

THE EFFECTS OF MAGNESIUM PEMOLINE ON THE
REHABILITATION OF INDIVIDUALS WITH
CENTRAL NERVOUS SYSTEM DISORDERS

by

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CHAPTER I

INTRODUCTION

Meaningful speech may be considered one of man's greatest achievements. Speech is the most important means by which man has to interact with his environment. By this extraordinary capacity, man has shaped the world in which he lives. Even the development and refinement of man's ideas are dependent upon his ability to speak. Speech structures our thinking and behavior.

When man speaks, he speaks with his entire body, that is, all of the major physiological systems interact in the process. All these processes must enter into superb integrations which are correlated with previous learning. Perhaps no other human activity requires greater co-ordination than speaking. It is man's advanced nervous system which has made this complex speaking process possible.

The central nervous system in man holds a vital role in his ability to speak. Without this complex central nervous system, man would be completely incapable of speaking. The important anatomical units of the central nervous system are the cerebral cortex, the cerebral ventricles, the basal ganglia, the thalamus, the mid brain, the pons, the medulla, the cerebellum, and the spinal cord.

Man's ability to remember and to adapt to new situations is largely the result of the development of the

cerebral cortex. The cortex is often referred to as the outer cover for the cerebrum and contains four lobes: frontal, parietal, temporal, and occipital. The cerebral ventricle's main function is to manufacture cerebrospinal fluid which circulates through the brain and spinal cord. The basal ganglia, located below the cerebral cortex, contains three gray nuclear masses. This is also known as the internal capsule which controls the thousands of pathways going to and from the cerebral cortex. The thalamus is known as the sensory "relay station" since all visual, auditory, somatic, and visceral impulses end or synapse here before continuing to the cerebral cortex. Thus, this part of the brain is sometimes called the "feeling" center of the brain. The midbrain originates the higher centers of the brain and is responsible for the finer motor co-ordination movements. The most important bridge between the brain stem, cerebellum, and cerebral cortex, is the pons which lies just below the midbrain. Within the pons are nuclear reflex centers for breathing and circulation. The medulla is an enlargement of the upper end of the spinal cord. The pathways from the midbrain now split into two pyramidal tracts. The cerebellum lies beneath the cerebrum and above the pons-medulla. The cerebellum receives information from all parts of the body. An extension of the medulla, the spinal cord decreases in diameter as it proceeds downward through the body. The spinal cord and spinal nerves receive and transmit sensory

impulses from the body to the brain. They assist in the out-going impulses from the brain to the muscles of the body. Also, they have sympathetic control of smooth muscles, circulation, and glandular function.

Within this complex overview of the general functioning of the central nervous system, specific functions are thought to be more directly related to speech. All the lobes of the cerebral cortex are important to speech since any sensory or incoming stimuli may make connection with the speech association areas and become part of the stimulation-integration-response arc of speech. The cerebral cortex has certain receptive areas that are significant for speech. The auditory receptive areas are located along the fissure of Sylvius and extend into the parietal lobe. When these receptive areas are intact, the individual can perceive speech sounds and is able to understand their meanings. The areas behind the fissure of Rolando makes possible the sense of touch and muscle movement, thus permitting precise tongue movements necessary for speech. Also in the cerebral cortex, is Broca's area with many underlying connecting fibers that control the muscles of speech. Related areas include memory, past experience, reasoning, and abstract thinking, which are all necessary in the total speech arc. The cerebral cortex, the basal ganglia, and the thalamus, which pertain to the speech arc, probably act as one unit. The midbrain acts as a "relay station" for hearing. Perception of loudness comes

from this area as well. The pons supplies a passageway for the sensory and motor pathways. The breathing rhythm, controlled by the medulla, becomes more dominant during speaking than in normal breathing. The cerebellum is of great importance to speech because it is the area of control of voluntary muscle movement. The sensory impulses from the body are transmitted through fiber bundles in the spinal cord. Some of these fibers will end in the cerebellum and thalamus and may effect the speech response either directly or indirectly.

The chemical compound magnesium pemoline, produced by Abbott Laboratories under the trade name Cylert, has been introduced as a central nervous system stimulant. Cylert is a combination of pemoline and magnesium hydroxide. This compound apparently stimulates the production of RNA, which in turn, stimulates the central nervous system. As discussed previously, the central nervous system controls the ability to produce meaningful speech. Therefore, the enhancement or stimulation of the central nervous system should facilitate this activity.

Magnesium pemoline has been shown to improve learning and retention ability in experimental animals.¹ It is not fully understood how this chemical actually works, but the

¹N. Plotnikoff, "Magnesium Pemoline: Enhancement of Learning and Memory of a Conditioned Avoidance Response," Science, 151 (February 11, 1966), 703-704.

predominant assumption is that Cylert has an ability to stimulate RNA polymerase. According to Glasky and Simon, magnesium pemoline facilitates the synthesis of nucleic acids in the brains of rats which enhances memory and learning.² In accordance with Glasky and Simon's biochemical findings, is the behavioral evidence of Plotnikoff who reports that magnesium pemoline facilitates the learning of a simple avoidance response in rats selected as "slow learners."³

In addition to these experiments with animals, human subjects have been treated with magnesium pemoline. Cameron has indicated that magnesium pemoline improves the memory of older patients suffering from intellectual deterioration.⁴ Burns, House, Fench, and Miller have found that in a normal population of young adults, magnesium pemoline did not facilitate learning.⁵ Magnesium pemoline has been found to exert a general alerting or anti-fatigue effect in a study done by

²A. V. Glasky and L. E. Simon, "Magnesium Pemoline: Enhancement of Brain RNA Polymerases," Science, 151 (February 11, 1966), 701-703.

³Plotnikoff, op. cit., p. 703.

⁴D. E. Cameron, "The Use of Nucleic Acid in Aged Patients with Memory Impairment," Journal of American Medical Association, 196 (29, 1966), 401.

⁵J. Burns, R. House, F. Fench, and J. Miller, "Effects of Magnesium Pemoline and Dextroamphetamine on Human Learning," Science, 155 (February 17, 1967), 849-851.

Lienert and Janke.⁶ Cameron, who has claimed to help patients with a severe memory deficit by orally administering RNA, has reported a similar success as a result of magnesium pemoline treatment.⁷ Several of his amnesic patients have improved their scores on Wechsler's Memory Quotient Test after prolonged medication with Cylert. Talland, Hagen, and James have tested the performance on the acquisition of new information and on its recall in chronic Korsakoff patients who had received Cylert.⁸

At the Veteran's Administration Hospital in Topeka, Kansas; Foster, Wing, and Goldstein are engaged in research using magnesium pemoline as an enhancer of memory and learning abilities in brain damaged patients.⁹ These researchers have found some preliminary evidence that magnesium pemoline has increased the memory and learning span of some of these patients. These promising results suggest that further

⁶G. A. Lienert, and W. Janke, "Pharmacologische Untersuchungen Über 5-Phenyl-imino-oxo-oxazotidine," Arzneimittel-Forsch. 7 (March, 1957), 436-439.

⁷D. E. Cameron and S. Sved, "Ribonucleic Acid and Psychiatric Therapy," Current Psychiatric Therapies, 4 (1964), 127-133.

⁸G. Talland, D. Hagen, and M. James, "Performance Tests of Amnesic Patients with Cylert," The Journal of Nervous and Mental Disease, 144 (5, 1967), 421-429.

⁹R. Foster, N. Wing, and J. Goldstein, "The Use of Magnesium Pemoline as an Enhancer of Memory and Learning Abilities in Brain Damaged Patients," (Project No. 379), Veteran's Administration Hospital, Topeka, Kansas.

research of the effects of Cylert would be worthwhile.

Statement of the Problem

Thus, the purpose of the present study is to test experimentally the effects of magnesium pemoline in central nervous system disordered patients on the expressive verbal aspects of speech. In light of this discussion, then, the primary questions to be considered in this study are:

1. Will magnesium pemoline significantly enhance verbal expressive speech in central nervous system disordered patients as measured by selected verbal tasks?
2. Will magnesium pemoline be significant in the rehabilitation therapy of central nervous system disordered patients?

Importance of the Study

There is an increasing need for rehabilitation of people who suffer from a central nervous system disorders. One of the most frequent central nervous system disorders is the cerebral vascular accident. In the United States, the cerebral vascular accident, or stroke, is considered one of the major diseases of America. Quite often the person who has suffered a cerebral vascular accident is middle aged and has many productive years remaining, if he can be rehabilitated. A needless loss of manpower is caused by speech disorders. With more intensive rehabilitation programs, many of these people perhaps could return to their previous normal patterns of life.

As a result of the Viet Nam Conflict, there have been many young men who have received severe head injuries causing some type of dysphasia. The importance of rehabilitating these young men cannot be underestimated. These individuals, without rehabilitation, would probably spend the rest of their lives being cared for in institutions.

Furthermore, automobile accidents have also accounted for an increasing number of people who suffer from severe head injuries or other types of central nervous system disorders. These accidents are happening everyday throughout the United States, and are effecting hundreds of individuals of all ages. These people, probably functioning as normal productive individuals before the car accident, should not be left to spend the rest of their lives in a disabled state. A rehabilitation program is definitely required.

Summary of Chapter

The present chapter has attempted to elaborate on the background of the problem under consideration, state the questions for experimental inquiry, and establish the need for the present investigation.

To recapitulate, speech, a very complex process, depends upon the proper functioning of the central nervous system. Only when the central nervous system functions properly, can man produce meaningful speech. Recently, a chemical compound magnesium pemoline, has been introduced

as a central nervous system stimulant. Researchers are interested in the effects that this drug has on speech. These investigators feel that the administration of magnesium pemoline will be of significance in the rehabilitation of central nervous system disorder patients.

The present study was designed to explore the effects of this agent on expressive verbal behavior in central nervous system disordered persons. The increasing number of persons afflicted with such disorders would appear to make any such investigation worthwhile.

CHAPTER II

REVIEW OF THE LITERATURE

The ability to produce meaningful speech is dependent in part upon the association areas of the brain. Through these areas, the stimuli which enter the brain are inter-related. There are three main neural pathways that are directly concerned with speech production: the pyramidal, the extrapyramidal, and the cerebellar motor pathway. These pathways contain billions of neurons. Each neuron has hundreds or thousands of tiny dendrites receiving contact from one or many other neurons. Within each neuron are units of free floating RNA molecules which have information processing functions. With the administration of certain drugs, the RNA synthesis is enhanced. A hypothetical relationship between increased RNA synthesis and learning and memory abilities has been postulated. Many investigators have attempted to establish a functional relationship between nucleic acid or protein metabolism to various aspects of brain functions. The reports have suggested that changes in the RNA and DNA content of the brain may be directly related to processes of learning and memory. If, indeed, learning and memory are enhanced by increased RNA synthesis caused by the administration of certain drugs, then this would seem likely to aid the patient who has a central nervous system disorder in his relearning and remembering of visual cues, speech,

and language. Thus, the development of an agent which stimulates synthesis of brain nucleic acid and enhances learning would further strengthen the hypothesis that nucleic acids function as the informational engram in the brain. Also, the development of this type of an agent would provide a valuable therapeutic aid.

Investigators have recently produced a great deal of research concerning the effect of drugs on speech. The drugs that have been found to produce the greatest effect on speech are mainly hallucinogenic drugs, stimulants, more specifically, central nervous system stimulants, and magnesium pemoline. Selected studies under each of the above mentioned groups are reviewed in the following section.

Hallucinogenic Drugs

Honigfeld used the cloze analysis to assess the "understandability" of the spontaneous speech of a normal subject who had received 9 mg. of psilocybin, an hallucinogenic drug.¹⁰ This drug seemed to exert an enhancing effect within the first one and one-half hours followed quickly by a deterioration in the quality of verbal communication for about the next two hours. Cloze analysis may be thought of as "an index of the overall correspondence or commonality

¹⁰George Honigfeld, "Effect of an Hallucinogenic Agent on Verbal Behavior," Psychological Reports, 13 (1963), 383-385.

between the language system of different individuals."¹¹ Although a deceptively simple procedure to administer and score, it has been described as having "the virtue of tapping, or being sensitive to, most of the psychological determinants of encoding and decoding."¹² The mechanics of the procedure involved the deletion of every fifth or nth word of a presented message.

It was interesting to observe that over time, the drug effects on language, and on other psychomotor skills, were strongly reminiscent of the effects of cerebral depressants, eg. alcohol. After an initial enhancing effect, greater "understandability" occurred, then a rapid deterioration occurred in communication ability which lasted approximately two hours, after which there occurred a rapid return to hypothetical baseline levels.

In a follow up study, Honigfeld again employed the cloze analysis to evaluate the temporal effects of LSD and epineprine on the "understandability" of verbal communication.¹³ Ten normal male subjects recorded spontaneous speech samples before, and at the eight fixed intervals after injection of each of the drugs. The order of drug

¹¹Ibid., 383.

¹²Ibid., 384.

¹³George Honigfeld, "Temporal Effects of LSD-25 and Epineprine on Verbal Behavior," Journal of Abnormal Psychology, 70 (1965), 303-306.

administration was varied randomly. Typescripts of these speech samples with every fifth word deleted were completed by 13 normal adults and scored according to the number of agreements with the original sources. The two drugs acted differentially and the expected interaction of drug and time effects was obtained. Compared with pre-drug level, LSD impaired "understandability." Peak effects for both drugs were noted about two hours after injection.

It is generally agreed that the identification processes are disturbed in the schizophrenic state. Abramson and his associates were interested in the stablemate concept of therapy as affected by LSD in schizophrenia.¹⁴ The frames of reference used by the nonpsychotic individual during the adaption process in daily living were replaced to a certain extent in the schizophrenic individual by internalized symbolic versions of the poignant personalized parts of the schizophrenic's environment. It appeared to the authors of this article, that a study of certain types of group processes might provide a better understanding of the nature of the distorted identification process, and improve techniques for communication with schizophrenic patients, thereby developing better methods of therapy. Although, group methods

¹⁴H. A. Abramson, M. P. Hewitt, H. Lennard, W. J. Turner, J. O'Neil, and S. Merlis, "The Stablemate Concept of Therapy as Affected by LSD in Schizophrenia," Journal of Psychology, 45 (1958), 75-84.

previously had been employed with the relatives of schizophrenic patients or with other psychotic patients, the present investigation was designed to avoid the conflict situation. The stablemate therapy placed a normal individual in the therapy situation with the schizophrenic.

The stablemate therapy concept investigation was conducted in the special section of the Research Division of the State Hospital at Central Islip, New York. A tape recorder, with its microphone concealed in a small radio cabinet, was in an adjoining room which was equipped with a one-way screen. Three elements were used to structure the interview: (1) the patient was given either a placebo or LSD-25 dissolved in water, (2) the questionnaire previously used to study LSD in non-psychotics was administered, and, (3) selected pictures of the Thematic Apperception Test were discussed.

In general, there was more behavior change under LSD for schizophrenic patients than for normal subjects. Communication between patient and stablemate during LSD sessions was characterized by a greater amount of other oriented references than during placebo sessions.

Lennard and his co-workers investigated some of the

group patterns of communication under LSD-25.¹⁵ These three conditions were identified:

- Condition I A typed script from a tape recording of a group of normal women under the influence of LSD-25 discussing the topic, "The Place of Women in Society."
- Condition II A typed script from a tape recording of a group of normal women with a placebo discussing the topic, "The Place of Women in Society."
- Condition III A typed script from a tape recording of the members individually under the influence of LSD-25 discussing the topic, "The Place of Women in Society."

In general, these statements could be made from the results of the study. Verbal output on the part of group members under LSD was restricted and shortened. In groups where some members received LSD and others the placebo, those who had not received the drug tended to increase their communication output. When all were on LSD there was a marked reduction in negative interpersonal responses. Despite the relatively high dosage of LSD-25 administered, the ratio between amounts of task activity and socio-emotional activity did not differ for the groups under LSD-25 and when under the normal condition. The ratio of questions

¹⁵H. Lennard, M. E. Jarvik, and H. A. Abramson, "Lysergic Acid Diethylamide (LSD-25) A Preliminary Statement of Its Effects Upon Interpersonal Communication," Journal of Psychology, 41 (1956), 185-198.

to answers, as well as the ratio of orientation to evaluative responses, was higher in the group under condition LSD-25 than under condition normal. The authors interpreted this as an attempt on the part of the group to restore cognitive clarity, despite the felt impairment.

Stimulant Drugs

The stimulant drugs have also received a great deal of interest. These researchers are mainly interested in the effect of the stimulant drugs on the individual's verbal output and behavioral patterns. The following section will discuss some of the more recent literature in this area.

Tourlentes and Hunsecker investigated the efficacy of chlorpromazine in facilitating communication processes.¹⁶ Thirty-four schizophrenic patients were divided into three groups. Two groups received 200 mg. of the drug and placebo during alternate six week periods, while the third group was a continuous control on the placebo. The groups were roughly equivalent for age, hospital duration, and intelligence. The drug and placebo tablets were coded by the manufacturer, and subjects were assigned at random to groups by a ward physician, so that the investigator and all ward personnel who worked with them were unaware of the drug groups. The

¹⁶T. T. Tourlentes and A. L. Hunsecker, "Chlorpromazine and Communication Process," Archives of Neurology and Psychiatry, 79 (1958), 468-472.

groups not on the drug at a particular period, as well as the controls, received a placebo tablet identical with the drug. Initially and at two subsequent six week intervals, various psychological tests, recorded psychiatric interviews, sociometric evaluation, and cinematographic sampling of spontaneous behavior in a relatively unstructured situation were undertaken for each subject. Results failed to establish that 200 mg. of chlorpromazine as prescribed, significantly altered communication process as measured in this study. Some evidence, however, supported the observation that there was a reduction in anxiety with this drug.

Fink investigated the effect of an anticholinergic agent, diethazine, on the EEG, behavior, and language patterns on 40 psychiatric patients at various stages in the course of electroconvulsive treatment.¹⁷ Alterations in EEG were concurrent with behavioral changes. In patients with delta activity, the time and voltage of delta activity decreased. The patients behavior showed increased restlessness and agitation, visual illusory sensation, and delusional thoughts about their illness. Syntactic patterns described for convulsive therapy were observed. Use of third person, qualification, and displacement decreased. In dyadic analysis there was a decrease in the coefficient

¹⁷M. Fink, "Effect of Anticholinergic, Diethazine on EEG and Behavior," Archives of Neurology and Psychiatry, 80 (1958), 380-387.

of variation. These observations were discussed in the framework of the neurophysiologic adaptive hypothesis of the action of convulsive therapy and it was concluded that the biochemical basis for convulsive therapy was similar to that of cranio-cerebral trauma. Changes in acetylcholine cholinesterase metabolism are intimately related to the behavioral effect and the EEG desynchronization may be a physiologic concomitant of hallucinogenic activity.

The purpose of a study by Gottschalk and his colleagues was to test the efficacy of a method of assessing the subject and behavioral effects of psychoactive drugs in the human subject.¹⁸ The method involved the psycholinguistic analysis of short samples of the subject's speech. Twenty dermatologic subjects at the Cincinnati General Hospital participated in a double-blind, placebo-crossover study in which the psychoactive drug administered was perphenazine. Five minute samples of their speech were elicited with standard instructions and recorded on tape at approximately the same time of day on five successive days. Analysis of the verbal sample showed a reduction of the median scores for 16 out of 20 patients in an index of "hostility directed outward," a scale which includes in its scoring

¹⁸L. A. Gottschalk, A. Gleser, C. Goldine, K. Springer, S. M. Kaplan, J. Shannon, and W. O. Ross, "Effects of Perphenazine on Verbal Behavior Patterns," Archives of General Psychiatry, 2 (1960), 632-639.

not only hostile, destructive references overtly originating from the speaker, but also displaced, projected, and denied references of this kind. Three of the patients, whose hostility scores increased while taking perphenazine, had scores below the median for this series of subjects while on the placebo. Furthermore, there was suggestive evidence that these four subjects had distinctive personality features other than those of subjects whose hostility-directed-outward scores decreased with perphenazine. This psychoactive drug had no notable effect on the hostility-directed-inward scores of the patients as a whole. Those patients, when on the placebo, who had free anxiety scores in the upper one-third range of the group, tended to show no consistent direction of change with perphenazine. Five of the six patients over 65 showed an increase of the free anxiety score while on perphenazine. Verbal content analysis revealed that there was a significant trend for dermatologic patients while on perphenazine, to make more references to feeling of personal bodily and emotional well-being. Also, with perphenazine the patients tended to use a greater number of words expressing positive, approving feelings such as "good," and "happy." The authors felt that this method of measuring the effects of psychoactive drugs by verbal content analysis could prove to be a useful therapeutic method for patients who have personality disorders.

The purpose of an experiment reported by Goldman,

Skarbek, and Henderson was to study the effect of chlorpromazine on such cognitive functions that have been shown by the investigator to be measurable in terms of verbal behavior.¹⁹ These were hesitation pauses in spontaneous speech which in previous work had been shown to reflect processes concerned with the selection of words and the formulation of meaning. The experiments consisted in evoking spontaneous utterances of speech at two levels of cognitive complexity involving descriptive and general statements in normal and highly intelligent adults. Speech of this kind had been studied before and the two levels were shown to differ widely in pause duration. In this investigation such speech was studied in conditions of no drug, sodium amytal, and chlorpromazine. The advantage of pause time in speech, as a measure of cognitive changes under these conditions, is that it makes possible a separation of the behavior accompanying the processes concerned with achieving cognitive results from the quality of the results themselves. This enables the researchers to gain a picture of the drug action in relation to the mechanism involved in cognitive activity apart from what it achieves. The latter was assessed independently from judges rating of the cognitive quality of the statements made, with the level of

¹⁹F. Goldman-Eisler, A. Skarbek, and A. Henderson, "The Effect of Chlorpromazine on Speech Behavior," Psychopharmacologia, 7 (1965), 220-229.

generalization being the criterion. Thus, the drug effects could be studied separately for cognitive labor and for its efficiency in terms of cognitive achievement.

The results showed the effect of chlorpromazine on pause time, in contrast to sodium amytal, to be selective, varying in direction with individuals. The effect on the cognitive quality of the linguistic product was shown to be linked to the effect of chlorpromazine on pause behavior, with the pause time appearing under chlorpromazine as under normal conditions, to be involved in generating complex verbal structures. Under sodium amytal, on the other hand, no such link between hesitation and information was found.

Central Nervous System Stimulants

Researchers interested in patients who demonstrated a central nervous system disorder, began experimenting with the effects of increased DNA and RNA in these individuals. By 1955, it had been shown that the amount of nucleic acid decreased with age. This fact was interpreted by the researchers as a possible connection between increased DNA or RNA as a hypothetical relationship to memory.

The effect of the administration of ribonucleic acid upon memory defect in the aged had been studied at the Allan Memorial Institute since 1965. These studies were initiated by a report made by Weiss, who, in summarizing his work about the neuron, pointed out that this structure is constantly

renewing itself; that the material necessary for its continued activity is produced at the nucleated end and passed toward the end plates.²⁰ He referred to the finding of Hyden, who induced a high rate of protein synthesis in the cell from the elevated nucleic acid concentration in and around the nucleus, and to the findings of Samuels that labelled phosphoprotein seemed to shift peripherally in nerves.^{21,22} Katz and Halstead had also proposed that, "neurons involved in memory become fully functional only after chemical structural changes" and had suggested that a neuron became operative in this regard through the formation of a new protein molecule.²³ They assumed that this molecule was a nucleoprotein acting as a template for the synthesis of protein replicas.

Hyden seems to have been the first to advance the hypothesis that the substrate of memory is ribonucleic

²⁰P. Weiss, "The Life History of the Neuron," Paper presented at the annual meeting of ARNMD (1955).

²¹H. Hyden, "Spectroscopic Studies on Nerve Cells in Development, Growth, and Function," Genetic Neurology (University of Chicago Press, 1950), pp. 177-193.

²²A. J. Samuels, "Distribution, Exchange and Migration of Phosphate Compounds in the Nervous System," American Journal of Physiology, 164 (1951), 1-15.

²³J. Katz and W. S. Halstead, "Protein Organization and Mental Function," Comparative Psychology Monographs, 20 (1950), 1-33.

acid.²⁴ He pointed out that the many combinations permitted by the rearrangement of its four bases provide a substance which in theory could encode 10^{15} or more bits of information.

Sved demonstrated that the blood ribonuclease level was significantly correlated with increased age, but he found no significant correlation between the blood ribonuclease level in aged individuals with memory deficit and those without.²⁵ After preliminary work on animals, Cameron, Sved, and Wainrib began in 1956 to study the effects of intravenous DNA and later RNA in the human subject.²⁶ It proved very difficult to get these substances into a satisfactory solution and, after approximately a one year trial, intravenous administration was abandoned in favor of oral RNA until 1961, when a satisfactory intravenous solution was achieved by a biochemical team under the leadership of Sved.

Cameron, Sved, Soloym, and Wainrib stated that no matter how ribonucleic acid was administered, little change

²⁴H. Hyden, "Nucleic Acids and Proteins," In Neurochemistry (Charles C. Thomas Publisher, 1955).

²⁵S. Sved and D. E. Cameron, "Ribonucleic Acid and Psychiatric Therapy," Current Psychiatric Therapies, 4 (1964), 127-133.

²⁶D. E. Cameron, S. Sved, and B. Wainrib, "Effects of Intravenous Administration of Ribonucleic Acid Upon Failure of Memory for Recent Events in Presenile and Aged Individuals," Recent Advances in Biological Psychiatry (Pleum Press, 1963).

of an ameliorative nature could be brought about in the mnemonic function if the memory deficit was severe.²⁷ The authors worked predominantly with three categories of patients: those suffering from presenile psychosis (primarily Pick's and Alzheimer's diseases), from senile psychosis, and from arteriosclerotic brain syndromes. A limited number of patients suffering from alcoholic Korsakoff psychosis also have been given ribonucleic acid. All patients under treatment were placed on two grams of RNA which was administered orally. The patients were, in addition, given intravenous RNA, past experience having shown this method to be considerably superior to the first type of oral administration. The amount of RNA given intravenously varied from two to ten grams depending upon the reaction of the patient; the frequency of administration varied from daily to once or twice per week. When ten grams were given, it was diluted in 1,000 cc's of 5 per cent glucose and normal saline and given usually over a five to six hour period. The patient was premedicated one-half hour before with atropine demoral magnesium. In some cases, the RNA administration was accompanied by intravenous ATP without, however, noticeable gain.

For the assessment of mnemonic function, the authors

²⁷D. E. Cameron, S. Sved, L. Solyom, B. Wainrib and H. Barik, "Effects of Ribonucleic Acid on Memory Defect," American Journal of Psychiatry, 120 (1963), 320.

employed the use of these four measures:

1. The Weschsler Memory Scale
2. A counting test
3. Six parameters of a conditioned reflex procedure
4. Tests based on the capacity for time estimation.

The EEG was used as one means of following the effects of ribonucleic acid.

Favorable changes were recorded in all three categories of mild organic deficit; brain arteriosclerotic, senile dementia, and presenile dementia. The results, however, were limited in moderate cases of organic involvement and were negligible in far advanced cases. Unfortunately, when one dealt with an organic brain syndrome, memory disturbance was only one of the deficits. If progression could be halted, or if reversal was brought about in the memory deficits, this did not necessarily affect the progression of the organic process as a whole. Hence in patients in whom favorable effects had been achieved with respect to mnemonic functioning, there could be, nonetheless, a continuing progression of defect in judgement, in the maintenance of socially acceptable behavior, and in motor and sensory functions.

Nevertheless, this procedure constituted the only method which has produced a halting and, in favorable cases, a reversal of deterioration in memorial function in organic brain syndromes. The procedure was, however, in the

experimental stages and information was being sought as to whether the effects were produced by the ribonucleic acid as a whole or whether some component thereof could be isolated which might have a still higher level of efficiency of operation. There were no leads as to how ribonucleic acid administered orally and intravenously produced this effect.

In a more recent series of experiments, RNA was administered to the patients, as earlier experimentation had proved it to be superior to DNA. After prolonged investigation, Cameron and Solyom found that the oral administration of a slowly dissolving tablet eliminated the occasional shocklike effect of intravenous treatment.²⁸ Also, the slowly dissolving pill was better than oral fluid administration because the latter sometimes produced abdominal discomfort, cramps, and diarrhea.

The total number of subjects involved in Cameron's experiments was 84.²⁹ These patients were divided into groups one and two. The first group consisted of 41 aged individuals who were then attending the Allan Memorial Institute of Psychiatry. In this selection, the authors excluded those who suffered from mood changes, recent

²⁸D. E. Cameron and L. Solyom, "Effects of Ribonucleic Acid on Memory," Geriatrics, 16 (1961), 74.

²⁹Ibid., p. 74-81.

cerebral accident, and/or undernourishment. The second group of patients were chosen from a geriatric ward of a provincial mental hospital. Their illnesses were much further advanced than those in group one. The second group was also divided into two subgroups, A and B. The first subgroup was given a placebo preparation, while the latter received RNA on a double-blind basis.

Assessment in group one was based on the Wechsler Memory Scale, a counting test, and information supplied by the patient and by his relatives. RNA was administered orally to the majority of patients in the form of a special, slowly dissolving pill, in dosages ranging from 2 to 75 grams daily. In 14 cases, however, daily intravenous injection of 50 to 2,000 mg. of RNA in a 10 per cent solution was administered. With group two, a conditional reflex test was added to the Wechsler Memory Scale and counting tests assessments before commencement of the drug and placebo experiments. Three months later, reassessment by the same method was repeated. All conditioning was carried out by the same psychiatrist and all testing by the same psychologist. The pattern of ribonucleic acid administration was three grams daily during the first week, six grams daily during the second week, and nine grams daily from the third to twelfth weeks. All medication was given orally and the placebo was administered in the similar manner.

The administration of RNA had a favorable general

effect upon memory retention failure in the aged. The earlier in the progress of the condition RNA was given, the more favorable the effects. Patients with moderately advanced memory failure did better on RNA than did patients with marked memory impairment. If the retention span was below 40 seconds according to the counting test, the result was apt to be either a slight improvement or a slowing down of the rate of progression of retention failure. Above 40 seconds, the higher the initial score, the more marked the improvement was apt to be. The dosage of RNA was highly individual to pace with the advancing aging process. In both experimental groups, arteriosclerotic patients responded more favorably to RNA than did senile dementia patients. In ten cases, suspension of treatment resulted in a further decline of memory, which was halted by reinstitution of RNA. RNA was given either in the form of a slowly dissolving tablet or intravenously. Intravenous administration was apt to be accompanied by disturbing side effects. Of the methods of assessment used, the counting test and the conditioned reflex test were most closely correlated. Among the favorable changes in addition to those affecting the memory, were increased alertness, interest, initiative, and confidence.

Magnesium Pemoline

From the results of the research done with RNA and

DNA, North Chicago Abbott Laboratories developed the compound magnesium pemoline under the trade name, Cylert. Cylert is a combination of 2-imino-5-phenyl-4-oxazolidinone and magnesium hydroxide.³⁰ The developers of magnesium pemoline felt that this compound could stimulate the production of the brain's RNA, thus improve learning and memory.

Simon studied the effect of magnesium pemoline on the systems in the brain that are responsible for both RNA and protein synthesis in vivo and vitro.³¹ By using C¹⁴ orthic acid, it was demonstrated that magnesium pemoline was capable of enhancing the quantity and specific activity of brain nuclear RNA in vivo. The inhibition of protein synthesizing system of the brain which was also observed, failed to be significant. Simon used the vivo test system to determine the effect of magnesium pemoline on the RNA synthesis of the rat brain. Male Sprague-Dawley rats were divided into two groups of six animals each. The animals were injected with magnesium pemoline or methocle, the placebo. After a 30 minute period all the animals were injected intracranially with orthic acid-2-C-14. At the end of an additional period of 60 minutes, the rats brains were

³⁰Abbott 304000: Cylert, a combination of 2-imino-5-phenyl-4-oxazolidinone and magnesium pemoline.

³¹L. Simon, "Magnesium Pemoline: Enhancement of Brain RNA Synthesis in Vivo," Permission to cite by the author.

removed and prepared for analysis. Each sample was analyzed for total RNA content by its absorption at 260 mm. and counted for radioactivity. Magnesium pemoline did not cause an increase in the specific activity of total brain RNA production, however, there was an increase in total micrograms of nuclear RNA/gram of brain tissue and an increase in the specific activity of nuclear RNA. Simon showed, then, by the vivo labeling technique, that magnesium pemoline increased the synthesis of brain nuclear RNA and supported the view that the main mode of action of magnesium pemoline was to enhance the synthesis of brain nuclear RNA. In addition, he found that magnesium pemoline had no effect on the major system in the brain responsible for protein synthesis.

Magnesium pemoline and dextroamphetamine, two central nervous system stimulants, were tested to see if they improved learning in human subjects. This study, by Burns and his associates dealt directly with the effect of these stimulants on the associative processes, specifically the acquisition rate in a learning task in a population that was intellectually above average.³² The subjects consisted of 30 male university students. A double-blind method was employed and each subject was given a single oral administration of one drug. The five drug conditions for this study were as

³²J. Burns, R. House, F. Fenoch, and J. Miller, "Effects of Magnesium Pemoline and Dextroamphetamine on Human Learning," Science, 155 (1967), 849-851.

follows:

1. Magnesium pemoline 25 mg.
2. Magnesium pemoline 12.5 mg.
3. Magnesium pemoline 6.25 mg.
4. Dextroamphetamine 15 mg.
5. Placebo

Two tasks were used in this experiment. The simpler one was a reaction time task in which the correct response for each light was to press the button directly in front of the light. The learning task required the subject to learn which single key was the correct response to each light when the keys were randomly assigned, except that the correct button was never immediately in front of the light associated with it. The subjects under the placebo learned faster than the subject under any of the several doses of magnesium pemoline, however, none of these differences reached statistical significance. The subjects who received dextroamphetamine learned significantly slower than those who received the placebo or the magnesium pemoline. Also, it was found that higher doses of magnesium pemoline in humans actually inhibits learning.

The purpose of an experiment by Talland, Hagen, and James was to determine the effect of a single dose of Cylert on the acquisition of new information and on its recall in patients diagnosed to be in the chronic phase of the

Korsakoff Syndrome.³³ The subjects were three women and one man who all had a record of alcoholism and had observable signs of Wernickes Syndrome prior to their admission to a mental hospital. Four different experimental conditions were employed in this study, however, the same basic tasks were used in all the experimental situations. The subjects were given a single, oral dose of 50 mg. of Cylert or a lactose placebo according to a double-blind procedure. There were three learning tasks required. The first task was to recall a newspaper report which was read only once by the experimenter and consisted of six sentences and divided into 20 units. The second task was that of learning a list of ten common monosyllabic CVC (consonant-vowel-consonant) words. The subjects were allowed three minutes to memorize the words. The last task for remembering called for memory of a series of eight figure drawings of familiar objects (eg. hammer, clock, cake, etc.) which were projected from prepared slides.

The purpose of the first experimental condition was to list the effect of Cylert on the acquisition of new information and on its recall. The second experimental condition served the same purpose as the previous one except that the dosage was decreased 25 mg. Also, a second

³³G. Talland, D. Hagen, and M. James, "Performance Tests of Amnesic Patients with Cylert," The Journal of Nervous and Mental Disease, 141 (1966), 421-429.

stimulant drug was used as a control, and a few added tasks were employed in order to test the drug's effect on a wider range of functions. The third experimental condition tested the effect of Cylert, administered regularly over a relatively long period of time, on learning, memory, and some basic functions. Any effect observed was compared with changes attributable to a single dose, as well as with performance on a prolonged placebo treatment. The fourth experimental condition tested the effect of Cylert, given in daily doses of 50 mg. for a period of three weeks, on performances in tasks of learning, memory, and other related functions.

In a follow up study by Talland to his first investigation, twenty-four student volunteers, between ages 21 and 25 years, served as subjects on three or four occasions at weekly intervals for periods of about three hours.³⁴ At the beginning of the experimental sessions, the subjects were administered a tablet of 25 mg. of Cylert or a lactose placebo, and then were given a rest period of 70 minutes which they spent reading. In the first session, the rest period lasted for 90 minutes, but in subsequent sessions, the time between 70 and 90 minutes was occupied by tests of delayed recall of a narrative text and of a maze learned the

³⁴G. Talland, "Tests of Learning and Memory with Cylert," Psychopharmacologia, 10 (1967), 445-451.

previous week. The time between 90 and 120 minutes was used for learning new tests. Then the subject received his second tablet, either Cylert or placebo, and five minutes later he started a test of sustained attention. This testing lasted 50 minutes and was followed by tests of recall and relearning. The drugs were administered by the double-blind procedure.

These experiments demonstrated that Cylert was capable of improving performance by human operators, though possibly only by mitigating fatigue effects. Talland's experiments reported the favorable drug effect was fairly instantaneous and manifest in an increase of correct responses to a class of visual patterns that were specified as signals, without an increase in false positive responses. The gain in performance attributable to the drug was, therefore, not achieved by lowering the criteria for responses but by the processes affected, namely those involving perception, short-term retention, and matching of data.

In summary of Talland's studies Cylert administered in single doses of 25 mg. improved accuracy in performance of a continuous attention task. This effect was strongest within an hour from oral administration of the drug, and on a task that involved a relatively difficult test in short term memory. These findings were considered as evidence for a non-specific alerting or anti-fatigue effect, as distinct from a specific effect on memory function attributed

to Cylert.

A survey of these experimental findings gave little, if any, confirmation of Cylert as a treatment of pathological memory disturbance. The few results that could suggest some benefit from this drug are offset by others that show improved performance with the placebo. Although the experimental procedures employed may not have probed all the functions impaired, they were sufficiently diverse and representative of those impaired functions to allow for a wide generalization of the negative results obtained. Clinical observations made by the experimenters and the ward personnel also failed to give significant reports of improvement of other changes in the patients behavior as a result of the experimental drug treatment. By the same token, there was no evidence of any side effect with the improved oral administration procedure, nor did the patients complain of discomfort or unusual sensations. Although there were some instances of improved performance with Cylert, none of the experiments furnished evidence that this effect is reliable under the conditions of the double-blind design which also controls for the practice element. Neither did the researchers indicate that Cylert exerted an adverse effect on performance. Therefore, whatever influence this drug may have on brain metabolism, it is unlikely to offer a pharmacological remedy for severe memory disorders.

Chapter Summary

This chapter was concerned with reviewing the literature concerning the effect of drugs on speech. The areas of drug research reviewed were hallucinogenic drugs, stimulant drugs, and central nervous system stimulant drugs. Of specific interest in the central nervous system stimulant drug area, was the effect of the chemical compound magnesium pemoline. This new drug, recently developed by Abbott Chicago Laboratories, created a great deal of interest for researchers who were concerned with the rehabilitative possibilities of Cylert. This chapter suggested the potential fruitfulness of investigation in the area of drug research and to the further understanding both of specific drug effects and of the speech processes.

CHAPTER III

PROCEDURE

Subjects

Six adult patients of the neurology service at the Veteran's Administration Hospital who exhibited some speech difficulty associated with a history of nervous system damage or injury were selected for this study. The subjects displayed different types of speech difficulty with varying degrees of severity. Patients taking certain anticonvulsents, psychotropic, or central nervous system stimulant drugs were excluded from the study. The patients were sufficiently intact psychologically and physically to be testable with speech tests such as the Halstead-Wepman Screening Tests for Aphasia, the Sklar Aphasia Scale, the Missouri Developmental Test for Articulation, the West, Kennedy, and Carr Sentences Survey, or by any standard language testing technique necessary for speech evaluation.

The patients had to be capable of giving their consent to participate in the experiment and signing Veteran Administration Form 10-3203, Consent for Use of Picture and Voice. Authorization was also secured from the ward physician and Service Chief.

Experimental Design

For the purpose of controlling order effects and

examiner bias, a double-blind procedure was utilized. The testing of each subject took approximately one-half hour per test run. However, if the subject was unable to work or perform for this length of time, then two, fifteen minute periods were employed. During the course of the experiment, each subject was tested five times. The subjects were assigned randomly to magnesium pemoline schedules or placebo schedules. The assignment of the subjects to magnesium pemoline schedules or placebo schedules was unknown to the test administrator.

During the magnesium pemoline schedule, each subject was administered the American measure of 50 milligrams of magnesium pemoline in tablet form each day. This dosage continued over a two week period. Since the Federal Drug Administration monitors all new drugs, the physical conditions of the subjects were carefully noted while receiving the experimental drug. All subjects signed an agreement in the presence of a witness that they understood that they were being given an investigational drug. The placebo was administered in a manner identical to the administration of the magnesium pemoline.

Before and after each pharmaceutical treatment, baseline tests were performed. Thus, five experimental conditions were established; two pharmaceutical, magnesium pemoline and placebo, and three baseline, no treatment. The entire group of subjects was pre-tested (Experimental

Condition I) and then administered either the placebo or magnesium pemoline for a two week period. During this period, all subjects were tested again (Experimental Condition II). After the two week period of placebo or magnesium pemoline administration, a week of no medication was allowed. This week between each of the pharmaceutical conditions was employed in order to minimize the effects of any residuals. At the end of this period, all subjects were retested (Experimental Condition III). Again, after this testing, the subjects were placed on magnesium pemoline schedules or placebo schedules. The new schedule was the opposite of the schedule that the subject was assigned for the preceding period. For example, if the subject had been administered magnesium pemoline for the first pharmaceutical condition, then he was given the placebo schedule for the second pharmaceutical period. However, if the subject had been given the placebo schedule first, he then would be given the magnesium pemoline schedule for the second pharmaceutical period. After the new schedules had begun, the subjects were tested again (Experimental Condition IV). When the final pharmaceutical period was complete and the subjects were no longer receiving any medication, drug or placebo, they were post-tested for the final baseline data (Experimental Condition V).

The same tests and testing order were utilized for all subjects in all experimental conditions.

In that changes resulting from medication are not always directly ascertainable from particular tests and become more obvious under conditions of observation of the person's behavior, the use of a systematic procedure for ward observation of experimental patients by nurses and nursing assistants was also utilized. This procedure was similarly carried out with the double-blind method. The nurses and nursing assistants reported their observations on particular patients to the ward physician upon request. The nurses and nursing assistants informally expressed what they had observed in the patient's general behavior or any noticeable change that had occurred.

Test Events

Each subject was administered the following battery of tests.

1. Sklar Identification of Objects Test³⁵
2. Schuell Object Naming Test³⁶
3. Recall Test
4. Oral Reading Test³⁷

³⁵Maurice Sklar, Sklar Aphasia Scale (Western Psychological Services, Beverly Hills, California, 1966).

³⁶Hildred Schuell, The Minnesota Test for Differential Diagnosis of Aphasia (Research Edition, Form 7).

³⁷Velma Avant and Charles Hutton, "Passage for Speech Screening in Upper Elementary Grades," Journal of Speech and Hearing Research, XXVII (February 27, 1962), 40-46.

5. Vocal Encoding Test³⁸

Each subject served as his own control for each test. The same patient was tested approximately at the same time of day under the five experimental conditions in order to reduce intra-individual variability related to fatigue.

Sklar Identification of Objects Test. The Sklar Aphasia Scale was developed by Maurice Sklar in 1948 to provide objective measurements and evaluations of speech and language disturbances resulting from brain damage.³⁹ The items in the subtest, Sklar Identification of Objects Test, measure auditory verbal comprehension as sampled by verbal stimuli requiring only gestural or motor responses that indicate recognition and comprehension. In the present investigation the examiner spread twenty common objects before the patient and then asked, "Do you see all these objects? I'm going to name them. I want you to point to the object or pick it up, after I say that object's name. Wait until I tell you the object's name, then show me. Are you ready?" The examiner stated one object's name at a time, "Show me the comb." The examiner allowed the subject to complete his response before he proceeded to the next object. If the subject did not respond to the first request, then the

³⁸James J. McCarthy and Samuel A. Kirk, Illinois Test of Psycholinguistic Abilities (University of Illinois, Urbana, Illinois, 1961).

³⁹Sklar, op. cit., p. 1.

sentence was repeated again, "Show me the comb." If, however, the subject still did not respond, the examiner proceeded to the next object, "Show me the pencil," counting the previous request as an error. Or, if the subject, after the first statement, "Show me the comb," pointed to an incorrect object, then the statement, "Show me the comb," was repeated. If the subject still pointed to an incorrect object, then the examiner proceeded to the next object, counting the previous response as an error. But, if the subject pointed to the correct object on the second request, the examiner asked for the third time, "Show me the comb." If he was correct the third time, his response was counted as correct, but if he was incorrect the third time, his response was counted as an error. The time taken for the completion of the task was also recorded.

Schuell Object Naming Test. The Schuell Test for Aphasia was developed by Hildred Schuell for adults whose language abilities became impaired after normal language functioning had been established.⁴⁰ The test is directed primarily toward obtaining essential information which could be useful for the rehabilitation of aphasic persons. A sub-test, the object naming test, examines the higher symbolic levels of expressive ability of the subject through word finding or picture naming methods.

⁴⁰Schuell, op. cit., p. 1.

The Schuell Object Naming Test, as used in the present study, required the subject to name the picture that was presented on a televiewer. The slides were simple, black and white pictures of common objects. A total of twenty slides was presented to the subject. The examiner said to the subject, "You will see a picture on the screen." (examiner pointed to the screen) "I want you to tell me the name of the picture." The first picture was then presented on the screen for the subject. The examiner presented the slides one at a time and allowed the subject to complete his response before proceeding to the next slide. If the subject mislabelled the picture, that item was scored as incorrect, and the next picture was presented. If no response was made, twenty seconds were allowed before presenting the next picture. The number of correct pictures identified was the total score. Also, the elapsed time necessary for the test completion was recorded.

Recall Test. The recall test was concerned specifically with the central nervous system disordered patients' ability to recall certain words. The examiner asked the subject, "Tell me as many words as you can think of beginning with the letter 'h'." The subject was allowed two minutes for this task. Once the test had begun, the examiner made no further statements until the test time period was completed. At the end of the test, the total number of words was counted. Repeated words were counted only once.

The score was recorded as the total number of "h" words recalled.

Oral Reading Test. The oral reading test developed by Avant and Hutton provided a measure of the subject's articulation in connected speech and for an evaluation of other factors such as rate, voice quality, voice pitch, loudness, and breathing.⁴¹ Words for the passage were selected from the vocabulary of the Row, Peterson basic primer and from the first 1,000 words of the Rinsland list. The 123 word passage was presented to the subject on a card in large print and double spaced in an effort to reduce the influence of possible visual problems. The examiner handed the card to the subject and said, "Read this paragraph aloud." If the subject asked for assistance on a particular word, the examiner supplied the correct word. The oral reading test was scored by the length of time required to read the paragraph. Originally, the oral reading test had been selected to give a measure of both the subject's articulation pattern and his response time. However, the articulation measure was excluded since the errors that were made on the oral reading test were felt to be those of misread words, rather than articulation errors. The misread words would have been scored as articulation errors, which would have presented inaccurate data.

⁴¹ Avant and Hutton, op. cit., p. 44.

Vocal Encoding Test

The Vocal Encoding Test was a section test taken from the Illinois Test for Psycholinguistic Ability developed by McCarthy and Kirk in 1961.⁴² The purpose of the Vocal Encoding Test was to determine the number of unique, meaningful ways in which the subject could verbally characterize a simple object like a ball or block. Each response by the subject had to be clearly understood by the examiner before it was scored. If the subject's response was unclear, then the examiner immediately questioned the subject about that response to determine the subject's meaning of his answer. The questions asked were, "What do you mean?" or, "Tell me more about that." This type of questioning did not lead the subject to a desired response, but simply informed him that his meaning was unclear.

One demonstration item was employed for this test. The subject was handed a blue marble and asked, "Tell me about this." The subject could handle the marble if he wished. If, however, he did not respond with a few meaningful characteristics of the marble, he was asked some leading questions such as, "What is it? What is it made of? What color is it? What do you use it for?" These questions were used only for the demonstration item. After the subject responded to these questions, the test began immediately.

⁴²McCarthy and Kirk, op. cit., p. 1.

The marble was placed aside, and the examiner handed the subject a ball and said, "Tell me all about this." After about one minute of response time, or sooner if the subject clearly indicated that he was finished, the examiner said, "Tell me something else." If the subject appeared to have exhausted his repertoire before one minute, even after the second statement by the examiner, the next item was presented to the subject. However, if the subject was not finished responding in a minute, the next item was not presented until the examiner had said, "Tell me something else," and the subject had clearly indicated that he was finished with his response. The major variable was the number of unique ways in which the subject responded; since the test was open ended, the subject could give any of an infinite number of responses. All responses were recorded verbatim as the subject talked about the object. The subject's score was determined by the total number of acceptable responses according to the scoring procedures of the test manual. Also, the time taken for the task was recorded.

The entire testing period was tape recorded except during the administration of the Sklar Object Identification Test.

Chapter Summary

The present chapter has described the subjects, the experimental design, test events, and the testing procedure

that were employed for the study.

The design of the investigation indicated that five experimental conditions were established to study the effects of magnesium pemoline on the speech of central nervous system disordered patients. The Experimental Conditions I, III, and V were developed to investigate baseline information and to study the effects of learning and practice. The purpose of the pharmaceutical conditions, Experimental Conditions II and IV, was to establish and investigate the effect of the magnesium pemoline and the effects of the placebo on speech. When the subject was receiving the magnesium pemoline, the effects of the drug would be measured by comparing the drug condition to the baseline conditions or to the placebo condition. Also, the placebo condition could be compared with the magnesium pemoline condition or with the baseline conditions to study the effects of the process of administering a "medication."

CHAPTER IV

RESULTS AND DISCUSSION

The basic purpose of this investigation was to determine the effects of magnesium pemoline on the speech of central nervous system disordered patients. The study was concerned also with the rehabilitative value of magnesium pemoline.

After completion of the testing for all experimental conditions, it was revealed that all subjects received magnesium pemoline during the first pharmaceutical condition. That is, Experimental Condition I established baseline data, Experimental Condition II was the testing during the administration of magnesium pemoline, and Experimental Condition III set baseline test results after the magnesium pemoline administration had been completed. The placebo administration occurred during the fourth experimental condition, and the final baseline testing for the investigation was completed in Experimental Condition V.

Because of the small number of subjects employed in this pilot study, the preliminary results of this investigation with the experimental drug seem best illustrated by the following case reports.

Subjects

Case I. Case I was a 60 year old veteran who suffered

a cerebral vascular accident approximately a year and a half ago. On the Sklar Object Identification Test, he maintained the maximum score possible under the five experimental conditions, however, the time taken to complete the task displayed some variability. During the magnesium pemoline testing and the fifth experimental condition testing, Case I required a shorter time period than in the remaining experimental conditions. The time decrease during the drug administration possibly may be explained by the effect of Cylert; the decrease in time during the fifth experimental condition could have been a function of practice and learning. During the Object Naming Test, the subject named all pictures correctly under each experimental condition. However, the time was considerably shorter during the second experimental condition, the Cylert trial. The Recall Test showed little variation of results in any of the experimental conditions. The Oral Reading Test produced similar test times for all experimental conditions except the placebo trial which took approximately twice as much time. The Oral Encoding Test demonstrated that with each successive experimental condition, the subject responded with fewer words. The time was similar for all experimental conditions except the placebo condition which was much shorter than the remaining trials. The results for Case I are presented graphically in Figure 1, page 51. The graph demonstrates the

percentage of increase or decrease in performance from Experimental Condition I. For this subject, there was some suggestion that he was able to respond more rapidly while under the influence of the experimental drug for tasks that required concrete recognition responses to specific stimuli but not for tasks requiring a formulated response to more abstract stimuli. In general, however, there was no sufficient evidence to permit inferences regarding the effects of the experimental drug.

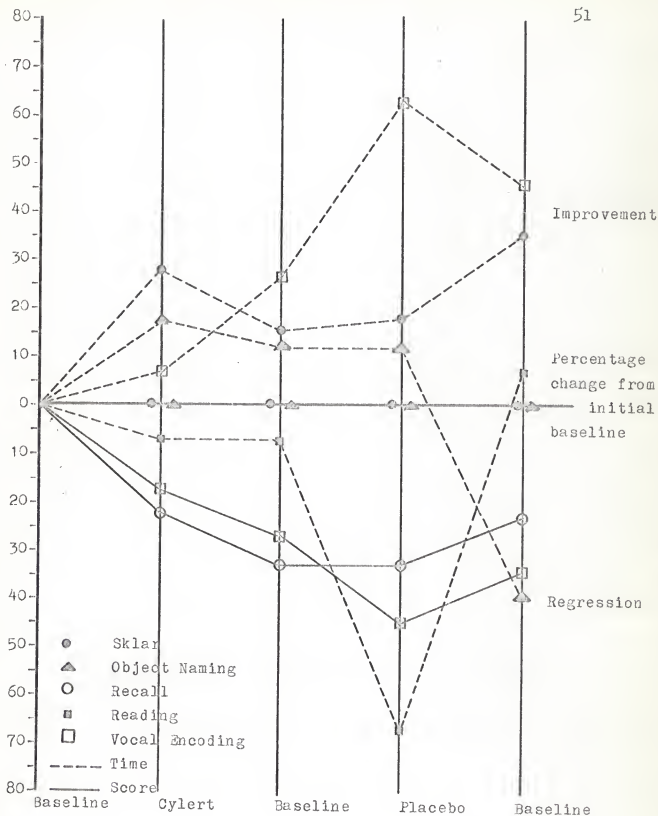


Figure 1. Case I. Percent of improvement or regression from the initial baseline on the test battery under pharmaceutical and additional baseline testing conditions.

Case II. The second subject, a 72 year old veteran, suffered a cerebral vascular accident about two years ago. This subject identified about half of the objects correctly on the Sklar Object Identification Test under all conditions. The time required for this task demonstrated improved response time on each successive testing session which may be due to a practice effect. On the Object Naming Test, Case II increased his score with each successive trial. This may have been due to the learning of the object's names. Furthermore, the time decreased as the successive conditions were presented. The first baseline condition took approximately three times as much time as the remaining four conditions. The Recall Test demonstrated that with each successive experimental condition, the subject responded with more words. The Oral Reading Test was not undertaken at this time because the task was too difficult for the subject. The scoring on the Vocal Encoding Test indicated that the placebo trial yielded the largest number of responses. During the magnesium pemoline condition, Case II made only one half of the number of responses made in the placebo trial. However, the time taken for this task was considerably shorter during the magnesium pemoline administration than for the other experimental conditions. The remaining experimental conditions required about twice to three times as much time to complete the task as the Cylert trial. The

results for Case II are presented graphically in Figure 2 on page 54. These results are plotted as a percentage of increase or decrease from Experimental Condition I. For this subject, there was some indication that he was able to respond more rapidly while receiving the experimental drug, Cylert. The subject appeared to improve in the number of responses to more concrete stimuli, however, the scores varied sufficiently so as to suggest nothing more than trends.

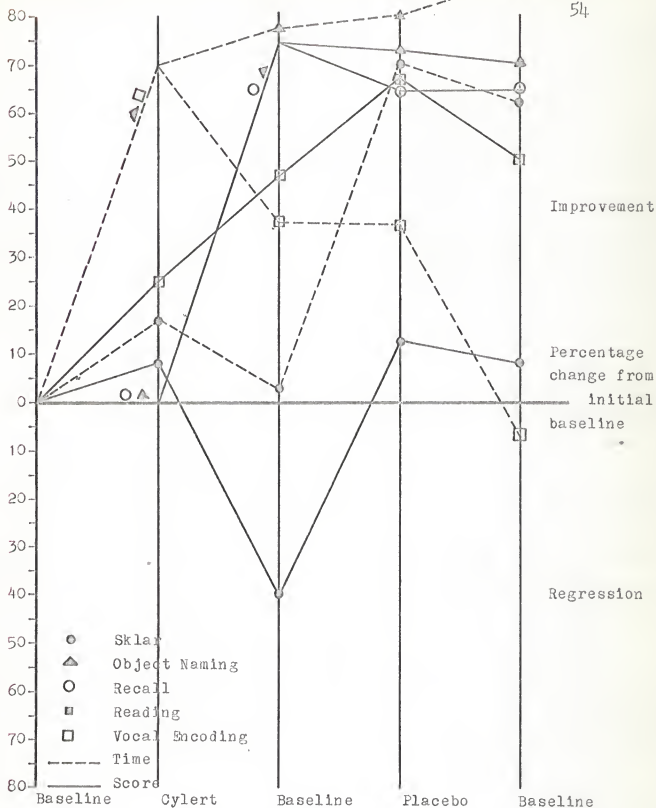


Figure 2. Case II. Percent of improvement or regression from the initial baseline on the test battery under pharmaceutical and additional baseline testing conditions.

Case III. The third subject, a 49 years old male veteran who suffered a cerebral vascular accident two and a half years ago, presented the following pattern of results. He obtained a high score on the Sklar Object Identification Test, however, he did not achieve the possible total of 20 correct. The magnesium pemoline conditions yielded results similar to experimental conditions one, three, and five. During the placebo condition, the subject scored less correct responses. The time varied for each trial with the magnesium pemoline condition requiring the most time. The subsequent trials generally decreased in the time required for that task. On the Object Naming Test, Case III increased his score with each successive trial. This may have been due to the learning of the object's names. Furthermore, time decreased as the conditions were presented, the first three conditions requiring twice as much time as the last two conditions. The Recall Test was quite difficult for this subject. He responded with two "h" words during the third experimental condition. For the other experimental conditions the subject gave no responses. The Oral Reading test also yielded few responses from the subject. The subject supplied no words from the test paragraph during the first trial; during the second and final experimental conditions, Case III read two words. During the placebo condition he achieved his highest score of four words. His response time

was approximately 40 seconds for each trial except the last condition when his time was 74 seconds for two responses. During the last test, the Vocal Encoding Test, the subject provided no correct responses except for the final baseline test when he gave two words in 60 seconds. On the third experimental condition, the subject attempted to verbalize about one of the objects but could not produce the name. The results for Case III are presented graphically in Figure 3 on page 57. The graph presents the scores in percentages of increase or decrease from Experimental Condition I. There was no general pattern of responding established for Case III. The magnesium pemoline condition indicated that no improvement occurred as a result of its administration.

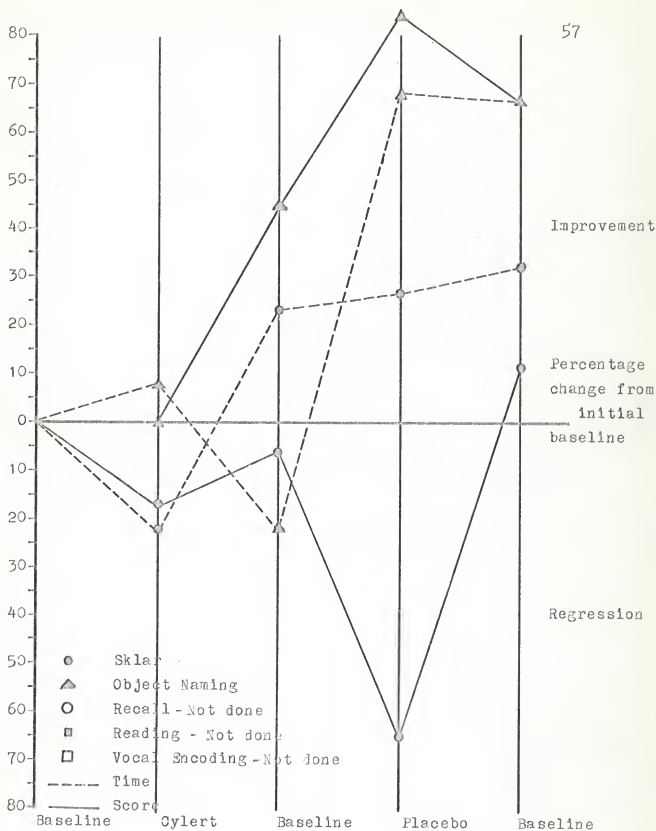


Figure 3. Case III. Percent of improvement or regression from the initial baseline on the test battery under pharmaceutical and additional baseline testing conditions.

Case IV. Case IV was a 94 years old male veteran who had Parkinson's Disease. This fourth subject yielded these results on the various tests. Case IV generally obtained a high score on the Sklar Object Identification Test. He scored 20, the total possible, on the magnesium pemoline and placebo conditions. On the other trials, the subject scored close to the possible total. The time factor varied a great deal. The magnesium pemoline and placebo conditions displayed the shortest time taken for the Sklar Object Identification Test. The other conditions required a longer period of time than the pharmaceutical conditions. The subject scored the maximum score under the various experimental conditions of the Object Naming Test except the placebo condition with the score there being slightly below the total score. The first condition required the longest amount of time for task completion. The remaining conditions took a shorter amount of time. None of these scores varied greatly among themselves. The results of the Recall Test showed that Case IV supplied the least number of correct responses during the magnesium pemoline condition. The remaining trials demonstrated approximately three times as many responses. For the Oral Reading Test, the subject averaged one minute for the completion of the task under the various conditions except the placebo trial which was not done by the subject. The scoring of the Vocal Encoding Test

displayed a relatively consistent pattern except for the placebo condition under which the subject gave considerably fewer responses than for the other testing conditions. The time was similar for all conditions except the placebo condition which was shorter as would be expected. This subject's performance is presented in Figure 4 on page 60. Case IV indicated a slight trend in improvement of response time during the Cylert administration. In general, there is not sufficient evidence to make a specific statement regarding the effects of magnesium pemoline.

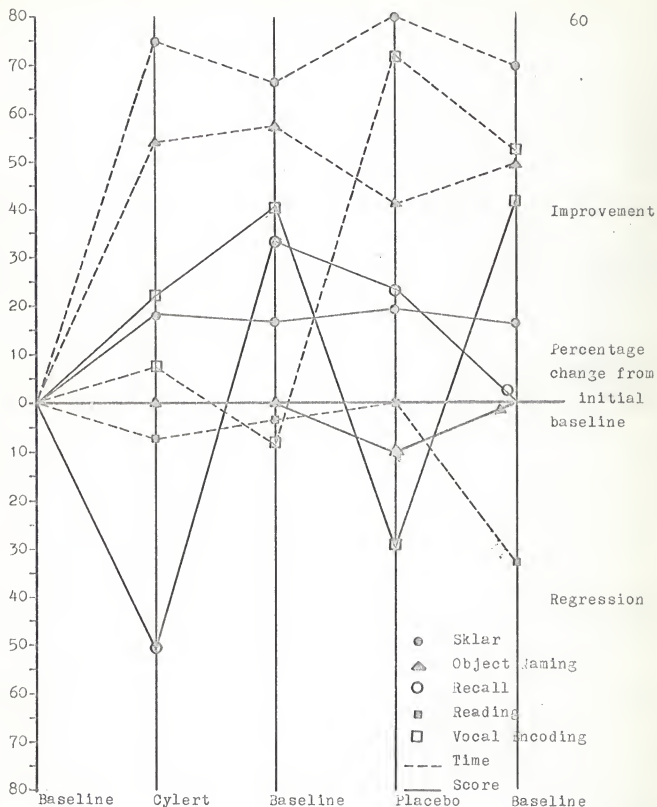


Figure 4. Case IV. Percent of improvement or regression from the initial baseline on the test battery under pharmaceutical and additional baseline testing conditions.

Case V. The fifth subject was a 41 year old male veteran who sustained a serious brain injury from an accident. The accident occurred about six years ago. This case performed as follows on the test battery. On the Sklar Object Identification Test, Case V scored the maximum total except on the third testing condition where he made one incorrect response. The time required on this task demonstrated improved response time on each successive testing session. Learning of the object's names due to practice may explain the general improvement. Again, the subject scored the total possible correct responses on the Object Naming Test except for the third condition where he made one incorrect response. The time taken to complete this test for the various trials was quite inconsistent. The first condition took the longest period of time; the magnesium pemoline testing trial decreased the time to less than half of that taken for the first trial. The third condition test time was similar to the Cylert condition test time. The placebo condition required slightly more time than the magnesium pemoline condition, and the last period was the shortest time necessary for this task. Thus, there was again no marked change in the performance score under the various conditions and no pattern of improvement in time was apparent to suggest positive effects from practice. The Recall Test varied from ten correct responses on the first trial to twenty correct

responses on the last trial. The Cylert condition had 19 correct responses. The third condition had fewer correct responses than the Cylert condition with the remaining conditions indicating general improvement. The Oral Reading Test indicated that Case V improved with each successive experimental condition and decreased the time required for each task. The Vocal Encoding Test showed little variability in the scoring. The first condition produced the fewest correct responses; the Cylert and third trials had the highest number of correct responses. The fourth and final conditions had fewer correct responses than the second and third trials. The magnesium pemoline condition test time was the longest of the various conditions. The other conditions were similar in test time. Figure 5 on page 63, presents the results for Case V. The scores are demonstrated in percentages of increase or decrease from Experimental Condition I. This subject demonstrated a slight trend for improvement of response time during the administration of the experimental drug. There was also a suggestion of enhanced ability to supply more responses for the tasks requiring abstract thinking. In respect to this observation, however, no generalization could be stated.

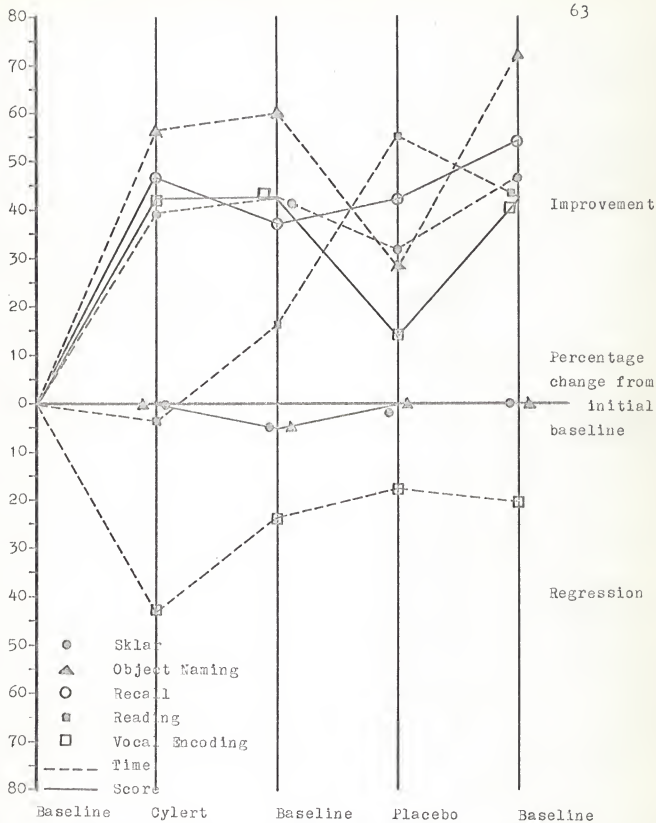


Figure 5. Case V. Percent of improvement or regression from the initial baseline on the test battery under pharmaceutical and additional baseline testing conditions.

Case VI. The sixth subject, a 52 year old veteran with Parkinson's Disease, performed in the following manner on the tests. Case VI identified correctly the 20 objects on the Sklar Object Identification Test. The time taken for the task varied slightly. The magnesium pemoline trial and the third experimental condition trials required the shortest amount of time taken for task completion. The other conditions required a slightly longer period of time. Again, the subject scored the total of 20 correct for each experimental condition on the Object Naming Test. The time taken for the task did not vary a great deal, the magnesium pemoline trial requiring the least amount of test time. However, the remaining conditions were only a few seconds longer than the magnesium pemoline condition. The Recall Test showed that the Cylert condition and the final condition yielded the most correct responses. The subject achieved the lowest time for task completion for the Oral Reading Test during the Cylert trial test time. The first condition test time was slightly longer than the magnesium pemoline condition. The remaining conditions required approximately twice as much time as the Cylert condition. The subject obtained a fairly consistent score for the Vocal Encoding Test. The time variable, however, was rather inconsistent. The magnesium pemoline and the placebo conditions required the least amount of time. Conditions one,

three, and five took a slightly longer period of time to complete the task. This subject's results are presented graphically in Figure 6 on page 66. The scores are presented in percentages of increase and decrease from Experimental Condition I. Case VI demonstrated some increased ability to respond more rapidly during the administration of the magnesium pemoline. Again, however, no generalization could be made from this observation.

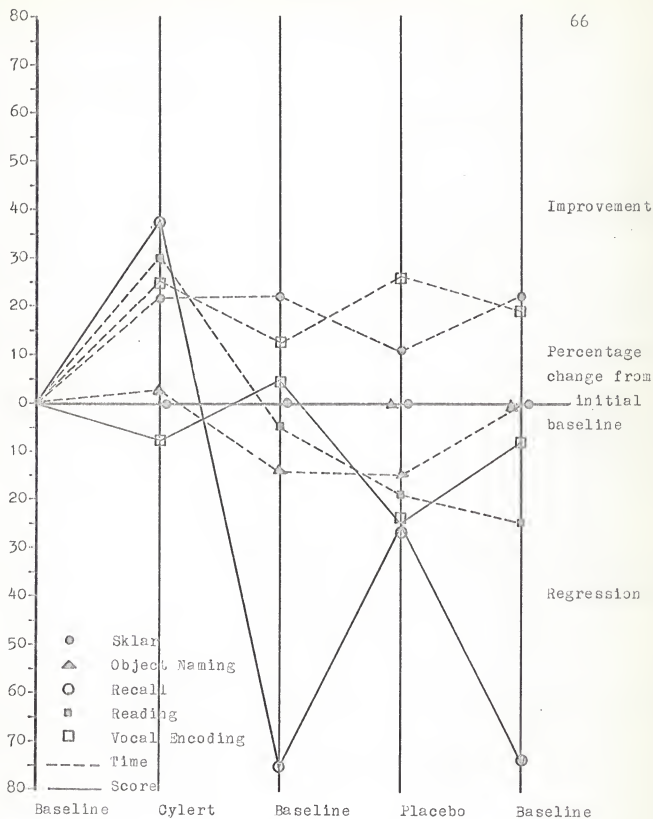


Figure 6. Case VI. Percent of improvement or regression from the initial baseline on the test battery under pharmaceutical and additional baseline testing conditions.

Tests

Sklar Object Identification Test. The Sklar Object Identification scores did not show any general pattern of improvement during the drug administration. The time required for this task under the magnesium pemoline condition generally required a shorter time period than for the first baseline condition. The subsequent time improvement for the following experimental conditions possibly may be explained as a function of a practice effect. Figure 7, page 68, presents percentage change of each subject's score to the Sklar Object Identification Test during the five conditions. Figure 8, page 69, presents the percentage change of each subject's response time required for the task completion.

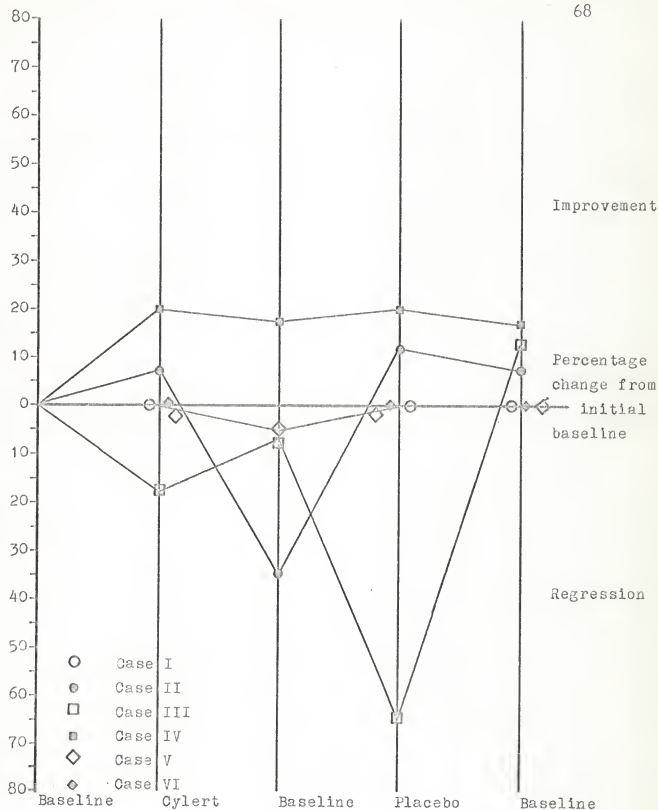


Figure 7. Percent of numerical improvement or regression from the initial baseline for all subjects on the Sklar Object Identification Test.

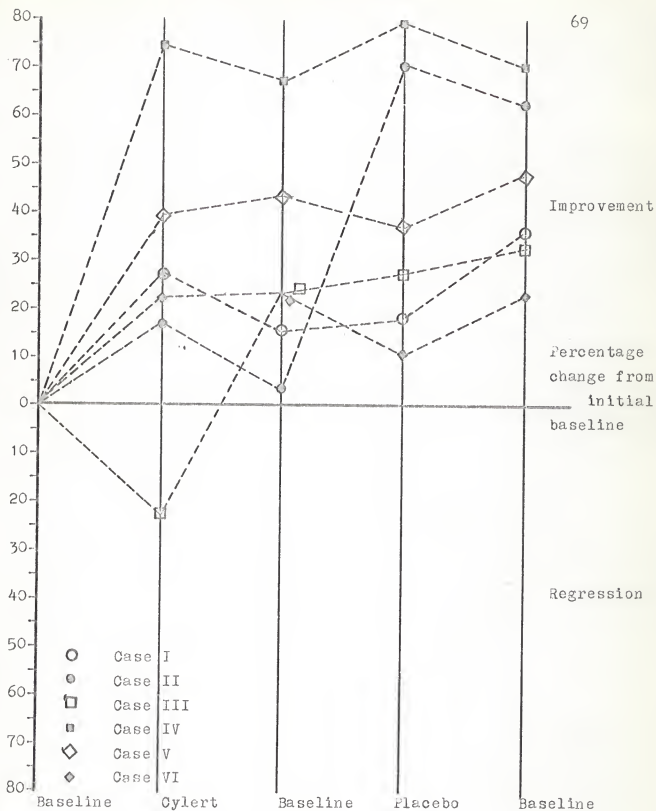


Figure 8. Percent of time improvement or regression from the initial baseline for all subjects on the Sklar Object Identification Test.

Object Naming Test. The Object Naming Test did not indicate any general pattern of improvement across subjects during the magnesium pemoline administration. The subjects' baseline scores, in all cases, were the same as the Cylert scores. In each case, however, the Cylert condition required less time than the first baseline condition. The subjects' scores varied, with Cases II, IV, and V presenting a more notable time decrease than Cases I, III, and VI. Figures 9 and 10, pages 71 and 72, graphically demonstrate the raw score change and time change percentages of each subject from Experimental Condition I.

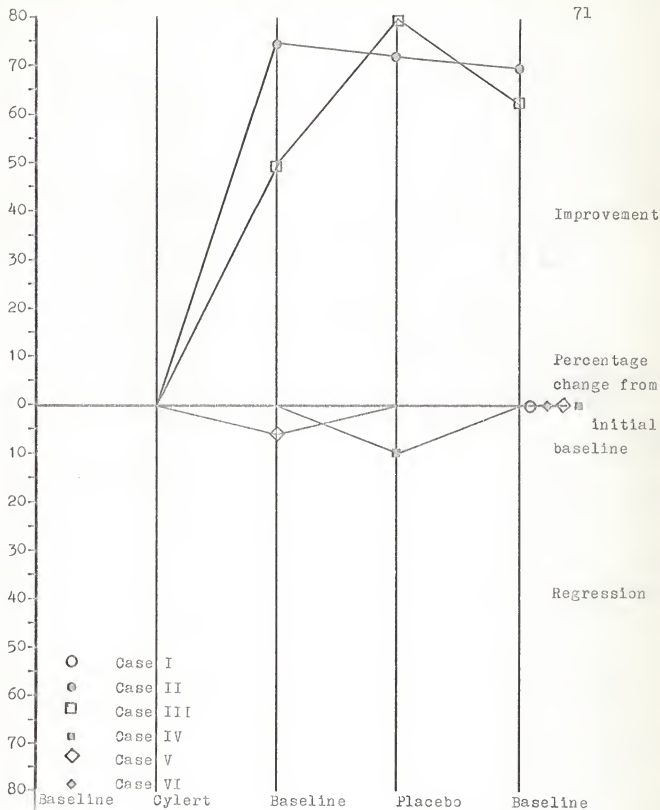


Figure 9. Percent of numerical improvement or regression from the initial baseline for all subject on the Object Identification Test.

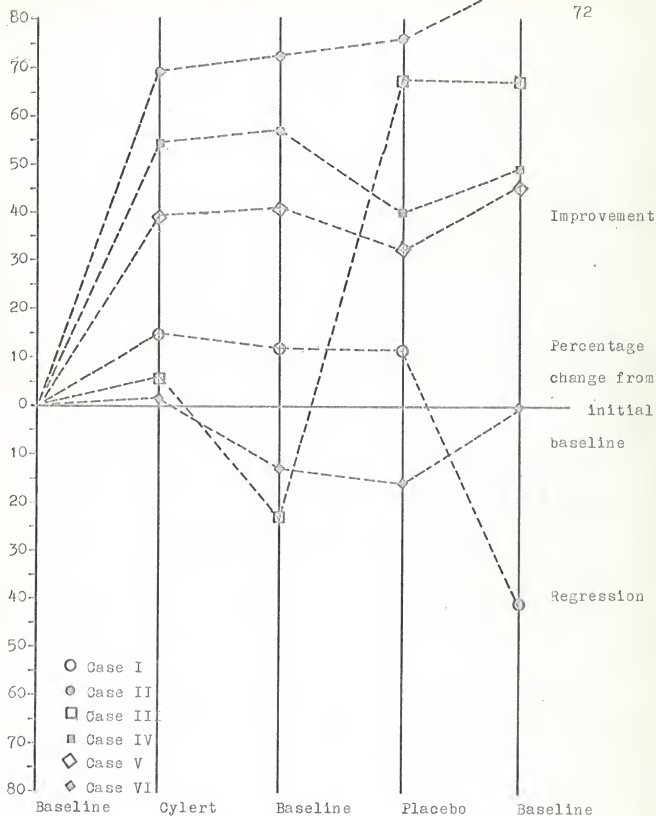


Figure 10. Percent of time improvement or regression from the initial baseline for all subjects on the Object Identification Test.

Recall Test. The Recall Test, completed by five subjects, demonstrated no pattern in the results that were obtained. Two subjects improved during the magnesium pemoline administration, one subject maintained his baseline rate; the remaining two subjects decreased in the recall of "h" words. Figure 11, page 74, graphically presents the results on this task.

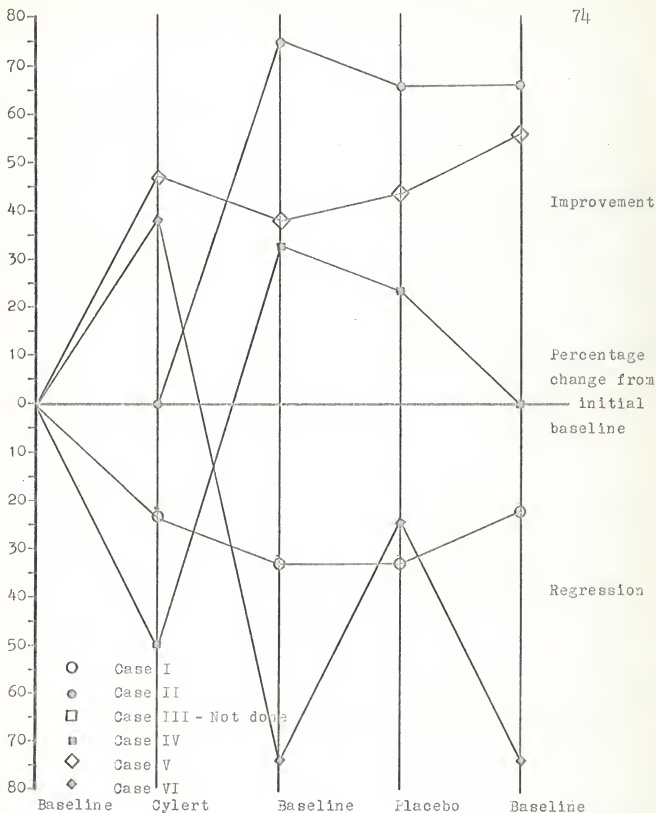


Figure 11. Percent of numerical improvement or regression from the initial baseline for the subjects that participated in the Recall Test.

Oral Reading Test. The Oral Reading Test presented only one instance where the subject improved during the Cylert administration, however, two subjects did not participate in the task. The time differences between Experimental Condition I and Experimental Condition II were relatively small. During the remaining experimental conditions, no pattern could be established. On page 76, Figure 12 graphically presents the results of each subject on the test.

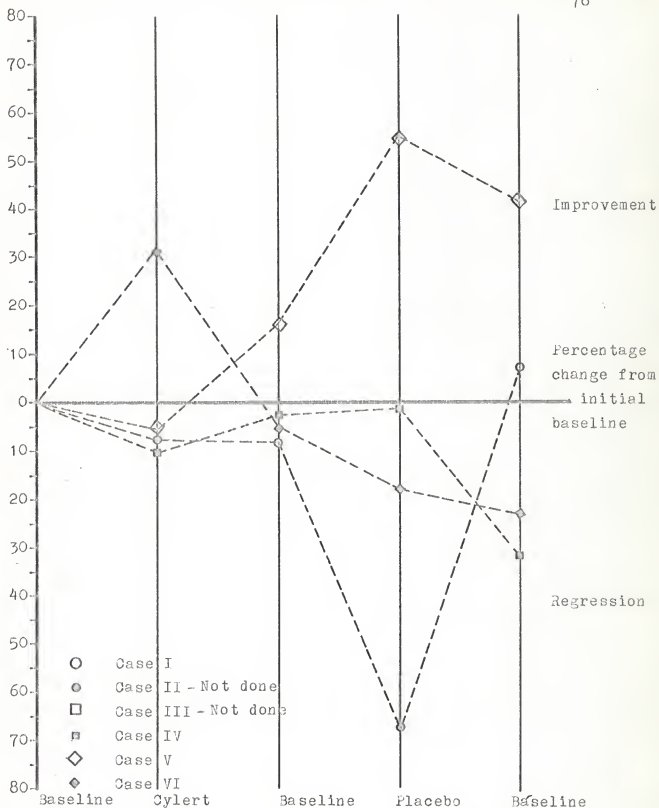


Figure 12. Percent of time improvement or regression from the initial baseline for the subjects that participated in the Oral Reading Test.

Vocal Encoding Test. The Vocal Encoding Test demonstrated that Cases II, IV, and V improved their numerical scores during the Cylert administration. However, this score was consistently improved during subsequent conditions. Cases I and VI decreased their scores during the drug administration, and Case III did not participate in the test. The test time indicated a slight trend for improvement during the Cylert condition, but no pattern could be established. Figures 13 and 14 on pages 78 and 79, graphically display the percentages of numerical response and test time change for each subject.

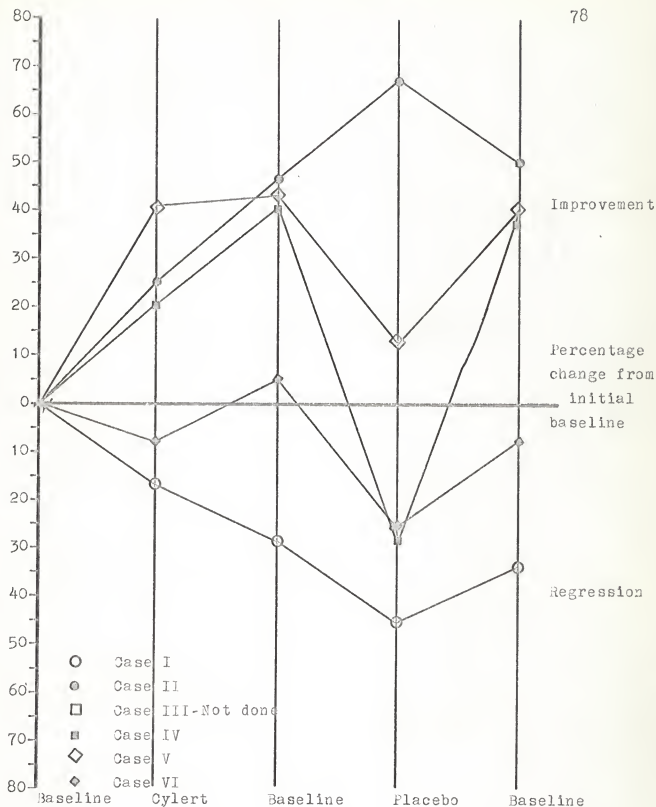


Figure 13. Percent of numerical improvement or regression from the initial baseline for the subjects that participated in the Vocal Encoding Test.

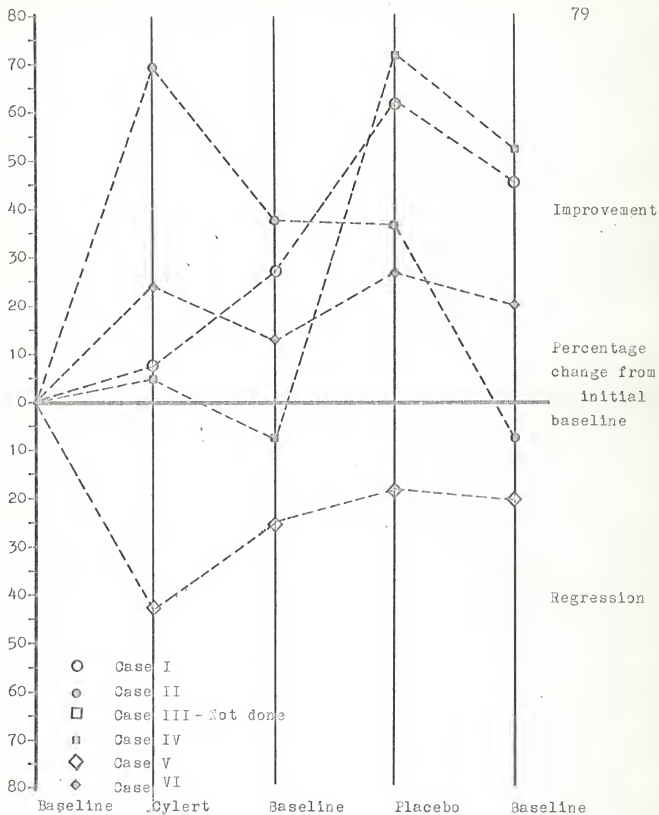


Figure 14. Percent of time improvement or regression from the initial baseline for the subjects that participated in the Vocal Encoding Test.

Chapter Summary

This chapter presented the performance results of central nervous system disordered patients on the tests employed in this investigation under five experimental conditions. The results were presented in respect to each subject and for each test.

In general, the performance of the subjects on the selected tests varied randomly with the experimental conditions which suggests that any differences among the experimental conditions occurred by chance. This would indicate that magnesium pemoline does not have any specific influence on central nervous system disordered patients as measured by the test battery employed in this investigation.

CHAPTER V

SUMMARY AND CONCLUSIONS

Man's central nervous system holds a vital role in his ability to speak. This advanced central nervous system has made the complex speaking process possible. Without this higher nervous system, man would be completely incapable of producing meaningful speech. Since the central nervous system controls the body functions that produce speech, agents acting upon the central nervous system could be expected to effect speech. Abbott Laboratories have introduced a chemical compound magnesium pemoline, as a central nervous system stimulant. It has been observed by employees at the Veteran Administration Hospital in Topeka, Kansas that the anticipated effect seemed to be present in the speech of central nervous system disordered patients while receiving magnesium pemoline during a pilot study. These informal observations have been cited by several people who worked closely with these patients and were generally regarded as enhancing speech. Chapter I stated that the purpose of the present study was to test experimentally the effects of magnesium pemoline in central nervous system disordered patients on the expressive verbal aspects of speech. The study was concerned also with the rehabilitative value of magnesium pemoline.

Investigators recently have concentrated a substantial amount of research on the effects of drugs on verbal output. Selected studies from the areas of hallucinogenic drugs, stimulants, central nervous system stimulants, and specifically, magnesium pemoline were reviewed in Chapter II.

Chapter III described the subjects, experimental design, test events, and the testing procedures that were employed for this investigation. Five experimental conditions were established to study the effects of magnesium pemoline. Experimental Conditions I, III, and V were developed to investigate baseline information. Experimental Conditions II and IV were established to investigate the effect of magnesium pemoline and the placebo on the speech of central nervous system disordered patients.

In Chapter IV, the results of the study were presented according to subjects, tests, and experimental conditions. The performances of the subjects on the selected tests varied randomly with the experimental conditions. In respect to the findings of the present study, it may be concluded either that (1) magnesium pemoline did not have any specific influence on the speech of central nervous system disordered patients as measured by the test battery employed in this investigation, or (2) if specific influences were present, the test battery employed was not adequate for

demonstrating these effects.

Although some researchers have found instances of improved performance with magnesium pemoline, none of these experiments furnished evidence that this effect was reliable under the conditions of a double-blind study. Therefore, whatever influence this drug may have on brain metabolism, its use as a pharmacological remedy for improving speech in central nervous system disordered patients does not appear promising. However, if observations of improved speaking ability from persons working with this drug persist, then further investigation of this drug should be undertaken. The present study may not have indicated the positive effects that magnesium pemoline may possess. Further investigation to study the effects of magnesium pemoline could be done employing different measures that may possibly better quantify the apparent speech differences. Spectrographic analysis of the voice quality would appear to be one possible direction for study. Other types of measures of expressive language abilities, such as mean length of response, would perhaps also be more fruitful in quantifying any real differences due to the action of pharmaceutical agents. Should future research contraindicate the result of the present study, this finding would be welcome by the rehabilitation workers concerned with central nervous system disordered patients.

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APPENDIX

Six adult patients of the neurology service at the Veteran's Administration Hospital who exhibited some speech difficulty associated with a history of nervous system damage or injury were selected for this study.

Case 1

General Information:

Case 1, a 60 year old Negro male, is a former maintenance worker. He was employed until his cerebral vascular accident on September 28, 1966.

Medical Diagnosis:

1. Cerebral thrombosis due to arteriosclerosis vessel indeterminate with right hemiparesis and focal motor seizures.

2. Chronic brain syndrome associated with arteriosclerosis.

Medical Prognosis:

The prognosis is favorable and rehabilitation work is recommended.

Case 2

General Information:

Case 2, a 72 year old male veteran, is a former foundry worker. This subject has a long history of various

earlier illnesses.

Medical Diagnosis:

1. Arteriosclerotic disease, generalized, moderate to severe with cardiac involvement and peripheral arterial disease.

2. Chronic brain syndrome, secondary to cerebral vascular accident, with right sided hemiplegia and mild left-sided hemiparesis and urinary incontinence.

3. GU tract infection, chronic.

4. Mild emphysema with intermittent mild pulmonary tract infection of a peripheral nature.

Medical Prognosis:

The prognosis for this patient is generally poor.

Case 3

General Information:

Case 3 suffered a cerebral vascular accident on October 31, 1965. Previously, he was self-employed as a grocer in Melvern, Kansas. This subject is 49 years old.

Medical Diagnosis:

1. Left internal carotid artery occlusion, manifested by a flaccid right-sided paralysis, aphasia, paresis of right conjugate gaze, right lower facial weakness.

Medical Prognosis:

The prognosis is exceedingly limited for any further degree of improvement of his muscular weakness or speech. However, at the present time he has the capacity to perform self-care activities.

Case 4

General Information:

Case four is a 94 year old male veteran who before retirement was employed as a meat inspector. The subject was admitted to the Veteran Hospital in February 1967.

Medical Diagnosis:

1. Basal artery insufficiency manifested by weakness in the left arm and leg, difficulty swallowing, chewing, and hoarseness.
2. Parkinson's Disease, likely on a atherosclerotic basis.
3. Acute bronchopneumonia, treated.
4. Prostatic hypertrophy, benign, treated.

Medical Prognosis:

The prognosis is uncertain as manifested by the patient's unpredictable course early in hospitalization.

Case 5

General Information:

Case five suffered a severe head injury in a car accident on July 7, 1962. He is a 41 year old male veteran.

Medical Information:

1. Post-traumatic encephalopathy chronic, severe, manifested by severe degree of organic dementia, expressive aphasia, some receptive aphasia, ataxia, and muscular weakness.

Medical Prognosis:

The prognosis for this patient is generally fair. The recommendation is for him to receive continuous treatment on an outpatient basis.

Case 6

General Information:

The sixth case is a 52 year old retired Army Major. This subject suffers from paralysis agitans.

Medical Diagnosis:

1. Paralysis agitans (Parkinson's Disease), chronic, bilateral, and severe.
2. Acute lumbosacral strain, associated with degenerative disc disease.

Medical Prognosis:

The prognosis for this subject is fair in regard to longevity but poor in regard for recovery.

THE EFFECTS OF MAGNESIUM PEMOLINE ON THE
REHABILITATION OF INDIVIDUALS WITH
CENTRAL NERVOUS SYSTEM DISORDERS

by

JANET BETH KUNTZ

B. S., Kansas University, 1966

AN ABSTRACT OF A MASTER'S THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF ARTS

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KANSAS STATE UNIVERSITY
Manhattan, Kansas

1968

The chemical compound, magnesium pemoline, produced by Abbott Laboratories under the trade name Cylert, has been introduced as a central nervous system stimulant. Cylert is a combination of pemoline and magnesium hydroxide. Although the specific action of this compound has not been determined, it apparently stimulates the specific activity of brain nuclear RNA, which in turn, stimulates the central nervous system. Since the central nervous system controls the ability to produce meaningful speech, the enhancement or stimulation of the central nervous system should facilitate speech.

Recent research at the Veteran's Administration Hospital in Topeka, Kansas has been concerned with magnesium pemoline as an enhancer of memory and learning in brain damaged patients. Preliminary evidence has suggested that magnesium pemoline increases the memory and learning span of some of these patients. Therefore, the purpose of the present study was to test experimentally the effects of magnesium pemoline in central nervous system disordered patients on the expressive verbal aspects of speech.

Six adult patients of the neurology service at the Veteran's Administration Hospital in Topeka, Kansas, who exhibited some speech difficulty associated with a history of nervous system damage or injury, were selected for this study. Five experimental conditions were established to study the effects of magnesium pemoline on the speech of

central nervous system disordered patients. The Experimental Conditions I, III, and V were developed to establish baseline information and to study the effects of learning and practice. The purpose of Experimental Conditions II and IV, pharmaceutical conditions, was to establish and investigate the effects of magnesium pemoline and the effects of a placebo on speech. When a subject was receiving magnesium pemoline, the effects of the drug were measured by comparing the drug condition to the baseline conditions or to the placebo condition.

The performance of the subjects on the selected tests appeared to vary randomly with the experimental conditions which suggests that any differences among the experimental conditions may have occurred by chance. This would indicate that magnesium pemoline does not have any specific influence on central nervous system disordered patients, as measured by the test battery employed in this investigation. However, the test battery employed in the present study may have been inadequate to indicate any positive effects that magnesium pemoline may possess. Further investigation to study the effects of magnesium pemoline, employing different measures, may possibly better demonstrate any differences in speaking ability that may exist.