Purkinje cells (*11*), which have been shown in the cat to be inhibitory to cerebellar nuclei (*13*), or by parallel-fiber activation of the small interneurones of the molecular layer (*5*) remain as possible components of this depression. On the other hand, even under conditions of low resting potential (Fig. 2, G–I), which are known to increase the electromotive force of Purkinje cell IPSP's in the cat (*11*), no IPSP's were recorded in frog Purkinje cells. This lack of inhibitory impingement was noted after graded Loc or WM stimulation or any combination of these two stimuli in over 20 Purkinje cells penetrated.

The fact that the cerebellum of the frog, which is known to have a definite regulatory action on the postural tonus of the animal (*14*), is devoid of long-lasting inhibition shows that an effective functioning of a primitive cerebellum can occur in the absence of the inhibitory regulation of Purkinje cells.

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Magnesium Pemoline: Lack of Facilitation in Human Learning, Memory, and Performance Tests

Abstract. *Either a placebo or 25 or 37.5 milligrams of magnesium pemoline was administered on a double-blind basis to three intelligence-matched groups of normal, adult males. Learning and 24-hour retention tests included verbal learning, motor learning, and classical conditioning. Short-term memory tests were administered through both the visual and auditory modalities. Arm-hand steadiness and visual reaction time performance tests were included. The only measures revealing significant group differences showed the performance of subjects given pemoline was inferior to that of subjects given a placebo.*

Recent animal studies with magnesium pemoline have indicated that this drug increases the amount of brain RNA (*1*), facilitates acquisition, and extends retention in shock avoidance learning (*2*). Methodological criticisms have been leveled at the interpretation of the animal retention data (*3*). Human tests of a similar drug, lacking only the magnesium constituent, have been performed in Europe over the last 5 years. In one case the findings indicated facilitation of a complex psychomotor task (*4*), while another study found the drug effect too variable to be of value in speeding the motor and auditory responses of jet pilots (*5*).

Although many stimulants have been shown capable of speeding reaction times and increasing vigilance, compounds have rarely appeared which could specifically enhance the rate of learning or the extent of retention in

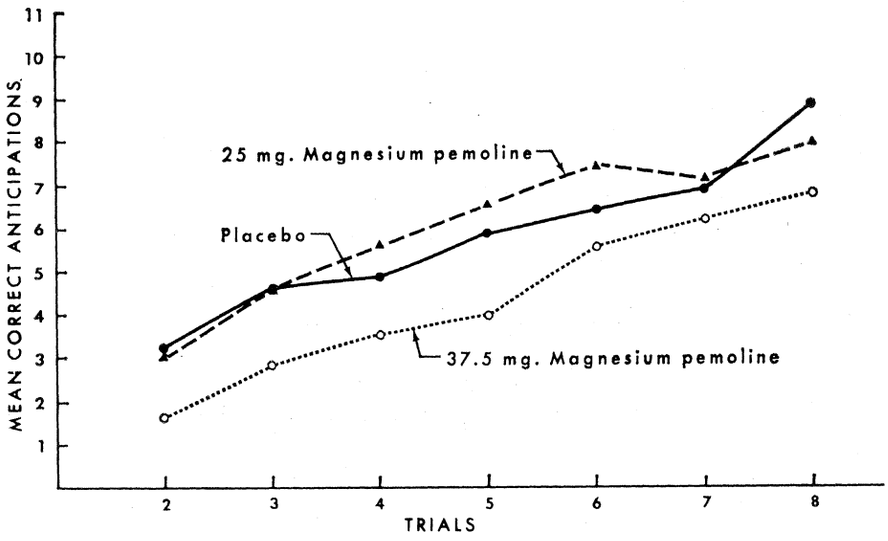

Fig. 1. Mean correct anticipations in verbal learning. (N = 12 per group). The group given placebo and the group given 25 mg of the drug did not differ significantly, but the 37.5-mg group performed significantly poorer than both of the other groups.

man. Working with RNA injections in geriatric patients has led one experimenter (*6*) to conclude that memory function can be most improved in patients having the least deterioration. If this is the case, subjects having normal brain functions might be expected to show even greater improvement.

The subjects used in this study were 39 young adult men, with carefully screened medical and psychological backgrounds. Subjects were tested in groups of three. Members within each group had scores within five points of each other on a test which assesses overall general intelligence (*7*). Each subject in a three-man group received an oral dose of either 25 or 37.5 mg of magnesium pemoline (*8*), or an identical-appearing placebo. Doses were administered on a double-blind basis 3 hours prior to the start of testing. For the purpose of controlling diets and off-test activities, subjects were kept on a hospital ward overnight preceding the 24-hour retention tests.

The verbal learning test consisted of two lists of three-letter, English-language words presented to the subjects for learning by the serial anticipation method (*9*). During the pre-drug familiarization phase, a seven-word list was used. The words were presented by tape recording to subjects wearing headphones. Subjects were instructed to listen to the list all the way through on the first trial, then to anticipate each word by saying it aloud before hearing it from the recording on successive trials. The words appeared at 3-second intervals with an 8-second intertrial interval. A 12-word list was used in the drug or placebo phase. The number of correct anticipations was recorded for each of eight trials. The 24-hour post-drug retention test consisted of a single trial with the 12-word list.

An analysis of variance of the acquisition trial data indicated the existence of significant group differences ($F = 4.91$, df = 2/33, $p < .05$, $N = 12$ per group). Post hoc comparisons among the groups revealed that no significant difference existed between the group that received a placebo and the group that received 25 mg of magnesium pemoline, but the group that received 37.5 mg of the drug performed significantly poorer than both the placebo group ($F = 32.79$, df = 1/231, $p < .01$) and the 25-mg group ($F = 46.56$, df = 1/321, $p < .01$). See Fig. 1. There were no significant group differences in the 24-hour retention test scores.

In the motor learning test the subject's task was to maneuver a stylus through a curved track without touching the sides or bottom. He could view his progress only by means of the mirror mounted above the track. The stylus acted as an electric contact whenever it touched a surface of the track, thus furnishing measures of the number of errors, the total duration of the errors, and the elapsed time from start to finish. Subjects were informed of errors by a light which came on whenever the stylus was in contact with a track surface. Pre-drug familiarization with the apparatus was given without the mirror. Each subject traced the track six times during the drug phase and six times during the 24-hour retention phase. The results of the analyses of variance for all three measures taken during the acquisition trials yielded no significant group differences. However, a significant interaction of trials and the total error time measure was found ($F = 2.41$, df = 10/179, $p < .05$, $N = 10$ per group). The simple main effects analysis indicated that this significant group

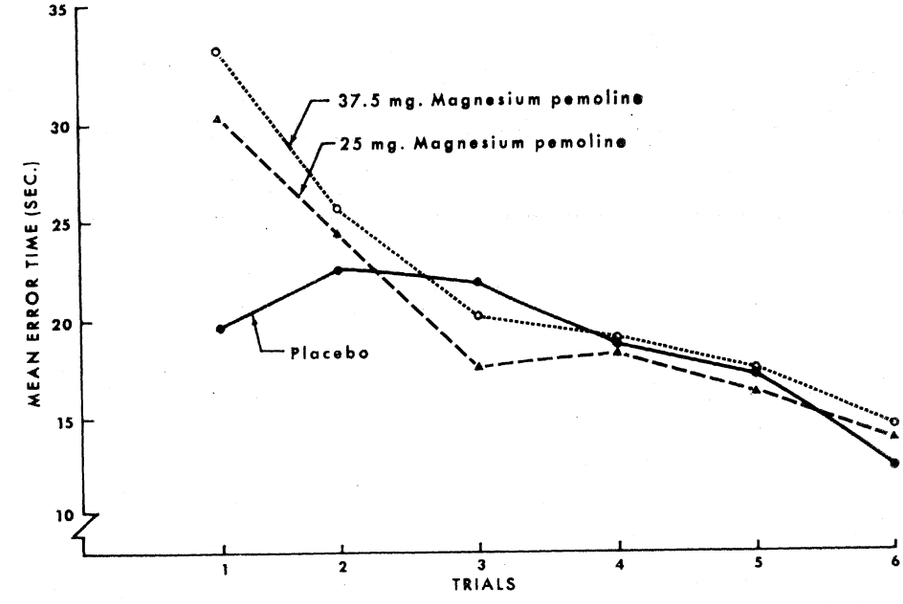

Fig. 2. Mean error time on the motor learning task (N = 10 per group). Both drug groups showed a steeper learning gradient because they did significantly poorer on the first trial.

difference existed only on the first trial ($F = 7.46$, df $= 2/27$, $p < .01$). Figure 2 shows that both of the drug groups have greater initial error times than the placebo group. This finding brings out the importance of viewing the data completely. For example, if one were to consider only the slopes of these plots, or the magnitude of the F-ratios obtained for their practice effects, or the percent improvement for each group, one could conclude that the drug groups showed stronger learning. However, these data show that on an absolute basis the drug groups were poorer in performance, at least initially. One may ask at this point whether the groups were adequately matched at the start of testing. A partial answer may be obtained by noting that the groups did not differ significantly during the familiarization trials without the mirror. Moreover, the drug group curves clearly paralleled each other for all the trials and traced a markedly steeper gradient than the curve generated by the placebo group. The three measures taken during the retention trials yielded no significant group differences or interactions.

Classical conditioning of the galvanic skin response was performed at 6 hours and again at 24 hours after drug administration. Both days' trials consisted of three phases. The first phase, habituation, consisted of 30 headphone presentations of a loud clicking sound 0.5 second in duration, occurring at variable intervals, the mean interval being 20 seconds. In the conditioning phase there were 22 clicker presentations, each followed immediately by a 0.5-second shock delivered to the finger tips. The shocks were adjusted to the individuals' tolerances and ranged from 1.5 to 3.0 a-c ma. During the conditioning phase, eight test trials occurred in which the clicker sounded without the shock. From one to four shock trials were interposed between the test trials.

The last phase on both days was extinction, in which 30 clicker presentations were made without the shock. Lykken zinc–zinc sulfate electrodes (*10*) were applied to the index and third fingers of the subject's left hand. Shock electrodes were applied to the fingers of the right hand. Although complete records were obtained, eight points in each phase were selected a priori for data analysis and were the same for all subjects. Resistance measurements were made to the nearest 0.5 kohm for most subjects. A few subjects who showed extreme responsiveness were measured to the nearest 1.0 kohm. Resistances were converted to log conductances and subjected to analyses of variance. The measures analyzed were the background log conductance levels at the point in time just prior to a click presentation, and the magnitude of the response defined as the maximum increase in the log conductance level which occurred within 6 seconds of the onset of the clicker. There were no significant group differences ($N = 12$ per group) in background conductance levels or in response magnitudes during any of three phases on either the drug test day or on the 24-hour retest.

The auditory short-term memory test consisted of four sets of random digits presented to the subject by tape recording. The first presentation of each set had four digits spoken at a rate of one digit per second. Each successive presentation in a set had an additional digit, up to a limit of eleven digits. The score obtained by the subject for each set was the number of digits in the last correctly recalled presentation after which he had two successive failures. No significant group differences ($N = 13$ per group) were found. Familiarization trial data indicated that the groups were matched.

The visual short-term memory test was developed to investigate the possibility of reduction of inhibition of memory traces by magnesium pemoline. It consisted of a series of random six-digit numbers which were projected tachistoscopically on a screen. One set of three digits appeared for 100 milliseconds and was immediately followed by a second three-digit set which also appeared for 100 milliseconds. These six digits were in turn followed by a pattern of crossed lines to reduce the afterimage of the second set. The subject's task was to recall all six digits in the correct order. Although the last three digits were recalled in a majority of the cases, considerable difficulty was encountered in recalling the first three digits. This was the desired effect and, presumably, was due to the inhibitory influence of the second set of digits upon the memory trace of the first set. The two measures obtained on this test were (i) the total number of digits correctly recalled in a series of 20 six-digit presentations, and (ii) the total number of times the subject correctly recalled the first of the two three-digit sets. Again, the analyses of variance yielded no significant group differences ($N = 11$ per group).

Arm-hand steadiness was tested with the same track-tracing device and three measures described above in the motor learning task, with the exception that subjects were allowed to view their work directly. Five pre-drug familiarization trials and two trials after drug administration were run. No significant group differences ($N = 13$ per group) were found on any of the three measures.

Visual reaction time was tested by having the subject place his index finger on a starting point and then move his hand quickly to a button 5.0 cm away whenever a light appeared on the panel. A trial consisted of ten variably spaced light presentations. The measure obtained for each trial was the total response time for all ten light presentations. Four pre-drug familiarization trials and two trials following drug administration were run. No significant group differences ($N = 12$ per group) were found for visual reaction time.

These data show that magnesium pemoline in the dose ranges tested does not facilitate learning, memory, or performance in normal, adult men. In fact, the only statistically significant effects indicate that the heavier dose is deleterious for verbal and motor learning. This study was concerned with acute effects of the drug. While chronic administration might yield different results, only acute doses were required for the effects reported with animals.

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