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Influences on Handedness of Local Application of Acetylcholine with Glutamic Acid to Cerebral Cortex of the Rat

Edward R. Suess

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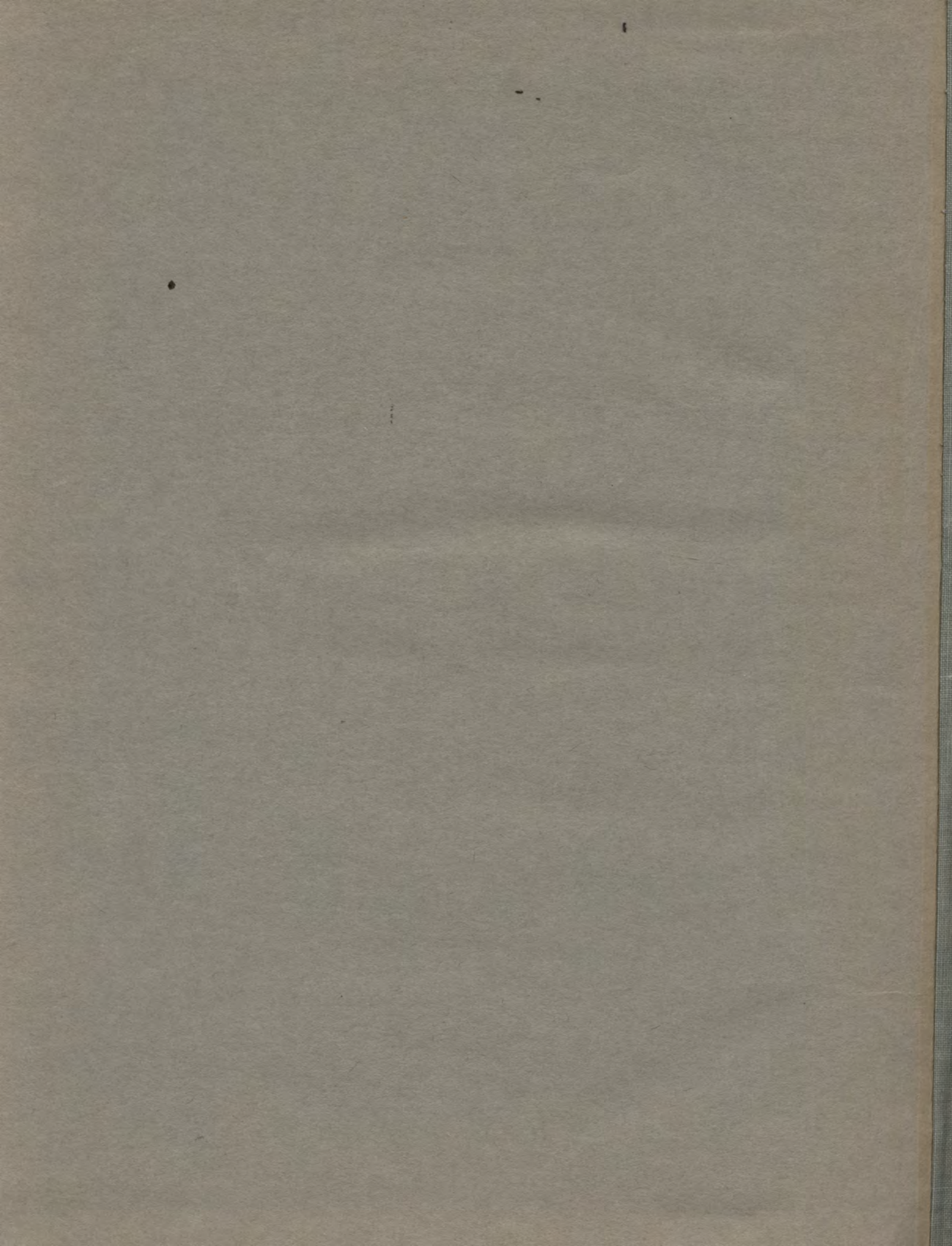
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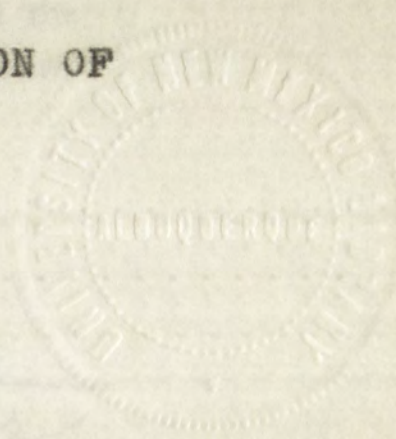
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**INFLUENCE ON HANDEDNESS OF LOCAL APPLICATION OF
ACETYLCHOLINE WITH GLUTAMIC ACID TO
CEREBRAL CORTEX OF THE RAT**



Aug 1, 1949

By

Edward R. Suess

From

A Thesis

W. Clayton

**In partial fulfillment of the
Requirements for the Degree of
Master of Science in Psychology**

W. Clayton

**The University of New Mexico
1949**



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MASTER OF SCIENCE

E. Castetter

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DATE

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CEREBRAL CORTEX OF THE RAT

BY

Edward R. Suess

Thesis committee

Gronlund Peterson

CHAIRMAN

Walter J. Kester

C. Clayton Hoff

This thesis directed and approved by the candidate's com-
mittee has been accepted by the Graduate Committee of the
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[Signature]
DATE

INFLUENCE OF RADIATION ON LOCAL APPLICATION OF

ACETYLCHOLINE WITH ORGANIC ACID TO

GENERAL CORTEX OF THE BRAIN

BY

Edward R. Squire

Thesis committee

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CHAPTER I

THE PROBLEM AND DEFINITION OF TERMS USED

This study is a continuation of investigation begun by Peterson and continued by Peterson and Rigney.¹ In an unpublished report to the AAAS in Philadelphia in 1940, Peterson first outlined the nature of the investigation of this problem.²

Essentially, it is to seek the neural equivalent of practice. Since the behavior of an organism is dependent upon organic structures, and since behavior changes with practice or experience, it may be assumed that some kind of organic change takes place within the organism, presumably in the nervous system, when such changes are manifested in behavior. What the nature of this change is, remains

¹ Geo. M. Peterson, and Joseph W. Rigney, "Influence on Handedness of Local Application of Acetylcholine with Other Chemicals to the Cerebral Cortex of the Rat," Jour. of Comp. and Physiol. Psychol., In Press.

² Geo. M. Peterson, "Acetylcholine as a Neurochemical Equivalent of Practice," Unpublished report to the AAAS, Philadelphia, December, 1940, p. 1.

CHAPTER I

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² Geo. M. Peterson, "Acetylcholine as a Neurotransmitter Equivalent of Practice," unpublished report to the AAS, Philadelphia, December, 1940, p. 1.

a persistent problem for psychology. Peterson selected an organic chemical, acetylcholine, as a promising drug to work with in attacking this problem. If it could be shown to have a facilitating effect upon a behavior trait subject to practice effects, this might be a first step in establishing a relationship between these behavior changes due to practice and physiological changes within the organism. Since acetylcholine does bear a close relationship to synaptic nerve conduction and since a particular behavior trait has definitely been established and localized as to function in the brain with a fairly accessible region for neurological work, it appears wholly warranted and feasible to approach the problem in the manner presented.

Handedness in the albino rat, a form of behavior easily observed and measured, is the particular trait selected for study.³ Methods and materials employed to determine handedness along with the frequency of occur-

³ Geo. M. Peterson, "Mechanisms of Handedness in the Rat," Comparative Psychology Monographs, Vol. 9, No. 6, Baltimore: The Johns Hopkins Press, April, 1934. Pp. 1-67.

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 No. 6, Baltimore; The Johns Hopkins Press, April, 1934.
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rence of predominantly single-handed and ambidexterous rats have been reviewed by Peterson.⁴ The rat, regardless of his original hand preference, can be taught the use of his non-preferred hand through application of forced practice. This is ordinarily accomplished by employing an off-set feeding dish which makes the use of the preferred inconvenient. Practice with the non-preferred hand may result in transfers to its use in the normal situation with the center food dish. Unpublished studies in the University of New Mexico laboratory indicate that anywhere from one hundred to one thousand reaches in this situation may cause a shift in handedness to the use of the non-preferred hand. The degree of shift when placed in the normal feeding situation may be anywhere from an occasional use of the non-preferred hand to a complete shift.⁵ Peterson attempted

⁴ Loc. cit.

⁵ Peterson, op. cit., "Acetylcholine as a Neurochemical Equivalent of Practice," Table I.

3

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⁴ loc. cit.

⁵ Peterson, op. cit., "Asymptotic as a Neuro-
... Chemical Equivalent of Practice," Table I.

to induce a similar shift in handedness in the rat by applying acetylcholine to that portion of the cerebral cortex which controls the use of this non-preferred hand. His design was planned to effect these changes and to observe any significant shifts through this drug application.

Preliminary work with acetylcholine gave no consistently positive results; however, some interesting and significant observations were made as to the effects of the application of this drug. One hundred and fifty rats were utilized. One hundred and eight were single-handed and forty-two were ambidexterous. Only two single-handed rats and fifteen ambidexters were influenced in a positive direction; however, some of the animals exhibited clonic movements of the contralateral forelimb a few minutes after acetylcholine was applied to the cortex.⁶ It can at least be assumed that the drug did reach the motor neurons of

⁶ Geo. M. Peterson, "Changes in Handedness in the Rat from the Local Application of Acetylcholine to the Cerebral Cortex," Jour. of Comp. and Physiol. Psychol., In press.

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that portion of the cortex responsible for the innervation of that particular limb.

Later work in this direction made use of other chemicals with acetylcholine.⁷ Those selected were inhibitors of cholinesterase, buffers, solvents natural to nerve tissue, and chemicals with parallel effects. One of the chemicals tested in combination with acetylcholine was glutamic acid. The natural glutamic acid was applied to three rats. A positive shift resulted in two instances, and no shift in one. Various combinations of other chemicals were also tried, none of which gave consistently positive results. It was found, however, that smaller concentrations of acetylcholine could be used to produce shifts than was previously used. One half of one percent to three percent solutions of acetylcholine were employed instead of the former five to ten percent concentrations.⁸

⁷ Peterson and Rigney, op. cit.

⁸ Ibid.

that portion of the cortex responsible for the control of that particular limb.
Later work in this direction was done by Peterson and Rigby. These authors have tested the effects of cholinesterase, buffers, solvents, and other substances, and chemicals with parallel effects. The natural glutamate acid was applied to the cortex. A positive shift resulted in two instances, but in only one. Various combinations of other chemicals were also tried, none of which gave consistently positive results. It was found, however, that smaller concentrations of glycocine could be used to produce similar results. One half of one percent to three percent solutions of acetylcholine were employed instead of the former five to ten percent concentrations.

Peterson and Rigby, *op. cit.*
8

I. THE PROBLEM

Statement of the problem. This study was undertaken to determine the effects on handedness in the rat upon application of glutamic acid and acetylcholine to the cortex.

Importance of the study. Since acetylcholine is a natural constituent of nerve tissue, it is more than feasible to explore the effects of this chemical. Its role of pre- and post-synaptic conduction and also the assumption of a similar role at synaptic surfaces has already been indicated.⁹ The literature is replete with the possibilities and potentialities of acetylcholine and its relationship and bearing to the nerve impulse. Recent investigations have pointed to glutamic acid as a chemical worth considering to aid in the facilitation of greater effects of acetylcholine.

⁹ T. H. Bullock, H. Grundfest, D. Nachmansohn, M. A. Rothenberg, "Generality of the Role of Acetylcholine in Nerve and Muscle Conduction," Jour. Neurophysiol., Vol. X, No. 1, January 1947, (Springfield: Charles C. Thomas), pp. 11-22.

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II. DEFINITION OF TERMS USED

Acetylcholine. This ester is a methylated quaternary ammonium base formed from choline and acetic acid. It is hygroscopic, soluble in alcohol and water; it is easily decomposed by heat or alkali.¹⁰ Acetylcholine, liberated between many conducting tissues throughout the body, is synthesized by an enzyme, choline acetylase.¹¹ It is a very unstable ester in living tissue, being split by another enzyme, choline esterase, in a matter of milliseconds at the site of action during transmission of nerve impulses.¹² Acetylcholine is formed in brain slices under aerobic conditions if glucose or pyruvate is present.¹³

Glutamic acid. Glutamic acid is a monoamine dicarboxylic acid, and is one of the amino acids present in

¹⁰ Goodman and Gilman, The Pharmacological Basis of Therapeutics, (New York: The MacMillan Company, 1941).

¹¹ David Nachmansohn, "Role of Acetylcholine in Nerve Activity," Vitamins and Hormones, Vol. III, (New York: The Academic Press, 1945), p. 365.

¹² Ibid., p. 341.

¹³ Ibid., p. 365.

Acetylcholine

ermy ammonia base found in the brain and nerves. It is hydrolyzed, and is easily decomposed by heat. It is liberated between the nerve and the body, in synapses, and is reabsorbed. It is a very unstable salt, and is broken down by another enzyme, cholinesterase, in the same manner as the other acetylcholine. Acetylcholine is a neurotransmitter, and is used in the nervous system. It is a very important substance in the nervous system, and is used in the treatment of various conditions.

Glutamic acid

carboxylic acid, and is one of the amino acids.

¹⁰ Gadow and O'Brien, The Biochemistry of Therapeutics, (New York: McGraw-Hill, 1951), p. 100.

¹¹ David R. Kandel, Nerve Activity, (New York: The Academic Press, 1968), p. 100.

¹² Ibid., p. 101.

¹³ Ibid., p. 102.

the body. The vast majority of amino acid molecules are derived from plant proteins where they are produced from their inorganic constituents by the action of photosynthesis.¹⁴

Glutamic acid is officially classified as a "non essential" amino acid; however, it is the only amino acid which is metabolized by brain tissue.¹⁵ It has important therapeutic properties in that the mild form of epilepsy known as petit mal is now treated with it.¹⁶ This acid is easily synthesized by the body.¹⁷

Glutamic acid is positively correlated with mental behavior. Statistically significant results were obtained for an increase in learning ability of rats to run a maze

¹⁴ R. A. Gortner, Outlines of Biochemistry, (New York: John Wiley and Sons, Inc., 1929), p. 423.

¹⁵ B. J. Harrow, Textbook of Biochemistry, (Philadelphia: W. B. Saunders Company, 1947), p. 537.

¹⁶ J. C. Price, H. Waelsch, and T. J. Putnam, "dl-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures," Jour. of Amer. Med. Assoc., Vol. 122, No. 17, (Chicago, 1943), p. 1153.

¹⁷ Harrow, op. cit., p. 537.

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¹⁴ H. A. Gardner, Outlines of Biochemistry, (New York: John Wiley and Sons, Inc., 1939), p. 483.

¹⁵ E. J. Harrow, Textbook of Biochemistry, (Philadelphia: W. B. Saunders Company, 1947), p. 537.

¹⁶ J. C. Price, H. Weisbach, and T. J. Putnam, "Glutamic Acid Hydroxide in Treatment of Petit Mal and Psychomotor Seizures," Jour. of Amer. Med. Assoc., Vol. 122, No. 17, (Chicago, 1935), p. 1153.

¹⁷ Harrow, op. cit., p. 537.

when the l(+) form of glutamic acid was administered.¹⁸ Glutamic acid contains a property not common to amino acids in general, since it cannot be replaced by glycine.¹⁹

Amino acids may act as buffers since they are amphoteric and can form fairly stable salts with either acids or bases. They may act both as acids and weak bases when in solution. Specifically, glutamic acid, existing in proteins in the form of an amide, is a stronger acid than base since it possesses the properties of two carboxyl groups.²⁰

The optically active glutamic acid forms both d and l acids. Upon alkaline hydrolyzation, this active amino acid becomes a racemic amino acid in that one of the unions of the double bond within glutamic acid

¹⁸ F. T. Zimmerman, and S. Ross, "Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat," Arch. of Neurol. and Psychiat., Vol. 51, (Chicago, 1944), pp. 446-51.

¹⁹ Harrow, op. cit., p. 537.

²⁰ R. J. Williams, An Introduction to Biochemistry, (New York: D. Van Nostrand Company, Inc., 1931), p. 93.

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¹⁸ E. T. Zimmerman, and E. Rose, "Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat," Arch. of Neurol. and Psychol., Vol. 21, (Chicago, 1927), pp. 48-51.

¹⁹ Hadow, op. cit., p. 237.

²⁰ H. J. Williams, An Introduction to Biochem-
istry, (New York: D. Van Nostrand Company, Inc., 1931), p. 22.

may later become attached to hydrogen; therefore, rather than an active amino acid, we find equal amounts of d and l acids.²¹ The symbols d and l indicate both the configuration and the direction of rotation. Thus, d(+) indicates d-configuration and dextrorotation. Various factors actually influence and determine the direction of rotation and subsequently the classification of amino acids. The d forms are usually represented in the literature as the natural forms. Glutamic acid pre-formed in the protein molecule has the same configuration around the alpha-carbon atom, namely, the l-form.²²

Handedness and Ambidexterity. When placed in a feeding situation where they must reach with their forepaws for food, rats exhibit a preference for one hand or the other.²³ About ninety percent of all rats will either be completely left handed or completely right handed. The

²¹ Gortner, op. cit., p. 406.

²² P. H. Mitchell, A Textbook of Biochemistry, (New York: McGraw-Hill Book Co., Inc., 1946), pp. 95-96.

²³ Peterson, op. cit., "Mechanisms of Handedness in the Rat," p. 1.

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1. The reaction of the amino acid with the

reaction and the reaction of the amino acid with the

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one actually involved in the reaction of the

rotation and absorption of the amino acid

acids. The α form is the most common in the

amino acid, and the β form is the

the protein molecule has the same structure

the alpha-carbon atom, which is the

Handbook of Chemistry and Physics

leading sites on which the amino acid

puts the amino acid, and the amino acid

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as completely into the amino acid

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remaining ten percent are more or less ambidexterous, although most of these continue to show a preference for one hand. Rats with greater degrees of ambidexterity presumably could be most easily influenced by drug application; therefore, these rats were more carefully sought for our study.

Practice. This is the repeated performance of the white rat in reaching for food, grasping it, and then conveying it to the mouth, as practiced in the forced reaching situation. Continued practice or use of the non-preferred hand brings about an inclination of the rat towards the use of this hand.

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CHAPTER II

REVIEW OF THE LITERATURE

The literature dealing with acetylcholine and its role as mediator of nerve impulses is voluminous. This work has been reviewed by Rigney.¹ What will be presented here is a brief discussion of its relationship to glutamic acid.

I. ACETYLCHOLINE

This ester is found within the parasympathetic nervous system as well as the central nervous system. Due to its presence at synapses and myoneural junctions at the time of nerve stimulation, it has received a great deal of attention in recent years. At least one investigator, Nachmansohn, regards it as the propagator as well as transmitter of the nerve impulse. His three lines of investigation center about the facts that cholinesterase

¹ Joseph W. Rigney, "Influence on Handedness of Local Application of Acetylcholine with DFP and Glycine to Cerebral Cortex of the Rat," (Unpublished Master's thesis, The University of New Mexico, Albuquerque, 1948).

CHAPTER II

REVIEW OF THE LITERATURE

The literature dealing with acetylcholine and its role as mediator of nerve impulses is voluminous. This work has been reviewed by Riggs.¹ What will be presented here is a brief discussion of its relationship to glaucoma.

I. ACETYLCHOLINE

This ester is found within the parasympathetic nervous system as well as the central nervous system. Due to its presence at synapses and neuromuscular junctions at the time of nerve stimulation, it has received a great deal of attention in recent years. At least one investigator, Bachmann,² regards it as the propagator as well as transmitter of the nerve impulse. His three lines of investigation center about the facts that cholinesterase

¹ Joseph W. Riggs, "Influence on Bandwidth of Local Application of Acetylcholine with DFP and Glycine to Cerebral Cortex of the Rat," (Unpublished Master's Thesis, The University of New Mexico, Albuquerque, 1948).

is present in high concentrations at the nerve during the time of neural activity; there is a definite localization of cholinesterase at the neuronal surface; and a close parallel exists between the action potential and the activity of this enzyme, as has been evidenced in the electric organs of certain fish.² Cholinesterase is also used as an index to measure, indirectly, the amount of acetylcholine present at the particular locus of nerve activity or transmission.³ Other investigations with acetylcholine include Elliot, working within the autonomic nervous system;⁴ the extensive work of Miller and his co-workers;⁵ Loewi's experiments with frog hearts and the study of transmission

² Nachmansohn, op. cit., p. 341.

³ Ibid., p. 342.

⁴ T. R. Elliot, "On the Action of Adrenalin," (J. Physiol., 31:XX), cited by Cannon and Rosenbleuth, Autonomic Neuro-Effector Systems, Experimental Biology Monographs, (New York: The MacMillan Co., 1937), p. 21.

⁵ F. R. Miller, G. W. Stravratsky, and G. A. Woonton, "Effects of Eserine, Acetylcholine and Atropine on the Electroencephalogram," Jour. Neurophysiol., Vol. III, No. 2, March, 1940, (Springfield: Charles C. Thomas), pp. 131-38.

is present in high concentrations at the nerve during the time of neural activity; there is a definite localization of cholinesterase at the neuronal surface; and a close parallel exists between the action potential and the activity of this enzyme, as has been evidenced in the effect of certain drugs. Cholinesterase is also used as an index to measure, indirectly, the amount of acetylcholine present at the particular focus of nerve activity or transmission. Other investigations with acetylcholine include Elliot, working within the autonomic nervous system; the extensive work of Miller and his co-workers; Lowy's experiments with frog hearts and the study of transmission

1. Nachmansohn, op. cit., p. 311.
 2. Ibid., p. 312.
 3. T. R. Elliot, "On the Action of Adrenalin," *J. Physiol.*, 31:XX, cited by Cannon and Rosenbluth, *Ano-*
malis Nervus-Effector System, Experimental Biology Mono-
graphs, (New York: The Macmillan Co., 1937), p. 21.
 4. T. R. Miller, G. W. Starvinsky, and G. A. Houston, "Effects of Histamine, Acetylcholine and Adrenaline on the Electroencephalogram," *Jour. Neurophysiol.*, Vol. III, No. 2, March, 1940, (Springfield: Charles C. Thomas), pp. 131-38.

at parasympathetic nerve endings;⁶ and Kibjakow and Dale's contributions to the theory of chemical transmission in the central nervous system.⁷ A recent review by Feldberg deals with acetylcholine and the problem faced in reconciling the chemical theory and the objections against such a theory.⁸ One of the most severe critics of the chemical mediation theory is Eccles, who lists several criticisms in one of his earlier reports.⁹ Work by Nachmansohn and his associates on the pharmacological effects of acetylcholine,¹⁰ and the studies of Sjostrand,¹¹ deal further with the prop-

⁶ Otto Loewi, Harvey Lectures, 28 (1932-33), 218 (1934), cited by Nachmansohn, op. cit., p. 338.

⁷ Nachmansohn, op. cit., p. 339.

⁸ W. Feldberg, "Present Views on the Mode of Action of Acetylcholine in the Central Nervous System," Physiol. Rev., Vol. 25, (Baltimore, Maryland, 1945), p. 596; also Nachmansohn, op. cit., p. 339.

⁹ J. C. Eccles, "Synaptic and Neuro-muscular Transmission," Physiol. Rev., Vol. 17, (Baltimore, 1937), pp. 538, ff.

¹⁰ M. A. Rothenberg, D. B. Sprinson, and D. Nachmansohn, "Site of Action of Acetylcholine," Journal of Neurophysiology, Vol. XI, No. 2, March, 1948.

¹¹ T. Sjostrand, Jour. Physiol., 90:41P., 1937, cited by Feldberg, op. cit., p. 598.

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⁶ Otto Loewi, Harvey Lectures, 28 (1932-33), 218 (1934), cited by Nachmansohn, *op. cit.*, p. 338.

⁷ Nachmansohn, *op. cit.*, p. 339.

⁸ K. Feldberg, "Present Views on the Mode of Action of Acetylcholine in the Central Nervous System," *Physiol. Rev.*, Vol. 25 (Baltimore, Maryland, 1945), p. 290; also Nachmansohn, *op. cit.*, p. 339.

⁹ J. C. Eccles, "Synaptic and Neuro-muscular Transmission," *Physiol. Rev.*, Vol. 17 (Baltimore, 1937), pp. 278, 279.

¹⁰ M. A. Rosenburg, D. E. Sarleson, and D. Nachmansohn, "Site of Action of Acetylcholine," *Journal of Neurophysiology*, Vol. XI, No. 2, March, 1948.

¹¹ T. Sjostrand, *Jour. Physiol.*, 90:419, 1937, cited by Feldberg, *op. cit.*, p. 340.

erties and effects of this chemical. A study of the synaptic region of the neuron is taken up by Gasser in his report.¹² Erlanger discusses the fundamental differences between nerve fiber and synapse conduction.¹³

It might be noted that due to recent discoveries by Nachmansohn, cited at the beginning of this chapter, a modified theory of the activity of acetylcholine in the nervous system has been introduced. He has replaced the older extracellular theory with an intracellular theory. This indicates a similar role for acetylcholine in conduction along fibers and across synapses.¹⁴

II. GLUTAMIC ACID

With the recent discovery through clinical observations that glutamic acid has a favorable effect on pat-

¹² H. S. Gasser, "Axons as Samples of Nervous Tissue," Synapse Symposium, Journal of Neurophysiology, Springfield, Illinois: Charles C. Thomas, September, 1939, Vol. 11, No. 5, pp. 361-69.

¹³ J. Erlanger, "Initiation of Impulses in Axons," Synapse symposium, Journal of Neurophysiology, Vol. 11, No. 5, Sept. 1939, (Springfield: Charles C. Thomas), pp. 370-78.

¹⁴ Nachmansohn, op. cit., p. 360.

erites and effects of this material. The
spillover region of the network is shown in the
report. It is clear that the relationship between
between nerve fibers and synapses is extremely
It might be noted that the present observations
by Neuhann, cited as the basis of our present
modified theory of the activity of synapses in the
nervous system has been discussed. The
older extracellular theory of the activity of
This indicates a similar relationship between
tion along fibers and across synapses.

II. DISCUSSION

With the recent discovery of the relationship
atoms that fibrillar cells have a large effect on

H. S. Gasser, "The Physiology of Nerve Fibers,"
Tissue, Synapse and Nerve, 1939, Chicago, Illinois,
Springfield, Illinois, 1939, Vol. II, No. 7, pp. 31-32.

J. V. Eisinger, "The Physiology of Nerve Fibers,"
Synapse Symposium, Journal of Neurophysiology, Vol. 2,
No. 2, Sept. 1939, pp. 370-78.

In Neuhann, et al., 1939.

ients suffering from petit mal, the mild form of epilepsy, further work has been taken up to test its effects on nerve activity and its relationship to acetylcholine.¹⁵ Nachmansohn and his associates found that l(+) glutamic acid in $2 \times 10^{-2}M$ concentrations increases the rate of formation of acetylcholine by about four to five times.¹⁶ The d(-) glutamic has a small effect. Of all other amino acids tested thus far, glutamic acid rates second only to cysteine in having the strongest effect on acetylcholine formation.¹⁷ As has been earlier mentioned in this report, Peterson used the natural glutamic acid in establishing two positive shifts in handedness upon application with acetylcholine to the cerebral cortex of three animals.¹⁸

It is view of the above facts that this study was run systematically to determine any possible effects of this amino acid with acetylcholine.

¹⁵ J. C. Price, H. Waelsch, and T. J. Putnam, loc. cit.

¹⁶ D. Nachmansohn, H. M. John, and H. Waelsch, "Effect of Glutamic Acid on the Formation of Acetylcholine," Journal of Biological Chemistry, Vol. 150, No. 2, October, 1943. Pp. 485-86.

¹⁷ Nachmansohn, op. cit., p. 367.

¹⁸ Peterson, op. cit., "Changes in Handedness in the Rat from the Local Application of Acetylcholine to the Cortex."

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III. HANDEDNESS AS A CRITERION OF

CEREBRAL FUNCTIONING

Handedness was chosen as a suitable trait to be observed and measured in testing the influence of drug application since it has been localized in the brain.

Locus on cerebral cortex which controls handedness of the white rat. Cerebral dominance of handedness and the effects of destruction in particular areas of the cortex of the rat has been the object of several studies.^{19,20} In later studies, the locus controlling handedness was more clearly specified. It was found that a small region in the contralateral frontal lobe of the cerebral cortex is essential for the control of handedness.²¹

¹⁹ Geo. M. Peterson, "A Preliminary Report on Right and Left Handedness in the Rat," Jour. of Comp. Psychol., Vol. XII, (Baltimore, Md., 1931), p. 248.

²⁰ Peterson, op. cit., "Mechanisms of Handedness in the Rat," pp. 1-67.

²¹ Geo. M. Peterson, and La Charles Fracarol, "The Relative Influence of the Locus and Mass of Destruction Upon the Control of Handedness by the Cerebral Cortex," Jour. of Comp. Neurology, Vol. 68, No. 2, (Philadelphia: The Wistar Institute Press), Feb., 1938, p. 189.

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observed and referred to as the ... application since it ...

Location of cerebral cortex in the rat

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Reliability of ambidexterity. The first fifty reaches during an observation period were found to be a good indication as to the variation expected from day to day.²² Statistical analysis confirmed the high reliability of these observations in a recent study.²³

²² Ibid., p. 176.

²³ Rigney, op. cit.

Reliability of Ambidexterity. The first fifty

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²² Ibid., p. 175.

²³ Higley, op. cit.

CHAPTER III

METHODS USED AND THE EXPERIMENTAL DESIGN

The procedure followed in this study is similar to that used by Rigney.¹ A factorial design was laid out according to Fisher.² Since d and l glutamic acid were both available, an additional measurable influence was possible regarding application to the left and right hemisphere.

Observation of Handedness. Rats were first observed and selected for varying degrees of ambidexterity. Since there were not a sufficient number of natural ambidexters available to complete the experimental design, it was necessary to place ten single-handed rats into a forced reaching situation whereby they eventually learned to make use of their non-preferred hand as well as the normally preferred hand. These artificial ambidexters were treated

¹ Rigney, op. cit.

² Ronald A. Fisher, The Design of Experiments, (London: Oliver and Boyd, 1947).

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¹ Higney, op. cit.

² Ronald A. Fisher, The Design of Experiments (London: Oliver and Boyd, 1937).

in the same manner as the normal ambidexters.

After selection, each rat was observed for three days prior to the operation day. These observations included two sets of fifty reaches for each day. On the fourth day, operation day, a set of fifty reaches was taken and the rat then immediately put through the operational procedures. After the operation, the rat was again placed into the feeding situation to be observed for fifty or more post-operational reaches. Fifty to one hundred reaches were also observed from three to five days after the operation.

Operational procedure. After the first fifty reaches on operation day, the animal was immediately anesthetized by ether. The hair was clipped from the top of the head where an incision was to be made. The skull was exposed and trephined at the frontal lobe. The drug or drug combinations were applied directly to the cerebral cortex by a small ball of cotton saturated with these solutions. The incision was again closed with wound clips and the rat placed once more into the feeding cage

in the same manner as the control group.

After section, each rat was placed in a separate cage.

Days prior to the beginning of the experiment, the rats

included two sets of fifty rats each, one set of fifty

fourth day, operation day, and the rat was placed in a

box and the rat was placed in a separate cage.

Operational procedures. The rats were placed in a

again placed into the same box and the rat was placed

for fifty or more post-operative days.

one hundred reached the end of the experiment.

days after the operation.

Operational procedures. The rats were placed in a

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clip and the rat placed in a separate cage.

from which he had previously been taken.

With a few rats, drugs were re-applied a few days after the initial operation. The procedure followed was much the same as that mentioned above.

Factorial design and drug combinations. A Fisher factorial design on analysis of variance technique made use of combinations of twelve rats or any multiple thereof. This design had one replication, thereby utilizing twenty-four animals. The limitation in number was due to the non-availability of ambidexters. The drug combinations used were assigned the following letters: Acetylcholine, A; l-glutamic acid, B; d-glutamic acid, B'. Operation and application to left and right hemisphere were assigned the letters C and c respectively. Total possible combinations are shown in table I. Small letters designated the absence of the drug in the various combinations.

The chemicals used were of approximately the following concentrations: Acetylcholine 3 to 5 percent, glutamic acid .1 M.

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Factorial design and drug combinations. A Fisher

factorial design or analysis of variance technique made use of combinations of twelve rats or any multiple thereof. This design had one replication, thereby utilizing twenty-four animals. The limitation in number was due to the non-availability of analgesics. The drug combinations used were assigned the following letters: Acetylsalicylic acid, A; I-glycine acid, B; 5-glycine acid, C; Operation and application to left and right hemispheres were assigned the letters D and E respectively. Total possible combinations are shown in table I. Small letters designated the absence of the drug in the various combinations.

The chemicals used were of approximately the following concentrations: Acetylsalicylic acid 5 percent, I-glycine acid 1 M.

TABLE I

RATS, COMBINATIONS, AND DRUGS

Rats		Combinations	Drugs
1M	13M	ABC	Acetylcholine, <u>l</u> -glutamic acid left hemisphere
2M	14M	AB'C	Acetylcholine, <u>d</u> -glutamic acid left hemisphere
3M	15M	ABc	Acetylcholine, <u>l</u> -glutamic acid right hemisphere
4M	16F	AB'c	Acetylcholine, <u>d</u> -glutamic acid right hemisphere
5M	17M	AbC	Acetylcholine, left hemisphere
6M	18F	Abc	Acetylcholine, right hemisphere
7M	19M	aBC	<u>l</u> -glutamic acid, left hemisph.
8M	20F	aB'C	<u>d</u> -glutamic acid, left hemisph.
9M	21F	aBc	<u>l</u> -glutamic acid, right hemisph.
10M	22M	aB'c	<u>d</u> -glutamic acid, right hemisph.
11F	23M	abC	control rats, left hemisphere
12F	24M	abc	control rats, right hemisphere

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CHAPTER IV

RESULTS, TABLES, AND ANALYSIS

The results to be discussed include the reliability of ambidexterity in the rat and the possible influence of orders; and the variances from the factorial design including the effects of acetylcholine and glutamic acid.

I. INFLUENCE OF ORDERS ON AMBIDEXTERITY

An analysis of variance was done on pre-operational data of twenty-four rats used in this study to determine the influence of orders on handedness. Results are shown in table II. The total contribution of orders to the total variance was non-significant. These results are in accord with those found by Rigney.¹ Since orders were judged to be two samples of the same distribution, it was justifiable to determine the contribution of drugs accounting for any differences between operation day orders.

¹ Rigney, op. cit.

RESULTS

The results of the analysis of variance are presented in Table I. The results show that the variance between orders is significant, indicating that the effects of order are significant.

I. INFLUENCE OF ORDER ON THE VARIANCE OF THE MEAN
An analysis of variance was conducted on the data of twenty-four pairs of orders. The results show that the influence of order is significant, as indicated by the F-test in Table II. The total variance was non-significant, and the variance was non-significant with those found by Higney. The two samples of the same order were found to determine the contribution of order to the total variance between orders.

Higney, op. cit.

II. THE DRUGS AND THEIR EFFECTS

Acetylcholine. The variance contributed by acetylcholine was only .04, which is considerably less than experimental error. Since this is the lesser mean square, it was used in the denominator to determine the F ratio. This ratio is significant at the five percent level, indicating, if this level of significance is accepted, that there is greater similarity between acetylcholine rats and non-acetylcholine rats than would be expected by chance. Since there is nothing in the experimental design to warrant such a result, we can only conclude that the one time in about twenty to be expected, has occurred here.

Glutamic acid. The variance contributed by glutamic acid was 9.30. This was significant at neither the one nor five percent level. See table IV.

With only one rat, number twenty female, was there a positive shift in handedness after application of this drug. Although this was only one rat of the total used that exhibited any curious effects, it is interesting to note that upon the application of d-glutamic acid to the left hemisphere,

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right and left rear spasticity became evident fifteen minutes after the operation, March 27. A shift did not show up in the first fifty reaches even though occasional incomplete right passes were made in the feeding situation. Subsequent post-operational reaches showed a marked shift to the use of the non-preferred hand. The following day, March 28, reaches were again comparable to pre-operational reaches. On March 29, the drug was re-applied. All reaches, pre-operational and post-operational, were consistent and showed no change. See table VI. Post-mortem examination of the brain revealed no mechanical damage to cortical tissue.

In a number of other rats, re-application was made a day or two after the original operation. All these cases showed no shift in handedness.

There was no significance for any of the interaction terms.

right and left rear quadrants became evident fifteen minutes after the operation, March 27. A shift did not show up in the first fifty reaches even though occasional incomplete right-paw reaches were made in the feeding situation. Subsequent post-operational reaches showed a marked shift to the use of the non-preferred hand. The following day, March 28, reaches were again comparable to pre-operational reaches. On March 29, the drug was re-applied. All reaches, pre-operational and post-operational, were consistent and showed no change. See Table VI. Post-mortem examination of the brain revealed no anatomical damage to cortical areas. In a number of other cases, re-application was made a day or two after the original operation. All these cases showed no shift in handedness.

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forms.

TABLE II

ANALYSIS OF VARIANCE OF SIX DAYS PRE-OPERATION DATA
FOR TWENTY-FOUR RATS

	Sum of Squares	D.F.	Mean of Squares
Total	88,959	143	622
Rats (i)	32,798	23	1426
Days (j)	760	2	380
Orders (k)	57	1	57
(Interactions)			
i j	5,053	46	110
i k	851	23	37
j k	241	2	121
i j k	49,199	46	1070

TABLE II

ANALYSIS OF VARIANCE OF SIX DAYS PRE-OPERATION DATA
FOR TWENTY-FOUR HATS

Sum of Squares	D.F.	Mean of Squares	
88,929	143	622	Total
35,798	23	1556	Hats (1)
760	5	380	Days (2)
27	1	27	Orders (K)
			(Interactions)
2,023	46	110	1 J
821	23	37	1 K
217	5	121	1 M
89,199	146	1070	1 J K

TABLE III

FACTORIAL DESIGN AND DIFFERENCES BETWEEN
PRE-AND POST-OPERATION PERIODS

Combinations	Rats	Reaches with Non-preferred Hand Pre-operation	Reaches with Non-preferred Hand post-operation	D
ABC	1M	4	0	4
	13M	0	0	0
AB'C	2M	30	26	4
	14M	1	0	1
aBC	7M	1	2	-1
	19M	37	49	-12
aB'C	8M	49	50	-1
	20F	3	8	-5
AbC	5M	1	0	1
	17M	3	0	3
ABc	3M	34	3	31
	15M	5	23	-18
AB'c	4M	20	10	10
	16F	39	48	-9
aBc	9M	0	0	0
	21F	26	9	17
aB'c	10M	17	0	17
	22M	25	4	21
Abc	6M	9	0	9
	18F	9	0	9
abC	11F	1	0	1
	23M	0	0	0
abc	12F	50	50	0
	24M	9	0	9

TABLE III

FACTORIAL DESIGN AND DIFFERENCES BETWEEN
PRE- AND POST-OPERATION PERIODS

Combin- ations	Rate	Resonance with Non-preferred Hand Pre-operation	Resonance with Non-preferred Hand Post-operation
ABC	IM	4	0
	JYM	0	0
AB'C	SM	30	25
	JJM	1	0
ABC	YM	1	2
	JYM	27	19
AB'C	BM	49	20
	SOP	3	8
ABD	SM	1	0
	JYM	3	0
ABD	SM	34	3
	JSM	2	23
AB'D	JM	20	10
	JOP	39	18
ABC	BM	0	0
	SJP	20	9
AB'D	JOM	17	0
	SJM	22	4
ABD	BM	9	0
	JBP	9	0
ABD	JJP	1	0
	SJM	0	0
ABC	JSP	20	20
	SJM	9	0

TABLE IV
ANALYSIS OF VARIANCE OF PRE-AND POST-OPERATION
PERIOD DIFFERENCES

Drugs	Sum of Squares	D.F.	Mean Squares	F
Total	2597.96	23		
Acetylcholine (A)	.04	1	.04	3453 *
Glutamic Acid (B)	18.59	2	9.30	
Hemisphere (C)	425.04	1	425.04	
(Interactions)				
AB	123.58	2	61.79	
AC	165.38	1	165.38	
BC	25.58	2	12.79	
ABC	182.25	2	91.13	
Estimate of Error	1657.50	12	138.13	

* smaller variance used as denominator - significant at 5% level.

TABLE IV

ANALYSIS OF VARIANCE OF PRE- AND POST-OPERATION PERIOD DIFFERENCES

Source	D.F.	Sum of Squares	Mean Squares	F
Total	23	2297.90		
Acetylcholine (A)	1	.04		0.01
Gluconic Acid (B)	2	18.59		0.30
Hexaphere (C)	1	122.04		122.04
(Interactions)				
AB	2	123.28		61.79
AC	1	162.38		162.38
BC	2	22.28		12.79
ABC	2	182.22		91.13
Residual Error	12	1671.20		138.13

Smaller variance used as denominator - significant at 5% level.

TABLE V (Contd.)

RECORDS OF REACHING

Days	Per- iods	Rats						Hands															
		6M	3M	4M	9M	1M	15M	5M	7M	R	L	R	L	R	L	R	L	R	L	R	L		
1	1	49	1	26	24	31	19	48	2	20	30	44	6	6	44	3	47						
	2	47	3	11	39	26	24	50	0	26	24	47	3	1	49	5	45						
2	1	49	1	21	29	32	18	47	3	27	23	49	1	1	49	9	41						
	2	50	0	32	18	30	20	50	0	13	37	50	0	0	50	4	46						
3	1	50	0	33	17	29	21	50	0	24	26	32	18	0	50	1	49						
	2	36	14	22	28	23	27	50	0	25	25	30	20	0	50	2	48						
4**	1	41	9	16	34	30	20	50	0	4	46	45	5	1	49	1	49						
	2	50	0	47	3	40	10	50	0	0	50	27	23	0	50	0	50						
	3	50	0	46	4	34	14	35	15	0	50	40	10	0	50	0	50						
	4	50	0	50	0	43	7	30	20	0	10	34	16	0	50	0	50						
	5	50	0	45	5	37	13	48	2	0	10	37	13	0	50	0	50						

TABLE V (Contd.)

RECORDS OF REACHING

Days	Per-iods	Rats															
		11F		16F		18F		12F		2M		8M		23M		10M	
		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	1	5	45	19	31	0	50	10	40	43	7	43	7	0	50	46	4
	2	0	50	3	47	2	48	7	43	39	11	49	1	1	49	47	3
2	1	0	50	13	37	0	50	1	49	47	3	48	2	0	50	50	0
	2	1	49	4	46	27	23	0	50	42	8	16	34	0	50	37	13
3	1	0	50	4	46	30	20	1	49	45	5	36	14	0	50	48	2
	2	0	50	6	44	37	13	0	50	38	12	46	4	0	50	36	14
4**	1	1	49	11	39	41	9	0	50	30	20	49	1	0	50	33	17
	2	0	50	2	48	50	0	0	50	26	24	50	0	0	50	50	0
	3	0	50	0	50					14	36	50	0	0	50	50	0
	4	1	49	1	49			22	28					0	50	32	18

TABLE V (continued)

RECORDS OF REACHING

Days	Per- iods	Rats															
		11F	16F	18F	12F	2M	8M	23M	10M	R	L	R	L				
		Hands															
		R	L	R	L	R	L	R	L	R	L	R	L				
5	1	0	50	0	50	10	0	2	48	22	28	45	5	0	50	37	13*
	2							11	39			7	0	0	50	19	1
6	1			1	49*	50	0*			20	30						
	2			0	50	0	0			14	36						
	3			0	50												

* Combination of drugs re-applied

** Operation day

TABLE A

Year	1946	1947	1948	1949	1950
...

Date 1946

RECORDS OF SEARCHING

VOLUME A (continued)

TABLE V

RECORDS OF REACHING

Days	Per-iods	Rats																	
		13M	17M	24M	19M	21F	22M	20F	14M	13M	17M	24M	19M	21F	22M	20F	14M		
		Hands																	
		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	1	7	43	40	10	5	45	23	27	38	12	1	49	44	6	1	49		
	2	12	38	32	18	29	21	35	15	35	14	47	3	35	15	14	36		
2	1	3	47	32	18	32	18	29	21	44	6	37	13	18	32	16	34		
	2	1	49	27	23	40	10	39	11	48	2	38	12	5	45	2	48		
3	1	2	48	20	30	46	4	45	5	48	2	43	7	2	48	3	47		
	2	0	50	4	46	48	2	43	7	41	9	27	23	2	48	5	45		
4**	1	0	50	3	47	41	9	37	13	24	26	25	25	3	47	1	49		
	2	0	50	0	50	50	0	49	1	33	9	18	1	8	42	0	9		
	3	0	50	0	50	50	0	48	2	0	0	28	3	38	12	0	24		
	4	0	50	0	50	50	0	50	0	0	0	43	0	36	14	0	24		
	5	0	50	0	50	50	0	50	0	0	0	43	0	46	14	0	24		
	6	0	50	0	50	50	0	50	0	0	0	43	0	35	15	0	24		

1900

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30

DATE	TIME	TYPE	SPM	AMT	SLS	SSP	SOE	TPH

RECORDS OF RESEARCH
LABORATORY

TABLE V (continued)

RECORDS OF REACHING

Days	Per- iods	Rats															
		13M	17M	24M	19M	21F	22M	20F	14M	R	L	R	L				
		Hands															
5	1	0	50	1	49*	20	30	33	17	8	0	42	8	5	45	0	17
	2	0	50	0	50	43	7	44	6								
	3					30	20	38	12								
	4					21	29	35	15								
6	1									46	4	49	1	16	34*	1	49
	2													16	34		
	3													16	34		
7	1									49	1					0	50

* Combination of drugs re-applied

** Operation Day

1 11-03-99-100-11

100 100 100 100
100 100 100 100
100 100 100 100

0 20 0 100 50
0 20 0 100 50

1 1 1 1 1 1 1 1 1 1

1 1 1 1 1 1 1 1 1 1

1 1 1 1 1 1 1 1 1 1

ИНТЕРЕСЫ ПО СЧЕТАМ

ЛИСТА А (продолжение)

TABLE VI

REACHING RECORD OF RAT NUMBER TWENTY, FEMALE

Day	Hand		Day	Hand	
	R	L		R	L
1	44 35	6 15	5	5	45
2	18 5	32 45	6 (re-application)		
			pre:	16	34
3	2 2	48 48	post:	16	34 34
4 (operation day)					
	pre:	3 47			
	post:	8 42			
		38 12			
		36 14			
		46 4			
		35 15			
		27 23			

The buffer, given as a result, turned out to be without significant effect on the reaching record of rat number twenty, female, and the results indicate a shift in the preference towards the use of the

TABLE VI

REACHING RECORD OF RAT HURBEN TWENTY, FEMALE

Day	Hand		Dry	Ear	
	R	L		R	L
1	14	15	5	5	15
2	18	18	6 (re-application)	10	10
3	2	2	10	10	10
4 (operation day)	3	3	10	10	10
	8	8			
	12	12			
	14	14			
	15	15			
	15	15			
	15	15			

CHAPTER V

SUMMARY AND CONCLUSIONS

Twenty-four rats were used in a factorial design to test the influence of acetylcholine and glutamic acid on handedness, when applied to the cerebral cortex, in the hemisphere homolateral to the preferred hand.

According to the analysis of variance on drugs used in this study, neither acetylcholine nor glutamic acid caused significant shifts in handedness when applied to the cerebral cortex of the albino rat. In fact, the difference between acetylcholine rats and non-acetylcholine rats was significantly less than expected from the experimental error. Since there is nothing in the experimental design to warrant this result, we are concluding that it is an exceptional occurrence which can only be accounted for by chance.

The buffer, glutamic acid, used in this study also turned out to be without significance. Only in one case, rat number twenty, female, was there a marked shift in handedness towards the use of the non-preferred hand.

11

... to test the influence of a variable was given in the
on handness, a variable of the research interest in
hemisphere control over the other hand.
According to the analysis of variance we have
in this study, either hemisphere for stimulus
caused significant effects in handness and in the
the cerebral cortex of the right hand. In fact, the dif-
ference between asymmetrical and symmetrical
tasks was significantly less than for the other hand.
In fact, since there is a right to left
design to report this result, we are convinced that
is an exceptional case as well as a
for by chance.
The latter, chance side, was
turned out to be a right hemisphere in a
for number theory, tasks, and there is a
handness toward the left hemisphere.

Upon re-application, however, pre-operation data for the first order was the same as the two post-operational orders.

All the interaction variances were also without significance.

With the drug concentrations used in this study, neither acetylcholine nor glutamic acid, singly or taken together, seemed to have an effect in influencing the rat to a shift in hand preference. This study appears to warrant further consideration of dosages and possibly a modification of technique before glutamic acid should again be utilized in a comparable study.

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Upon re-application, however, post-operative data for the
This order was the same as the two post-operative
orders.

All the interaction variables were also significant.

With the drug concentrations used in this study,
neither acetylcholine nor ginseng acid, singly or taken
together, seemed to have an effect in influencing the rat
to a shift in hand preference. This study appears to war-
rant further consideration of dosages and possibly a sub-
stitution of technique before ginseng acid should again
be utilized in a comparable study.

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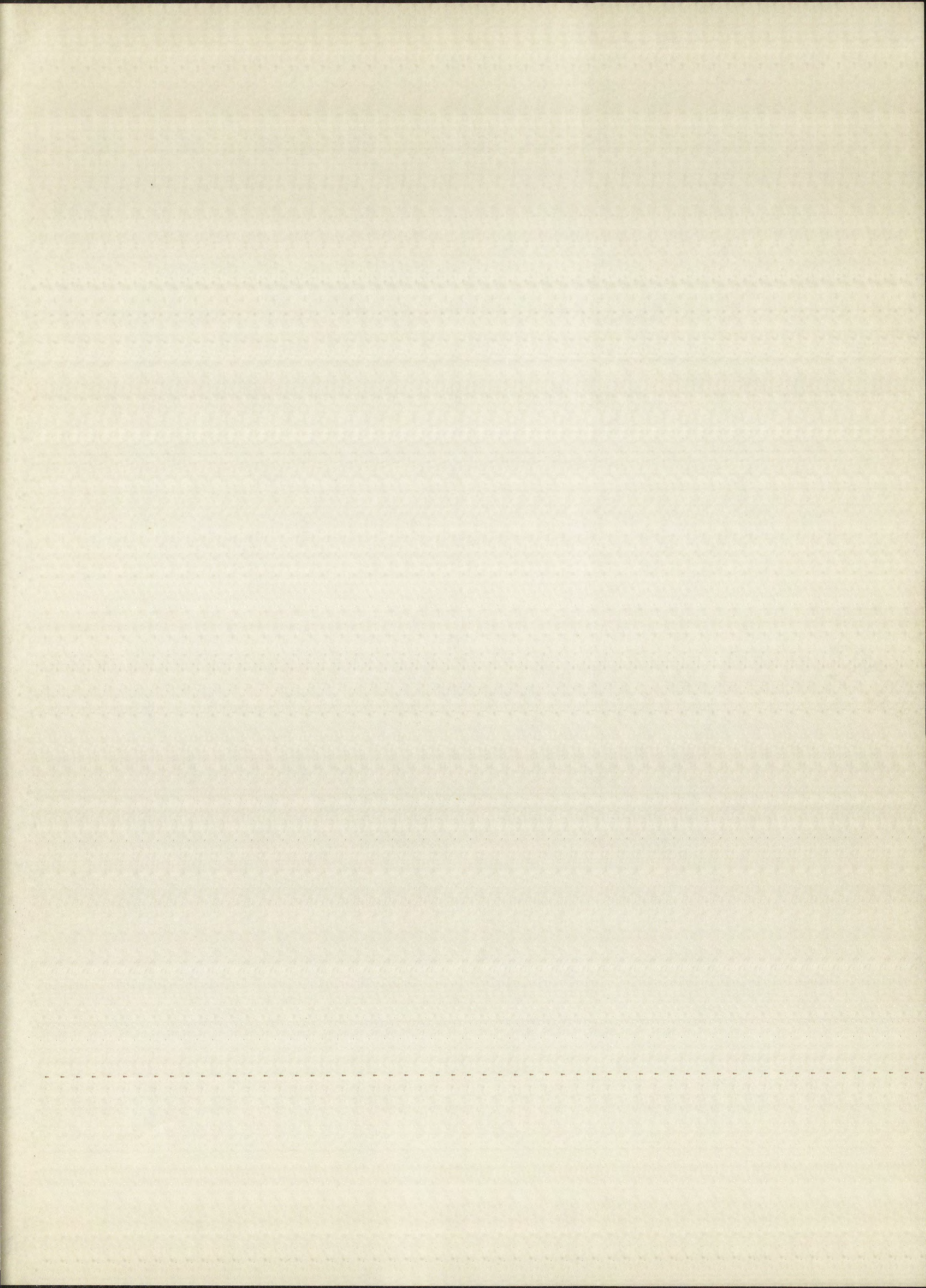
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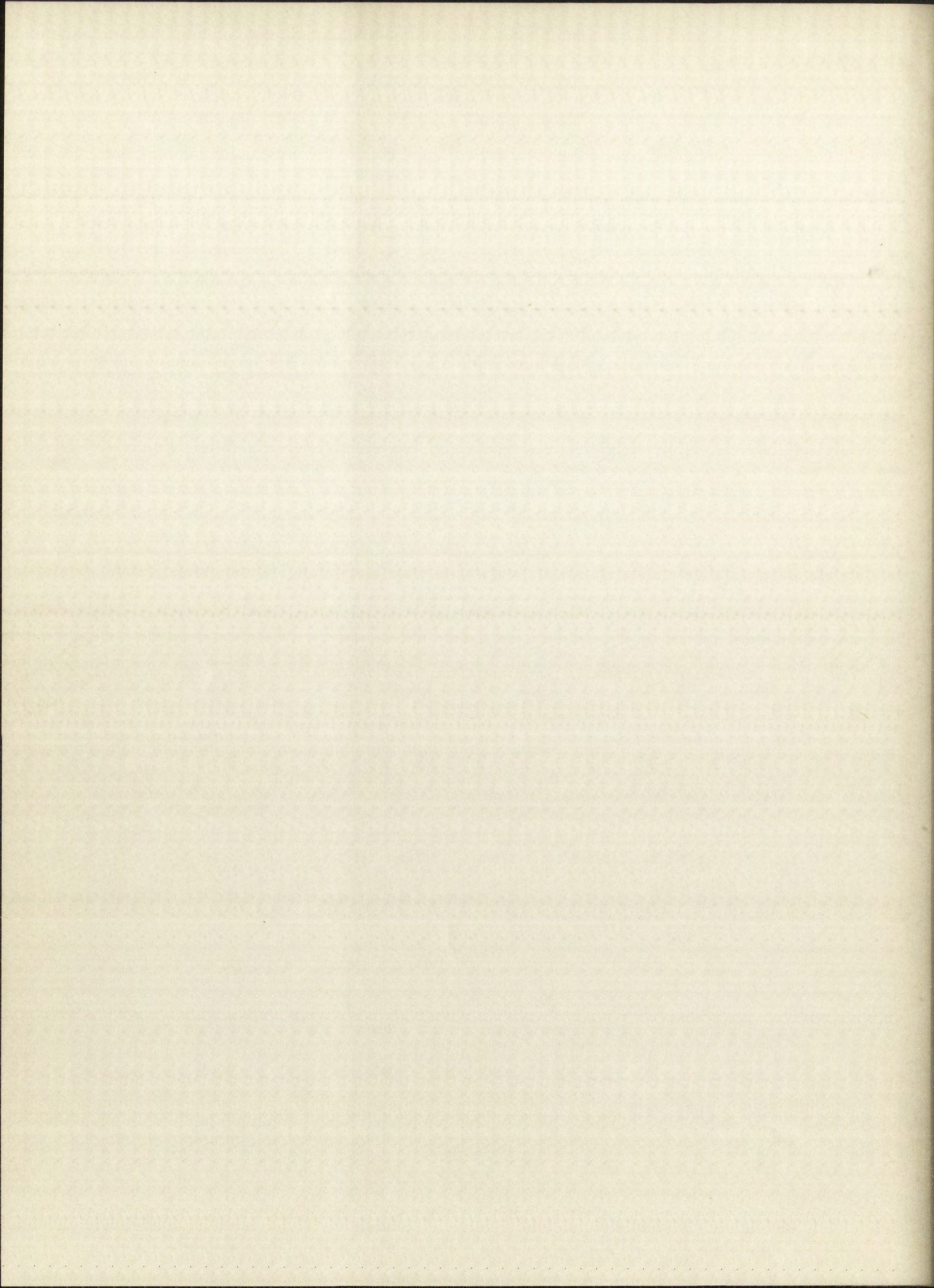
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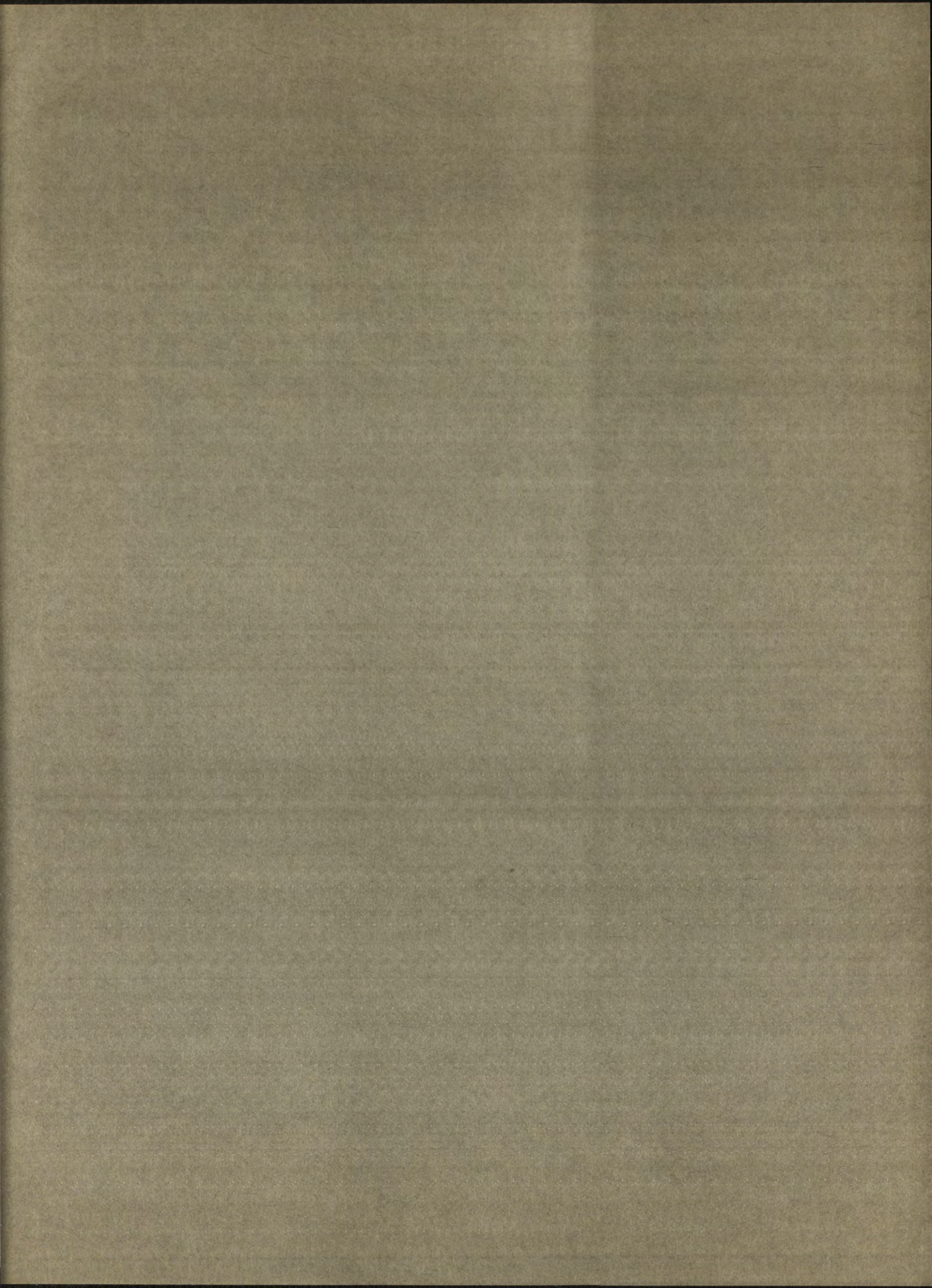
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