# THE EFFECT OF MAGNESIUM PEMOLINE UPON SPEECH DISCRIMINATION ABILITY OF INDIVIDUALS WITH CENTRAL NERVOUS SYSTEM DISORDERS

by

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# CHAPTER I

## THE PROBLEM

### Introduction

> Pongileoni's blowing and the scraping of the anonymous fiddlers had shaken the air in the great hall, had set the glass of the windows looking on to it vibrating; and this in turn had shaken the air in Lord Edward's apartment on the further side. The shaking air rattled Lord Edward's membrana tympani; the interlocked malleus, incus, and stirrup bones were set in motion so as to agitate the membrane of the oval window and raise an infinitesimal storm in the fluid of the labyrinth. The hairy endings of the auditory nerve shuddered like weeds in a rough sea; a vast number of obscure miracles were performed in the brain, and Lord Edward ecstatically whispered "Bach!"[1]

The preceding quotation limns normal auditory communication. Sound waves enter the ear mixed with ambient noise present in the communication channel. The ear analyzes the auditory information and recodes this in the form of nerve impulses in the fibers of the auditory nerve. The nerve fibers converge and branch as they ascend along an elaborate pathway to the brain. Analysis, perception, and apperception of the impulses probably take place in the subcortical and the cortical brain areas. Damage to any part of this hearing circuit, as a lesion, would have a deleterious effect on the processing of the auditory signals.

Fairbanks has studied the speech mechanism and has

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[1] Aldous Huxley, Point Counter Point (New York: Harper and Row, 1956), pp. 34-35.

interpreted it as a closed cycle system, or servosystem.[2] The servosystem employs feedback of the output signal to the place of control, comparison of the output to the input, and such manipulation of the output producing device as will cause the output to have the same functional form as the input. The system involves sensor units which relay data to the controller unit in the form of feedback signals. The controller unit includes a storage device which receives and stores the input and gives off an input signal which is sent to a comparator and mixer. The comparator functions to form a calculation between the feedback from the input to derive an error signal which is fed to the mixer. The error signal combines with the input to produce the effective driving signal which is modified so that the future output more closely approximates the functional form of the input. The input, then, has been received, compared, and reproduced in this model.

An important feature of this phenomenon is the storage system which stores all of the past auditory impressions of the individual. The auditory impressions are received, catalogued, associated, retained, and capable of reactivation by current auditory impressions in this component of

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[2]Grant Fairbanks, "Systematic Research in Experimental Phonetics: 1. A Theory of the Speech Mechanism as a Servosystem," Journal of Speech and Hearing Disorders, 19 (1954), 133-139.

the model. Reactivation of past auditory events for comparison with current auditory impressions in the controller unit, and more specifically the storage system, would constitute auditory discrimination.

The perception and discrimination of auditory stimuli is believed to be located in the temporal lobe. Burr suggested that the capacity of memory is located in the temporal lobe also.[3] He felt that memory lies in a reverberating neuron circuit, or in a feedback system.

In understanding the concept of auditory discrimination, it is necessary to understand the functioning brain and its relationship specifically to auditory discrimination. Luria viewed the neural organization of the cerebral cortex as a complex hierarchical system based on the interaction of separate analysers, the separate parts connected by vertical and horizontal linkages.[4] Underlying each of the fundamental sections of the cerebral cortex are the "primary" or "extrinsic" zones, overlaid by "secondary" or "projectional-associative" zones and a third level of organization named "tertiary" or "intrinsic" zones, entailing several analysers.

Reflecting on contemporary psychology and linguistics,

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[3]Harold S. Burr, The Neural Basis of Human Behavior (Springfield, Ill.: Thomas Co., 1960).

[4]Ciba Foundation Symposium: Disorders of Language, ed. A. V. S. De Reuck and Maeve O'Connor (Boston, Massachusetts, 1964), pp. 143-150.

Luria viewed language behavior as a complex system of codes, organized into a system of phonemes, each of which singles out definite and persistent sound cues from the flow of speech. By auditory and articulatory (phonemic) evaluation, there may be selection (discrimination) of the definite units of speech. A small change in an essential phonemic cue may lead to a change in the perception of the word as in "fan" and "van". The phonemes being stable units of speech once learned, implying retention in the neuronal network of the brain, form the basis for comparison and categorization of the sound system of language. Phonemic codes then depend on the auditory and kinesthetic analysers. When these forms of analysers are disturbed, the sound organization of speech may break down.

With an impairment in "phonemic" hearing, an individual may lose his differential cues between voiced and unvoiced consonants. The impaired individual has difficulty in discriminating the acoustic cues. In auditory testing, the impaired individual may quickly master the instructions to lift the right hand upon hearing a high frequency tone and the left upon hearing a low frequency tone, performing these actions without error. However, the individual is unable to perform the same actions in identifying speech sounds. There is no pure-tone hearing deficit, but a disturbance in the analysis of sounds.

Reflecting on the servosystem, with the impairment

of the auditopsychic areas of the controller unit, there is limited action causing disturbances in the reactivation of past auditory events in the storage system. Therefore, comparison between past and current auditory impressions is less accurate. The degree of accuracy of judgment in a discrimination task would be diminished.

From the discussion of the central auditory nervous system it is certain that there must be increasing interaction and synchronization of the nerve impulses as they ascend the auditory pathway. Studies by Bocca and Calearo, Goetzinger, and Jerger support this contention by relating central auditory dysfunction to poor auditory response on difficult tasks of auditory discrimination.[5, 6, 7] Cases of pathology of the higher auditory pathways were observed in the greater than normal breakdown in auditory discrimination between distorted speech and ordinary speech. Central nervous system destruction or impairment in any zone in the brain stem and cerebral cortex interferes with the work of the analysers which participate in the speech and hearing process and leads

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[5] E. Bocca and C. Calearo, "Central Hearing Processes," Modern Developments in Audiology (New York: Academic Press, 1963), pp. 337-370.

[6] C. P. Goetzinger, et al., "A Study of Hearing in Advanced Age," A. M. A. Archives of Otolaryngology, 73 (1961), 662-674.

[7] James Jerger, "Observations on Auditory Behavior in Lesions of the Central Auditory Pathways," A. M. A. Archives of Otolaryngology, 71 (1960), 797-806.

to disintegration of all functioning systems of speech and hearing. Any reactivation or stimulation of damaged zones in the rehabilitation process might provide for more accurate analysis, better discrimination, or more accurate recall of past auditory events thus establishing a more competent speech and hearing system.

Statement of the Problem

In light of current theory regarding central nervous system processing of auditory information, the present use of drugs in the study of central nervous system disorders, and the ever-present need for further research, the present study will investigate the effects of magnesium pemoline on speech discrimination on individuals with disorders of the central nervous system.

The null hypothesis may be stated as such: there will be no change in speech discrimination ability in subjects with central nervous system disorders upon the administration of magnesium pemoline. An alternate hypothesis would be: there will be a change in speech discrimination ability in subjects with central nervous system disorders upon the administration of magnesium pemoline. More specifically, it is the purpose of this study to determine if there is a significant improvement in speech discrimination tasks in subjects with central nervous system disorders upon the administration of magnesium pemoline.

Importance of the Study

The problem of central nervous system disorders and their effects is being studied continuously. A number of factors serve to stimulate further research. Firstly, the expanding dimensions of warfare lead to brain injuries of young, productive servicemen. In a society which places a premium on productivity, rehabilitation for these individuals and the general welfare of all involved will be a decisive factor in the role of self-dignity and self-support.

Secondly, the mounting toll of traffic accidents each year increases the number of severe head injuries resulting in central nervous system dysfunction. The abrupt and impartial selection of the victims of these accidents disrupts the precious normalcy with rehabilitation offering hope to regain normal functioning.

Thirdly, modern preventive and curative medicine is providing an increase in the life expectancy among the older citizens and a concomitant increase in the number of patients with central nervous system damage as coronary disease or hypertension with frequent resultant cerebral impairment. There has been an estimate that 1,500,000 mature persons in the United States have survived cerebral vascular accidents who have varying degrees of impairment.[8] Hudson reports

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[8]Margaret C. Lefevre, "Speech Therapy for the Geriatric Patient," Geriatrics, 12 (1957), 691-695.

that by 1975 there will be an estimated 20 million aged persons in the United States.[9] Today, there is serious consideration of the socio-economic conditions and opportunities that confront elderly persons. The recent instigation of medical and supportive aid through federally sponsored welfare programs available to the aged and others affects the economy as a whole. Previously these programs were not available, but now with the available assistance and guidance to provide for needed treatment, rehabilitation is of paramount importance in offering the individual the opportunity to continue his life, not as a subordinate to society, but as a member of society. As there is a paucity of information available on the rehabilitation of central nervous system impairments affecting the speech and hearing functioning, there is a definite need to further investigate the variables that affect the rehabilitation process for these impairments.

Recently, research of various pathologies has involved drug experimentation and investigation. In a relatively uninvestigated area, Cameron reported on the administration of ribonucleic acid polymerase (RNA) to patients with memory

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[9]Atwood Hudson, "Communication Problems of the Geriatric Patient," Journal of Speech and Hearing Disorders, 25 (1960), 236-248.

deficits.[10] Favorable results were noted in many patients; changes occurred in patients having severe memory deficits and marked confusion. Orientation returned and there was considerable restoration of retention. Cameron and Solyom administered RNA on a double-blind basis to individuals who suffered cerebrovascular accidents or senile dementia.[11] After a three week period, the Wechsler Memory Scale and a counting test were administered to these patients. The results showed a higher attention span, less confusion, and more purposeful activity. In many cases, suspension of the treatment resulted in further decline of memory which was halted by the reinstitution of RNA.

More recently, investigators have been concerned with a chemical compound consisting of pemoline and magnesium hydroxide, tradenamed Cylert by Abbott Laboratories of Chicago, Illinois.[12] Glasky and Simon have studied the effects of stimulation by magnesium pemoline upon systems that synthesize brain nucleic acid with rats in vivo and in vitro.[13]

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[10] D. Ewen Cameron, "The Use of Nucleic Acid in Aged Patients with Memory Impairment," American Journal of Psychiatry, 114 (1958), 943.

[11] D. Ewen Cameron and Leslie Solyom, "Effects of Ribonucleic Acid on Memory," Geriatrics, 16 (1961), 74.

[12] Abbott 30400: Cylert, a combination of 2-imino-5 phenyl-4-oxazolidinone and magnesium hydroxine.

[13] Alvin J. Glasky and Lionel N. Simon, "Magnesium Pemoline: Enhancement of Brain RNA Polymerases," Science, 155 (February 11, 1966), 702-703.

The investigators found that there were differential effects between true RNA and pseudo-polymerase, but the mechanism by which magnesium pemoline activates the nuclear aggregate enzymes responsible for RNA synthesis could not be determined definitely.

Foster, Wing, and Goldstein have engaged in research in administering the drug magnesium pemoline to study memory and learning abilities in brain injured patients.[14] With incomplete results as yet, they recognize the need to continue investigation into many areas of central nervous system impairment with magnesium pemoline.

The late D. E. Cameron encouraged further research by saying,

> It (magnesium pemoline) opens the way to an almost limitless exploration of new methods of modifying this extraordinary system whereby we can bring forward continually the experiences of the past to modify present actions and future plans.[15]

Summary

In this chapter an attempt was made to introduce the problem of impairment in speech discrimination ability in central nervous system disorders. The need for further

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[14] D. B. 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, Veterans Administration Hospital, Topeka, Kansas.

[15] "Neurology" (anon. rev.), Time (June 24, 1966), 56.

research of this problem was discussed. A statement of the problem was presented in an effort to structure the direction of the present investigation for further study of the use of pharmaceutical agents in central nervous system disorders.

## CHAPTER II

## REVIEW OF THE LITERATURE

The direction of the present investigation requires some acquaintance with relatively complex and esoteric information concerning the functioning of the central auditory nervous system and the biological ramifications of the relationships between nucleic acids, magnesium pemoline, and central nervous system dysfunction. A review of some of the literature representative of these areas will be presented.

### Central Auditory Function

The auditory nerual pathway is made up of a series of nerve fibers beginning at the cochlea containing afferent neurons of the first order.[16] An afferent neuron and hair cell that excite this neuron constitute a sensory unit. The sensory units (i.e. hair cells, cilia) somehow initiate nerve impulses in the fibers of the auditory nerve. The sensory units are activated in spatial and temporal patterns relating to frequency, intensity, and timing in cochlear functioning. Auditory nerve axons conduct these nerve impulses and group together forming the cochlear nerve, the root of the auditory nerve. The cochlear nerve runs dorsally and caudally and laterally to the medial part of the ventral cochlear nucleus.

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[16] S. A. Sarkisov, The Structures and Functions of the Brain (Indiana University Press, 1966), pp. 111-116.

The axons of the cochlear nerve then divide into ascending and descending branches, in turn giving off numerous collaterals. Axons of the second order, arising in the dorsal and ventral cochlear nuclei, may run to the region of the superior olivary complex, mainly on the contralateral side terminating in the superior olive and in the nucleus of the trapezoid body. Other fibers run into axons of the third order from nuclei of the superior olivary complex and pass through the lateral leminiscus to the inferior colliculi. Generally then, the pathways of auditory conduction consist of four consecutively joined neurons. The first pass from the organ of Corti to the primary cochlear nuclei, the second run from the cochlear nuclei to the inferior colliculus, the third extend from the inferior colliculus to the medial geniculate body, and the fourth pass from the medial geniculate body to the auditory cortex ending in the temporal region. Additional subcortical structure relaying central auditory fibers suggests different orders of neurons may run parallel in the auditory system.

In addition to the anatomical location of auditory functioning, Burr emphasized the importance of the concept of memory.[17] Into the gray matter of the cortex come a number of auditory stimuli as intensity, pitch, timbre, location, and rhythm. Here the immediate coordinations and

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[17]Burr, p. 101.

correlations are carried out making it possible to discriminate the various kinds of sound the ear picks up. He points out that this discrimination property of the nervous system, or the cerebral hemispheres as a whole, shows up clearly in the auditory field. Memory functioning also has been located in the temporal lobe. With the concept of a feedback arrangement, a neuron once activated by a given bit of information can move to the output and back to the input in a continuously operating circuit. The basis of memory is thought to be this reverberating circuit. Therefore, the temporal lobe not only receives auditory stimuli coming into the nervous system, but also stores this information.

Bocca and Calearo believed that investigations of the central auditory system should be based upon the evaluation of disorders of pattern formation and integration.[18] That is, perception of a sound message does not seem to be a choice between single elements, but a choice between integrated units of sound elements. Therefore, the central auditory function is an organization of simultaneous or successive elements into definite patterns. One sound element has a certain relationship to another sound element. In terms of this concept of "redundancy" the audito-psychic area allows total recognition of a message only partially presented. This redundancy and perception is a function of the

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[18] E. Bocca and C. Calearo, pp. 337-370.

auditory centers in the integration and definition of form. The integration at the central level involves peripheral repertoires as well as the dynamic fluctuations in the duration, intensity, and frequency of stimuli. While the pattern of the verbal message is rigidly structured, so is the pattern of the activity of the message itself at various auditory stations and centers. This concept constitutes an intrinsic redundancy allowing patterns of neural activity to be discriminated. This redundancy is based on the criterion of order in the succession and distribution of incoming verbal stimuli afforded by the multiplicity of neural patterns. From their viewpoint, investigations of the central auditory system should be based on less structured material, in order to competently evaluate discrimination ability. By lowering the redundancy then, the individual with a central auditory lesion would have a more demanding discrimination task.

Schuknecht viewed the intelligibility of auditory functioning to be located at the central level.[19] Auditory systems in patients with temporal lobe lesions, acoustic neuroma, or presbycusis infer that lesions involving the auditory pathway allow reception of a simple pure tone signal, but do not handle the complex signals of speech.

Jerger related that, in general, neither cochlear,

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[19]Harold F. Schuknecht, "Perceptive Hearing Loss," Laryngoscope 68 (March, 1958), 429-439.

nor cortical lesions appreciably impair ordinary speech discrimination scores, but that lesions at various sites within the auditory nervous system may be demonstrated only by the more subtle demands of certain kinds of hearing tests.[20] Acuity for pure tones seems to be maximally affected by peripheral lesions, while speech discrimination is reduced in the bottleneck region of the eighth nerve and in the brain stem. Therefore, as the site and/or extent of the lesion is more central to the eighth nerve or brain stem, there is a concomitant decrease in the successful transmission of complex auditory stimuli.

Central Auditory Dysfunction

Jerger studied unilateral lesions in the central auditory system in observing a left temporal gliobstoma, a left temporal epilepsy, and a left frontal meningioma in the region of the sphenoid wing.[21] The audiograms evidenced no abnormalities. Conventional discrimination scores were satisfactory. However, in all cases, discrimination scores for distorted speech evidenced a performance which was considerably poorer on the ear ipsilateral to the affected temporal lobe. The alternate loudness matches might infer that the right ear evoked less intensity than stimuli delivered to

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[20] Jerger, pp. 797-806.

[21] James Jerger, "Auditory Manifestations of Lesions in the Auditory Nervous System," Laryngoscope 70 (1960), 417-425.

the same ear at comparable sensation levels. Jerger suggested that unilateral lesions of the temporal lobe at the cortical or subcortical level may impair the integrating and synthesizing function of the central auditory system.

Bocca and others further studied the integrative function of the cortex on 18 patients who suffered from cerebral tumors affecting one side of the temporal cortex.[22] Results showed in nearly all cases the failure of normal tone and speech audiometry to reveal deviations from the normal in either ear; however, discrimination of distorted voice was poorer in the ear contralateral to the cortical lesions. Therefore, it seems that these functional disorders are seen in the upper stations of the auditory pathways.

Goetzinger and others explored the effects of the differences between the sexes and aging on hearing discrimination and hypothesized additionally that hearing loss and poor discrimination are of a cortical nature and there would be a significant relationship between chronological age and the difficulty of the discrimination test; a simpler discrimination task would show little or no relation to chronological age.[23] Their findings seemed to support the hypothesis. Discrimination scores decreased as a function of old age and

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[22]E. Bocca, et al., "Testing 'Cortical' Hearing in Temporal Lobe Tumours," Acta Oto Laryngologica 45 (1955), Fasc. 4, 289-304.

[23]Goetzinger, pp. 662-674.

this appeared to reflect a cortical dysfunction. However, the findings indicated that discrimination problems of the aged are a composite of several factors and could not be localized to any one level of the auditory system.

Walsh and Goodman also investigated the diagnostic implications in the relationships between the discrimination scores and the loss of hearing for speech.[24] By exploring one case diagnosed as multiple sclerosis, it appeared that there was a loss for speech of only seven per cent. However, discrimination scores were 54 per cent and 58 per cent in the ear contralateral to the central auditory lesion. The authors stated that it appeared as if central auditory lesions resulted in poor speech discrimination no matter what the hearing loss.

Schuknecht, in reviewing clinical investigations, tenated that poor discrimination associated with small pure tone loss is characteristic of neural degeneration.[25] By experimentation on cats, 75 per cent of the ganglion cells could be lost to certain areas of the cochlea without creating threshold elevations for frequencies of excitation in those areas. Further auditory studies on human patients with acoustic neuroma have shown that while there was only

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[24]T. E. Walsh and A. Goodman, "Speech Discrimination in Central Auditory Lesions," Laryngoscope 65 (1955), 20-25.

[25]Schucknecht, p. 800.

a small pure tone threshold loss, there was decreased speech discrimination. In relating this finding, it could be implied that only a few fibers are needed to carry impulses of threshold magnitude.

Goetzinger and Rousey believed that speech discrimination difficulties of the aged could be attributed to a degenerative reduction in the number of ganglion cells and fibers of the auditory tract.[26] Degenerative changes of a cortical nature may also reflect poor speech discrimination. In either case, there seems to be no hearing loss for pure tones.

In recognizing the importance of central nervous system functioning in auditory discrimination, the following review of the literature concerning the effects of certain independent variables upon central nervous system functioning should be of particular interest.

Nucleic Acids and Mental Functioning

Cameron investigated the hypothesis that increased RNA ingestion can reverse or arrest progression of memory retention failure in the aged.[27] RNA was administered orally to patients in a pill form in dosages from 2 to 75 grams (gm.) daily. In 14 cases, daily intravenous injections of

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[26] C. P. Goetzinger and C. L. Rousey, "Hearing Problems in Later Life," Medical Times 87 (1959), 771-780.

[27] D. E. Cameron, et al., pp. 74-81.

50 to 2,000 milligrams (mg.) of RNA in a 10 per cent solution were given. Three months after the first experiment, re-assessment was repeated by the same method. The pattern of administration of RNA was as follows: 3 gm. daily during the first week, 6 gm. daily during the second week, and 9 gm. daily from the third to twelfth weeks. All medication was administered orally to a total of 693 gm. Tests measuring the degree of memory failure were the Wechsler Memory Scale, the Counting Test, and the Conditioned Reflex Test. Also reports of careful observations were obtained from relatives and friends. The 84 patients studied were divided into two groups. Group I consisted of 41 aged individuals with brain arteriosclerosis, senile dementia, and Korsakoff's psychosis. Group II consisted of advanced cases of these disorders. Results showed that in Group I improvement in retention span was noted after the first three weeks of treatment with RNA. Reports from medical staff members and relatives gave much evidence of memory improvement taking place during treatment. Also the general condition of each patient improved in alertness, interest, initiative, and confidence. In Group II, results obtained with RNA were comparable to those results obtained in the first group. Arteriosclerotic patients were found to be improved, but to a lower degree in comparison to the similar categories in Group I. Favorable results were not obtained in the senile patients on RNA or on placebo. In observing the results, the authors suggested that

increased RNA administration may serve to arrest a progressing memory deficit as improvement of memory was realized with a mean maximal daily dose of 10.2 gm. which is approximately twice as much as the daily intake of RNA from natural sources. While many individual differences were observed, the authors could not suggest an optimal dosage, but it seemed that a certain degree of saturation of RNA was necessary to obtain improvement with later reduction to a maintenance dosage. Withdrawal of RNA caused a decline in memory and treatment was reinstituted for these individuals.

Currently there is revitalized interest in drug experimentation with the impaired and unimpaired organism. A particular area of drug investigations has concerned central nervous system functioning and the drug magnesium pemoline. Theoretical speculations about RNA as a substrate of memory traces and experimentally demonstrated correlations with the administration of magnesium pemoline has stimulated lively research with propitious expectations. In that this is a relatively new and lightly studied area, particularly in respect to speech and hearing, the representative literature will be presented in some detail for more complete understanding.

Drug research with animals. One of the first efforts to demonstrate the effectiveness of magnesium pemoline was

studied by Glasky and Simon.[28] With a continued interest in attempting to establish a functional relation between nucleic acid or protein metabolism and brain function and to strengthen the hypothesis that nucleic acid functions as the information engram in the brain, the researchers studied, *in vivo* and *in vitro*, the stimulation by magnesium pemoline of systems that synthesize brain nucleic acids. Magnesium pemoline was administered intraperiotoneally to Sprague-Dawley white rats. The activity was measured both in the presence of true RNA polymerase and in the presence of pseudo-RNA polymerase. At various intervals, groups of 6 to 10 animals were sacrificed after treatment with magnesium pemoline. The brain tissue of both the control and treated group was collected and the nuclear aggregate preparation was assayed from both groups for true and pseudo-RNA polymerase activities. Results indicated that pseudo-RNA polymerase activity was slower than its counterpart, but showed a continued linear increase in activity as a function of time. In studying the effect of magnesium pemoline added *in vitro* on the activity of an aged enzyme preparation from brain tissue of nontreated animals by various methods of isolation, results showed that there was selective enhancement of the enzyme activity and particularly an enhancement of true RNA polymerase activity. The effect of magnesium

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[28] A. J. Glasky and L. N. Simon, pp. 702-703.

pemoline was not observed to be specific and was not necessarily related to the general pharmacological properties of psychotropic drugs. The data offered no definite information concerning the mechanism by which magnesium pemoline activates the nuclear aggregate enzymes for RNA synthesis. Possible explanations were: a direct activation of the enzyme(s), an allosteric alteration of a single enzyme protein molecule, or an activation of the DNA primer to make it a more effective template.

Interested in conflicting research results with magnesium pemoline, Simon investigated the effect of magnesium pemoline on RNA synthesis in rat brain using a completely in vivo test system.[29] Male Sprague-Dawley rats were divided into two groups of six animals each. The animals were injected with either magnesium pemoline (10 mg./kg., i.p.) or vehicle (0.25% 2-C-14 methocel). After 30 minutes, oratic acid was injected intercranially into each animal. At the end of an additional 60 minutes, each animal was decapitated. The brains were rapidly removed, chilled, and washed. A 20 per cent homogenate was prepared from each individual brain. Each sample of each homogenate and purified nuclei were analyzed for total RNA microgram content. The results indicated that magnesium pemoline did not cause

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[29]Lionel N. Simon, "Magnesium Pemoline: Enhancement of Brain RNA Synthesis: in vivo." Permission to cite the article from the author.

an increase in the specific activity of total brain RNA, when the comparisons were made on samples of homogenates prepared from whole brain tissues; however, different results were obtained when the same measurements were made on purified nuclei from whole brain homogenates. The administration of magnesium pemoline caused an 87 per cent increase in total micrograms of nuclear RNA/g. of brain tissue and a 114.5 per cent increase in the specific activity of nuclear RNA.

In this report, Simon cited arguments from other researchers whose findings essentially demonstrated that magnesium pemoline did not cause any increase in RNA activity in the brain. One contrary finding showed no increase in specific activity of total brain RNA activity after magnesium pemoline administration. The particular explanation offered the only possible conclusion — that there is a "special class of RNA" of the brain which might increase the turnover of brain RNA. Simon supported this observation by presenting the findings of Volkin and Strackan which designated a "messenger RNA" having the characteristics of being rapidly turned over and present mainly in the nucleus for short time periods. Another contrary finding reported that magnesium pemoline was incapable of stimulating rat brain RNA polymerase in vivo or in vitro and that it was ineffective in stimulating in vivo synthesis of both RNA and protein in chosen cells measured by nucleotide (NT) activity.

Simon observed that: firstly, while there was an initial precipitous drop in the (4)-NT activity, there was a slow increase for a period of 2 hours, and there was a threefold increase in the (1)-NT reaction over the 0 to 2 hour time period — the conclusion concerning the effectiveness of the drug does not seem to be justified in recognizing the apparent three-fold increase in (1)-NT activity in preparations isolated from treated animals; secondly, the untreated preparations may have indicated that the researchers had physically removed some substance present in the preparation which inhibited the enzyme and thus the possibility of seeing additional activation by pemoline was greatly diminished. More accurate and comprehensive investigation of the significance of the results and the importance in the method of isolation of brain nuclear RNA polymerase were felt to be of considerable importance in determining the results of the administration of magnesium pemoline.

In further investigation of the ribosomal system in the central nervous system mainly involved in protein synthesis, Simon studied the effects of magnesium pemoline on a cell-free ribosomal system isolated from a rat brain.[30] The results showed that magnesium pemoline had no effect in vivo or in vitro on the ribosomal system isolated from rat brain. Simon concludes by experimenting with in vivo

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[30]Simon, p. 7.

labeling techniques formulating that magnesium pemoline increases the synthesis of brain nuclear RNA supporting the activation of brain RNA polymerase and that the main mode of action of magnesium pemoline is to enhance the synthesis of brain nuclear RNA. In addition, he concludes that magnesium pemoline has no effect on the major system in the brain responsible for protein synthesis.

Plotnikoff studied the comparative effects of magnesium pemoline and methamphetamine, methylphenidate, and saline placebo controls on the acquisition and retention of a conditioned avoidance response in rats.[31] Male Sprague-Dawley rats were used. Magnesium pemoline was given orally 30 minutes prior to the first acquisition trial. Methamphetamine and methylphenidate were administered to a second and third group. The testing equipment consisted of a grid flooring and an escape platform above the grid floor. The first day rats were given a series of three trials, with 30 second sequencing: 15 seconds inside the chamber without shock or buzzer, 10 seconds with buzzer, and 5 seconds of shock with buzzer. These three test trials were used to select slow learners for subsequent studies. The second day the rats were given the drug orally 30 minutes prior to the first acquisition trial of a ten-trial sequence. The third

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

day retention of the escape response was measured by placing the test rat inside the chamber for 30 seconds without any buzzer or shock stimulation. Results of the study showed that rats treated with magnesium pemoline acquired the proper response by the second to the third acquisition trial of a ten-trial sequence, while saline-treated controls only reached the criterion of learning by the seventh trial. Controls failed to maintain their learned escape response on the retention trials and there was a rapid decline in performance. Both methamphetamine and methylphenidate were completely ineffective in altering acquisition or retention responses in contrast to magnesium pemoline. Methamphetamine and methylphenidate did not alter retention rates as compared to the controls. Thus, it was experimentally demonstrated that magnesium pemoline enhances the acquisition and retention of a conditioned avoidance response in rats.

Drug research with humans. One of the initial attempts to examine the effectiveness of magnesium pemoline with humans was investigated by Cameron.[32] He administered magnesium pemoline to twenty-four men aged 49 to 85 whose memories had been impaired by severe hardening of the arteries — senile psychosis. By using a double-blind approach, one half of the patients received magnesium pemoline for the first week while the other half received a placebo;

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[32]"Neurology," p. 56.

the conditions were reversed for the second week. The results recorded on motion picture film, showed that some patients after taking magnesium pemoline made more accurate drawings of objects recently shown to them, showed more decisiveness in what they remembered, and recalled things faster than the placebo group. There was significant improvement for men under 70 for visual presentations and pairings of words. Dr. Cameron's striking findings and other neurological research suggests that memory is not a biochemical system and is more than a mere pattern of behavior. A recent finding that Cameron cited, observed that the nerve cell is not, as previously held, a fixed and static structure, but one that continually forms new connections and breaks up old ones while producing biochemical substances to regulate faraway organs. Cameron suggested the possibility of a completely new system of medicine based, not on conventional drugs and surgery, but on the RNA mediated "memory" inside every one of the trillions of cells in the body.

Burns and others comparatively investigated the effects of magnesium pemoline and dextroamphetamine on learning in 30 male university student volunteers.[33] Using a double-blind procedure, each subject was given a single oral administration of one drug. The five conditions used in the

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[33] John T. Burns, et al., "Effects of Magnesium Pemoline and Dextroamphetamine on Human Learning," Science 155 (1967), 849-851.

study were: (1) magnesium pemoline, 25 mg.; (2) magnesium pemoline, 12.5 mg.; (3) magnesium pemoline, 6.25 mg.; (4) dextroamphetamine, 15 mg.; and (5) placebo. The subjects receiving 12.5 mg. and 6.25 mg. of magnesium pemoline were tested after the tests of other drug conditions were completed. The simpler task was a reaction-time task in which the correct response to different lights was to press the button in front of it. The learning task required the subject to learn which single key was the correct response to each light when the keys were randomly assigned. Any errors were related to the subject over an earphone by a brief tone. The first day of the experiment was a training session. The first problem was a reaction-time task. Following this, the subject was instructed to strive for maximum accuracy. The learning session consisted of 840 trials which were balanced for frequency of stimuli. In observing the learning curve it could be seen that the period of greatest learning occurred on Trial 8. Therefore, the period of greatest learning was the average of proportions of correct responses in Trials 2 through 9. Results showed that mean learning rate was fastest under placebo and increasingly slower under the conditions of magnesium pemoline and dextroamphetamine. It was further found that the rate of learning for any of the doses of magnesium pemoline was not significantly different from the placebo treatment. The higher the dosage of magnesium pemoline, the greater was the reduction in the mean rate

of learning. While subjects on dextroamphetamine learned more slowly than subjects on placebo, the dextroamphetamine group in the simpler reaction-time task had significantly faster reaction times than the placebo group with no decrease in accuracy. Dextroamphetamine was the only drug condition significantly different from the placebo, but even so showed a slower rate of learning than the placebo group. The behavioral effects of magnesium pemoline in animals have shown that higher doses inhibit learning. Apparently, the direction of the differences between placebo and the various doses of magnesium pemoline is in agreement with this finding. The results of the study indicated that in the subjects tested, magnesium pemoline did not enhance learning.

Talland investigated the effects of magnesium pemoline in the performance of a continuous attention task.[34] The subjects consisted of 24 student volunteers aged between 21 and 24 years. The subjects were administered a tablet of 24 mg. of magnesium pemoline or lactose placebo and were given a rest period for 90 minutes. In subsequent sessions, the interval between 70 and 90 minutes was used for testing delayed recall of a narrative text and of a maze learned in the previous week. The time between 90 and 120 minutes was used for new learning tests. Then, the subject received his

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[34]George A. Talland, "Improvement of Sustained Attention with Cylert," Psychonomic Science 6 (1966), 493-494.

second tablet of either placebo or magnesium pemoline and five minutes later he started a test of sustained attention for 50 minutes. Test of recall and relearning followed these tests. The test of sustained attention consisted of a continuous series of patterns of digits projected on a screen from slides. The task was to count the number of digits in view and to respond each time the number was the same as in the previous displays. Results showed that both drug schedules resulted in a reduction in the number of errors. This reduction and difference in scores between placebo and placebo conditions and magnesium pemoline and placebo conditions and the interaction between treatment and tasks was not statistically significant. The difference between placebo and placebo conditions and placebo and magnesium pemoline conditions was significant as was also the interaction between treatment and tasks. Generally, it was concluded that magnesium pemoline enhances performance in tasks requiring continuous attention. More specifically, the improvement in task-efficiency supports the general stimulant or anti-fatigue properties attributed to the drug. The authors suggest that the noted favorable influence that magnesium pemoline has on learning and remembering may reflect an increase in the level of general alertness rather than an effect specific to the processes involved in learning and memory.

Talland and McGuire investigated the effects of

magnesium pemoline on learning and memory.[35] The subjects for the experiment were 24 student volunteers between the ages of 21 and 24 years. The drug was administered orally in doses of 25 mg. each at the beginning or 120 minutes later. A lactose placebo was also given. The two experimental schedules were (1) magnesium pemoline and placebo and (2) placebo and magnesium pemoline and the control schedule placebo and placebo. After 90 minutes, the subject being administered either agent, was given three learning tasks: a maze test, a narrative text, and a set of figure drawings. A second agent was administered at the end of the period and after five minutes of rest, the subject was tested for sustained attention. Following, there was a test of retention of newly learned material. The results showed that administration of magnesium pemoline did not improve or speed up learning. Also magnesium pemoline did not seem to exert a systematic influence on those delayed effects of learning which would allow for inferences to the mental processes of consolidation or retention. Gains measured in the difference between information recalled after initial and repeated learning could be demonstrated only on trials of relearning. Savings in the number of trials required to reach criterion performance were greatly increased in the maze learning test

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[35]George A. Talland and Michael T. McGuire, "Tests of Learning and Memory with Cylert," Psychopharmacologia (Berl.) 10 (1967), 445-451.

by the administration of magnesium pemoline before relearning. It was implied by the authors that the drug affected performance in the repeated learning task rather than retention tasks by strengthening a consolidation process after original learning. The authors strongly recognize a probable general stimulant or anti-fatigue effect attributable to magnesium pemoline rather than any influence on learning and remembering.

Talland and others were interested in the effects of magnesium pemoline on performance of chronic Korsakov patients under experimentally controlled conditions.[36] The performance tasks tested the processes involved in various aspects of learning and memory. Experiment I investigated the effect of magnesium pemoline on the acquisition of new information and on its recall in four patients. Single oral doses of 50 mg. and placebos were given on a double-blind procedure. Learning and recall were observed. Results showed no systematic change in scores among the three treatments, magnesium pemoline, placebo, and no medication, nor any change attributable to repeated trials. Experiment II involved three people in the previous experiment excluding the oldest (fourth) member. Dosage was cut to half (25 mg.) for magnesium pemoline and also included methamphetamine

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[36]George A. Talland, et al., "Performance Tests of Amnesic Patients with Cylert," The Journal of Nervous and Mental Disease 141 (1967), 421-429.

(10 mg.) and lactose. Experimental procedures again investigated aspects of learning and memory. One subject showed improved performance with magnesium pemoline on a continuous attention task. All subjects improved with magnesium pemoline on the succeeding sessions of a running memory span test. Experiment III investigated similar aspects of learning and memory with the same four patients over a relatively longer period of time. Results were varied, but offered no trend for the effects of magnesium pemoline.

Recently Foster, Wing, and Goldstein initiated a pilot study to investigate the effects of magnesium pemoline on aphasic patients.[37] Objective and subjective evaluations suggested that the patients on this drug improved noticeably over placebo controls in mental functioning and noticeably in speech and language behavior. Interest was stimulated to manage a more experimentally controlled study of this drug upon central nervous system disorders.

While no research has directly examined the effect of magnesium pemoline on speech sound discrimination in central nervous system disorders, the preceding, similar studies have direct references to the questions which this present study will examine in depth.

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[37] D. B. Foster, et al.

Summary

This chapter has presented a selected review of the literature relating to the problem under investigation. A discussion of the function and the dysfunction of the central auditory system was presented. The relationship between nucleic acids and mental functioning was discussed. Information was presented concerning drug research with animals and humans. The review of the pertinent literature has involved the material concerning speech discrimination and, although indirectly related to speech discrimination, the state of knowledge concerning the nature of magnesium pemoline integral to the appreciation and evaluation of the present study.

# CHAPTER III

## PROCEDURES

The research design of the present investigation entails a description of the size of the experiment, the experimental material, and the experimental treatment. By following these procedures, it was possible to study the problem which is the concern of the investigation.

### Subjects

The subjects used for the present study were six male outpatients of the Veterans Administration Hospital at Topeka, Kansas. The subjects were tested previously for auditory sensitivity in the hospital admittance testing battery and were selected because of their central nervous system disorder and their inability to evaluate accurately acoustic or auditory stimuli. The subjects had sufficient hearing acuity to permit supra-threshold discrimination testing. The verbal responses of the subjects infrequently contained misarticulations. The subjects were adequately intact, both physiologically and psychologically, to participate in the study.

The subjects could not take any anti-convulsant, psychotropic, or central nervous system stimulant drug for the duration of the study. In compliance with the regulations set forth by the Federal Drug Administration, the

physical condition of each subject was monitored carefully while on the experimental drug. Each subject selected for this study was informed of its investigational purposes and signed an agreement (Veterans Administration Form, Number 10-3203, Consent for Use of Picture and Voice), with proper witnesses, that he understood the use of his performance for educational and research purposes.

Tests

In observing the difficulty in discriminating auditory stimuli, simple amplification of speech does not provide an adequate measure for this impairment. Therefore, the test events were selected respective to three considerations: (1) the general hearing sensitivity of the subject, (2) the speech discrimination ability of the subject, and (3) the time length of the test session to prevent general physical fatigue for the patient.

Audiometric pure tone. This test is a psychophysical measure to obtain the lowest intensity of a stimulus required to produce a sensation in a subject or elicit a response from a subject in relation to normal thresholds of audibility as specified by the American Standards Association. The particular procedure used was the Carhart and Jerger modification of the Hughson-Westlake technique for obtaining pure tone thresholds. In this procedure, the subject was given a tone presentation at 70 decibels hearing level to evoke a response.

A descent was made from that point in ten decibel steps until there was no response. Ascents were made in five decibel steps from the level of inaudibility to the level of the first response. Threshold was located in ascending trials and was defined as the minimal level evoking two responses out of three tone presentations. While the attenuator was being adjusted for the next level there was a toneless interval. Tone presentations were for a duration of not less than one second and not more than two seconds. Test frequencies administered were 500 Hz., 1000 Hz., 2000 Hz., and 4000 Hz.

Discrimination. Discrimination tests evaluate the ability of the listener to understand speech material presented at an optimum hearing level. A discrimination loss for speech is the difference between 100 per cent and the per cent of the given speech material that a listener identifies or repeats correctly at a level that is sufficiently high so that a further increase in intensity is not accompanied by a further increase in the amount of speech material repeated correctly.

The first discrimination test used was the C.I.D. Auditory Test W-22, List 2E. This test consists of 50 phonetically balanced (PB), monosyllabic words. The list contains the various speech sounds of English in the relative frequency of occurrence that approximates the distribution of speech sounds that would be found in ordinary conversation.

The second discrimination test used was the Rush Hughes recording of the Harvard P.A.L. Phonetically-Balanced Word List 7B. The criteria for the selection of words for this list additionally considers words of equal average difficulty, equal range of difficulty, representative of English speech, and in common usage. No particular criteria were employed in selecting either list, except for the popularity the lists have enjoyed as clinical tools, especially the Rush Hughes recording.

Instructions for List 2E and List 7B were as follows:

> Directions: You will hear some one-syllable words on this recording. You will hear them at approximately the same loudness. Listen carefully and repeat as many of the words as you can. If you are not sure of the word, make a guess. Do not pay attention to any of the phrases before the words, just repeat the words. Let's try some words for practice:
>
> You will say . . . soup
> You will say . . . park
> You will say . . . lake
>
> Here are some others:
>
> Number 1 . . . man
> Number 2 . . . car
> Number 3 . . . run

The third discrimination test used was the Wepman Auditory Discrimination Test, Form I. The test consists of a list of forty word pairs. The word pairs may be identical or they may be minimal pairs — two words that are alike in all but a single phonetic feature. The test was selected to study the phenomenon of "phonemic deafness" in speech discrimination ability. The subject must discriminate

between sound elements in the word pair.

The following instructions were read before the test:

> Directions: On this recording you will hear two words at a time. I want you to tell me whether the two words are the same word read twice or two different words read to you. If the two words are exactly the same say, "Same"; if the two words are not exactly the same say "Different". Do not pay attention to the phrases before the words, just answer whether the words are the same or different. Let's try some words for practice:
>
> Number 1 . . . man, man
> Number 2 . . . hat, pat
> Number 3 . . . dog, hog

A previous recording of the two PB lists used in this study completed by another examiner were borrowed for use in this study.[38] List 2E and List 7B were transcribed from new disc recordings to magnetic recording tape to preserve the effects of recording conditions and the speakers. The Wepman test was recorded by a linguist under regulated conditions at 3 3/4 ips onto the master tape. Word pairs were read with a carrier phrase and approximately a one second pause between words. The 1000-cycle calibration tone was recorded for each test in order to adjust the speech gain of the audiometer. The tests and order of words in the tests were not varied in sequence of presentation for the duration of the study.

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[38] Robert S. Brooks and C. P. Goetzinger, "Vocabulary Variables and Language Skills in the PB Discrimination of Children," The Journal of Auditory Research 6 (1966), 357-370.

Instrumentation

The test events for this study were conducted in a test and control unit, I.A.C. Model 1203. The auditory pure tones were generated by a Beltone Model 15C clinical audiometer located in the control room. The headphones were TDH-39 receivers in MX-41/AR ear cushions located in the test room. The remaining three discrimination tests were from a master tape recording played on an Eico RP/100 tape deck. The tape deck was jacked through a Grason Stadler Speech Audiometer, Model 162. The speech audiometer signal was amplified by a Citation B, Harmon Kardon solid state stereo power amplifier which was broadcast over an AR 3, Inc. extension speaker located in the test room.

Scotch Brand magnetic recording tape, Number 141 was used in the transcription of the W-22, Rush Hughes, and Wepman recordings. The tape is a heavy duty, silicone lubricated product of the Minnesota Mining and Manufacturing Company.

Drug Administration

Each subject received a prescription of a two week supply of medication dispensed by the hospital pharmacy. Magnesium pemoline was of white tablet form in the amount of 50 mg. per tablet. The placebo was in identical white tablet form also. The subjects in the study were accustomed to taking medication and were instructed to take the tablet

every morning for a period of fourteen consecutive days.

Experimental Design

Each subject acted as his own control for the experimental purposes of this investigation. Following a double-blind procedure, the subjects and examiner were unaware of the type of drug being administered for the respective conditions. Two conditions were studied: Medication Condition I, consisting of the administration of either magnesium pemoline or placebo and Medication Condition II, consisting of the administration of the remaining medication, either magnesium pemoline or placebo. The auditory test battery was given during each of these medication conditions and baseline testing was done before and after each treatment constituting pre- and post-baseline measures. This design thus yielded five test battery runs as follows:

Trial A. Pre-baseline

Trial B. Medication Condition I, (magnesium pemoline or placebo)

Trial C. Post- and Pre-baseline

Trial D. Medication Condition II, (magnesium pemoline or placebo)

Trial E. Post-baseline

Following this procedure, the resulting data provided information about the effectiveness or ineffectiveness of the drug magnesium pemoline upon speech discrimination ability on individuals with central nervous system disorders.

Research Questions

The following questions were formulated to explore the results in detail:

1. Is there a statistically significant difference between either the Medication Conditions I and II or between the Medication Conditions I and II and the various baselines, Trials A, C, and E for List 2E of the C.I.D. Auditory Test W-22?

2. Is there a statistically significant difference between either the Medication Conditions I and II or between the Medication Conditions I and II and the various baselines, Trials A, C, and E for List 7B of the Rush Hughes version of the Harvard P.A.L. PB words?

3. Is there a statistically significant difference between either the Medication Conditions I and II or between the Medication Conditions I and II and the various baselines, Trials A, C, and E for the Wepman Auditory Discrimination Test, Form I?

These particular questions were designed to examine either (a) the effects of the experimental drug relative to performances during no particular treatment or (b) the effects of the process of merely administering a "medication" relative to no treatment. By comparing Medication Conditions I and II, the real effect of the experimental drug was contrasted with the possible effects of "medication" by the use of the placebo.

Summary

The present chapter has endeavored to describe the experimental sample, the test materials employed, the instrumentation, and experimental design and procedures of the investigation. In addition, specific research questions were raised for the purpose of examining in detail the results of the investigation.

# CHAPTER IV

## RESULTS AND DISCUSSION

The purpose of this study was to investigate the effects of the experimental drug, magnesium pemoline, upon speech discrimination ability on individuals with central nervous system disorders.

### Analysis of the Results

The feature investigated in this analysis was auditory behavior measured by three tests of speech discrimination. Performances were measured for each subject and test for the medication conditions which involved the administration of magnesium pemoline and placebo. Baseline performances were collected for each subject and test before and after each of the two medication conditions. The performances of the subjects, in terms of the average percentage of correct responses, have been presented graphically for the three tests in the different trials, (see Figure 1). The raw data have been presented in Appendix B.

The Friedman Two-Way Analysis of Variance was selected to determine the statistical significance of differences in the response of the subjects for each test and the different

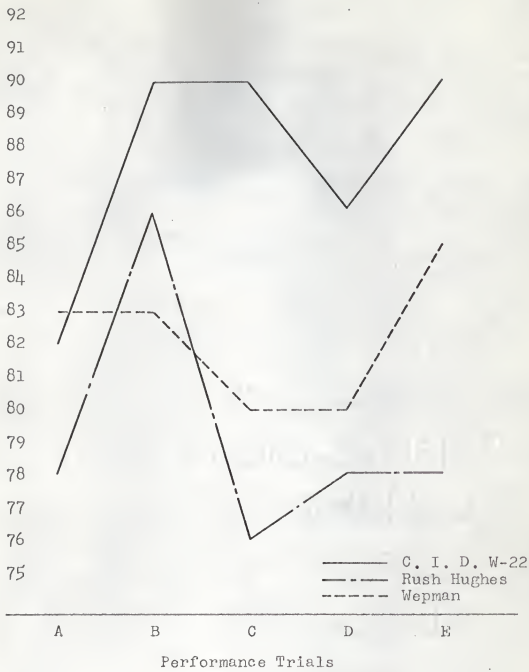


Figure 1. Average Percentage of Correct Responses for Three Speech Discrimination Tests: Trial A, Pre-baseline; Trial B, Magnesium Pemoline; Trial C, Post- and Pre-baseline; Trial D, Placebo; Trial E, Post-baseline.

trials.[39] This particular statistical device is useful for studying a small sample as used in this study. The scores for each subject were converted to ranks for each of the five test trials and cast into a subject by conditions table. If the scores of the subjects are independent of the conditions, the distribution of ranks among the conditions would be essentially random. If the scores of the subjects are dependent upon the conditions, then the sum of the ranks for the respective conditions could be expected to vary significantly. The Friedman test determines whether the rank totals under the various conditions do, in fact, vary significantly. This type of analysis was done for each auditory test.

C.I.D. W-22 Test, List 2E. The data on speech discrimination ability from this test were obtained for each subject on the five trials by recording the number of correct responses to the PB words presented. Examination by inspection of the scores between trials showed small differences except in Trial B which involved the administration of magnesium pemoline. Trial B showed the greatest difference in that, generally, there was an increase in the number of correct responses. However, the differences among the five trials were not statistically significant.

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[39] Sidney Siegel, Nonparametric Statistics for the Behavioral Sciences (New York: McGraw-Hill Book Company, Inc., 1956), pp. 166-173.

Rush Hughes Test, List 7B. The data on speech discrimination ability from this test were obtained for each subject on the five trials by recording the number of correct responses to the PB words presented. Examination by inspection of the scores between trials again showed small differences except in Trial B which involved the administration of magnesium pemoline. Trial B showed increases in the number of correct responses, especially for subject number six, (see Appendix B). As with the W-22, however, the differences for the five trials were not statistically significant.

Wepman Auditory Discrimination Test, Form I. The data on speech discrimination ability from this test were obtained for each subject on the five trials by recording the number of correct identifications for the word pairs presented. Examination by inspection of the scores between trials showed slight differences in responses, but no pattern was evident as with the W-22 and Rush Hughes tests. In comparison with the inspection of differences for these tests, the differences in performances did not show changes of the magnitude previously noted. As might be expected, the five trials did not yield statistically significant differences.

Analysis of the Subjects. Similar analyses of variance were performed for examination of subject variation to determine if there were significant differences between the subjects. The scores for each subject were converted to ranks for each of the five trials and cast into a conditions

by subjects table for each auditory test. If the scores for the conditions are independent of subject variation, the distribution of ranks among the subjects would be essentially random. If the scores of the conditions are dependent upon systematic variation among the subjects, however, the sum of the ranks among the subjects would vary significantly.

All three tests of speech discrimination yielded subject differences significant at the .0001 level. Although there was no way to attribute these significant differences to any particular subject except by inspection of the data, much of the variation observed seemed to be a function of subject six. This subject scored second lowest on the W-22 test. He obtained the poorest scores on the Rush-Hughes test under all conditions. The Wepman test did not clearly reveal variations attributable to a single subject.

Discussion of the Results

The findings for this study revealed that there were no statistically significant differences in test responses for the subjects under the various baseline and pharmaceutical conditions. However, observation by inspection of the data revealed that there were noticeable differences in performance levels for the different tests and subjects under the various conditions.

By inspection of the data for the C.I.D. W-22 Test, a general increase was observed in the average number of

correct responses from Trial A, initial baseline, to Trial B, Medication Condition I (magnesium pemoline). In further inspection of the data for the Rush Hughes Test, it may be observed that a greater number of correct responses were measured for Trial B, Medication Condition I (magnesium pemoline), than were measured for any other trial; in fact, the remaining baseline and placebo trials did not exceed the initial baseline number of correct responses for this test. By inspection of the data for the Wepman test, some slight differences were seen between trials, but these differences were not of the magnitude as seen in the previous two tests.

In dealing with auditory dysfunction, Schuknecht reported that auditory systems in patients with temporal lobe lesions, presbycusis or acoustic neuroma which involve the auditory pathway allow the reception of simple pure tone signals, but do not handle the complex signals of speech.[40] From these observations auditory functioning is placed at the central level. Jerger reported that acuity for pure tones seems to be maximally affected by peripheral lesions, while speech discrimination is reduced in the bottleneck region of the eighth nerve and in the brain stem.[41] Therefore, as the site and/or extent of the lesion is more central to the eighth nerve or brain stem, there is a concomitant decrease

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[40]Schuknecht, pp. 429-439.

[41]Jerger, pp. 797-806.

in the successful transmission of complex auditory stimuli. Examination by inspection of the performances for the various conditions of the study did not seem to demonstrate any variations in performances upon the administration of magnesium pemoline except for subject number six. This subject, in addition to having more central lesions, had an impairment of the eighth cranial nerve, (see Appendix C). This subject showed a noticeable improvement in speech discrimination ability upon the administration of magnesium pemoline. Perhaps the action of this agent somehow facilitated functioning of the cranial nerve system. It may be speculated that magnesium pemoline may affect the first order neuron, but not higher ones. The research on this one subject may indicate that the drug, magnesium pemoline, is selective to the eighth cranial nerve and facilitates its functioning yielding improved speech discrimination ability. It is suggested that further research should investigate the administration of magnesium pemoline to individuals with impairments from lesions of a peripheral level to lesions of the central level. In particular, from the results exhibited by the subject with a lesion of the eighth cranial nerve, further research is encouraged to examine the effects of magnesium pemoline upon these lesions and/or individuals with more generalized deficits that also involve eighth nerve lesions.

Bocca and Calearo reported that investigation of the central auditory system should be based upon the evaluation

of pattern formation and integration because of the remarkable "redundancy" of the auditory system.[42] By lowering the redundancy of an auditory discrimination task, the individual would have a more demanding discrimination task. Jerger related that lesions at various sites within the auditory nervous system may be demonstrated only by the more subtle demands of certain kinds of hearing tests.[43] It was seen that in subject number six, there was the greatest increase in performance of speech discrimination ability for Trial B, Medication Condition I (magnesium pemoline) for the Rush Hughes Test in comparison with the other subjects and tests used in this study. The Rush Hughes Test has enjoyed popularity as a clinical tool because of its apparent greater difficulty due to the verbal presentation and recording characteristics. Subject number six exhibited a lesion of the eighth cranial nerve and also showed the greatest improvement in speech discrimination ability on the Rush Hughes Test upon the administration of magnesium pemoline. In reference to the preceding finding, it may be speculated that the effects of the drug were real, but that the other tests used in this study did not provide the necessary more subtle and demanding tasks to elicit a breakdown in speech discrimination ability

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[42]Bocca and Calearo, pp. 337-370.

[43]Jerger, pp. 797-806.

for those subjects with only the highest level lesions.

Goetzinger and Rousey reported in their testing of elderly subjects that it is not uncommon to find a "difference score" of approximately 20 per cent between the Hirsh recordings of the C.I.D. W-22 PB lists and the more difficult Rush Hughes recordings of the Harvard PB lists.[44] When this normal difference is exceeded the authors suggested there may be dysfunctions of the higher auditory pathway. It is curious to notice that the subjects in the present study seem to be almost equal in the performances on the W-22 and Rush Hughes tests; even subject number six, although exhibiting the greatest change for the Rush Hughes test upon drug administration, did not yield a 20 per cent difference score between the two trials. For the subjects tested in this study, the identical two tests did not elicit a breakdown in speech discrimination ability. Therefore, it is suggested that future attempts to investigate the effect of magnesium pemoline upon speech discrimination ability in central nervous system disorders consider the implementation of more demanding tasks of speech discrimination.

Summary

The results of the study revealed by inspection that there were differences in responses for the subjects upon

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[44]Goetzinger and Rousey, pp. 771-780.

the administration of magnesium pemoline. Upon statistical analysis, however, the responses for the subjects on the baseline and medication conditions were not significantly different. It was concluded that the experimental drug either (a) had no effect upon speech discrimination ability in individuals with central nervous system disorders as investigated in this study, or (b) that the tests employed were not sufficient for demonstrating any effects present. It was further speculated on the basis of the performance of one subject that there may be a differential effect on the eighth cranial nerve upon the administration of magnesium pemoline suggesting that this agent is selective in acting upon first order neurons, but not on higher pathways. Suggestions were made for implementing more demanding tests and for the selection of a more specific test sample.

## CHAPTER V

## SUMMARY AND CONCLUSIONS

In light of the current theory regarding central nervous system processing of auditory information, the current use of drugs to study central nervous system disorders, and the need for further research in this area, the present study investigated the effects of magnesium pemoline upon speech discrimination ability on individuals with central nervous system disorders. This study investigated the null hypothesis that there would be no change in speech discrimination ability in subjects with central nervous system disorders upon the administration of magnesium pemoline.

A selected review of the literature presented a discussion of the function and dysfunction of the central nervous system. Information was presented concerning nucleic acids and the experimental drug, magnesium pemoline.

In this study six subjects were used who were outpatients at the Veterans Administration Hospital in Topeka, Kansas. The subjects were selected because of their central nervous system disorder and their inability to evaluate accurately acoustic or auditory stimuli. Each subject received a two week supply of medication of either magnesium pemoline or placebo as the condition required. Each subject acted as his own control. The subjects and examiner were unaware of the type of drug being administered for the

respective conditions. An auditory test battery comprised of three tests of speech discrimination was during the magnesium pemoline and placebo conditions. Testing was done before and after each medication condition.

The findings of this study indicated that upon the application of the Friedman Two-Way Analysis of Variance to the data, the performances of the subjects with central nervous system disorders did not yield statistically significant differences for any of the tests used in the study. Therefore, the null hypothesis of this study was confirmed and it was concluded that there was no increase in speech discrimination ability upon the administration of magnesium pemoline to individuals with central nervous system disorders.

In relating the present study to the results reported by other authors investigating the effects of magnesium pemoline (Burns, Talland, and Talland and McGuire) the present study revealed results which are similar to the reports by those authors. Generally the results of the previous and present study seem to conclude that magnesium pemoline has no effect specific to the processes involved in learning and memory.

In observing the results of this study, it was seen that there is a need for further more specific research. More demanding examination of speech discrimination ability

upon the administration of this drug may provide promising areas for research in the future. Further attempts to investigate the effectiveness of this drug should consider the particular sample of subjects to provide for the eventual exposition of this potentially valuable recourse for rehabilitation purposes.

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# APPENDIX A

C.I.D. Auditory Test W-22, List 2E

1. that
2. ill
3. knee
4. pew
5. star
6. and
7. tree
8. odd
9. dumb
10. ham
11. smart
12. with
13. off
14. thin
15. gave
16. now
17. send
18. move
19. ice
20. eat
21. rooms
22. cars
23. air (heir)
24. new (knew)
25. jaw
26. well
27. die (dye)
28. one (won)
29. then
30. own
31. bin (been)
32. key
33. oak
34. young
35. live (verb)
36. hit
37. by (buy)
38. chest
39. show
40. cap
41. ail (ale)
42. tare (tear)
43. hurt
44. way (weigh)
45. else
46. does
47. yore (your)
48. too (two, to)
49. flat
50. ease

Rush Hughes PB 50, List 7B

1. fling
2. pig
3. aim
4. though
5. coast
6. gun
7. act
8. grade
9. roar
10. dope
11. rash
12. wire
13. shave
14. raid
15. fort
16. quiz
17. woe
18. shaft
19. knit
20. comes
21. but
22. sag
23. pounce
24. him
25. scout
26. rich
27. gasp
28. fake
29. nine
30. mud
31. south
32. sledge
33. siege
34. cook
35. chop
36. woo
37. dwarf
38. sniff
39. plod
40. by
41. meet
42. pent
43. am
44. sin
45. whip
46. off
47. range
48. cut
49. dose
50. jug

Wepman Auditory Discrimination Test
Form I

| | | | | | |
|---|---|---|---|---|---|
| 1. | tub | - tug | 21. | cat | - cap |
| 2. | lack | - lack | 22. | din | - bin |
| 3. | web | - wed | 23. | lath | - lash |
| 4. | leg | - led | 24. | bum | - bomb |
| 5. | chap | - chap | 25. | clothe | - clove |
| 6. | gum | - dumb | 26. | moon | - noon |
| 7. | bale | - gale | 27. | shack | - sack |
| 8. | sought | - fought | 28. | sheath | - sheaf |
| 9. | vow | - thou | 29. | king | - king |
| 10. | shake | - shape | 30. | badge | - badge |
| 11. | zest | - zest | 31. | pork | - cork |
| 12. | wretch | - wretch | 32. | fie | - thigh |
| 13. | thread | - shred | 33. | shoal | - shawl |
| 14. | jam | - jam | 34. | tall | - tall |
| 15. | bass | - bath | 35. | par | - par |
| 16. | tin | - pin | 36. | pat | - pet |
| 17. | pat | - pack | 37. | muff | - muss |
| 18. | dim | - din | 38. | pose | - pose |
| 19. | coast | - toast | 39. | lease | - leash |
| 20. | thimble | - symbol | 40. | pen | - pin |

# APPENDIX B

TABLE I

INTELLIGIBILITY SCORES FOR THREE SPEECH DISCRIMINATION TESTS FOR SIX SUBJECTS DURING FIVE TEST TRIALS

| Trials | Tests | Subjects | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| A | (W-22) | 84 | 78 | 86 | 92 | 90 | 66 |
| Pre-baseline | (RH) | 76 | 78 | 80 | 88 | 92 | 56 |
| | (Wepman) | 85 | 80 | 90 | 90 | 65 | 78 |
| B | (W-22) | 92 | 82 | 94 | 98 | 90 | 80 |
| Cylert | (RH) | 76 | 78 | 88 | 88 | 88 | 74 |
| | (Wepman) | 90 | 73 | 95 | 90 | 55 | 88 |
| C | (W-22) | 88 | 76 | 94 | 96 | 92 | 88 |
| Post- and | (RH) | 66 | 64 | 82 | 92 | 90 | 64 |
| Pre-baseline | (Wepman) | 58 | 83 | 93 | 88 | 65 | 93 |
| D | (W-22) | 90 | 78 | 92 | 96 | 96 | 62 |
| Placebo | (RH) | 76 | 68 | 82 | 86 | 92 | 62 |
| | (Wepman) | 90 | 68 | 95 | 98 | 63 | 73 |
| E | (W-22) | 88 | 76 | 94 | 98 | 96 | 86 |
| Post-baseline | (RH) | 70 | 64 | 80 | 90 | 90 | 76 |
| | (Wepman) | 88 | 78 | 95 | 90 | 63 | 90 |

NOTE: Wepman scores are ordinarily presented as raw scores, whereas W-22 and Rush Hughes (RH) scores are usually expressed in percentages. All scores are presented as percentage scores for comparison purposes.

APPENDIX C

Subject 1

Subject 1 was a 68 year old, white male. During his working life, he served in the positions of a coach and an athletic director. He was married. He had a fifteen year history of high blood pressure and arteriosclerosis. He suffered a heart attack in 1949 and a coronary thrombosis in 1951. The individual suffered a cerebral thrombosis in 1965 resulting in speech impairment and right hemiplegia which is presently in almost complete remission. The subject suffered a cerebral vascular accident in 1966. He also exhibited an acute involutional psychotic reaction to his condition manifested by moderate to severe depression.

Diagnosis: (1) Chronic brain syndrome

(2) Hypertensive arteriosclerotic heart disease

(3) Osteoarthritis

(4) Residual right hemiplegia

Prognosis: Good

Subject 2

Subject 2 was a 58 year old, white male. He completed a high school education. His occupations included a psychiatric aide and welder. He was married and a parent. In December, 1965 the subject suffered a sudden onset of severe weakness of the left arm and leg.

Diagnosis: (1) Cerebral vascular accident, probably secondary to thrombosis of right middle cerebral artery with left hemiparesis severe

(2) Depressive reaction, mild, associated with diagnosis (1)

Prognosis: Fair for improvement in the left paresis

Subject 3

Subject 3 was a 60 year old, Negro male. The subject did not complete high school, but has completed several correspondence courses. He was a former maintenance worker. He was married. The subject suffered a cerebral vascular accident in September, 1966 resulting in right hemiparesis predominant in the distal right arm.

Diagnosis: (1) Cerebral thrombosis due to arteriosclerosis vessel indeterminate with right hemiparesis and focal motor seizures

(2) Chronic brain syndrome associated with arteriosclerosis

Prognosis: Favorable

Subject 4

Subject 4 was a 46 year old, white male. He completed a high school education. He was formerly employed as a salesman. He was married. The subject had a documented history of neurological problems including leg weakness and Bell's Palsy intermittent since 1942. In 1963, there was a general muscle weakness. Examination showed signs of brain stem

involvement along with some loss of cortical functioning and emotionallability. There was mild impairment of higher integrative functioning. The neurological examination showed spotty sensory and motor deficits in both hemispheres, mostly on the left.

Diagnosis: (1) Multiple sclerosis, manifested by a spastic ataxic gait

Prognosis: Fair adjustment

Subject 5

Subject 5 was a 46 year old, white male. The subject had a high school education. He was twice-divorced. The subject had experienced 15 years of progressive muscle wasting and gradual restriction of life. Neurological examination indicated some mild impairment of auditory discrimination. He exhibited a combination of mild intellectual impairment and generalized muscular atrophy.

Diagnosis: (1) Myotonia atrophica, chronic, unimproved

Prognosis: Poor

Subject 6

Subject 6 was a 56 year old, white male. The subject was a college graduate. He formerly was employed as an accountant. He was married and a parent. The subject experienced a gradual progression of hearing loss and anomalies since 1947. In September, 1965, a right sub-occipital

craniotomy was completed with total removal of an acoustic neuroma. The subject also had emphysema and diabetes mellitus controlled by diet. The subject exhibited memory impairment and higher cognitive impairment reflected by the extremely concreistic nature of his thought processes. Examination showed VII, VIII, IX, and X cranial nerve damage on the right side.

Diagnosis: (1) Right acoustic neuroma, improved post-operatively

Prognosis: Not available

# THE EFFECT OF MAGNESIUM PEMOLINE UPON SPEECH DISCRIMINATION ABILITY OF INDIVIDUALS WITH CENTRAL NERVOUS SYSTEM DISORDERS

by

BARRY R. MOLINEUX

B. A., University of Kansas, 1966

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The purpose of the present study was to investigate the effects of magnesium pemoline upon speech discrimination ability of individuals with central nervous system disorders. Language is behavior viewed as a complex system of codes organized into a system of phonemes, each of which singles out definite and persistent sound cues from the flow of speech. By phonemic evaluation, there may be discrimination of the definite units of speech. With a disturbance in the sensory analyses of sounds, there is difficulty in discriminating the acoustic cues. Central nervous system destruction or impairment in any zone in the brain stem and cerebral cortex interferes with the work of the analysers which participate in the speech and hearing process leading to disintegration of all functioning systems of speech and hearing.

Studies of the hearing system have placed the intelligibility of auditory functioning at the central level. Temporal lobe lesions, acoustic neuroma, or presbycusis infer that lesions involving the auditory pathway allow the reception of simple pure tone signals, but do not handle the complex signals of speech.

Investigators have been studying the effects of the chemical compound magnesium pemoline. There have been theoretical speculations about ribonucleic acids as a substrate of memory traces and experimentally demonstrated correlations with the administration of magnesium pemoline. It has been

reported that upon the administration of magnesium pemoline to animals that there is an increase in the acquisition and retention of learned behavior. Other research with humans presented conflicting reports about the effect of magnesium pemoline upon learning. Some investigators reported that magnesium pemoline may act as a general stimulant or have an anti-fatigue effect property, rather than have any direct effect on learning and memory.

The present study used six subjects who were out-patients at the Veterans Administration Hospital at Topeka, Kansas. Each subject exhibited a central nervous system disorder and an inability to evaluate accurately acoustic or auditory stimuli. Each subject received a two week supply of medication, either magnesium pemoline or placebo as the test condition required. The study was directed on a double-blind basis. Each subject acted as his own control. An auditory test battery comprised of three tests of speech discrimination was administered during the medication conditions. Baselines were administered before and after each medication condition.

The results of the study indicated that there was no increase in speech discrimination ability upon the administration of magnesium pemoline to individuals with central nervous system disorders. Upon the application of the Friedman Two-Way Analysis of Variance to the data, the performances of the subjects did not yield statistically

significant differences for any of the tests used in the study.

In observing the results from other investigators, it was concluded that either the experimental drug had no effect upon the subjects used in the present study or that the tests employed in the study were not sufficient for demonstrating any effect present. From the data of one subject with a lesion of the eighth cranial nerve, a speculation was made that this drug may be selective in acting upon first order neurons, but not on higher pathways. Further attempts to study this drug should consider the implementation of more demanding tests and the selection of a more specific test sample.