

THE ROLE OF ACETYLCHOLINE IN BEHAVIOUR  
SUPPRESSING MECHANISMS

---

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BY

HUGH BROWN

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## ABSTRACT

TITLE OF DISSERTATION: THE ROLE OF ACETYLCHOLINE IN BEHAVIOUR  
SUPPRESSING MECHANISMS

HUGH BROWN, DOCTOR OF PHILOSOPHY, 1970

A SERIES OF STUDIES WERE CONDUCTED TO ASSESS CARLTON'S (1963) HYPOTHESIS THAT, "A CHOLINERGIC SYSTEM IN THE BRAIN ANTAGONIZES A SECOND SYSTEM WHICH ACTIVATES BEHAVIOR". THE APPROACH BEHAVIOUR OF WATER DEPRIVED MICE TO A DRINKING TUBE (OR, IN SOME INSTANCES, FOOD DEPRIVED MICE, AND A FOOD CONTAINER) AS A FUNCTION OF PREVIOUS (HABITUATING) EXPERIENCE IN THE CHAMBER CONTAINING THE TUBE, WAS CONSIDERED FROM EACH OF FOUR ASPECTS: 1.) PHARMACOLOGICAL, 2.) MOTIVATIONAL, 3.) STIMULUS, AND 4.) RESPONSE. IT WAS FOUND THAT MUSCARINIC ANTICHOLINERGIC AGENTS DO INHIBIT THE INFLUENCE OF PREVIOUS EXPERIENCE, THAT THE SITE OF THE DRUG ACTION IS PROBABLY THE CNS, BUT DIMINUTION OF CHOLINERGIC ACTIVITY ALONE IS NOT A SUFFICIENT CONDITION. IT WAS ALSO FOUND THAT MOTIVATIONAL AND EXTRANEOUS ENVIRONMENTAL FACTORS CONTRIBUTE SIGNIFICANTLY TO THE EFFICACY OF THE DRUG ACTION. IN ADDITION, IT WAS SHOWN THAT A MEASURE OF GENERAL MOTOR ACTIVITY OFFERS A COMPARABLE, IF NOT SUPERIOR, METHOD OF ASSESSING THE DESCRIBED DRUG EFFECTS. ON THE BASIS OF THESE FINDINGS, AN ALTERNATIVE HYPOTHESIS IS OFFERED THAT TAKES ALL THE FACTORS INTO ACCOUNT.

FURTHER, THE NEW HYPOTHESIS AVOIDS THE CONCEPTUAL DIFFICULTIES INHERENT IN "BIOCHEMICAL LOCALIZATION", I.E., THE ATTEMPT TO CONSIDER SPECIFIC BIOCHEMICAL SYSTEMS AS THE PHYSIOLOGICAL SUBSTRATES OF SPECIFIC BEHAVIOURAL PHENOMENA.

## TABLE OF CONTENTS

	PAGE
LIST OF TABLES . . . . .	VI
LIST OF FIGURES . . . . .	IX
CHAPTER	
I. INTRODUCTION . . . . .	1
ESTABLISHMENT OF NEUROHUMOURAL TRANSMISSION THEORY . . . . .	1
NEUROHUMOURAL TRANSMISSION IN THE CENTRAL NERVOUS SYSTEM . . . . .	3
BEHAVIOURAL STUDIES OF CENTRAL NEUROHUMOURAL TRANSMISSION . . . . .	9
GENERAL ORIENTATION . . . . .	9
THE ROLE OF NEUROHUMOURAL TRANSMISSION IN BEHAVIOURAL HABITUATION . . . . .	19
II. METHODS . . . . .	35
THE GENERAL PROCEDURE FOR MEASURING APPROACH LATENCY . . . . .	35
SUBJECTS . . . . .	35
APPARATUS . . . . .	35
OPERATIONS . . . . .	36
PHARMACOLOGICAL PROCEDURES . . . . .	40
PARAMETRIC VARIATIONS . . . . .	40
PHARMACOLOGICAL ASSESSMENT OF DRUG AND DOSAGE VARIATIONS . . . . .	40
MOTIVATIONAL INFLUENCES INVOLVING DEPRIVATION, TIME AND INCENTIVE . . . . .	44

CHAPTER	PAGE
TESTS OF GENERALIZATION ACROSS STIMULUS CONDITIONS . . . . .	46
GENERAL ACTIVITY MEASUREMENT . . . . .	47
ANCILLARY MEASUREMENTS . . . . .	50
III. RESULTS . . . . .	51
PHARMACOLOGICAL PARAMETERS . . . . .	51
MOTIVATIONAL PARAMETERS . . . . .	59
STIMULUS PARAMETERS . . . . .	65
RESPONSE PARAMETERS . . . . .	70
ANCILLARY DATA . . . . .	77
IV. DISCUSSION . . . . .	80
PHARMACOLOGICAL CONSIDERATIONS . . . . .	80
MOTIVATIONAL ASPECTS . . . . .	89
THE DRUG-STIMULUS INTERACTION PROBLEM . . . . .	95
THE SUPERIORITY OF GENERAL MOTOR ACTIVITY AS A MEASURE OF THE INFLUENCE OF PREVIOUS EXPERIENCE . . . . .	100
SOME CONCLUSIONS AND AN ALTERNATIVE HYPOTHESIS . . . . .	103
REFERENCES . . . . .	108

## LIST OF TABLES

TABLE	PAGE
1. DRUGS EMPLOYED IN THE VARIOUS EXPERIMENTS AND THEIR RELEVANT CHARACTERISTICS . . . . .	41
2. DRUGS AND DOSE RANGES EMPLOYED IN APPROACH LATENCY EVALUATION . . . . .	43
3. DRUG ANTAGONISM RELATIONSHIPS STUDIED IN APPROACH LATENCY PROCEDURE . . . . .	44
4. CHARACTERISTICS OF FILTERS USED TO VARY CHAMBER ILLUMINATION . . . . .	46
5. DRUGS AND DOSE RANGES EMPLOYED IN ACTIVITY EXPERIMENTS . . . . .	49
6. MEAN APPROACH LATENCY VALUES (0.01 MINS.) FOR SELECTED DRUGS AND DOSES . . . . .	52
7. ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING APPROACH LATENCY MEASURE . . . . .	53
8. MEAN APPROACH LATENCY VALUES (0.01 MINS.) FOR VARIOUS DOSES OF SEVERAL DRUGS . . . . .	56
9. THE ANTAGONISTIC RELATIONSHIP BETWEEN SCOPOLAMINE OR DITRAN AND ESERINE OR TACRINE AS MEASURED BY APPROACH LATENCIES (MEAN PER GROUP IN 0.01 MINS.) . . . . .	57
10. MEAN APPROACH LATENCY VALUES (0.01 MINS.) FOLLOWING INTRACRANIAL INJECTIONS OF SCOPOLAMINE, ATROPINE AND METHYL-ATROPINE . . . . .	58
11. MEAN APPROACH LATENCY VALUES (0.01 MINS.) FOLLOWING DOSAGE WITH SCOPOLAMINE OR ATROPINE AND VARIOUS HOURS OF WATER DEPRIVATION . . . . .	60

TABLE	PAGE
12. MEAN APPROACH LATENCY VALUES (0.01 MINS.) FOR FOOD REINFORCEMENT FOLLOWING DOSAGE WITH SCOPOLAMINE OR ATROPINE AND VARIOUS HOURS OF DEPRIVATION . . . . .	61
13. MEAN VOLUME OF WATER CONSUMED (CC/SS) BY EACH EXPERIMENTAL GROUP DURING PERIOD BETWEEN DRUG DOSAGE AND INITIATION OF DEPRIVATION PERIOD . . . . .	62
14. ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING WATER CONSUMPTION MEASURE . . . . .	62
15. MEAN VOLUME OF WATER CONSUMED (CC/SS) AT VARIOUS TIMES DURING PERIOD BETWEEN DRUG DOSAGE AND INITIATION OF DEPRIVATION PERIOD (CUMULATIVE OVER SUCCESSIVE 24 HOUR PERIODS) . . . . .	63
16. MEAN NUMBER OF LICKS ON DRINKING TUBE PER 15.0 MINUTES FOLLOWING DOSAGE WITH SEVERAL DRUGS . . . . .	66
17. ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING LICKING RATE MEASURE . . . . .	67
18. MEAN APPROACH LATENCIES (0.01 MINS.) FOLLOWING DOSAGE WITH SCOPOLAMINE AND ATROPINE WITH DRINKING TUBE PRESENT DURING INITIAL EXPOSURE PERIOD . . . . .	67
19. EFFECT OF COLOURED ILLUMINATION ON MEAN APPROACH LATENCY VALUES (0.01 MINS.) FOLLOWING A DOSE OF 0.32 MG./KG. SCOPOLAMINE . . . . .	68
20. EFFECT OF INTERMITTANT ILLUMINATION (3.0 FLASHES PER SECOND) ON SCOPOLAMINE-MODIFIED APPROACH LATENCY VALUES (0.01 MINS.) . . . . .	69
21. EFFECT OF VARIOUS CONDITIONS OF "WHITE NOISE" ON SCOPOLAMINE MODIFIED APPROACH LATENCY VALUES (0.01 MINS.) . . . . .	71

TABLE	PAGE
22. MEAN AND STANDARD DEVIATION FOR NUMBER OF PHOTOBAM INTERRUPTIONS PER 15 MINUTES FOLLOWING VARIOUS DOSES OF SEVERAL DRUGS . . . . .	72
23. MEAN NUMBER OF PHOTOBAM INTERRUPTIONS UNTIL DRINKING TUBE APPROACH FOR SEVERAL DOSES OF SCOPOLAMINE . . . . .	75
24. ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING PHOTOBAM MOTOR ACTIVITY MEASURE . . . . .	75
25. MEAN AND STANDARD DEVIATION FOR PHOTOBAM INTERRUPTIONS AT VARIOUS DERIVATION LEVELS FOR WATER, CONDENSED MILK AND LABORATORY CHOW . . . . .	76
26. MEAN AND STANDARD DEVIATION FOR NUMBER OF PHOTOBAM INTERRUPTIONS PER 15 MINUTES FOLLOWING INTRACRANIAL DOSES OF ATROPINE AND METHYLATROPINE . . . . .	77
27. SYMPTOMATOLOGICAL SUMMARY OF THE EFFECTS OF THE DRUGS EMPLOYED IN THE VARIOUS EXPERIMENTS . . . . .	78



## LIST OF FIGURES

FIGURE	PAGE
1. SCHEMATIC DIAGRAM OF THE APPARATUS USED TO MEASURE APPROACH LATENCY. THE LIGHT SOURCE FOR CHAMBER ILLUMINATION IS NOT REPRESENTED AS IT WOULD OBSCURE THE WATER BOTTLE-DRINKING TUBE . . . . .	37
2. THE EXPERIMENTAL PARADIGM EMPLOYED IN ASSESSING THE EFFECTS OF DRUGS AND PRIOR EXPOSURE ON APPROACH LATENCY . . . . .	38
3. SCHEMATIC DIAGRAM OF THE ARRANGMENT USED TO MEASURE GENERAL ACTIVITY . . . . .	48
4. MEAN LATENCY INDICES FOR EACH GROUP IN THE INITIAL DOSE EVALUATIONS. LATENCY INDEX IS THE LATENCY VALUE IN 0.01 MINS. DIVIDED BY 10 . . . . .	54
5. MEAN AMOUNT OF WATER CONSUMED BY EACH EXPERIMENTAL GROUP (CC/SUBJECT) WITHIN VARIOUS TIME PERIODS FOLLOWING DOSAGE WITH 0.32 MG./KG. SCOPOLAMINE; I.P., OR 10.0 MG./KG. ATROPINE, I.P. . . . .	64
6. DOSE-EFFECT CURVES FOR GENERAL ACTIVITY AT VARIOUS TIMES FOLLOWING SCOPOLAMINE, ATROPINE, METHYLATROPINE, DITRAN, D-AMPHETAMINE, AND METHYLPHENIDATE, ALL ADMINISTERED INTRAPERITONEALLY . . . . .	74

## CHAPTER 1

### INTRODUCTION

#### ESTABLISHMENT OF NEUROHUMOURAL TRANSMISSION THEORY

CHEMICAL MEDIATION OF IMPULSE TRANSMISSION THROUGH THE NERVOUS SYSTEM WAS SUGGESTED AS LONG AGO AS 1650 BY DESCARTES (KANTOR, 1947). YET, UNTIL LOEWI'S (1921) CLASSIC DEMONSTRATION OF "VAGUSSTOFF" AS A CHEMICAL TRANSMITTER NEARLY 300 YEARS LATER, THE NOTION WAS NOT GIVEN SERIOUS CONSIDERATION BY MOST PSYCHO- AND NEUROPHYSIOLOGISTS. INDEED, AS RECENTLY AS 1950, A POPULAR PHYSIOLOGICAL PSYCHOLOGY TEXTBOOK IN ITS DISCUSSION OF NEUROHUMOURAL TRANSMISSION STATED;

ACCORDING TO THIS NOTION, SYNAPTIC TRANSMISSION WAS ACHIEVED BY THE RELEASE AT THE NERVE ENDINGS OF CERTAIN BIOCHEMICAL SUBSTANCES THAT SET UP THE IMPULSE IN THE NEXT CELL. NOWADAYS, HOWEVER, WE ARE QUITE SURE THAT THE ACTIVITY AT THE SYNAPSE IS BASICALLY NO DIFFERENT FROM THE ACTIVITY IN THE NERVE FIBER (MORGAN AND STELLAR, 1950, P. 98).

IN THE YEARS SINCE 1950, EXPERIMENTAL AND THORETICAL ADVANCES HAVE EFFECTED MARKED RE-EVALUATION OF SUCH CONCLUSIONS. A MORE RECENT EDITION OF THE SAME TEXT ADDRESSING ITSELF TO THE SAME TOPIC NOW CONCEDES;

IT IS NOW GENERALLY AGREED AMONG INVESTIGATORS IN THE FIELD THAT [THERE ARE] DIFFERENT MEANS OF TRANSMISSION AT SYNAPSES. THE MESSAGE AT THE SYNAPSE IS CHEMICAL, WHEREAS THAT IN AN ELECTRICALLY STIMULABLE MEMBRANE IS ELECTRICAL (MORGAN, 1965, P. 72).

THE POINT IS FURTHER ELABORATED BY A PHARMACOLOGICAL TEXTBOOK WHICH STATES UNEQUIVOCALLY THAT:

THERE IS NOW GENERAL ACCEPTANCE BY THE GREAT MAJORITY OF PHYSIOLOGISTS AND PHARMACOLOGISTS OF THE THEORY OF NEUROHUMOURAL TRANSMISSION, THAT IS, THAT NERVES TRANSMIT THEIR IMPULSES ACROSS MOST SYNAPSES AND NEUROEFFECTOR JUNCTIONS BY MEANS OF SPECIFIC CHEMICAL AGENTS KNOWN AS NEUROHUMORAL TRANSMITTERS (KÖELLE, 1965, p. 399).

THAT SUCH EMPHATIC SUPPORT COMES FROM PHARMACOLOGY AND NOT PSYCHOPHYSIOLOGY IS QUITE IN KEEPING WITH THE ORIGIN OF THE MORE CONTEMPORARY FORM OF THE THEORY. LOEWI'S NOTION OF CHEMICAL TRANSMISSION WAS ANTICIPATED BY SEVERAL YEARS, BUT THE DATA, POSSIBLY BECAUSE IT WAS PHARMACOLOGICAL IN NATURE, ESCAPED GENERAL BIOLOGICAL ATTENTION. REFERRING TO THIS STATE OF AFFAIRS, LOEWI HIMSELF SAID:

THE REPORTS OF BOTH ELLIOT AND DIXON WERE PUBLISHED SO INCONSPICUOUSLY THAT THEY ESCAPED GENERAL ATTENTION AS WELL AS MY OWN. THE EARLIER RESULTS WERE ONLY REDISCOVERED, SO TO SPEAK, SOME YEARS AFTER MY DISCOVERY OF THE CHEMICAL TRANSMISSION OF THE NERVE IMPULSE WHICH WAS MADE IN 1921 (1945, p. 159).

ELLIOT'S (1905) STUDY SUGGESTED THAT EPINEPHRINE WAS INVOLVED IN TRANSMISSION ACROSS POSTGANGLIONIC SYMPATHETIC SYNAPSES, AND DIXON (1907) REPORTED HIS SUSPICION CONCERNING A SUBSTANCE RELEASED FOLLOWING STIMULATION OF THE VAGUS NERVE. BURN (1963) IS EVEN HISTORICALLY MORE DEFINITIVE IN THAT HE CITES EXPERIMENTAL EVIDENCE WHICH SUGGESTS THAT A DEMONSTRATION OF NEUROHUMORAL TRANSMISSION EXISTED AS EARLY AS 1863.

IN ADDITION, DEFINITION OF THE PHARMACOLOGICAL ACTIVITIES

OF ACETYLCHOLINE ALSO PREDATED LOEWI'S (1921) DEMONSTRATION. THIS WAS THE RESULT OF DALE'S (1914) WELL-KNOWN CARDIOVASCULAR ASSESSMENT OF THE SUBSTANCE. THE RELATIONSHIP BETWEEN ACETYLCHOLINE AND NEURAL TRANSMISSION WAS ESTABLISHED IN 1926 WHEN LOEWI AND NAVRATIL IDENTIFIED "VAGUSSTOFF" AS ACETYLCHOLINE ON THE BASIS OF THE FACILITORY EFFECTS OF PHYSOSTIGMINE ON VAGAL STIMULATION.

THESE FINDINGS PROVIDED THE BASIS FOR MANY SIGNIFICANT ADVANCES IN UNDERSTANDING DRUG ACTION. SINCE ONLY A FEW DRUGS (E.G., CYANIDE - GROLLMAN, 1965) ACT DIRECTLY ON CELL METABOLISM, NEUROHUMOURAL TRANSMISSION THEORY IS VERY BASIC TO DEFINING DRUG ACTIONS ON THE NERVOUS SYSTEM. THUS, A COMPLEMENTARY RELATIONSHIP IS ESTABLISHED IN THAT PHARMACOLOGY VERIFIES THE THEORY AND, SIMULTANEOUSLY, EMPLOYS IT AS A FUNDAMENTAL TENET.

### NEUROHUMOURAL TRANSMISSION IN THE CENTRAL NERVOUS SYSTEM

SHERRINGTON SUGGESTED AS EARLY AS 1906 THAT THE MECHANISM OF TRANSMISSION, WHATEVER IT MIGHT BE, WAS SIMILAR FOR ALL SYNAPSES. CONSEQUENTLY, FOLLOWING LOEWI'S (1921) VERIFICATION OF PERIPHERAL CHEMICAL TRANSMISSION, IMMEDIATE SPECULATION CENTRED ON THE ROLE OF ACETYLCHOLINE (AND SUBSEQUENTLY, OTHER SUBSTANCES) IN REGARD TO SYNAPTIC TRANSMISSION WITHIN THE CENTRAL NERVOUS SYSTEM (CNS).

INITIALLY, ELUCIDATION OF CNS NEUROHUMOURAL TRANSMISSION SEEMED EXPERIMENTALLY SIMPLE - NOT ANY MORE RIGOROUS THAN APPLICATION OF THE TECHNIQUES ALREADY EVOLVED FOR DELINEATING

PERIPHERAL TRANSMISSION. LOEWI SUGGESTED TWO MODES OF APPROACH:

...IT MUST BE SHOWN, FIRST, WHETHER OR NOT ACETYLCHOLINE ACTS LIKE NERVOUS STIMULATION UPON THE EFFECTOR ORGANS WITHIN THE CNS AND, SECONDLY, WHETHER OR NOT ACETYLCHOLINE IS LIBERATED DURING STIMULATION OF THE CNS AS IT IS IN THE PERIPHERAL NERVOUS SYSTEM (1945, p. 167).

HOWEVER, A RECENT REVIEW OF EFFORTS TO IDENTIFY CENTRAL SYNAPTIC TRANSMITTERS HAD TO CONCLUDE THAT:

A NUMBER OF CRITERIA HAVE BEEN SUGGESTED FOR THE CHARACTERIZATION OF A GIVEN SUBSTANCE AS A TRANSMITTER AT A GIVEN SYNAPSE. UNFORTUNATELY, SOME OF THESE CRITERIA CANNOT BE MET AT THE PRESENT TIME FOR CENTRAL SYNAPSES, AND IT MAY BE UNREALISTIC TO REQUIRE THAT THEY SHOULD BE. NEVERTHELESS, THREE MAJOR CRITERIA, EACH AMENABLE TO FURTHER SUBDIVISION, CLEARLY STAND OUT: (A) THE SUBSTANCE AND THE APPROPRIATE ENZYME SYSTEMS FOR ITS BIOSYNTHESIS AND ITS METABOLISM MUST BE PRESENT AND IN THE RIGHT LOCALE; (B) THE SUSPECTED SUBSTANCE AND THE TRANSMITTER MUST HAVE IDENTICAL ACTIONS AND SIMILAR PHARMACOLOGICAL CHARACTERISTICS ON THE POSTSYNAPTIC CELL; AND (C) THE TRANSMITTER RELEASED FROM THE NERVE ENDING MUST BE SHOWN TO BE IDENTICAL TO THE SUSPECTED SUBSTANCE (SALMOIRAGHI, COSTA AND BLOOM, 1966, p. 224).

THUS, AFTER TWENTY YEARS, THE GOALS REMAIN ESSENTIALLY THE SAME.

PROGRESS HAS CONSISTED OF AN ADMISSION THAT OBTAINING THEM

"...MAY BE UNREALISTIC."

THREE DIFFICULTIES HAVE CONTRIBUTED TO THE CONTEMPORARY IMPASSE. IN MOST INSTANCES, THE COMPLICATIONS ARE EQUALLY APPROPRIATE TO CONSIDERATIONS OF PERIPHERAL TRANSMISSION. INDEED, THEIR ELUCIDATION AND ELABORATION BASICALLY ARISE FROM EXPERIMENTS AND OBSERVATIONS CONCERNING TERMINAL AUTONOMIC SYNAPSES (THE SITE FROM WHICH ALMOST ALL TECHNOLOGY REGARDING NEUROHUMOURAL TRANSMISSION HAS BEEN EVOLVED). THE COMPLICATING FACTORS ARE: 1.) THE

POSSIBLE EXISTENCE OF MULTIPLESTEP TRANSMISSION SEQUENCES. A NUMBER OF STUDIES (BURN, 1963; BURN, 1961; BURN AND RAND, 1959; KOELLE, 1962) HAVE INDICATED THAT THE ACTION OF ACETYLCHOLINE AT VARIOUS PERIPHERAL SITES, RATHER THAN SIMPLY PROCEEDING TRANS-SYNAPTICALLY, MAY FUNCTION PRE-SYNAPTICALLY TO ACTIVATE OTHER NEUROHUMOURAL TRANSMITTERS SUCH AS NOREPINEPHRINE. AS WELL, EVIDENCE EXISTS TO INDICATE POST-SYNAPTIC STORAGE AND RELEASE OF TRANSMITTER SUBSTANCES AT PERIPHERAL ENDINGS (NACHMANSOHN, 1959). SIMILAR CIRCUMSTANCES MAY OCCUR CENTRALLY, OTHER TRANSMITTERS, AND MORE STEPS MAY BE INVOLVED AT OTHER SYNAPSES. 2.) ANATOMICAL EVIDENCE INDICATES THAT THERE ARE AXO-SOMATIC, AXO-AXONIC, AND ENDO-DENDRITIC AS WELL AS THE MORE PROTOTYPIC AXO-DENDRITIC SYNAPSES (STEVENS, 1966). ALL TYPES ARE REPRESENTED IN THE CNS, THE LATTER BEING TYPICAL ONLY PERIPHERALLY. AS SALMOIRAGHI ET AL. (1966) CONCLUDED, "THE MORPHOLOGICAL AND FUNCTIONAL COMPLEXITY OF CENTRAL SYNAPSES IS HARDLY AMENABLE TO BROAD GENERALIZATION."

3.) METHODOLOGICAL LIMITATIONS. FOR DEMONSTRATING THE ROLE OF A SUBSTANCE IN PERIPHERAL NEUROHUMOURAL TRANSMISSION, SEVERAL TECHNIQUES ARE CHARACTERISTICALLY EMPLOYED (KOELLE, 1965). THESE ARE: A.) RECOVERY OF THE SUBSTANCE FROM THE PERFUSATE OF AN INNERVATED STRUCTURE WHILE THE NERVE IS BEING STIMULATED (THE TECHNIQUE, IT WILL BE RECALLED, USED BY LOEWI), B.) IDENTIFICATION OF THE SUBSTANCE BY APPROPRIATE ANALYSES, C.) EVIDENCE THAT THE SUBSTANCE WILL PRODUCE THE SAME RESPONSE AS NERVE STIMULATION AND, D.) DEMONSTRATION THAT THE RESPONSE FOLLOWING EITHER NERVE

STIMULATION OR INJECTION OF THE SUBSTANCE IS MODIFIED IN THE SAME WAY BY VARIOUS DRUGS. THESE METHODS DO NOT NECESSARILY FOLLOW FOR CENTRAL TRANSMITTERS. ESPLIN PUTS THE MATTER SUCCINCTLY:

THE CRITERIA FOR PROOF THAT A SPECIFIC SUBSTANCE HAS A TRANSMITTER FUNCTION AT A PARTICULAR SYNAPSE WERE ELABORATED IN CONNECTION WITH INVESTIGATIONS OF PERIPHERAL SYNAPTIC TRANSMISSION.... THESE CRITERIA ARE NOT WHOLLY APPLICABLE TO THE CNS BECAUSE OF THE DIFFICULTY IN PERFUSING OR ACTIVATING A HOMOGENEOUS COLLECTION OF SYNAPSES. (1965, PP. 38-39).

AS ALREADY SUGGESTED, THESE LIMITATIONS HAVE BEEN SEVERE ENOUGH TO SERIOUSLY COMPROMISE PROGRESS IN DEFINING CENTRAL NEUROHUMOURAL TRANSMISSION. IN A RECENT SYMPOSIUM CONCERNING THE ROLE OF ACETYLCHOLINE IN THE CNS, KRNEVIC STATED:

IN SPITE OF MANY SUGGESTIONS OVER A PERIOD OF MORE THAN 30 YEARS THAT ACH IS LIKELY TO BE A CENTRAL SYNAPTIC TRANSMITTER - SOME OF THE EARLIEST SUGGESTIONS CAME FROM THE DISCOVERY OF THE ROLE OF ACH IN PERIPHERAL STRUCTURES - AND THE MARSHALLING OF A VAST AMOUNT OF DATA ON THE DISTRIBUTION OF ACH AND RELATED ENZYMES, AND ON CENTRAL ACTIONS OF ACH, THERE IS STILL NO CLEAR EVIDENCE THAT CHOLINERGIC NERVE FIBERS PLAY A MAJOR ROLE IN THE OPERATION OF THE CENTRAL NERVOUS SYSTEM. ONE CANNOT ASSUME INDEFINITELY THAT THE IDENTIFICATION OF CHOLINERGIC SYSTEMS IS IMPOSSIBLE OR VERY DIFFICULT FOR TECHNICAL REASONS (1969, P. 113).

IN EFFECT, ALL EVIDENCE ACCUMULATED TO DATE, IS INDIRECT. PERUSAL OF ANY OF A NUMBER OF RECENT REVIEWS MAKES THE POINT ABUNDANTLY CLEAR (E.G., SEE GERBRANDT, 1965; KRNEVIC, 1969; REEVES, 1966; SALMOIRAGHI, ET AL. 1966).

A WIDELY CITED EXCEPTION TO THESE LARGELY NEGATIVE CIRCUMSTANCES INVOLVES ECCLES (1957, 1964, 1969) CONTENTION THAT ACETYLCHOLINE IS THE TRANSMITTER SUBSTANCE BETWEEN THE RECURRENT

COLLATERALS OF MOTOR FIBRES AND THE RENSHAW CELLS. ECCLES ARGUES ON THE BASIS OF PARSIMONY IN THE FORM OF "DALE'S PRINCIPLE" (DALE, 1934) THAT A GIVEN NEURONE WILL HAVE THE SAME TRANSMITTER SUBSTANCE AT ALL ITS AXONIC TERMINATIONS. ECCLES HAS DEMONSTRATED THAT THE POSTSYNAPTIC IMPULSE IS PROLONGED AND INTENSIFIED BY ANTICHOLINESTERASES AND DEPRESSED BY SOME, BUT NOT ALL, CURARE-LIKE COMPOUNDS. SOME QUATERNARY AMMONIUMS ARE ALSO WITHOUT A DEPRESSING EFFECT.

DESPITE NEAR DOGMATIC ACCEPTANCE BY SOME TEXTBOOK AUTHORS (E.G., THOMPSON, 1967), IT IS OBVIOUS THAT THE VERIFICATION IS FAR FROM DEFINITIVE. WEIGHT (1967) EVEN DISPUTES THE EXISTENCE OF RENSHAW CELLS. INSTEAD OF PRESUMING A COMPLETELY SEPARATE NEURONE, HE SUGGESTS THAT THE RECURRENT INHIBITION ARISES FROM A COLLATERAL FIBRE OF THE MOTONEURONE, AND ACETYLCHOLINE LIBERATED AT THE COLLATERAL TERMINALS, INSTEAD OF IMMEDIATELY ACTING POSTSYNAPTICALLY, INITIALLY REMAINS PRESYNAPTIC THEREBY MAINTAINING A TERMINAL POTENTIAL WHICH ONLY SUBSEQUENTLY BECOMES POSTSYNAPTIC. THE FORMER APPEARS EXCITATORY AND NICOTINIC, THE LATTER INHIBITORY AND MUSCARINIC. IN EFFECT, THE TIMING OF THE ACTIVITY CAN BE ACCOUNTED FOR WITHOUT POSTULATING AN ADDITIONAL NEURONE. CURTIS AND DAVIS (1963) AND KRNEVIC AND PHILLIS (1963) HAVE POINTED OUT THAT MOST CENTRAL CHOLINOCEPTIVE SITES ARE MUSCARINIC WHILE THE MOTONEURONE RECURRENT COLLATERAL-RENSHAW CELL SYNAPSE APPEARS TO BE NICOTINIC. THE SIGNIFICANCE OF THIS IS EXPLAINED BY KRNEVIC:

THE DISCOVERY OF SPINAL ACH-SENSITIVE CELLS  
INNERVATED BY RECURRENT COLLATERALS OF MOTOR



FIBERS WAS A STRIKING CONFIRMATION OF THE EXISTENCE OF THE POSTULATED CENTRAL CHOLINERGIC MECHANISMS. IT SEEMED AS IF THIS MUST BE MERELY THE PRELUDE TO THE SYSTEMATIC DEMONSTRATION OF MANY OTHER CHOLINERGIC SYNAPSES. BUT THIS IMPRESSION WAS QUITE WRONG. AFTER A PROLONGED AND WIDESPREAD SEARCH THROUGHOUT ALL PARTS OF THE CNS FOR CELLS WHICH RESPOND TO ACh IT IS CLEAR THAT RENSHAW CELLS IN SEVERAL RESPECTS ARE QUITE UNTYPICAL OF CENTRAL CHOLINOCEPTIVE NEURONES. THEY DIFFER FROM ALL OTHER TYPES OF NEURONES BY THEIR CONSISTENTLY HIGH SENSITIVITY TO ACh, THE RAPID TIME COURSE OF THE EXCITATORY EFFECT AND THE PREDOMINANTLY NICOTINIC CHARACTER OF THEIR ACh RECEPTORS (1969, p. 113).

THUS, MANY IMPORTANT QUESTIONS REMAIN TO BE ANSWERED BEFORE THE RENSHAW ARC CAN BE ACCEPTED AS A POSITIVE EXAMPLE OF CENTRAL CHOLINERGIC NEUROHUMOURAL TRANSMISSION.

ANOTHER CONTENTION, ALSO WIDELY CITED, SUGGESTS THAT ACETYLCHOLINE PARTICIPATES IN THE GENERATION OF NERVE IMPULSES LEADING TO THE COCHLEAR MICROPHONIC (VINNIKOV & TITOVA, 1964). THE NOTION IS GIVEN EXPERIMENTAL CREDENCE ON THE BASIS OF FINDINGS THAT PHYSOSTIGMINE LENGTHENS THE LATENCY OF THE COCHLEAR POTENTIAL. OTHER INVESTIGATORS HAVE BEEN UNABLE TO VERIFY THIS FINDING (DAVIS, 1957, 1961), STILL OTHERS HAVE CORRELATED THE EFFECT WITH AMBIENT TEMPERATURE RATHER THAN DRUGS PER SE (GANNON, LASZLO & MOSCOVITCH, 1966). AGAIN, NUMEROUS POINTS NEED ADDITIONAL EMPHASIS BEFORE DEFINITIVE CONCLUSIONS CAN BE ESPOUSED.

A NUMBER OF SUBSTANCES OTHER THAN ACETYLCHOLINE HAVE BEEN PROPOSED AS POTENTIAL CENTRAL NEUROHUMOURAL TRANSMITTERS. SOME, SUCH AS ADENOSINE TRIPHOSPHATE (ATP), "SUBSTANCE P", EPINEPHRINE, HISTAMINE, HOMEOCYSTEIC ACID AND N-METHYL-D-ASPARTIC ACID ARE SAID

TO BE PRIMARILY EXCITATORY. OTHERS, SUCH AS "FACTOR I", GAMMA-AMINO-BUTYRIC ACID (GABA), AND 5-HYDROXYTRYPTAMINE (SEROTONIN) APPEAR TO INDUCE AN INHIBITORY ACTION (BUDAY, 1960; CURTIS, 1963; ECCLES, 1964).

## BEHAVIOURAL STUDIES OF CENTRAL NEUROHUMOURAL TRANSMISSION

### GENERAL ORIENTATION

FEW CONTEMPORARY INVESTIGATORS QUESTION THAT BEHAVIOUR IS REGULATED AND MEDIATED BY THE CENTRAL NERVOUS SYSTEM. FOR EXAMPLE, HILGARD AND BOWER UNRESERVEDLY STATE THAT:

NOTHING IS MORE CERTAIN THAN THAT OUR BEHAVIOR IS A PRODUCT OF OUR NERVOUS SYSTEM. THE PROPOSITION IS ALMOST MORE TAUTOLOGICAL THAN FACTUAL (1966, p. 425).

INDEED, ELABORATION OF THE RELATIONSHIP BETWEEN THE NERVOUS SYSTEM AND BEHAVIOUR IS THE RAISON D'ETRE OF PHYSIOLOGICAL PSYCHOLOGY (E.G., TEITELBAUM, 1967). RECOGNITION OF THE INTEGRATION OF THE "PHYSICAL AND THE PSYCHICAL", THE "ORGANIC AND THE MENTAL", OR THE "BODY AND THE MIND", AS IT IS VARIOUSLY CALLED, IS HISTORICALLY CREDITED TO BAIN (KANTOR, 1947). HOWEVER, PRECISE DEFINITION OF NERVOUS SYSTEM-BEHAVIOUR INTEGRATION WAS FORMULATED BY SHERRINGTON. HE SAID:

THERE REMAINS YET ANOTHER TYPE OF INTEGRATION WHICH CLAIMS CONSIDERATION... INTEGRATION HAS BEEN TRACED AT WORK IN TWO GREAT, AND IN SOME RESPECTS COUNTER-PART, SYSTEMS OF THE ORGANISM. THE PHYSIOCOCHEMICAL (OR FOR SHORT PHYSICAL) PRODUCED A UNIFIED MACHINE FROM WHAT WITHOUT IT WOULD BE MERELY A COLLOCATION OF COMMENSAL ORGANS. THE PSYCHICAL CREATES FROM PSYCHICAL DATA, A PERCIPIENT THINKING AND ENDEAVOURING MENTAL INDIVIDUAL. THOUGH OUR EXPOSITION KEPT THESE TWO SYSTEMS AND THEIR

INTEGRATIONS APART, THEY ARE LARGELY COMPLEMENTAL AND LIFE BRINGS THEM CO-OPERATIVELY TOGETHER AT INNUMERABLE POINTS (1906, PP. XV-XVI).

THEN, HE CONCLUDES THAT THE NERVOUS SYSTEM:

....WELDS IT TOGETHER FROM COMPONENTS AND CONSTITUTES AN ANIMAL INDIVIDUAL FROM A MERE COLLECTION OF ORGANS (1906, P. 234).

THE INTEGRATION PROPOSITION IN COMBINATION WITH THE SIMULTANEOUSLY EMERGING NOTION OF STRUCTURE-FUNCTION LOCALIZATION WITHIN THE NERVOUS SYSTEM (E.G., GALL & SPURZHEIM, 1809; JACKSON, 1873; SEE GRAY, 1948; MURPHY, 1948) HAS GIVEN RISE TO A BASIC METHODOLOGICAL PRESUMPTION THAT CNS STRUCTURE AND FUNCTION CAN BE ANALYZED BY OBSERVING BEHAVIOURAL CHANGES FOLLOWING THE CONTROLLED ALTERATION OF A SPECIFIC CNS SYSTEM. PAVLOV GAVE INITIAL EXPRESSION TO THE APPROACH. BY WAY OF INTRODUCING HIS ELABORATION OF CONDITIONED SALIVARY REFLEXES, HE STATED EMPHATICALLY THAT:

THE CEREBRAL HEMISPHERES STAND OUT AS THE CROWNING ACHIEVEMENT IN THE NERVOUS DEVELOPMENT OF THE ANIMAL KINGDOM. THESE STRUCTURES IN THE HIGHER ANIMALS ARE OF CONSIDERABLE DIMENSIONS AND EXCEEDINGLY COMPLEX, BEING MADE UP IN MAN OF MILLIONS UPON MILLIONS OF CELLS - CENTRES OR FOCI OF NERVOUS ACTIVITY - VARYING IN SIZE, SHAPE AND ARRANGEMENT, AND CONNECTED WITH EACH OTHER BY COUNTLESS BRANCHINGS FROM THEIR INDIVIDUAL PROCESSES. SUCH COMPLEXITY OF STRUCTURE NATURALLY SUGGESTS A LIKE COMPLEXITY OF FUNCTION WHICH IN FACT IS OBVIOUS IN THE HIGHER ANIMAL AND MAN...THE HIGHEST NERVOUS ACTIVITY IS DEPENDENT UPON THE STRUCTURAL AND FUNCTIONAL INTEGRITY OF THE CEREBRAL HEMISPHERES (1927, P. 1).

THE CONCEPT, STILL TODAY, REMAINS BASIC TO MOST CONCLUSIONS REGARDING BEHAVIOURAL FUNCTION THAT HAVE BEEN DRAWN FROM

SURGICAL AND/OR ELECTRICAL MANIPULATIONS OF THE BRAIN, AND, MORE RECENTLY (ALTMAN, 1966), IT HAS FOUND UTILITY IN THE INTERPRETATION OF CHEMICAL MANIPULATIONS SUCH AS DRUG ADMINISTRATION. HOWEVER, LOCALIZATION, IN THIS TRADITIONAL LIMITED SENSE, HAS BEEN CHALLENGED AS AN ADEQUATE FOUNDATION FOR FUNCTIONAL PRESUMPTIONS

LASHLEY STATED:

NEUROLOGICAL THEORY HAS BEEN DOMINATED BY THE BELIEF THAT THE NEURONS OF THE CENTRAL NERVOUS SYSTEM ARE... LINKED IN RELATIVELY ISOLATED CONDITIONED REFLEX ARCS AND THAT THEY ARE ACTIVATED ONLY WHEN THE PARTICULAR REACTIONS FOR WHICH THEY ARE SPECIFICALLY ASSOCIATED ARE CALLED OUT. SUCH A VIEW IS INCOMPATIBLE BOTH WITH THE WIDESPREAD EFFECTS OF STIMULATION...AND WITH RECENT EVIDENCE FROM ELECTRICAL RECORDING OF NERVOUS ACTIVITY... IT IS PROBABLY NOT FAR FROM THE TRUTH TO SAY THAT EVERY NERVE CELL OF THE CEREBRAL CORTEX IS INVOLVED IN THOUSANDS OF DIFFERENT REACTIONS (1951, PP. 135-136).

THUS, EFFORTS TO ASSIGN SPECIFIC BEHAVIOURAL ACTION TO DISCRETE NERVOUS SYSTEM STRUCTURES MUST BE CONSIDERED LIMITED AT BEST.

DESPITE THE DIFFICULTY INHERENT IN EMPLOYING SUCH A CONFINING ASSUMPTION AS A CONCEPTUAL FOUNDATION, ATTEMPTS HAVE BEEN MADE TO CORRELATE BEHAVIOUR WITH SPECIFIC CENTRAL NEUROHUMOURAL TRANSMITTERS. RUSSELL (1958) EVEN TALKS IN TERMS OF CORRELATING "BIOCHEMICAL LESIONS" WITH BEHAVIOURAL CHANGES. AS A SPECIFIC EXAMPLE, CONSIDER THE FOLLOWING STATEMENT FROM A RECENT REVIEW CONCERNING CENTRAL CHOLINERGIC TRANSMISSION-BEHAVIOUR RELATIONSHIPS:

.... THE AMOUNT AND DISTRIBUTION OF ACH IN THE BRAIN MAY BE BASIC FACTORS IN SOME PSYCHOLOGICAL PROCESSES, AND MAY BE AN IMPORTANT SOURCE OF INDIVIDUAL DIFFERENCES (REEVES, 1966, P. 321).

OR, THE MCGAUGH AND PETRONOVICH CONTENTION THAT:

....THE ACETYLCHOLINE-ACETYLCHOLINESTERASE SYSTEM IS CRITICALLY INVOLVED IN LEARNING AND MEMORY (1965, p. 159).

POPULAR UTILIZATION OF THE CONCEPT MAY DERIVE FROM THE FACT THAT IT PERMITS RELATIVELY SIMPLE EXPERIMENTAL DESIGNS. IT IS ONLY NECESSARY TO EMPLOY BEHAVIOUR AS THE DEPENDENT OR INDEPENDENT VARIABLE RELATIVE TO NEUROHUMOURAL LEVELS. THAT IS, ONE CAN PHARMACOLOGICALLY ALTER THE EXISTING HUMOURAL LEVEL (E.G., DOSING THE ORGANISM WITH AN ANTICHOLINERGIC DRUG) AND OBSERVE BEHAVIOURAL CHANGES (E.G., RESPONSE RATE), OR ONE CAN EFFECT CHANGES IN BEHAVIOUR (E.G., CONDITIONING) AND OBSERVE CHANGES IN HUMOURAL LEVELS (E.G., ACETYLCHOLINESTERASE BLOOD LEVELS). BOTH HAVE BEEN ACCOMPLISHED MANY TIMES, PARTICULARLY IN RESPECT TO ACETYLCHOLINE. THERE ARE ALSO METHODOLOGICAL DIFFICULTIES WITHIN THE VARIOUS EXPERIMENTS (E.G., THE FAILURE TO CLEARLY DISTINGUISH BETWEEN ACETYLCHOLINESTERASE AND BUTYROCHOLINESTERASE IN USING ESTERASE LEVELS AS AN INDICATION OF ACETYLCHOLINE LEVELS: BENNETT, DIAMOND, KRECH, AND ROSENZWEIG, 1964; RUSSELL, 1969), BUT THE CONCEPTUAL FALLACY DISCUSSED EARLIER IS PARAMOUNT TO THESE. THAT IS, THE ASSUMPTION OF A ONE TO ONE RELATIONSHIP BETWEEN ACETYLCHOLINE LEVELS AND SPECIFIC BEHAVIOURS WHICH IS, IN EFFECT SAYING THAT THE CHOLINERGIC SYSTEM IS THE "CENTRE" FOR A GIVEN BEHAVIOUR. EXPRESSED IN SUCH TERMS IT CAN BE SEEN THAT ANY CONCLUSIONS DERIVING FROM THESE EXPERIMENTS ARE NO MORE THAN A CONTEMPORARY RESTATEMENT OF THE OLDER LOCALIZATION CONCEPT IN

CHEMICAL TERMS. BIOCHEMICAL "LESIONS" OF METABOLIC CYCLES HAVE REPLACED ANATOMICAL LESIONS OF BRAIN PARTS AS THE STRUCTURAL CORRELATES OF BEHAVIOURAL FUNCTION.

IN A MORE SPECIFIC MANNER, PHARMACOLOGY HAS UTILIZED A SIMILAR FALLACIOUS APPROACH IN DEVELOPING THE NOTION OF "CENTRALLY ACTIVE ANTICHOLINERGIC AGENTS" (E.G., HOFFMEISTER, KREISKOTT & WIRTH, 1964). THESE COMPOUNDS, PRIMARILY THE MORE TYPICAL TROPIC ACID ESTERS (E.G., N-ALLYLNORATROPINE; SOYKA AND UNNA, 1964, 1965) AND THE LESS FAMILIAR GLYCOLIC ACID ESTERS (E.G., DITRAN, OR N-ETHYL-3PIPERIDYL-PHENYLCYCLOPENTYL GLYCOLATE; ABOOD & BIEL, 1962; DEVITO & FRANK, 1964), HAVE MOST OF THE PROPERTIES CHARACTERISTIC OF PERIPHERAL MUSCARINIC ANTICHOLINERGIC SUBSTANCES AS WELL AS MARKED, OFTEN DRAMATIC (E.G., PSYCHOTOMIMETIC) BEHAVIOURAL EFFECTS. FOLLOWING THE PREVIOUSLY DESCRIBED LOCALIZATION CONCEPT, IT IS PRESUMED THAT THE LATTER - THE BEHAVIOURAL EFFECTS - ARE DUE TO THE ACTION OF THE DRUG ON SPECIFIC CNS SITES. IT IS FURTHER PRESUMED THAT THE ACTION IS OF AN ANTICHOLINERGIC NATURE SINCE THE DRUGS HAVE SUCH AN EFFECT PERIPHERALLY. IN REGARD TO THE GLYCOLATES, ABOOD (1961) STRONGLY REJECTS SUCH A NOTION. TAKING RECOGNITION OF THE LACK OF ANY EVIDENCE TO INDICATE THAT NEUROHUMOURAL AMINES ARE CNS TRANSMITTERS, HE SUGGESTS THAT THE BEHAVIOURAL ACTIONS OF THE GLYCOLATES MAY RESULT FROM A DIRECT EFFECT AT THE RECEPTOR SITE, THUS ACETYLCHOLINE WOULD MERELY DEFINE THE CHEMICAL CONFIGURATION OF THOSE SITES.

THE REVERSE ARGUMENT IS LIKEWISE EMPLOYED. IT IS SAID,

FOR EXAMPLE, THAT METHYLATROPINE, BECAUSE IT DOES NOT PASS THE BLOOD BRAIN BARRIER, HAS NO CENTRAL EFFECT AND THUS DOES NOT AFFECT BEHAVIOUR. FOR EXAMPLE, MCGAUGH AND PETRONOVICH DISCUSSING THE EFFECTS OF ATROPINE AND SCOPOLAMINE ON LEARNING AND RETENTION CONCLUDE:

THE PERFORMANCE IMPAIRMENT FOUND WITH THESE ANTI-CHOLINERGICS IS MOST LIKELY DUE TO EFFECTS ON THE CENTRAL NERVOUS SYSTEM, FOR PERIPHERALLY ACTING QUATERNARY COMPOUNDS SUCH AS METHYLSCOPOLAMINE AND METHYLATROPINE HAVE NOT BEEN FOUND TO IMPAIR EITHER LEARNING OR PERFORMANCE (1965, P. 160).

THESE CONCLUSIONS, OF COURSE, ALSO EXCEED THE DATA SINCE THEY ARE, AGAIN, DEPENDENT ON ASSUMING THAT CENTRAL CHOLINERGIC TRANSMISSION IS AN ESTABLISHED FACT, AND THAT THAT TRANSMISSION HAS A SPECIFIC BEHAVIOURAL CORRELATE. IN ADDITION IT IS ALSO AGAIN PRESUMED THAT THE CENTRAL ACTION OF A DRUG IS, IN FACT, SIMILAR TO ITS PERIPHERAL EFFECTS. THE FALLACY OF THAT PRESUMPTION HAS RECENTLY BEEN ELABORATED BY KARCZMAR:

ONE OF THE DANGERS OF THIS SITUATION IS THAT [DRUGS] ACTIVATE HALF A DOZEN OR MORE MECHANISMS AND EXHIBIT AS MANY SITES OF ACTION...MANY...SITES AND MECHANISMS PERTINENT TO THE ACTIONS OF CHOLINERGIC DRUGS MAY BE ENUMERATED. THUS, A GIVEN EFFECT OF A CHOLINERGIC OR ANTICHOLINERGIC DRUG MAY LEAD TO WRONG CONCLUSIONS WITH REGARD TO THE CHOLINERGIC TRANSMISSION. THE ERROR MAY BE AS SERIOUS AS TO POSTULATE A CHOLINERGIC SYNAPSE WHERE THERE IS NONE (1969, PP. 147-148).

SIMPLY, THE LATTER ASSUMPTION, AS WITH THE FORMER ASSUMPTION, IS NOT CONVERSANT WITH FACT.

IT WOULD SEEM, THEN, THAT DRUG-BEHAVIOUR CORRELATION STUDIES HAVE NOT BEEN ANY MORE CONTRIBUTORY TO ESTABLISHING

CENTRAL NEUROHUMOURAL TRANSMISSION THAN HAVE BEEN THE MORE TRADITIONAL PHYSIOLOGICAL METHODS. THE REASONS FOR THE LACK OF DEFINITION APPEAR TO BE TWOFOLD: 1.) CONCEPTUAL FALLACY AND 2.) LACK OF PARAMETRIC SPECIFICATION. AS WEISS AND HELLER CONCLUDED AFTER A REVIEW OF BEHAVIOURAL STUDIES CONCERNED WITH CHOLINERGIC TRANSMISSION:

WE CANNOT AVOID THE FACT THAT THE PROBLEMS OF SECURING CONTROL OF THE FUNDAMENTAL PROCESSES OF BEHAVIOR AND ELIMINATING SPURIOUS VARIABLES ARE MUCH MORE FORMIDABLE THAN WE RECOGNIZE. WE ARE CONFRONTED WITH THE TOTAL NERVOUS SYSTEM, NOT AN ISOLATED COMPONENT. AND IT IS A SYSTEM, MOREOVER, WITH A HISTORY THAT PLAYS A MAJOR ROLE IN DETERMINING THE CONSEQUENCES OF ALTERING THE NORMAL PHYSIOCHEMICAL PROCESSES THAT SUSTAIN IT. THE ANATOMICAL COMPLEXITY OF THE BRAIN, ITS RELATIVE INACCESSIBILITY, AND THE PRESENCE OF A BLOOD-BRAIN BARRIER ADD TO THE COMPLEXITY OF THE PROBLEM. BUT THE OBSTACLES ARE NOT INSUPERABLE. SCALING THEM DEMANDS MAINLY THAT WE CONFRONT THE COMPLEXITIES AND PROBLEMS DIRECTLY, RATHER THAN FALLACIOUSLY ELIMINATING THEM BY PRETENDING THAT THEY DO NOT EXIST (1969, P. 145).

IN BEHAVIOURAL STUDIES ONE IS NOT ONLY CONFRONTED WITH THE, "...TOTAL NERVOUS SYSTEM", BUT WITH THE TOTAL ORGANISM IN ITS TOTAL ENVIRONMENT. NEVERTHELESS, THE CIRCUMSTANCES IMPLY THAT IF THE ABOVE ELABORATED DIFFICULTIES COULD BE OVERCOME, IT WOULD BE POSSIBLE TO BEHAVIOURALLY DEFINE THE ROLE OF ACETYLCHOLINE IN CNS FUNCTIONING.

THE ROLE OF ACETYLCHOLINE RELEVANT TO CNS ACTIVITY HAS BEEN ASSESSED IN NUMEROUS EXPERIMENTS. THE FIRST EXPERIMENT TO SPECIFICALLY ASSESS THE EFFECTS OF ACETYLCHOLINE ON BEHAVIOUR