ANNEX I

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SAINT FRANCIS MEMORIAL HOSPITAL
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CURRENT PROBLEMS IN RESEARCH

Influence of Magnesium Pemoline on Learning to Read

Progress Report

This paper is a preliminary report on an experiment designed to test the influence of magnesium pemoline on a complex learning task, learning to read.

Learning may be defined as the modification of behavior by experience, or stated more simply, the acquisition of skill or knowledge. Memory is the capacity to recall past thoughts, ideas and mental images. Sometimes the definition of memory is extended to include the capacity to perform previously learned skills. For practical purposes, the words learning and memory describe similar or identical things. Learning is a process; memory is a capacity or a storage bank.

For the past five decades it has been accepted generally that the process of learning must be a chemical or a physical and chemical phenomenon. However, very little was known about its details. Quite recently, a mass of research has converged on the problem, as illustrated by one bibliography of 571 papers (1).

The vast majority of the reports in this area deal with experiments on animal subjects and in most instances the learning tasks are extremely simple, such as learning T-mazes and learning a conditioned avoidance response in a jump-out apparatus. Where human subjects have been used, learning tasks have been limited to problems such as those using a discrimination-reaction apparatus, or by reproduction of a design or picture, exposed and then removed from sight. Many investigators exhibit an understandable tendency to interpolate data from experiments of this kind to practical problems of education, mental retardation or senile memory deficits.

It is now feasible to test the interpolations from simple learning tasks to a complex, time-extended learning problem, specifically, learning to read. A new system of instruction, Conversational Reading, provides a means for accelerated reading instruction(2). Persons who are literate but who are not necessarily trained teachers perform the teaching role. Reading skills can improve up to several

grade levels during an 8-12 weeks teaching period. The system of instruction is well adapted to prison teaching situations and was used in a prison, the California Medical Facility at Vacaville, for the present study.

There is not complete unanimity of opinion regarding the action of magnesium pemoline. Plotnikoff reported that the drug enhanced the acquisition and retention of a conditioned avoidance response to electric shock in rats, in contrast to methamphetamine, which did not enhance this response (3). Beach and Kimble, using a similar apparatus, found that rats injected with magnesium pemoline had an increased spontaneous activity, that they tended to jump more quickly at a conditioned stimulus, but they did not exhibit "enhancement by magnesium pemoline" of learning and memory (4).

Concurrently, observations were being made on the effects of magnesium pemoline on human subjects. Cameron administered the drug to a group of patients with senile brain changes and found an increase in alertness and a reported improvement in the ability of subjects to reproduce geometric drawings (5). Ronald Smith, using refined psychological methods for measuring short-term memory, found no facilitation of learning, memory or performance in normal adult men (6). Cameron criticized Smith's conclusions, stating that Smith tested his subjects 3 hours after drug administration, whereas Cameron felt that the drug achieved statistically significant "improvement" only after one month of administration (7). Cameron submitted a table in this paper which showed an increase of "Mean I.Q." from 73.5 to 82.2 over a month. Also, Cameron implied that "brain-damaged humans" might respond better to magnesium pemoline than normal subjects.

The literature regarding magnesium pemoline which has been cited may be summarized as sometimes open to criticism of experimental method, sometimes contaminated by anecdotal material, and generally contradictory. One of the most interesting controversial points in the literature was the question of whether magnesium pemoline acted to stimulate RNA polymerase activity. Glasky and Simon reporting in the affirmative (8), and Morris, et.al. defending the negative (9).

Experimental Procedures

The present study was undertaken at the California Medical Facility at Vacaville, a state prison*. Volunteer

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subjects were selected from the prison population according to the following criteria: I.Q. 85 or above and 2 or more years below the level of reading skill which would be expected from schooling and I.Q. From a pool of 50 subjects, 20 pairs of men were selected, so that each member of a pair was as close as possible to his opposite number in I.Q., schooling, measured reading skill, race and cultural background. Through a system of random numbers, the men in each pair were split to form the experimental and control groups. Thus, in the beginning, experimental and control groups were made as comparable as possible. Later losses of men, principally through transfers out of the institution, but in some cases because of abnormal initial laboratory findings such as elevated SGOT, resulted in some replacements which were not paired as accurately as the original group. Members of the experimental group received a 25 mg. tablet of magnesium pemoline each morning; members of the control group received a placebo. Throughout the experiment there was no instance wherein any individual, subject, inmate teacher, or investigator broke the code. All subjects were led to believe that they were taking the drug; no subject ever questioned this. There were no illnesses attributable to the drug, and no complaints of adverse reactions.

The principal teaching activity was carried out between 6 P.M. and 9 P.M. evenings. Individual instruction was supplemented by language laboratory tapes and by coordinated assigned reading. Enthusiasm for the program was great. One 17 year-old, deemed unable to sign a waiver for liability immunity because of his age, carried his petition to remain in the study to such an administrative level that he was allowed to remain in the teaching program, without medication or placebo. He is not included in the statistics.

Most subjects completed the entire 60 lessons of the Basic Program of Conversational Reading, approximately 12 weeks. They were tested prior to the experiment, at the 40th Lesson (8 weeks), and after the 60th Lesson. A few subjects were transferred out of the institution before completing the 60 Lessons, and for these men, test scores run only to Lesson 40.

Measurement of reading skills deserves some discussion. A cardinal rule, often disregarded, is that a method for teaching a skill such as reading must be measured by an instrument or by instruments extrinsic to the method being studied. Otherwise, if the measurement is intrinsic to the method, such as a vocabulary test made up of words taught, spuriously high improvement scores are found. In the

present study, two quite different commercially-available tests were used, the Stanford Achievement Test for Reading and the Gilmore Oral Reading Test. The former has a word-meaning or vocabulary section and a paragraph-meaning, or comprehension section. The Gilmore is a test wherein the subject reads selected and standardized material aldud and is questioned on content. It is scored according to vocabulary and comprehension. All subjects were tested with both of these instruments before medication or instruction began, at the 40th Lesson, and at the end of the experiment after completion of the study. A few subjects were transferred from the institution after the 40th Lesson and had no testing after the 60th Lesson.

Results

The results of this experiment are expressed in reading test scores, or measures which are designed to indicate the grade level of a subject, measure his improvement with training, and in this experiment determine if magnesium pemoline has a measurable effect on the learning process. Measuring instruments are two commercially-available tests, one of which (Stanford Achievement Test) is directed toward silent reading skills, the other (Gilmore Oral) is based on oral reading, followed by questioning to determine comprehension. Alternate forms of the tests are used to avoid practise effects.

The actual scores of the tests are expressed in grade levels. Thus if a subject scored 4.0 before training and 5.5 at the end of 60 lessons, it would be concluded that he increased in reading skill, according to the test, by 1 1/2 years.

Experimental and control groups in this experiment were compared with regard to both tests and at testing after the 40th Lesson and after the 60th Lesson. Both groups improved, but there was a consistent tendency for the control group to improve more than the experimental group. Although the average differences sometimes appeared to be appreciable, simple statistical measures of significance of difference failed to show that any single difference was significant. It was our opinion that the array of differences favoring the control group could not be manipulated statistically as a set of independent variables, since all were part of a single experiment.

It is possible that there are more appropriate ideas regarding statistical interpretation. Therefore, we have decided to confine ourselves to presentation of raw data and means in this preliminary report.

Table I indicates the grade level reading scores of 22 experimental subjects on the Stanford Achievement Reading Test, and the Gilmore Oral Reading Test before training or medication, after forty lessons (8-10weeks) and after sixty lessons (12 or more weeks). Table II is similar to Table I, except that control group data are presented. Table III presents the means of the Stanford and Gilmore tests for experimental subjects. Table IV presents the means of the Stanford and Gilmore tests for control subjects.

Finally, Table V presents the mean grade level gains in reading for the control and the experimental groups, after forty lessons and after sixty lessons, on the Stanford, the Gilmore and the means of the two independent tests. This table represents the average gain in grade level years. The average gains range from .61 years to 1.77 years for the learning period. Comparison of the control group scores with the magnesium pemoline experimental group scores indicates an 11 out of 12 superiority of control group gains over experimental group gains.

One question of experimental design was thought to deserve consideration. It was stated earlier that the original experimental and control groups were set up with subjects in each group paired for I.Q., tested reading level and other pertinent variables. Later, with drop-outs and transfers, it was necessary to introduce new subjects in one or the other groups who did not have opposite numbers. To check the possibility that these changes may have introduced new factors, a table was made which included only subjects who were among the original pairs. Table VI presents the means of the Stanford and Gilmore tests for paired individuals only. Members of each pair are opposite one another. It will be noted that controls improved on the average by 1.32 years, while experimental subjects improved .67 years, at the 40th Lesson. Similar differences are seen at the 60th Lesson level although there were 4 drop-outs among the control group. It is thus apparent that the observed but not statistically significant differences between experimental and control group exists when the cases are limited to those originally paired.

Discussion

One interpretation of the data presented in this paper is that no evidence is adduced to support the hypothesis that magnesium pemoline, administered in a daily dose of 25 mg. over a period of many weeks, facilitates learning in a complex, long-range learning situation, specifically a reading training program. The conclusion suggests itself that generalization regarding the functions of "learning" and "memory" from earlier experiments may have been premature. The possibility suggests itself that the animals in Plotnikoff's experiment and the human subjects in Cameron's experiment may have performed as they did because they were stimulated or made more alert, and not because their learning was reinforced. A controlled human experiment reported by Gelfand et al., demonstrates the stimulant effects of magnesium pemoline of fatigued subjects (10).

Close examination of the data reported here leads to another interpretation. At Lesson 40 and again at Lesson 60, both the Stanford and the Gilmore measures of reading proficiency consistently show the control group to be leading the experimental group in reading improvement. Preliminary calculations not reported here indicated that no single comparison of control and experimental groups was statistically significant. No final conclusion can be made that the control group subjects in this experiment were better learners than those given magnesium pemoline. However, the consistency of the data could lead to the speculative hypothesis that magnesium pemoline could have a deleterious effect on learning and memory.

A modern view of learning is that it can be divided into at least two phases, an early, largely electrochemical or reverberation circuit phase, and a later consolidation phase which depends on the synthesis of specific neuronal nucleoproteins (11). Conceivably, a drug could have a favorable effect on the first phase and a deleterious effect on the second phase.

The data presented in this paper which are at most suggestive that magnesium pemoline may have an adverse effect on learning could be related to the findings of Burns et al. (12). Subjects were required to learn a complex discrimination-reaction problem. Magnesium pemoline, as well as amphetamine were reported to have a possible deleterious effect on learning, although there was an insufficient number of cases to afford statistically significant results. The Burns experiment would certainly be an example of first-phase memory, while the experiment reported here, dealing with long-term acquisition of reading-skills, is an example of second-phase memory.

One criticism of this study would be that the dose of magnesium pemoline was insufficient. It is possible that administration of larger amounts of the drug would clarify some of the problems which have been raised, and at the same time afford an opportunity to search for side-actions of magnesium pemoline.

Summary

Prisoner volunteers, interested in improving educational deficiencies in reading, were given an intensive program in reading training over a period of 10-12 weeks and concurrently given a daily dose of 25 mg. of magnesium pemoline. Control subjects, equally motivated and similarly selected, received the same training and placebo medication. The tested reading skills of both groups of subjects improved markedly. By test, control group subjects improved consistently more than experimental group subjects but the differences in improvement did not reach levels of statistical significance.

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Table I

Grade Level Reading Scores

Magnesium Pemoline

Subject	Stanford Reading Achievement			Gilmore Reading Test		
	Base Score	After Lesson Forty	After Lesson Sixty	Base Score	After Lesson Forty	After Lesson Sixty
r 13	4.5	6.7	7.5	5.1	5.2	5.5
16	2.5	3.5	3.9	4.5	4.4	4.4
os 17	4.3	5.3	4.3	4.1	5.2	5.5
n 21	5.9	6.4	7.1	5.2	6.6	7.1
23	4.2	5.1	5.1	4.2	4.7	5.2
za 25	5.7	7.2	7.5	3.2	5.4	7.4
6	5.5	7.1	7.3	5.3	6.6	6.5
a 28	5.9	4.9	5.5	4.5	4.8	4.9
38	5.4	4.7	5.2	4.3	5.0	6.1
tte 45	5.1	4.9	5.1	4.4	5.1	5.6
ld 47	4.1	4.2	4.6	4.5	5.5	5.3
49	5.2	5.4	6.7	4.1	5.4	6.2
50	2.1	3.0	3.3	3.1	3.3	3.6
el 51	5.9	5.1	5.2	5.0	5.8	5.6
52	5.1	5.3	5.5	5.2	6.0	5.6
an 59	2.3	3.6	3.9	2.8	4.0	4.5
ngs 60	4.9	4.9	5.3	3.6	5.5	6.1
48	5.1	6.5		3.8	5.8	
52	3.5	4.3	5.6	3.6	4.9	5.1
ns 54	4.8	6.3	6.5	4.1	4.7	5.2
on JC	2.9	3.4	4.5	1.0	1.5	3.0
YC	3.9	4.3	5.1	3.8	3.9	4.2
Sum	988	1121	1147	894	1093	1126
Mean	4.49	5.10	5.46	4.06	4.97	5.36
N	22	22	21	22	22	21
Improvement		.61	.97		.91	1.30

Table II

Grade Level Reading Scores

Control Group

Subject	Stanford Reading Achievement			Gilmore Oral Reading Tes		
	Base Score	After Lesson Forty	After Lesson Sixty	Base Score	After Lesson Forty	After Lesson Sixty
12	5.2	5.1	6.1	5.9	5.0	5.5
14	3.7	3.5	5.0	3.2	5.5	5.5
15	5.7	8.0	6.9	4.2	5.9	6.9
rd 18	5.1	6.4	5.9	4.9	5.8	5.8
rt 22	4.3	6.8	9.0	4.7	6.2	5.8
s 30	4.9	4.7	5.2	5.4	4.9	5.3
e 31	4.0	7.8	9.5	4.5	5.9	6.8
33	1.9	4.9	6.1	2.2	4.6	4.5
35	5.3	5.2	6.8	4.2	5.5	5.4
1 36	4.2	5.8	6.1	4.3	5.2	5.5
37	5.3	6.3	7.0	4.3	5.3	5.8
n 46	5.2	6.3	6.1	3.4	6.4	5.5
58	4.1	5.5	7.4	4.4	5.8	6.0
61	4.6	4.2	3.2	4.4	4.5	4.1
son 63	4.9	7.2	6.1	4.8	6.1	6.5
65	5.4	6.4	6.7	4.6	6.4	6.8
24	4.6	7.3		4.7	6.6	
27	4.5	4.2		4.3	4.4	
32	6.0	5.9		5.8	7.1	
41	4.7	5.8		4.7	5.2	
57	3.2	5.8		3.4	5.2	
SP	4.6	4.7	5.3	4.4	4.5	5.0
Sum	1014	1278	1084	967	1220	967
Mean	4.61	5.81	6.38	4.40	5.55	5.69
N	22	22	17	22	22	17
Improvement		1.20	1.77		1.15	1.29

Table III

Grade Level Reading Scores

Magnesium Pemoline

Subject Number	Mean of Stanford and Gilmore Tests		
	Base Score	After Lesson Forty	After Lesson Sixty
13	4.7	5.9	6.5
16	3.5	3.9	4.1
17	4.2	5.2	4.8
21	5.6	6.5	7.3
23	4.2	4.8	5.2
25	4.5	6.3	7.6
26	5.4	6.8	6.9
28	5.2	4.9	5.2
38	4.9	4.9	5.7
45	4.7	5.0	5.4
47	4.3	4.8	5.0
49	4.6	5.4	6.5
50	2.6	3.2	3.4
51	5.5	5.5	5.4
53	5.2	5.7	5.5
59	2.6	3.8	4.2
60	4.2	5.2	5.7
48	4.5	5.9	6.2
52	3.5	4.6	5.3
54	4.4	5.5	5.8
JC	1.9	2.5	3.8
YC	3.9	4.1	4.7
Sum	941	1104	1202
Mean	4.28	5.02	5.46
N	22	22	22
Improvement		.74	1.18

Table IV

Grade Level Reading Scores

Control Group

Subject Number	Mean of Stanford and Gilmore Tests		
	Base Score	After Lesson Forty	After Lesson Sixty
12	5.5	5.1	5.8
14	3.4	4.5	5.3
15	4.9	6.9	6.9
18	5.0	6.1	5.9
22	4.5	6.5	7.5
30	5.1	4.9	5.3
31	4.3	6.9	8.1
33	2.1	4.8	5.3
35	4.7	5.3	6.1
36	4.2	5.5	5.8
37	4.7	5.8	6.5
46	4.3	6.4	5.8
58	4.2	5.6	6.7
61	4.5	4.3	3.7
63	4.9	6.6	6.3
65	5.0	6.4	6.8
24	4.7	7.0	
27	4.4	4.3	
32	5.9	6.5	
41	4.7	5.5	
57	3.3	5.5	
SP	4.5	4.6	5.2
Sum	988	1250	1030
Mean	4.49	5.68	6.02
N	22	22	17
Improvement		1.19	1.53

Table V

Mean Grade Level Gains in Reading

	Control Group		Magnesium Pemoline	
	Forty Lessons	Sixty Lessons	Forty Lessons	Sixty Lessons
Stanford Achievement	1.20	1.77	.61	.97
Gilmore Oral	1.15	1.29	.91	1.30
Mean of Stanford and Gilmore	1.19	1.53	.74	1.18

Table VI

Comparison of Subjects Originally Paired

Mean of Stanford and Gilmore Tests

Control Group				Magnesium Pemoline			
Subject	Base Score	After Lesson Forty	After Lesson Sixty	Subject	Base Score	After Lesson Forty	After Lesson Sixty
24	4.7	7.0	---	13	4.7	5.9	6.5
12	5.5	5.1	5.8	51	5.5	5.5	5.4
46	4.3	6.4	5.8	59	2.6	3.8	4.2
27	4.4	4.3	---	16	3.5	3.9	4.1
18	5.0	6.1	5.9	26	5.4	6.8	6.9
14	3.4	4.5	5.3	45	4.7	5.0	5.4
41	4.7	5.5	---	17	4.2	5.2	4.8
30	5.1	4.9	5.3	28	5.2	4.9	5.2
31	4.3	6.9	8.1	53	5.2	5.7	5.9
22	4.5	6.5	7.5	60	4.2	5.2	5.7
57	3.3	5.5	---	47	4.3	4.8	5.0
58	4.2	5.6	6.7	25	4.5	6.3	7.6
37	4.7	5.8	6.5	38	4.9	4.9	5.7
63	4.9	6.6	6.3	21	5.6	6.5	7.3
15	4.9	6.9	6.9	50	2.6	3.2	3.4
65	5.0	6.4	6.8	49	4.6	5.4	6.5
Sum	729	940	769		717	830	896
Means	4.56	5.88	6.41		4.48	5.18	5.60
N	16	16	12		16	16	16
Improvement		1.32	1.85			.70	1.12