THE ROLE OF ACETYLCHOLINE IN BEHAVIOUR SUPPRESSING MECHANISMS

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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.

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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 <u>CHEMICAL</u>, WHEREAS THAT IN AN ELECTRICALLY STIMULABLE MEMBRANE IS <u>ELECTRICAL</u> (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 (KOELLE, 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 NEUROHUMOURAL 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 DENDO-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 ACETYCHOLINE IN THE CNS, KRNJEVIC 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 <u>INDIRECT</u>. PERUSAL OF ANY OF A NUMBER OF RECENT REVIEWS MAKES THE POINT ABUNDANTLY CLEAR (E.G., SEE GERBRANDT, 1965; KRNJEVIC, 1969; REEVES, 1966; SALMOIRAGHI, <u>ET AL</u>. 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 ACETYCHOLINE 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 KRNJEVIC 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 KRNJEVIC:

> THE DISCOVERY OF SPINAL ACH-SENSITITIVE 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 COUNTERPART, 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 BUTYROCHOLIN-ESTERASE IN USING ESTERASE LEVELS AS AN INDICATION OF ACETYCHOLINE 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

(AND THEREBY PRESUMABLY IMPLICATING THE CNS) WAS REPORTED BY ESSIG, HAMPSON, MCCANLEY, AND HIMWICH IN 1950. LOWER DOSES OF DIISOPROPYLFLUOROPHOSPHATE (DFP, AN ANTICHOLINESTERASE AGENT), ADMINISTERED INTRACAROTIDLY, EFFECTED CONTRAVERSIVE CIRCLING (I.E., ROTATING CONTRARY TO THE INJECTED SIDE). HIGHER DOSES WERE CONVULSIVE. BOTH EFFECTS WERE ANTAGONIZABLE BY ATROPINE OR SCOPOLAMINE. SINCE ACETYLCHOLINESTERASE ACTIVITY WAS FOUND TO BE LOWER IN THE CAUDATE NUCLEUS AND CORTEX OF THE INJECTED SIDE FOLLOWING THE LOWER DOSES, IT WAS ASSUMED THAT THE RESULTANT INCREASED CHOLINERGIC ACTIVITY WAS INDUCING CONTRALATERAL MUSCLE CONTRACTIONS, HENCE CONTRAVERSIVE CIRCLING. WITH THE HIGHER, CONVULSION PRODUCING, DOSES ACETYLCHOLINESTERASE LEVELS WERE LOW IN BOTH BRAIN HEMISPHERES.

SIMILARLY, A NUMBER OF EXPERIMENTS HAVE BEEN REPORTED TO SHOW VARIATION IN ACETYLCHOLINESTERASE LEVELS AS A FUNCTION OF "ENRICHED EXPERIENCE" (THE STUDIES ARE REVIEWED BY BENNETT, ET AL. 1964). RATS MAINTAINED IN LARGE GROUP CAGES, HAVING MANY NOVEL MANIPULABLE OBJECTS AVAILABLE, AND SUBJECTED TO FREQUENT MAZE TRAINING WERE REPORTED TO HAVE A GREATER SUBCORTICAL ACETYL-CHOLINESTERASE CONTENT THAN RATS MAINTAINED UNDER LESS "FAVOURABLE" CIRCUMSTANCES. MEMBERS OF THE "ENRICHED" GROUP ALSO HAD HIGHER TOTAL BRAIN WEIGHTS WHICH COULD ACCOUNT FOR THE HIGHER ENZYME LEVELS. IN FACT, IN RELATION TO TOTAL BRAIN WEIGHT, THE "ENRICHED" SUBJECTS HAD LOWER ACETYLCHOLINESTERASE LEVELS. AGAIN, THE IMPLICATION DRAWN WAS THAT CHOLINERGIC ACTIVITY IN THE CNS IS

ASSOCIATED WITH BEHAVIOURAL VARIATIONS AND WITH EXPOSURE TO PARTICULAR KINDS OF STIMULI.

IT SHOULD BE POINTED OUT HERE THAT STUDIES, SUCH AS THOSE JUST DISCUSSED, WHICH INVOLVE ACETYLCHOLINESTERASE TITRATIONS ASSUME THAT THE MEASURE IS AN ACCURATE REFLECTION OF ACETYLCHOLINE CONCENTRATIONS. TOWER (1958), AMONG OTHERS, HAS EMPHASIZED THE QUESTIONABLE CHARACTER OF SUCH AN ASSUMPTION. FIRST, ACETYLCHOLINESTERASE IS USUALLY PRESENT IN THE CNS AT CONCENTRATIONS FAR GREATER THAN THE MINIMAL AMOUNT NECESSARY FOR THE HYDROLYSIS OF ACETYLCHOLINE, I.E., THERE IS NO STRICT QUANTITATIVE RELATIONSHIP BETWEEN THE TWO SUBSTANCES. SECONDLY, THE ACETYLCHOLINESTERASE ASSAYS EMPLOYED IN SUCH STUDIES GENERALLY INDICATE TOTAL CHOLINESTERASE; I.E., THERE IS NO DISTINCTION BETWEEN ACETYLCHOLINESTERASE, AND NON-NEURAL BUTYROCHOLINESTERASE. THUS, SUCH STUDIES ARE NOT ONLY INCONSISTENT BUT BASED ON UNTENABLE BIOCHEMICAL ASSUMPTIONS.

IN REGARD TO EXPERIMENTALLY CONDITIONED BEHAVIOUR, THE FINDINGS ALMOST UNIVERSALLY SUGGEST THAT ACETYLCHOLINE IS IMPORTANT TO THE ACQUISITION OF RESPONSES (I.E., LEARNING). MOST TYPICALLY, THE EVIDENCE DERIVES FROM THE EFFECT OF ANTICHOLINERGIC DRUGS WHICH CHARACTERISTICALLY IMPAIR ACQUISITION AND/OR ESTABLISHED BEHAVIOUR (E.G., BIGNAMI, 1964; BOREN AND NAVARRO, 1959; BROWN, 1967; BUROSOVA, BOHDANECKY & WEISS, 1964; CARLTON, 1961, 1962, 1963, 1966A; CARLTON & DIDAMO, 1961; CHALMERS & ERICKSON, 1964; DOUGLAS & ISSACSON, 1966; GERBRANDT, 1965; GLOW,

Richardson & Rose, 1967; Hamilton & Grossman, 1969; Hearst, 1959, 1964; Herrnstein, 1958; Herz, 1959, 1960; Holten & Sonne, 1955; Innis & Staddon, 1969; Jung & Boyd, 1966; Leaf & Muller, 1966; Leaton, 1968a,b, 1969; Meyers & Domino, 1964; Myers, Roberts, Riciputi & Domino, 1964; McGaugh & Petronovich, 1965; Sepinwall, 1969; Squire, 1969; Stratton & Petronovich, 1963; Tapp, 1965; Warburton, 1969; Whitehouse, 1964).[1]

Acquisition is a term commonly employed to describe the process by which an organism comes to perform adaptive, positive, directed actions upon the environment with increasing efficiency as a function of previous experience. The action may, of course, be overt (e.g., motor activity) or covert (e.g., thinking, problem solving). In effect, the term can be considered synonymous with conditioning or learning. Many behavioural adaptations, however, involve the active restraint or suppression of any positive manipulation of the environment (e.g., "stand still!", "be quiet!", "stop thinking such things!", "ignore it!"). These behaviours, which are also acquired (or learned, or conditioned) through experience, are subsumed under a different set of terminology. Depending on the operations involved in their establishment, they are variously referred to as extinction, inhibition, passive avoidance, or habituation. Their presence in an organism's

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[1] The single exception noted in the present review was Dews (1958) report that scopolamine did not affect the acquisition or retention of a reversal problem in pigeons.

BEHAVIOURAL REPERTOIRE SEEMS TO FOLLOW SPECIFIC LAWS OF CONDITIONING (DEESE, 1958). HOWEVER, THEY ALL INVOLVE A CERTAIN TYPE OF LEARNING - LEARNING TO NOT PERFORM SOME ACT WITHIN A GIVEN SET OF CIRCUMSTANCES (BROWN, 1966B; 1967; CARLTON, 1963; HEARST, 1968; RESCORLA, 1969). CONSIDERED FROM THIS POINT OF VIEW, IT WOULD FOLLOW THAT ANTICHOLINERGIC AGENTS MIGHT ALSO RETARD "LEARNING TO SUPPRESS ACTION", AND INDEED THE PREPONDERANCE OF EXPERIMENTAL EVIDENCE, INCLUDING MANY OF THE EXEMPLIFYING REFERENCES CITED ABOVE, SUGGEST THAT SUCH IS THE CASE.

THE ROLE OF NEUROHUMOURAL TRANSMISSION IN BEHAVIOURAL HABITUATION

OF THESE JUST DISCUSSED ACTIVE-SUPPRESSION BEHAVIOURS, THE ONE CALLED HABITUATION IS OF PARTICULAR INTEREST IN REGARD TO NEUROHUMOURAL TRANSMISSION - PARTICULARLY CHOLINERGIC. THORPE HAS DEFINED BEHAVIOURAL HABITUATION AS:

> ....LEARNING TO NOT RESPOND TO STIMULI WHICH TEND TO BE WITHOUT SIGNIFICANCE IN THE LIFE OF THE ANIMAL (1956, P. 27).

GROSSMAN (1967) ATTRIBUTES THE FIRST OBSERVATIONS OF BEHAVIOURAL HABITUATION TO PAVLOV'S (1927) DISCUSSION OF THE "ORIENTING REFLEX". THE PHENOMENUM WAS, HOWEVER, REPORTED AS EARLY AS 1887 BY PECKHAM AND PECKHAM WHO NOTICED IT IN RELATION TO SPIDERS RESPONDING TO SOUNDS FROM A TUNING FORK. DEFINITIVE DESCRIPTION AND PARAMETRIC SPECIFICATION OF HABITUATION WAS ACCOMPLISHED BY HUMPHREY (1933) USING SNAILS AS EXPERIMENTAL SUBJECTS.

IT IS SIGNIFICANT TO NOTICE THAT THE DEFINITION OF THE

TERM RECOGNIZES HABITUATION AS AN ACQUISITION PROCESS, NOT JUST PASSIVE ADAPTATION OR FATIGUE. GROSSMAN MAKES THE DISTINCTION PHYSIOLOGICALLY:

> HABITUATION...DOES NOT REPRESENT A BREAKDOWN OF RECEPTOR OR TRANSMITTER FUNCTION. RATHER THE SENSORY MECHANISMS SEEM TO BE ACTIVELY INHIBITED BY SOME CENTRAL PROCESS WHICH IS ITSELF SUBJECT TO EXTINCTION OR 'DISINHIBITION'. THE ORGANISM APPEARS TO LEARN NOT TO RESPOND OR NOT TO TRANSMIT SENSORY INFORMATION WHICH HAS BEEN WITHOUT SIGNIFICANCE OR CONSEQUENCE IN THE PAST... HABITUATION MAY REPRESENT A SIMPLE LEARNING PROCESS...(1967, P. 641).

DEESE MAKES THE SAME DISTINCTION, BUT IN TERMS OF CONDITIONING VARIABLES:

> IF THE INTENSITY OF THE STIMULUS IS INCREASED, THE RESPONSE WILL REAPPEAR, ONLY TO DISAPPEAR WITH FURTHER REPETITIONS. A PERIOD OF REST WILL ALLOW THE RESPONSE TO RECOVER SPONTANEOUSLY, BUT AS IN THE CASE OF THE SPONTANEOUS RECOVERY OF EXTINCTION, REPEATED EXPERIMENTAL SESSIONS WILL FINALLY CAUSE THE BEHAVIOUR TO DISAPPEAR MORE OR LESS PERMANENTLY. THIS LAST POINT IS ESPECIALLY IMPORTANT BECAUSE IT IS THIS WHICH DIFFERENTIATES HABITUATION FROM SIMPLE FATIGUE. (1958, P. 318).

AN ATTEMPT TO CONCEPTUALIZE A RELATIONSHIP BETWEEN HABITUATION AND CENTRAL CHOLINERGIC TRANSMISSION HAS BEEN PUT FORTH BY CARLTON (1966B, 1968). BRIEFLY, HIS EXPERIMENTAL EVALUATION (DESCRIBED IN DETAIL IN THE NEXT CHAPTER) INVOLVED MEASURING THE LENGTH OF TIME A RAT EMPLOYED IN APPROACHING A DRINKING TUBE AS A FUNCTION OF PREVIOUS (72 HOURS) EXPOSURE (HABITUATION) OR NON-EXPOSURE TO THE CHAMBER IN WHICH THE TUBE WAS CONTAINED. THE ANIMALS WERE DEPRIVED OF WATER 24 HOURS BEFORE

TESTING. ANTICHOLINERGIC DRUGS ADMINISTERED JUST PRIOR TO THE INITIAL EXPOSURE ATTENUATED THE SUBSEQUENT RAPID APPROACH TO THE TUBE CHARACTERISTIC OF UNTREATED ANIMALS DURING THE SECOND EXPOSURE. NON-EXPOSED SUBJECTS, COULD NOT BE DISTINGUISHED (DRUG-TREATED FROM UNTREATED) ON THE BASIS OF APPROACH LATENCY. IT WAS CONCLUDED THEREFROM THAT ANTICHOLINERGIC DRUGS DISRUPT HABITUATION.

THE RELATIONSHIP IS SUGGESTED AS FOLLOWING FROM CARLTON'S EARLIER (1963) CONTENTION THAT A CENTRAL CHOLINERGIC SYSTEM EXISTS WHICH ANTAGONIZES A SECOND SYSTEM THAT FUNCTIONS TO ACTIVATE BEHAVIOUR. CARLTON OFFERS SEVERAL LINES OF EXPERIMENTAL EVIDENCE IN SUPPORT OF HIS HYPOTHESIS. HE REASONED THAT, IF THE NOTION WERE CORRECT, INCREASED ACTIVATION AND DECREASED CHOLINERGIC ACTIVITY SHOULD PRODUCE QUALITATIVELY SIMILAR EFFECTS. INDEED, HE HAD EARLIER FOUND (CARLTON AND DIDAMO, 1961) THAT ATROPINE OR SCOPOLAMINE WAS SYNERGISTIC WITH THE EFFECT OF AMPHETAMINE IN REGARD TO INCREASING RESPONSE RATES IN A CONTINUOUS AVOIDANCE PROCEDURE (IT IS ASSUMED BY CARLTON THAT THE ACTIVATING SYSTEM IS ADRENERGIC). FURTHER, CARLTON CITES SIDMAN'S (1953) FINDING THAT ATROPINE DISRUPTED CONTINUOUS AVOIDANCE RESPONDING; I.E., IT PRODUCES EXCESSIVE PRE-APPROPRIATE RESPONDING, A "LOSS OF INHIBITION". HE ALSO DESCRIBED THE NUMEROUS FINDINGS (E.G., BRADY, 1959; HEARST, 1959; HERRNSTEIN, 1958) THAT RESPONDING DURING EXTINCTION IS PROLONGED FOLLOWING TREATMENT WITH SCOPOLAMINE, AND BOREN AND NAVARRO'S (1959) REPORT THAT

SCOPOLAMINE FACILITATES ACQUISITION (PRESUMABLY BY INHIBITING NON-SIGNIFICANT RESPONDING). ON THE BASIS OF SUCH FINDINGS CARLTON CONCLUDED:

> THUS, LEVEL OF ACTIVATION COULD BE VIEWED AS CONTROLLING THE TENDENCY FOR ALL RESPONSES TO OCCUR WHEREAS AN INHIBITORY CHOLINERGIC SYSTEM WOULD ACT TO ANTAGONIZE THIS ACTION ON NON-REINFORCED RESPONSES. THE NET RESULT OF THIS INTERACTION WOULD BE THAT CHANGES IN ACTIVATION WOULD RESULT IN CHANGES IN THE LIKELIHOOD OF OCCURRENCE OF ONLY A FEW RESPONSES, THOSE THAT WERE REINFORCED (1963, P. 27).

THE EXPERIMENTAL EVIDENCE IS CONSISTENT IN SUPPORT OF THE HYPOTHESIS, BUT THE CONCEPTUAL ASPECTS ARE LACKING IN SEVERAL INSTANCES.

IT IS POSSIBLE (AS WAS DISCUSSED IN DETAIL ABOVE) THAT THE BEHAVIOUR DESIGNATED AS HABITUATION CAN BE CONSIDERED AS ONE TYPE OF "SUPPRESSING ACTION" BEHAVIOUR SIMILAR TO EXTINCTION, INHIBITION, ETC. IN FACT THE POINT IS ESSENTIALLY WHAT LED CARLTON TO A CONSIDERATION OF THE RELATION BETWEEN HABITUATION AND CHOLINERGIC TRANSMISSION. YET, AFTER DOING SO, CARLTON THEN TRIES TO LIMIT HIS DEFINITION OF HABITUATION. FOR EXAMPLE, IN COMPARING HABITUATION AND A TYPE OF EXTINCTION, HE SAYS:

> ....THERE SEEMS TO BE A RATHER THIN LINE BETWEEN HABITUATION AND 'EXTINCTION OF FEAR'. IN BOTH CASES AN ANIMAL COMES TO A NEW SITUATION WITH A SET OF RESPONSES TO STIMULI. AS A CONSEQUENCE OF EXPOSURE TO THESE STIMULI, THE INITIAL RESPONSES DISAPPEAR. A DISTINCTION CAN, HOWEVER, BE MADE.
>
> A RAT MAY DO ONE OF TWO ANTAGONISTIC THINGS IN A NOVEL ENVIRONMENT. HE MAY SUPPRESS BEHAVIOR (BECAUSE OF FEAR) OR HE MAY MOVE ABOUT THE ENVIRONMENT AND THEREBY EXPLORE IT. AS A

> CONSEQUENCE OF THIS EXPLORATION, THE ANIMAL FINDS THAT SOME STIMULI ARE NEITHER BIOLOGICALLY SIGNIFICANT THEMSELVES NOR CORRELATED WITH OTHERS HAVING SUCH SIGNIFICANCE. THESE STIMULI THUS LOSE THEIR INITIAL CONTROL OF BEHAVIOR, THE ANIMAL NO LONGER EXPLORES THEM. IT IS IN THIS SENSE, RATHER THAN ONE HAVING TO DO WITH SUPPRESSION DUE TO FEAR THAT I HAVE USED THE TERM HABITUATION (1968, P. 14).

BOTH "EXTINCTION OF FEAR" AND HABITUATION AS DEFINED BY CARLTON DO, IN FACT, INVOLVE ACTIVE SUPPRESSION THUS, TOPOGRAPHICALLY, THEY ARE NOT MUTUALLY EXCLUSIVE TYPES OF BEHAVIOUR. FEAR-INDUCED SUPPRESSION OF BEHAVIOUR ("FREEZING") HAS BEEN ATTENUATED BY ATROPINE IN A CAR SITUATION (PFEIFFER AND JENNY, 1957). THUS, THE "NON-BIOLOGICALLY SIGNIFICANT STIMULI" DO NOT LOSE THEIR, "CONTROL OF BEHAVIOR", THEY SIMPLY SHIFT TO CONTROLLING THE BEHAVIOUR OF NOT ATTENDING WHICH IS MOTORICALLY EXPRESSED AS ACTIVITY OR INACTIVITY AS THE CASE MAY BE. BEHAVIOUR BEING A DYNAMIC PROCESS CHARACTERISTICALLY DOES NOT OCCUR IN VACUO (I.E., IT ALWAYS HAS DETERMINANTS; EVEN THE ETHOLOGICAL CONCEPT OF "VACUUM ACTIVITY" IS NOT SO CONCEIVED; LORENZ, 1967). CONSEQUENTLY, THE DISTINCTION BETWEEN NOT RESPONDING DUE TO FEAR OR DUE TO HABITUATION IS NOT NECESSARY EXCEPT POSSIBLY FOR OPERATIONAL SPECIFICATION.

CARLTON (1968) DEFINES "BIOLOGICAL SIGNIFICANCE" IN THE DARWINIAN SENSE OF THE TERM (GIVEN NEUROPHYSIOLOGICAL RELEVANCE BY MCLEAN, 1958); I.E., A STIMULUS HAS BIOLOGICAL SIGNIFICANCE IF IT FUNCTIONS IN EITHER SELF OR SPECIES PRESERVATION. THEREFORE, IT WOULD ONCE AGAIN FOLLOW THAT HABITUATED STIMULI DO NOT LOSE CONTROL OVER BEHAVIOUR ONCE THEY ARE DETERMINED TO HAVE NO

"BIOLOGICAL SIGNIFICANCE", BUT RATHER THAT THE ORGANISM'S TOTAL ENVIRONMENT ALWAYS HAS "BIOLOGICAL SIGNIFICANCE", AND THAT "NOT RESPONDING" IN RELATION TO SOME OF THE STIMULI THEREIN FACILITATES HOMEOSTATIC CONSERVATION AND IS MORE EFFICIENT IN GENERAL. SO, AGAIN, THE ORGANISM ACTIVELY DOES NOT ATTEND TO CERTAIN STIMULI, THUS THOSE STIMULI DO CONTROL ITS BEHAVIOUR.

FURTHER EVIDENCE TO SUPPORT THE ACTIVE SUPPRESSION INTERPRETATION COMES FROM NEUROPHYSIOLOGICAL CORRELATIONS (THOMPSON AND SPENCER, 1966). IT SEEMS RATHER WELL ESTABLISHED THAT THE CNS EXERTS CONSIDERABLE CONTROL OVER ITS SENSORY INPUT PATHWAYS (GROSSMAN, 1967; HERNANDEZ-PEON, 1961; HERNANDEZ-PEON & BRUST-CARMONA, 1961; KIMBLE, 1965). A RECEPTOR INPUT IS SUBJECT TO ENHANCING OR INHIBITING INFLUENCES AT SEVERAL POINTS ALONG THE SENSORY PATHWAY, ALTHOUGH INHIBITION SEEMS TO BE THE MOST CHARACTERISTIC ACTION [TRADITIONALLY THE RETICULAR FORMATION WAS CONSIDERED THE PRIMARY SOURCE OF SUCH MODIFYING IMPULSES (LIVINGSTON, 1959); HOWEVER, RECENT EVIDENCE SUGGESTS THAT SEVERAL OTHER PROJECTION SYSTEMS ARE EQUALLY INVOLVED (MESCHERSKY & ROZENSCHTEIN, 1969)]. THE FUNCTIONING OF THIS SYSTEM IS ELECTROPHYSIOLOGICALLY CORRELATED TO BOTH THE TEMPORAL AND SPATIAL COURSE OF BEHAVIOURAL RESTRAINT. FOR EXAMPLE, AT VARIOUS POINTS ALONG THE SENSORY PATHWAY, NEURAL ACTIVITY CAN BE OBSERVED UNDERGOING VARIOUS DEGREES OF MODIFICATION IN ACCORDANCE WITH SIMULTANEOUSLY OCCURRING BEHAVIOURAL HABITUATION (GROSSMAN, 1967). THE PROCESS, BOTH NEURALLY AND BEHAVIOURALLY, CAN BE TEMPORARILY

REVERSED BY DISTRACTION (SUCH AS FOOTSHOCK OR STIMULATION OF THE RETICULAR FORMATION), AND MOST EVIDENCE SUGGESTS THAT HABITUATION, AND ITS CORRESPONDING NEURAL ACTIVITY, IS TOTALLY LOST IF THE HABITUATED STIMULI ARE SUBSEQUENTLY UTILIZED IN CONDITIONING (GRANT, HAKE, RIOPELLE & KOSTLAN, 1951; GRANT, HAKE & SCHNEIDER, 1948; SUBOSKI, DILOLLO & GORMEZANO, 1964). CONSEQUENTLY, CESSATION OF RESPONDING IS CORRELATED WITH ONGOING NEURAL ACTIVITY (INHIBITION) WHICH IN NO WAY APPEARS VACUOUS (I.E., IT IS NOT A LACK OR ABSENCE OF ACTIVITY). "NOT RESPONDING" - INCLUDING HABITUATION - THEN, HAS AN ACTIVE NEURAL SUBSTRATE. HOWEVER, IT IS STILL NOT CLEAR WHETHER THE INHIBITORY ACTION IS EXPRESSED AFFERENTLY OR EFFERENTLY.

FINALLY, THE WELL-ESTABLISHED BIPHASIC ACTION OF SEVERAL NEUROHUMOURAL TRANSMITTERS, INCLUDING ACETYLCHOLINE, MAKE THE POSTULATION OF TWO NEUROTRANSMITTER SYSTEMS INTERACTING TO REGULATE ACTIVATION NON-PARSIMONIOUS. DIFFERENT CONCENTRATIONS OF THE SAME NEUROHORMONE CAN, UNDER RELEVANT CONDITIONS, FUNCTION AS EITHER AN INHIBITOR OR A FACILITATOR (E.G., THE MUSCARINIC AND NICOTINIC ACTIONS OF ACETYLCHOLINE, BURN, 1963), THUS THE POSTULATED BEHAVIOURAL-NEUROHUMOURAL INTERACTION COULD BE COMPLETELY CHARACTERIZED BY THE DIFFERENTIAL ACTION OF ONLY ONE SYSTEM (E.G., CHOLINERGIC). THE BEHAVIOURAL CHANGES FOLLOWING DOSAGE WITH MUSCARINIC ANTICHOLINERGICS, FOR EXAMPLE, COULD CONCEIVABLY BE DUE TO A NICOTINIC ACTION (BOVET-NITTI, 1966).

WITH INCORPORATION OF THE ABOVE DISCUSSED CONSIDERATIONS,

CARLTON'S (1963) HYPOTHESIS AND HABITUATION MEASURE (1968) OFFERS A PLAUSIBLE BASIS FOR ASSESSING THE VALIDITY OF BEHAVIOURAL APPROACHES TO DEFINING THE ROLE OF ACETYLCHOLINE IN CNS FUNCTIONING, AND CONVERSELY, THE ROLE OF ACETYLCHOLINE IN BEHAVIOURAL PROCESSES. THESE MODIFICATIONS RENDER THE CONCEPT ESSENTIALLY INDEPENDENT OF ANY LOCALIZATION FALLACY. HABITUATION BECOMES MERELY REPRESENTATIVE (I.E., THE BEHAVIOUR CHOSEN FOR MEASUREMENT) OF ONE SIDE OF THE DICHOTOMY OF TOTAL POSSIBLE BEHAVIOUR (I.E., BEHAVING ACTIVELY OR SUPPRESSING ACTION). IT CAN THEN BE POSTULATED THAT THE LEVELS OF ACTIVATION ENCOMPASSED BY THIS RANGE MAY VARY IN A SYSTEMATIC AND PREDICTABLE WAY WITH CHANGES IN THE TOTAL LEVEL OF CHOLINERGIC ACTIVITY. KEEPING WITH THE NEUROLOGICAL ANALOGY, A BIOCHEMICAL "MASS ACTION" CONCEPT (LASHLEY, 1947) HAS THUS BEEN INTRODUCED.

CLARIFYING THE NOTION EXPERIMENTALLY REQUIRES A NUMBER OF PARAMETRIC SPECIFICATIONS WHICH, CONSIDERED AS A TOTALITY, SHOULD REVEAL THE NATURE OF THE RELATIONSHIP. THE PARAMETRIC VARIATIONS THAT REQUIRE SUCH ELABORATION CAN BE SUBSUMED WITHIN FOUR GENERAL CLASSES: 1.) PHARMACOLOGICAL, 2.) MOTIVATIONAL, 3.) STIMULUS VARIABLES AND 4.) RESPONSE CHARACTERISTICS. IN HIS STUDIES, CARLTON (1968) PRESENTS EXPERIMENTAL ASSESSMENTS OR EXPLANATORY ELABORATIONS OF A FEW RELEVANT POINTS, BUT MOST MAJOR ISSUES ARE LEFT UNRESOLVED.

IN REGARD TO PHARMACOLOGICAL CONSIDERATIONS, CARLTON (1968) WAS FIRST CONCERNED WITH WHETHER THE EFFECT SIMPLY REFLECTED SOME

IDIOSYNCRATIC CENTRAL OR PERIPHERAL ACTION OF SCOPOLAMINE; HE CONCLUDED IT DOESN'T BECAUSE ATROPINE HAS THE SAME EFFECT. THE NON-EFFECTIVENESS OF METHYLSCOPOLAMINE WAS OFFERED AS SUFFICIENT VERIFICATION THAT THE EFFECT OF THE NON-METHYLATED CONGENERS WAS SPECIFICALLY CENTRAL. THE LACK OF EFFECT OF SODIUM PENTOBARBITAL AND AMPHETAMINE WAS CONSIDERED ADEQUATE VERIFICATION THAT THE INCREASED APPROACH LATENCY WAS UNIQUE TO THE ANTICHOLINERGIC DRUGS EMPLOYED. THESE ISSUES ARE OBVIOUS AND BASIC, BUT CARLTON'S ATTEMPTED RESOLUTION IS FAR FROM ADEQUATE FOR AN UNCOMPROMISED CONCLUSION THAT ATTENUATION OF HABITUATION IS DUE TO ATTENUATION OF A CENTRAL CHOLINERGIC MECHANISM. PRIMARY TO ESTABLISHING THAT A DRUG EFFECT (OF ANY KIND) IS IN FACT DUE TO PHARMACOLOGICAL ACTIONS OF A NON-ARTIFACTUAL NATURE INVOLVES THE GENERATION OF A DOSE-EFFECT CURVE. BECAUSE OF THEIR NOTORIOUS BIPHASIC ACTIONS (GOTH, 1968), THIS IS EXTREMELY IMPORTANT IN REGARD TO THE EFFECTS OF CHOLINERGIC AGENTS. FOR EXAMPLE, MERRILL (1969) FOUND THAT LOW AND HIGH DOSES OF ESERINE IMPAIRED PLACE LEARNING BY MICE WHILE INTERMEDIATE DOSES HAD NO EFFECT. IN THEIR RECENT DISCUSSION OF THE PROBLEMS INVOLVED IN ASSESSING CHOLINERGIC-BEHAVIOURAL RELATIONSHIPS, WEISS AND HELLER EMPHASIZE THE POINT MOST STRONGLY:

> THE EVALUATION OF DOSE-RESPONSE FUNCTIONS IS INDISPENSABLE IN STUDIES OF DRUG-BEHAVIOR INTERACTIONS. ALMOST EVERY PHARMACOLOGICAL ACTION MUST BE DEALT WITH IN SUCH TERMS, OF COURSE. BUT IT IS MORE THAN A CLICHE. IN STUDIES AIMED AT BEHAVIORAL MECHANISMS, THERE ARE BOUND TO BE COMPLEX DOSE-BEHAVIOR FUNCTIONS THAT, MOREOVER, CHANGE IN CHARACTER WITH THE BEHAVIORAL PARAMETERS. IT IS ALWAYS A GREAT TEMPTATION TO AVOID THE TEDIOUS SAMPLING OF A WIDE RANGE OF DOSE LEVELS....UNFORTUNATELY, THERE ARE

> SIMPLY NO SHORTCUTS. PICKING JUST ONE TREATMENT LEVEL, ESPECIALLY FROM A NON-MONOTONIC FUNCTION, CAN EASILY MISLEAD THE INVESTIGATOR, BECAUSE HIS INTERPRETATION DEPENDS UPON THE POINT ON THE FUNCTION HE HAPPENS TO CHOOSE (1969, P. 135).

THUS, ALL OF CARLTON'S (1968) CONCLUSIONS ARE SERIOUSLY COMPROMISED BY A DEFICIENCY IN REGARD TO THE FUNDAMENTAL POINT THAT HE OFFERS NO DOSE-EFFECT DATA. ANY CONTENTIONS THAT DEVELOP FROM HIS STUDIES MUST BE CONSIDERED IN THIS PERSPECTIVE. CONVERSELY, STABLE MONOTONIC DOSE-EFFECT RELATIONSHIPS (OR THEIR LACK) BETWEEN HABITUATION AND TREATMENT WITH THE VARIOUS DRUGS WOULD GREATLY SUBSTANTIATE CLAIMS RELEVANT TO SPECIFICITY OF ACTION.

EVEN DOSE-EFFECT CURVES ARE NOT SUFFICIENT EVIDENCE OF A FUNCTIONAL RELATIONSHIP BETWEEN DRUG ACTION AND CHANGES IN AN ORGANISM'S STATE (E.G., IN THE INSTANCE OF COMPETITIVE ANTAGONISM, HALASZ, FORMANEK, & MARRAZZI, 1969). ADDITIONAL VERIFICATION CAN BE OBTAINED FROM AN ASSESSMENT OF ANTAGONISM RELATIONSHIPS (BOUTHILIT, 1961; BROWN, 1963, 1966A; DAVIS, 1965; HEISE & BOFF, 1962; JENNY & HEALY, 1959). INSTEAD, CARLTON (1968) UTILIZES THE CONTENTION THAT ANTAGONISTS SHOULD HAVE DIAMETRICALLY OPPOSITE EFFECTS ON THE BEHAVIOUR, BEING MEASURED (I.E., IF ANTICHOLINERGIC DRUGS DISRUPT A BEHAVIOUR, PARASYMPATHOMIMETIC AGENTS SHOULD FACILITATE THAT BEHAVIOUR). THE HABITUATION TECHNIQUE OBVIOUSLY DOES NOT LEND ITSELF TO AN ANALYSIS OF THIS TYPE, THEREFORE CARLTON OFFERS RELATED, BUT CIRCUMSTANTIAL, DATA AS SUPPORT. SPECIFICALLY HE USED WHITEHORSE'S (1959) REPORT THAT PRE-TREATMENT WITH ATROPINE RETARDS DISCRIMINATION LEARNING WHILE ESERINE

FACILITATES IT, AND A FINDING BY RUSSELL (1958) THAT AN ANTI-CHOLINESTERASE AGENT FACILITATES LEARNING. AS POINTED OUT EARLIER, HOWEVER, MERRILL (1969) FOUND THAT ESERINE IMPAIRS LEARNING. IN ANY INSTANCE, CARLTON'S MEASUREMENT OF HABITUATION DOES ALLOW A DIRECT ASSESSMENT OF ANTAGONISTIC INTERACTIONS. IN ADDITION SUCH AN APPROACH WOULD BE ESPECIALLY APPROPRIATE TO MUSCARINIC ANTI-CHOLINERGIC AGENTS SINCE IT HAS BEEN LONG ESTABLISHED (FRAZIER, 1870) THAT THEY ARE VERY SPECIFIC IN THEIR ANTAGONISM RELATION-SHIPS (INNES & NICKERSON, 1965). IF THE ANTICHOLINERGICALLY-INDUCED ATTENUATION OF HABITUATION COULD BE SELECTIVELY ANTAGONIZED BY PARASYMPATHOMIMETIC AGENTS, A COGENT ARGUMENT FOR EXISTANCE OF THE POSTULATED ACTION WOULD BE ACCOMPLISHED.

A VERY IMPORTANT ASPECT NOT CONSIDERED IN THE FORMULATION OF CARLTON'S HYPOTHESIS INVOLVES THE PROFOUND EFFECT THAT MANY ANTICHOLINERGIC SUBSTANCES HAVE ON THE INGESTION OF FOOD AND WATER (CICERO & MYERS, 1968; COHEN, 1966; GROSSMAN, 1967; SCHMIDT, MOAK & VANMETER, 1958); I.E., THE MOTIVATIONAL ASPECTS. THESE EFFECTS COULD VERY POSSIBLY ACCOUNT FOR MANY BEHAVIOURAL CHANGES PRESUMED TO BE DIRECTLY AFFECTED BY VARIATIONS IN CHOLINERGIC LEVEL - ESPECIALLY WHEN THE BEHAVIOUR BEING MEASURED IS CONTINGENT ON DEPRIVATION-INDUCED DRIVE (AS IS CERTAINLY THE CASE WITH CARLTON'S HABITUATION MEASURE). HOWEVER, IN GENERAL, THE RELEVANT EXPERI-MENTAL EVIDENCE IS NOT CONDUCIVE TO AN EXPLANATION OF THE EFFECTS IN TERMS OF INTERACTION WITH THE PERIPHERAL ACTIONS OF ANTI-CHOLINERGIC DRUGS (E.G., THE MYDRIATIC, ANTISPASMOTIC, HYPOTENSIVE

OR ANTISIALAGOGUE EFFECTS OF THE TROPIC ACID ESTERS), THUS SUGGESTING POSSIBLE IMPLICATION OF THE CNS. IN FACT, THE EFFECT OF ANTICHOLINERGIC DRUGS ON BEHAVIOUR IS QUITE OFTEN OPPOSITE TO WHAT WOULD BE PREDICTED FROM THE CONCOMMITANT PERIPHERAL ACTIONS (BOREN & NAVARRO, 1959). IN VIEW OF THE METHODOLOGICAL SIMPLICITY THAT SUCH STUDIES ENTAIL (SUCH AS VARIATIONS IN DEPRIVATION TIMES, VARIATIONS IN TYPE OF REINFORCEMENT, DETERMINATION OF CONSUMPTION CURVES, ETC.), THEIR NON-CONSIDERATION REPRESENTS AN UNTENABLE OMISSION AND NEGLECTS A STRONG LINE OF EVIDENCE FOR CLARIFYING THE ASSOCIATION BETWEEN THE ANTICHOLINERGIC ACTION AND THE CNS.

STIMULUS SPECIFICATION IS BASIC TO AN ANALYSIS OF ANY BEHAVIOUR, INCLUDING HABITUATION (DEESE, 1958; FERSTER & SKINNER, 1957; PAVLOV, 1927), AND DRUG-BEHAVIOUR INTERACTIONS ARE FUNDAMENTAL TO ANY PSYCHOPHARMACOLOGICAL EVALUATION (BROWN, 1965; 1967; BROWN & RICHARDS, 1966; GOLLUB & BRADY, 1965; KIERMAN, 1965; PENICK & FISHER, 1965; SIDMAN, 1953; WEISS & LATIES, 1959). DEMONSTRATION OF STIMULUS CONTROL (I.E., THE RESPONSE VARIES SYSTEMATICALLY AND PREDICTABLY WITH VARATIONS OF A STIMULUS PARAMETER) ALLOWS STIMULUS SPECIFICATION, AND DRUG-BEHAVIOUR INTERACTIONS ARE SHOWN BY MODIFICATION OF AN ESTABLISHED DRUG EFFECT AS A FUNCTION OF STIMULUS ALTERATIONS. (A CLASSIC EXAMPLE IS THE AGGREGRATE TOXICITY EFFECT OF AMPHETAMINE, THIESSEN, 1964). CARLTON'S ANALYSIS OF STIMULUS INFLUENCE CENTRES ON THREE ASPECTS: 1.) MEMORY DEFICIT, 2.) DISSOCIATION, AND 3.) EMOTIONAL CONTEXT.

THERE IS CONSIDERABLE CLINICAL EVIDENCE TO SUGGEST THAT ANTICHOLINERGIC DRUGS ARE AMNESIC AGENTS (INNES & NICKERSON, 1965). SOME ANIMAL STUDIES SUPPORT THE CONTENTION, (CARLTON & VOGEL, 1965), OTHERS DO NOT (E.G., HAMBURG, 1967, REPORTS THAT ANTI-CHOLINESTERASES, NOT ANTICHOLINERGICS PRODUCE RETROGRADE AMNESIA). CARLTON (1968) PRESENTS EVIDENCE WHICH ALLOWS HIM TO CONCLUDE THAT ANTICHOLINERGICS DO NOT PRODUCE AMNESIA (SCOPOLAMINE-TREATED RATS EXPOSED TO AN AUDITORY STIMULUS ASSOCIATED WITH FOOTSHOCK SHOWED EVIDENCE OF RETENTION IN TERMS OF AVOIDANCE BEHAVIOUR 48 HOURS LATER), AND THEREFORE THE EFFECT IN THE HABITUATION TEST IS NOT SIMPLY DUE TO AMNESIA.

IT HAS BEEN DEMONSTRATED THAT CONDITIONING EXPERIENCE DURING THE COURSE OF A DRUG'S EFFECT DOES NOT "TRANSFER" TO THE NON-DRUG STATE - I.E., THE CONDITIONING BECOMES DISSOCIATED BETWEEN THE DRUG AND NON-DRUG STATES. (BELLEVILLE, 1964; CLARK, BUTLER & ROSNER, 1969; HEISTAD, 1958; OVERTON, 1964; SACHS, WEINGARTEN, & KLEIN, 1966). IT THUS APPEARS THAT THE DRUG EFFECT ACTS AS A DISCRIMINATIVE STIMULUS FOR THE CONDITIONED BEHAVIOUR. OBVIOUSLY THESE CIRCUMSTANCES OFFER A POSSIBLE EXPLANATION OF THE EFFECT OBTAINED IN CARLTON'S HABITUATION CIRCUMSTANCES. HOWEVER, CARLTON CONTENDS THAT THE OBTAINED EFFECT IS NOT DISSOCIATION BECAUSE NON-ANTICHOLINERGIC DRUGS (AMPHETAMINE, PENTOBARBITAL) ARE INEFFECTIVE. THE CONTENTION IS BASED ON THE ASSUMPTION THAT DRUG EFFECTS - AT LEAST WHEN ACTING AS INTEROCEPTIVE DISCRIMINA-TIVE STIMULI - ARE QUALITATIVELY AND QUANTITATIVELY IDENTICAL;

SUCH AN ASSUMPTION IS BOTH PHARMACOLOGICALLY AND PSYCHOPHYSICALLY DUBIOUS.

FINALLY, CARLTON OFFERS EXPERIMENTATION DESIGNED TO SHOW THAT SCOPOLAMINE DOES NOT INHIBIT THE EXTINCTION OF CONDITIONED FEAR. THE DIFFICULTY IN ATTEMPTING TO MAKE A DISTINCTION BETWEEN "EXTINCTION OF FEAR" AND HABITUATION HAS BEEN PREVIOUSLY DISCUSSED. AS EXPECTED THE DIFFERENCE CANNOT BE CLEARLY ESTABLISHED. CARLTON HIMSELF STATES:

> THERE IS A FINAL QUALIFICATION. THIS EXPERIMENT INVOLVED CONDITIONED FEAR, WHEREAS THE FEAR, IF ANY, THAT COULD OPERATE IN OUR EARLIER STUDIES IS OF THE UNCONDITIONED VARIETY. THUS, IF ONE IS TO ACCEPT THE LACK OF EFFECT OF SCOPOLAMINE ON EXTINCTION OF FEAR AS NOT AN IMPORTANT FACTOR IN THE EARLIER WORK, IT MUST BE ASSUMED THAT RULES ABOUT ONE KIND OF FEAR WILL APPLY TO THE OTHER. THE BEST THAT ONE CAN SAY AT THIS POINT IS THAT INTERPRETATION OF THE EFFECT OF SCOPOLAMINE IN TERMS OF HABITUATION (AS I AM USING THE TERM) IS AT LEAST NOT CONTRADICTED BY THE LACK OF EFFECT OF SCOPOLAMINE ON THE EXTINCTION OF CONDITIONED FEAR (1968, PP. 16-17).

JUST AS IT IS PHARMACOLOGICALLY IMPRUDENT TO ASSIGN AN EFFECT TO A DRUG ON THE BASIS OF ONE DOSE, IT IS BEHAVIOURALLY INCAUTIOUS TO ASSUME AN EFFECT ON THE BASIS OF ONE RESPONSE MEASURE. CARLTON (1968) EMPLOYED APPROACH TO THE DRINKING TUBE AS THE ONLY MEASURE OF HABITUATION. THERE IS, HOWEVER, AT LEAST ONE ADDITIONAL CONSIDERATION INVOLVED IN THE UTILITY OF THIS MEASURE. IT IS WELL ESTABLISHED THAT MOST TYPES OF ANTI-CHOLINERGIC DRUGS EFFECT INCREASES IN SPONTANEOUS OR GENERAL MOTOR ACTIVITY (MEYERS, ROBERTS, RICIPUTI & DOMINO, 1964; LIPMAN, SHURRAGER & ABOOD, 1963; WAKELY & O'SULLIVAN, 1969). SUCH AN

ACTION COULD HAVE PROFOUND INFLUENCES ON THE APPROACH LATENCY MEASURE. DURING INITIAL EXPOSURE TO THE STIMULUS - THE HABITUATING EXPERIENCE - INCREASED GENERAL ACTIVITY COULD RESULT IN EITHER INCREASED HABITUATION, BECAUSE THE ORGANISM ENCOUNTERS AND INVESTIGATES MORE OF THE RELEVANT ENVIRONMENT PER UNIT TIME, OR DECREASED HABITUATION, BECAUSE OF DECREASED EXPOSURE PER UNIT OF STIMULATION (I.E., LESS TIME TO ATTEND ANY ONE ASPECT). THE FORMER ASSUMPTION, AND THE ONE COMPATIBLE WITH THE OBTAINED RESULTS, INDEED SEEMS TO BE THE MOST PLAUSIBLE IN THAT THE EFFECT OF BEHAVIOURALLY STIMULATING DRUGS (AT DOSES THAT INCREASE GENERAL ACTIVITY) SEEMS TO ALSO BE LARGELY FACILITATING IN RESPECT TO ATTENDING (DOMINO, CALDWELL & HENKE, 1965; DOYLE, 1961; DUREMAN, 1962; GOLLUB & BRADY, 1965; HEARST & WHALEN, 1963; HUNT & KRIVANEK, 1966; JARVIK, 1964; KORNETSKY, 1958; KOSMAN, 1964; TALLAND, 1966; WENZEL & RUTHLEDGE, 1962). HOWEVER, IT WOULD BE IMPORTANT TO DIRECTLY EVALUATE THE INTERACTION BETWEEN THE HABITUATION MEASURE AND THE ORGANISM'S GENERAL ONGOING ACTIVITY LEVEL.

IT IS ALSO POSSIBLE THAT THE LATENCY RESPONSE ITSELF IS A DIRECT RESULT OF DRUG ACTION RATHER THAN PREVIOUS EXPOSURE CONDITIONS. THERE IS EVIDENCE THAT BOTH THE PERIPHERAL (INNES & NICKERSON, 1965) AND BEHAVIOURAL (BROWN, 1967) EFFECTS OF ATROPINE AND SCOPOLAMINE ARE OF SUFFICIENT DURATION (UP TO 72 HOURS) TO HAVE SUCH AN INFLUENCE. AN ANCILLARY RESPONSE MEASURE, SUCH AS MOTOR ACTIVITY, WOULD PROVIDE AN EVALUATIVE BASIS FOR ASSESSING

THAT POSSIBILITY.

BY EMPLOYING ONLY ONE DOSE OF A STIMULANT (AMPHETAMINE) AND A DEPRESSANT (PENTOBARBITAL) DRUG TO DEMONSTRATE THEIR COMPARATIVE LACK OF EFFECT ON HABITUATION, AND TO THEREBY SUPPOSEDLY RULE OUT ANY POSSIBLE INTERACTION WITH GENERAL LEVELS OF ACTIVITY, CARLTON HAS ONLY CONFOUNDED ANY CONCLUSIONS. BOTH DRUGS ARE BEHAVIOURALLY BIPHASIC IN ACTION (I.E., EFFECT DOSE-DEPENDENT INCREASES OR DECREASES OF ACTIVITY) AND THOSE ACTIONS DIFFER WITH DIFFERENT RESPONSE MEASURES (BROWN, 1963, 1966A; GOLLUB & BRADY, 1965; OWEN, 1960; SHARPLESS, 1965). THUS, CONSIDERABLE ADDITIONAL EVALUATION IS NECESSARY TO ANY CONCLUSIONS CONCERNING RESPONSE VARIABLES.

CONSEQUENTLY, AS WAS SUGGESTED ABOVE, IF EACH OF THE PARAMETRIC ISSUES CAN BE RESOLVED, COLLECTIVE CONSIDERATION WOULD ALLOW A GENERAL CONCLUSION REGARDING THE PROBABILITY OF THE ANTICHOLINERGIC EFFECT ON BEHAVIOURAL SUPPRESSION BEING CENTRAL. THE PURPOSE OF THE EXPERIMENTATION REPORTED IN THE FOLLOWING SECTIONS IS TO LEND SUCH PARAMETRIC SPECIFICATION, THEREBY ASSESSING THE EFFICACY OF CARLTON'S (1963) HYPOTHESIS (AT LEAST TO THE EXTENT OF THE CONCEPTUAL MODIFICATIONS DETAILED EARLIER).

CHAPTER II

METHODS

THE GENERAL PROCEDURE FOR MEASURING APPROACH LATENCY

THE EXPERIMENTAL MANIPULATIONS TO BE DESCRIBED ALL REPRESENT VARIATIONS OF, OR ARE DIRECTLY RELATED TO SOME ASPECT OF THE METHOD DEVELOPED BY CARLTON (1966B, 1968; CARLTON & VOLGEL, 1965). CONSEQUENTLY IT IS BENEFICIAL TO FIRST CONSIDER THE BASIC TECHNIQUE PER SE.

SUBJECTS

CF_1 MALE ALBINO MICE WEIGHING 18-25 GRAMS WERE OBTAINED FROM QUEBEC BREEDING FARMS. SINCE CARLTON USED ALBINO RATS, THIS REPRESENTS A DEPARTURE FROM HIS TECHNIQUE. THE ANIMALS WERE HOUSED IN CLEAR PLASTIC MOUSE CAGES (TEN PER CAGE) WITH AD LIBITUM ACCESS TO PURINA MOUSE CHOW AND WATER. THE CAGES WERE CLEANED DAILY AND STORED IN THE SAME ROOM IN WHICH THE EXPERIMENTATION WAS CONDUCTED. TEMPERATURE, HUMIDITY AND ILLUMINATION WERE NEARLY CONSTANT (WITHIN THE RANGES SPECIFIED BELOW).

APPARATUS

THE EXPERIMENTAL CHAMBER WAS A SMALL (30.0 x 15.0 x 10.0 CMS.) NON-GLOSSY BLACK PLASTIC MICROBIOLOGICAL MOUSE CAGE.

THE LID AND FLOOR WERE COMPOSED OF 18 GAUGE STAINLESS STEEL WIRE MESH HAVING 1.27 CM. OPENINGS. THE WIRE FLOOR STOOD 1.0 CM. ABOVE THE PLASTIC FLOOR. THE LID WAS TOTALLY REMOVABLE PROVIDING ACCESS TO THE INTERIOR. A DRINKING TUBE APERTURE WAS SITUATED IN THE CENTRE, 1.75 CM. ABOVE THE WIRE FLOOR, OF ONE OF THE 15 CM. LONG SIDE WALLS.

THE STAINLESS STEEL DRINKING TUBE AND WIRE FLOOR WERE WIRED TO A PULSE OPERATED DRINKOMETER WHICH, BY WAY OF CONVENTIONAL ELECTROMECHANICAL RELAY APPARATUS, ACTIVATED APPROPRIATE RECORDING DEVICES.

DIM CHAMBER ILLUMINATION WAS PROVIDED BY A 1.25 X 1.75 CM. SQUARE DIFFUSE WHITE LIGHT CENTRED 1.75 CM. ABOVE THE WIRE FLOOR AND 4.29 CM. TO THE RIGHT OF THE DRINKING TUBE. THE LIGHT SOURCE WAS AN 1EE MINIATURE READOUT (SERIES 350) EMPLOYING A1 (0.5 WATT) BULBS.

FIGURE 1 PROVIDES A SCHEMATIC REPRESENTATION OF THE APPARATUS.

OPERATIONS

A TYPICAL ASSESSMENT WAS CONDUCTED IN TWO PHASES. THE BASIC SCHEME CAN BE FOLLOWED BY REFERENCE TO FIGURE 2. AS CAN BE SEEN, THERE WERE TWO CONTROL GROUPS AND TWO TEST GROUPS. A GROUP CONSISTED OF SIX ANIMALS, THUS UTILIZING 24 SUBJECTS FOR EACH ASSESSMENT. ONE OF EACH OF THE TWO GROUPS WITHIN A CONDITION WERE EXPOSED TO THE CHAMBER FOR 15 MINUTES AFTER TREATMENT WITHOUT

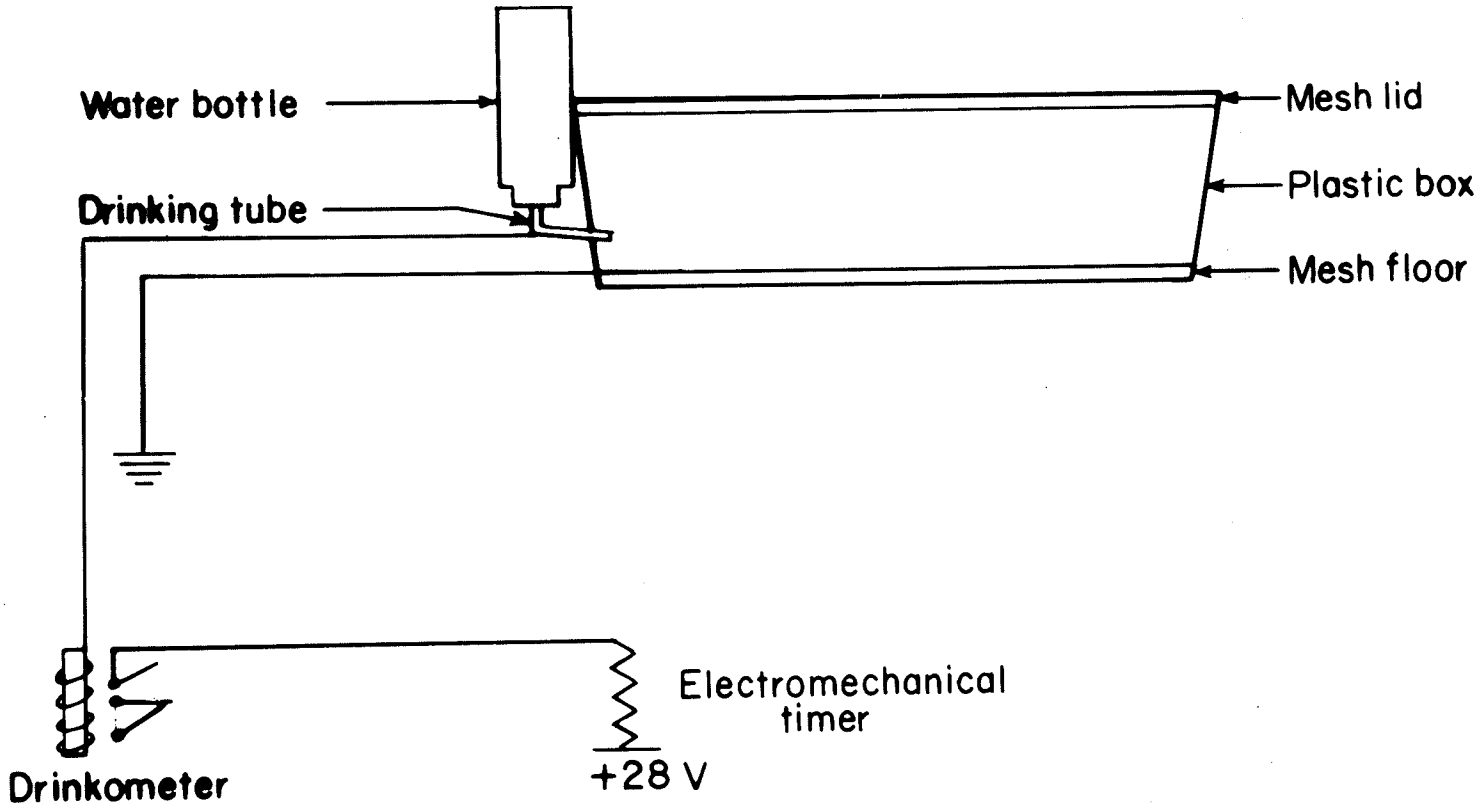

Fig. 1 Schematic diagram of the apparatus used to measure approach latency. The light source for chamber illumination is not represented as it would obscure the water bottle drinking tube.

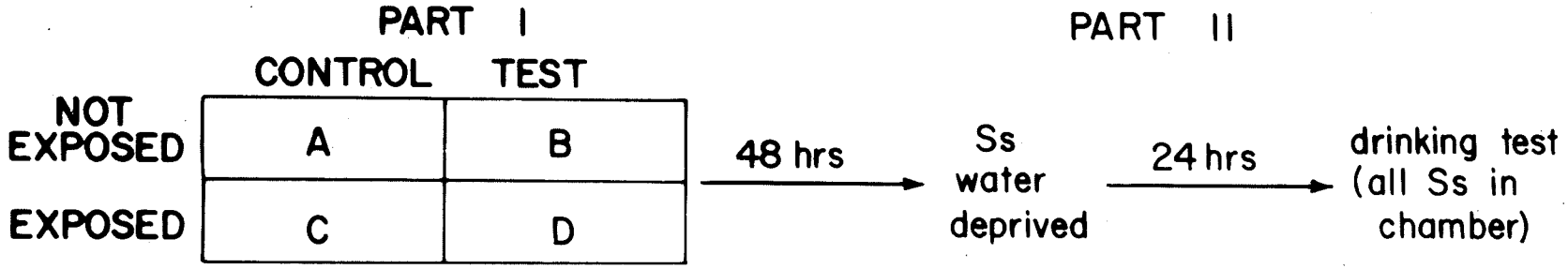

Fig. 2 The experimental parodigm employed in assessing the effects of drugs and prior exposure on approach latency.

THE DRINKING TUBE BEING PRESENT.[2] THEREFORE IN THE FIRST PHASE TWO GROUPS WERE DOSED WITH A DRUG. EACH MEMBER OF ONE OF THESE GROUPS WAS INDIVIDUALLY PLACED IN THE RIGHT REAR CORNER OF THE CHAMBER FOR 15 MINUTES; THE MEMBERS OF THE OTHER GROUP WERE IMMEDIATELY RETURNED DIRECTLY TO THEIR HOME CAGE. THE CONTROL GROUPS, WHICH CONSISTED OF SALINE TREATED SUBJECTS WERE IDENTICALLY HANDLED.

TREATMENTS WERE ADMINISTERED TEN MINUTES PRIOR TO THE INITIAL EXPOSURE. THE NON-EXPOSED ANIMALS WERE TREATED AT THE SAME TIME AS THE EXPOSED ANIMALS.

ASSESSMENTS WERE MADE AT VARIOUS TIMES OF THE DAY IN A TOTALLY NON-SYSTEMATIC MANNER. ROOM TEMPERATURE AND HUMIDITY WERE MAINTAINED CONSTANT AT 21°C ($\pm$ 3°) AND 30% RELATIVE HUMIDITY ($\pm$ 10%). A 12 HOUR OFF-ON LIGHT CYCLE WAS IN EFFECT AT ALL TIMES EXCEPT DURING EXPERIMENTAL SESSIONS WHICH WERE CONDUCTED WITH ONLY CHAMBER ILLUMINATION. ROOM LIGHT WAS TOTALLY ARTIFICIAL.

THE SECOND PHASE BEGAN 48 HOURS LATER WITH THE INITIATION OF WATER DEPRIVATION. AFTER 24 HOURS DEPRIVATION, ALL SUBJECTS, BOTH PREVIOUSLY EXPOSED AND NOT PREVIOUSLY EXPOSED WERE AGAIN PLACED IN THE RIGHT REAR CORNER OF THE CHAMBER, WHICH THEN CONTAINED THE DRINKING TUBE. THE TIME FROM INTRODUCTION INTO THE CHAMBER UNTIL DRINKING BEHAVIOUR OCCURRED (CONTACT WITH THE TUBE) WAS RECORDED (AND REFERRED TO AS LATENCY). ANIMALS THAT DID

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[2] AS WILL BE OBVIOUS, THIS IS SIMPLY A MEANS OF ELIMINATING THE INFLUENCE OF ANY APPROACH LEARNING IN THE ESTIMATE OF HABITUATION THAT WILL FOLLOW.

NOT RESPOND WITHIN FIFTEEN MINUTES WERE REMOVED AND ASSIGNED A LATENCY VALUE OF FIFTEEN MINUTES.

PHARMACOLOGICAL PROCEDURES

THE DRUGS EMPLOYED IN THE VARIOUS EXPERIMENTS ARE LISTED, ALONG WITH RELEVANT ANCILLARY INFORMATION, IN TABLE I. DOES WERE USUALLY ADMINISTERED INTRAPERITONEALLY (I.P.) AS SOLUTIONS IN 0.9% NACL AT A VOLUME OF 0.1 CC PER 10 GMS. BODY WEIGHT. DOSAGE WAS EQUILIBRATED TO MILLIGRAMS OF DRUG PER KILOGRAM OF TOTAL BODY WEIGHT. CONTROL ANIMALS RECEIVED SIMILAR VOLUMES OF 0.9% NACL (HEREAFTER CALLED "SALINE"). THE EXCEPTION TO THIS PROCEDURE WAS AN EXPERIMENT INVOLVING INTRACRANIAL DOSAGE WHICH WILL BE DESCRIBED ELSEWHERE. ALL SOLUTIONS WERE PREPARED FROM POWDERED SALTS IMMEDIATELY BEFORE DOSAGE BY APPROPRIATE ANALYTICAL TECHNIQUES.

DOSAGE WAS ACCOMPLISHED WITH STANDARD 1.0 CC CAPACITY HYPRODERMIC SYRINGES ATTACHED TO 5/8 INCH 27 GAUGE HYPODERMIC NEEDLES (EXCEPT FOR THE INTRACRANIAL INJECTIONS FOR WHICH AN 0.1 CC MICROLITER SYRINGE WAS EMPLOYED).

AS WAS INDICATED ABOVE, TEN MINUTE PRETREATMENT TIMES WERE EMPLOYED FOR ALL DOSES OF DRUGS.

PARAMETRIC VARIATIONS

PHARMACOLOGICAL ASSESSMENT OF DRUG AND DOSAGE VARIATIONS

COMPATABILITY WITH CARLTON'S (1966, 1968; CARLTON & VOGEL,

TABLE 1

DRUGS EMPLOYED IN THE VARIOUS EXPERIMENTS AND THEIR RELEVANT CHARACTERISTICS

GENERIC NAME	PREPARATION	PHARMACOLOGICAL ACTION	CHEMICAL CHARACTERISTIC
ATROPINE	SULFATE	MUSCARINIC ANTICHOLINERGIC[A]	TROPIC ACID ESTER
SCOPOLAMINE	HYDROBROMIDE	MUSCARINIC ANTICHOLINERGIC[A]	TROPIC ACID ESTER
METHYLATROPINE	SULFATE	MUSCARINIC ANTICHOLINERGIC[A] (DOES NOT PASS BLOOD-BRAIN BARRIER)	TROPIC ACID ESTER
DITRAN	HYDROCHLORIDE	MUSCARINIC ANTICHOLINERGIC[A] PSYCHOTOMETIC	GLYCOLIC ACID
HEMICHOLINIUM (H_3)	BROMIDE	NEUROMUSCULAR BLOCKING (PRESYNAPTICALLY)	BIS-HEMIACETAL
ESERINE (PHYSOSTIGMINE)	SALICYLATE	ANTICHOLIN-ESTERASE	ALKALOID

TABLE 1 (CONTINUED)

GENERIC NAME	PREPARATION	PHARMACOLOGICAL ACTION	CHEMICAL CHARACTERISTIC
D-AMPHETAMINE	SULFATE	SYMPATHOMIMETIC	PHENYLISOPROPYL-AMINE
METHYLPHENIDATE	HYDROCHLORIDE	CNS STIMULANT	METHYL α-PHENYL-2-PIPERIDINE
TACRINE (THA)	HYDROCHLORIDE	ANTIPSYCHOTO-MIMETIC	INDOLE ALKALOID

[A] STRICTLY SPEAKING THE ACTION OF THESE DRUGS IS ANTI-MUSCARINIC ANTI-CHOLINERGIC. IN KEEPING WITH CONVENTIONAL TERMINOLOGY, HOWEVER, THEY WILL BE REFERRED TO HEREIN AS SIMPLY MUSCARINIC ANTI-CHOLINERGIC.

1965) TECHNIQUE WAS ASSESSED BY EMPLOYING DRUGS AT DOSES APPROXIMATING THOSE REPORTED BY HIM. SPECIFICALLY THESE WERE SCOPOLAMINE (0.32 MG./KG.); ATROPINE (10.0 MG./KG.); METHYLATROPINE (10.0 MG./KG.); D-AMPHETAMINE (1.0 MG./KG.); AND CHLORPROMAZINE (3.2 MG./KG.). IN ADDITION, DITRAN (1.0 MG./KG.), ESERINE (0.32 MG./KG.) AND HEMICHOLINIUM (0.5 MG./KG.) WERE TESTED AT THIS TIME.

DOSE-EFFECT DETERMINATIONS WERE THEN ESTABLISHED FOR SCOPOLAMINE, ATROPINE, METHYLATROPINE AND D-AMPHETAMINE. DOSES EMPLOYED WERE AT 0.5 LOG_{10} INTERVALS AS OUTLINED IN TABLE 2.

TABLE 2

DRUGS AND DOSE RANGES EMPLOYED IN APPROACH LATENCY EVALUATION

DRUGS	DOSE RANGE (MG./KG.)
SCOPOLAMINE	0.032 - 3.2
ATROPINE	1.0 - 32.0
METHYLATROPINE	0.32 - 32.0
D-AMPHETAMINE	0.32 - 10.0

ANTAGONISM STUDIES WERE CONDUCTED USING THE COMBINATIONS OUTLINED IN TABLE 3. THE AGONIST WAS ADMINISTERED SIMUTANEOUSLY WITH THE ANTAGONIST. BOTH, THUS, HAD A 10 MINUTE PRETREATMENT TIME.

IN ADDITION SCOPOLAMINE AND ESERINE WERE TESTED FOLLOWING INTRACRANIAL INJECTIONS. DOSING WAS ACCOMPLISHED BY THE METHOD OF HALEY & MCCORMICK (1957). A 27 GAUGE NEEDLE WAS PASSED PERPENDICULARLY THRU THE CRANIUM INTO THE BRAIN FROM A POINT

2.0 MM TO EITHER SIDE OF THE MIDLINE PARALLEL TO THE ANTERIOR BASES OF THE PINNA. INJECTIONS WERE IN A VOLUME OF 0.01 CC. WHICH CONTAINED 0.0005 MG. SCOPOLAMINE OR 0.0001 MG. ESERINE. A COMBINATION OF INTRACRANIALLY ADMINISTERED METHYLATROPINE (0.001 MG.) AND INTRAPERITONEALLY ADMINISTERED ESERINE (0.1 MG./KG.) WAS ALSO EVALUATED.

TABLE 3

DRUG ANTAGONISM RELATIONSHIPS STUDIED IN APPROACH LATENCY PROCEDURE

AGONIST		ANTAGONIST	
DRUG	DOSE (MG./KG.)	DRUG	DOSE (MG./KG.)
SCOPOLAMINE	0.32	ESERINE	0.1
SCOPOLAMINE	0.32	TACRINE	1.0
DITRAN	1.0	TACRINE	1.0

MOTIVATIONAL INFLUENCES INVOLVING DEPRIVATION, TIME AND INCENTIVE

THE INFLUENCE OF DEPRIVATION LEVEL WAS EVALUATED BY ASSESSING THE LATENCY ATTENUATING EFFECT OF 10.0 MG./KG. ATROPINE FOLLOWING 3, 6, AND 12 HOURS DEPRIVATION AS WELL AS THE USUAL 24 HOURS. SCOPOLAMINE WAS SIMILARLY TESTED AT A DOSE OF 0.32 MG./KG. AS WELL AS AFTER 48 AND 72 HOURS DEPRIVATION.

THE INCENTIVE ASPECTS OF REINFORCEMENT WERE ASSESSED BY EMPLOYING CARNATION CONDENSED MILK OR PURINA MOUSE CHOW IN PLACE OF WATER. IN THE INSTANCE OF THE CONDENSED MILK, IT WAS SUBSTITUTED IN PLACE OF CHOW AS THE ONLY AVAILABLE FOOD FOR FOUR DAYS PRIOR TO TESTING. CHOW WAS TESTED BY PLACING A POWDERED

QUANTITY IN A SMALL WATCH GLASS UNDER THE APERTURE THROUGH WHICH THE WATER TUBE WOULD ORDINARILY PROJECT. BOTH FOODS WERE TESTED, FOLLOWING 24 HOURS DEPRIVATION, IN CONJUNCTION WITH SCOPOLAMINE (0.32 MG./KG.) AND ATROPINE (10. MG./KG.). IN ADDITION, EVALUATIONS FOLLOWING 48 AND 72 HOURS DEPRIVATION WERE MADE WITH 0.32 MG./KG. SCOPOLAMINE. WATER WAS ALSO TESTED WITH 48 AND 72 HOURS DEPRIVATION.

WATER CONSUMPTION FROM TIME OF DRUG OR SOLVENT INJECTION UNTIL THE INSTIGATION OF DEPRIVATION WAS MEASURED BY RECORDING THE WATER LEVEL IN 10.0 CC GRADUATED CYLINDERS AFFIXED WITH DRINKING TUBES AT 3, 6, 12, AND 24 HOUR INTERVALS OVER EACH OF TWO SUCCESSIVE DAYS. EACH SUBJECT WAS ISOLATED AND HAD ACCESS ONLY TO ITS OWN INDIVIDUAL WATER TUBE. THE CYLINDERS WERE REFILLED AFTER THE FIRST 24 HOUR PERIOD AND REMOVED AFTER THE SECOND 24 HOUR PERIOD.

WATER CONSUMPTION DURING A 15 MINUTE EXPOSURE IN THE PERIOD NORMALLY TERMINATED BY LATENCY RESPONDING WAS ASSESSED BY EMPLOYING LICKING RATE (NUMBER OF LICKS PER 15 MINUTES). MEASUREMENT WAS ACCOMPLISHED BY RECORDING DRINKOMETER PULSES ON AN ELECTROMAGNETIC COUNTER. THE DRUGS TESTED WERE SCOPOLAMINE (0.32 MG./KG.), ATROPINE (10.0 MG./KG.), D-AMPHETAMINE (1.0 MG./KG.), AND METHYLATROPINE (10.0 MG./KG.).

A COMPARISON WAS MADE OF THE EFFECTS OF 0.32 MG./KG. SCOPOLAMINE, WITH AND WITHOUT THE DRINKING TUBE BEING PRESENT DURING THE INITIAL EXPOSURE.

Tests of Generalization Across Stimulus Conditions

The colour of the chamber illumination was varied by interspersing Kodak Wratten filters into the chamber illumination. The specific variations employed are detailed in Table 4. No correction was made for intensity. Tests were conducted with one of each of these colours being present either during initial exposure or during the habituation test in subjects dosed with 0.32 mg./kg. scopolamine.

Table 4

Characteristics of Filters Used to Vary Chamber Illumination (Eastmen Kodak Co., 1965)

Colour	Filter No.	Dominant Wavelength (mu)	% Transmittance
Red	29F	632.7	11.0
Yellow	4	569.6	87.7
Blue	45	486.6	2.8

Flickering white light was also tested in groups dosed with 0.32 mg./kg. scopolamine. The flicker was present during initial exposure and/or during the habituation test. Flicker was maintained at a rate of three flashes per second (fps) by paralleling the chamber light circuit with the external syncronization output of a physiological stimulator.

Extraneous auditory stimulation was introduced by directing the output of a "white" noise generator (Gerbrands, Model 455C,

FREQUENCY SPECTRA 20-20,000 CPS, 3DB DOWN AT 20 AND 20,000 CPS., OPTIMUM LV RMS INTO 600 OHMS, CONTINOUSLY VARIABLE) THROUGH AN 8-OHM 3 INCH SPEAKER AFFIXED TO THE CENTRE OF THE TOP OF THE CHAMBER. THE NOISE WAS MAINTAINED AT A CONSTANT LEVEL (68DB ±3 AS READ ON SCALE B OF A BRUEL & KJAER MODEL 2203 SOUND-LEVEL METER) FOR SOME GROUPS AND "FLICKERED" FOR OTHERS (ALTERNATELY OFF-ON AT A RATE OF TWO PER SECOND; SWITCHING WAS ACCOMPLISHED USING THE PHYSIOLOGICAL STIMULATOR AS DESCRIBED ABOVE). THESE CONDITIONS WERE IMPOSED EITHER DURING INITIAL EXPOSURE, DURING THE HABITUATION TEST, OR BOTH.

GENERAL ACTIVITY MEASUREMENT

THE SPONTANEOUS, RANDOM, GENERAL ACTIVITY OF INDIVIDUAL MICE WAS MEASURED BY MEANS OF A PHOTOCELL DEVICE (DAVIS, 1967; HALL, 1961; ISSAC & ROOT, 1956). A CADMIUM SULFIDE PHOTOCELL (CLAIREX CL-3) WAS AFFIXED TO THE RIGHT SIDE OF THE PREVIOUSLY DESCRIBED CHAMBER. IT WAS PLACED IN THE EXACT CENTRE 15.0 CM. FROM EITHER END AND 1.75 CM. ABOVE THE FLOOR. DIRECTLY OPPOSITE, ON THE LEFT SIDE, A SMALL LIGHT SOURCE (1.5 V. PENLIGHT) WAS ATTACHED SUCH THAT IT FOCUSED DIRECTLY ON THE PHOTOCELL. INTERRUPTIONS OF THE LIGHT BEAM WERE RECORDED, BY WAY OF APPROPRIATE CIRCUITY, ON AN ELECTROMECHANICAL COUNTER. FIGURE 3 PRESENTS A SCHEMATIC REPRESENTATION OF THE APPARATUS.

ALL EXPERIMENTS WERE CONDUCTED WITH SIX SUBJECTS PER TREATMENT. EACH INDIVIDUAL ANIMAL WAS PLACED IN THE CHAMBER FOR 15 MINUTES WITH THE TOTAL NUMBER OF BEAM INTERRUPTIONS BEING

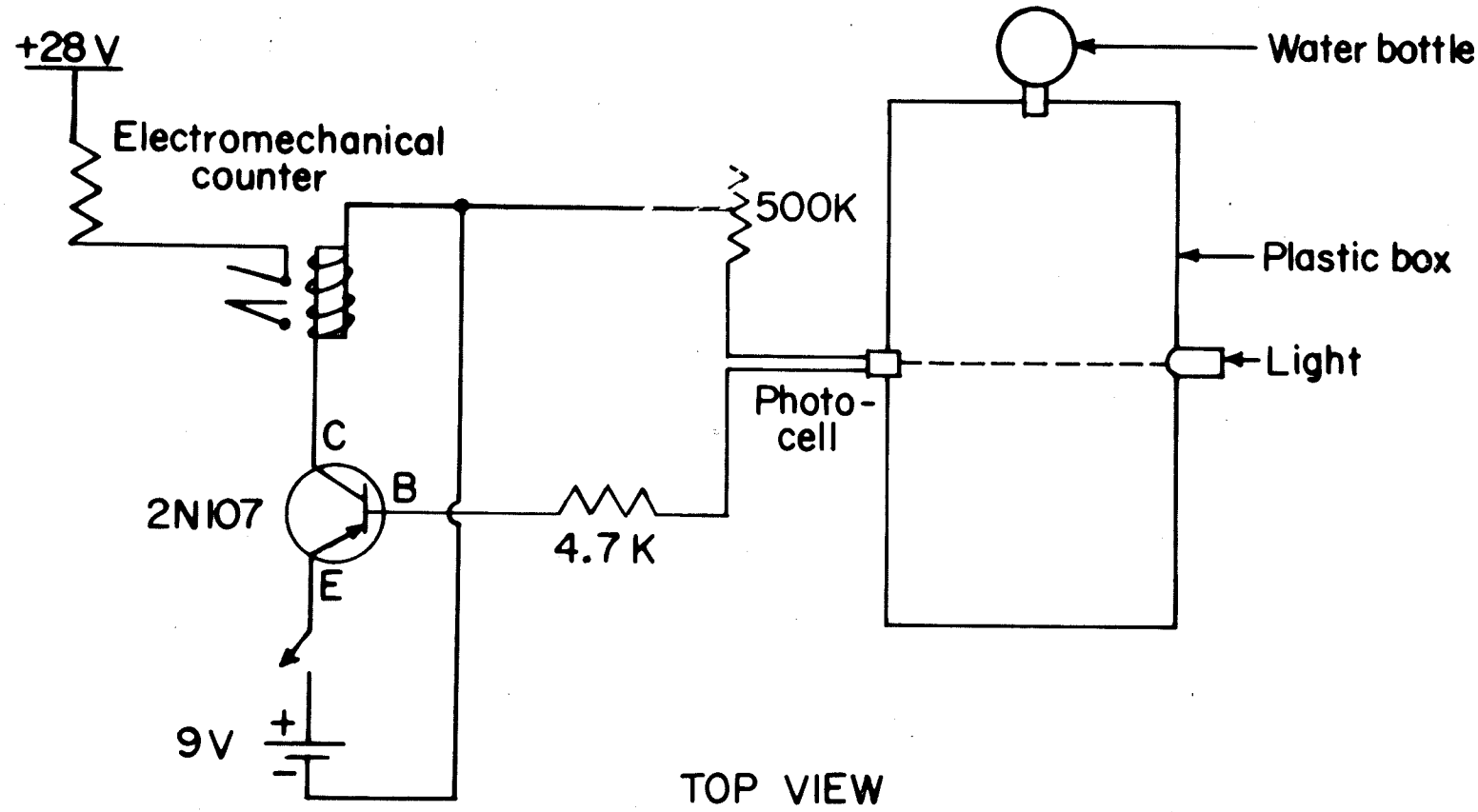

Fig. 3 Schematic diagram of the arrangement used to measure general activity.

RECORDED.

DOSE-EFFECT CURVES EMPLOYING THE DRUGS AND DOSES (IN 0.5 $\log_{10}$ INTERVALS) LISTED IN TABLE 5 WERE ESTABLISHED WITH A TEN MINUTE PRETREATMENT TIME. SIMILAR DETERMINATIONS WERE MADE WITH A 72 HOUR PRETREATMENT TIME EMPLOYING MICE THAT HAD NOT BEEN EXPOSED TO THE CHAMBER PREVIOUSLY, AND THOSE THAT HAD BEEN TESTED AT TEN MINUTES (I.E., PREVIOUSLY EXPOSED). A GROUP OF SALINE TREATED CONTROL SUBJECTS WERE TESTED UNDER THE SAME PRETREATMENT CONDITIONS IN CONJUNCTION WITH EACH DRUG.

TABLE 5

DRUGS AND DOSE RANGES EMPLOYED IN ACTIVITY EXPERIMENTS

DRUGS	DOSE RANGE (MG./KG.)
SCOPOLAMINE	0.1 - 3.2
ATROPINE	1.0 - 32.0
METHYLATROPINE	0.32 - 10.0
D-AMPHETAMINE	0.32 - 10.0
METHYLPHENIDATE	0.32 - 10.0
DITRAN	0.1 - 3.2

DOSE-EFFECT DATA FOR ATROPINE AND METHYLATROPINE WERE SIMILARLY OBTAINED EXCEPT ONLY THE TEN MINUTE PRETREATMENT TIME WAS EMPLOYED AND THE DRUGS WERE ADMINISTERED INTRACRANIALLY BY THE METHOD PREVIOUSLY DESCRIBED. THE DOSES USED WERE 0.001, 0.003, AND 0.01 MG.

GROUPS OF MICE WERE ALSO TESTED FOLLOWING EITHER 3, 6, 12,

24, 48 OR 72 HOUR DEPRIVATION OF EITHER WATER, CONDENSED MILK OR LABORATORY CHOW. SEPARATE GROUPS WERE USED FOR EACH DETERMINATION (I.E., NONE WERE PREVIOUSLY EXPOSED).

THE SCHEME (I.E., UTILIZATION OF EXPOSED, NON-EXPOSED SALINE AND DRUG TREATED GROUPS) USED TO ASSESS APPROACH LATENCY WAS REPEATED WITH 0.32 AND 1.0 MG./KG. SCOPOLAMINE. INSTEAD OF LATENCY, HOWEVER, ACTIVITY WAS RECORDED UNTIL INSTANT OF CONTACT WITH THE DRINKING TUBE.

ANCILLARY MEASUREMENTS

SYMPTOMATOLOGICAL ASSESSMENTS WERE ROUTINELY CARRIED OUT ON EVERY MOUSE THAT WAS DOSED. THESE WERE ACCOMPLISHED BY A QUALIFIED OBSERVER IN ACCORDANCE WITH ACCEPTED PHARMACOLOGICAL METHODS (BASTIAN, 1961; BROWN & REMFRY, 1964). THE PRECISE NATURE OF THE ASSESSMENTS MAY BE SEEN BY REFERENCE TO TABLE 27.

CHAPTER III

RESULTS

PHARMACOLOGICAL PARAMETERS

THE INITIAL STUDIES WHICH REPLICATED CARLTON'S (1966B, 1968) EXPERIMENTS RESULTED IN SCOPOLAMINE, ATROPINE OR DITRAN TREATED PRIOR EXPOSED GROUPS RESPONDING NEARLY IDENTICAL TO NON-EXPOSED SUBJECTS, I.E., THE HABITUATING INFLUENCE OF PRIOR EXPOSURE WAS ABOLISHED. METHYLATROPINE, ESERINE, D-AMPHETAMINE, CHLORPROMAZINE AND HEMICHOLINIUM TREATED AND EXPOSED SUBJECTS SHOWED THE RELATIVELY SHORT LATENCIES TYPICAL OF SALINE TREATED PRIOR-EXPOSED ANIMALS. EXACT VALUES ARE SUMMARIZED IN TABLE 6.

SIGNIFICANCE WAS DETERMINED BY EMPLOYING A DOUBLE-CLASSIFICATION (DRUG-EXPOSURE) ANALYSIS OF VARIANCE (SPENCE, UNDERWOOD, DUNCAN & COTTON, 1968), THE RESULTS OF WHICH ARE SUMMARIZED IN TABLE 7. IN ALL INSTANCES, THERE WAS A SIGNIFICANT ($P < 0.01$) DIFFERENCE BETWEEN EXPOSED AND NON-EXPOSED GROUPS AND BETWEEN SCOPOLAMINE, ATROPINE AND DITRAN TREATED AND SALINE TREATED GROUPS. THESE DRUGS ALSO REVEALED A SIGNIFICANT INTERACTION BETWEEN DRUG AND EXPOSURE TREATMENT. THAT THE SIGNIFICANT F FOR INTERACTION WAS, IN FACT, PRIMARILY DUE TO THE MARKED CHANGE IN THE SALINE EXPOSED GROUPS (OR ATTENUATION OF CHANGE IN THE DRUG EXPOSED GROUPS) CAN BE CLEARLY SEEN FROM FIGURE 4.

TABLE 6

MEAN APPROACH LATENCY VALUES (0.01 MINS) FOR SELECTED DRUGS AND DOSES

DRUG[A]	DOSE (MG./KG.) I.P.	NOT EXPOSED		EXPOSED		EFFECT[B]
		SALINE	DRUG	SALINE	DRUG	
SCOPOLAMINE*	0.32	136.6	142.9	28.2	137.0	+
ATROPINE*	10.0	133.8	159.1	24.6	132.8	+
METHYLATROPINE*	10.0	128.0	121.5	25.6	25.6	-
DITRAN	1.0	129.0	128.1	20.3	129.4	+
ESERINE	0.32	129.3	130.4	20.3	25.8	-
D-AMPHETAMINE*	1.0	132.6	127.0	28.1	25.7	-
CHLORPROMAZINE*	3.2	142.4	139.1	26.3	28.3	-
HEMICHOLINIUM	0.5	128.9	131.3	27.4	31.9	-

A. *INDICATES DRUGS EMPLOYED IN CARLTON'S (1966B, 1968) STUDIES.

B. +INDICATES THAT DRUG-TREATED EXPOSED VALUES ARE NOT SIGNIFICANTLY DIFFERENT FROM THE NON-EXPOSED VALUES; - INDICATES THAT DRUG-TREATED EXPOSED VALUES ARE NOT SIGNIFICANTLY DIFFERENT FROM THE SALINE-TREATED EXPOSED VALUES.

TABLE 7

ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING APPROACH LATENCY MEASURE

DOSE/DRUG	SOURCE	DF	MS	F*
0.32. MG./KG. SCOPOLAMINE	DRUG (A)	1	157.91	25.46
	EXPOSURE (B)	1	141.76	22.86
	INTERACTION(AXB)	1	269.55	43.48
10.0 MG./KG. ATROPINE	DRUG (A)	1	328.12	43.91
	EXPOSURE (B)	1	281.63	35.24
	INTERACTION(AXB)	1	174.21	28.96
10.0 MG./KG. METHYLATROPINE	DRUG (A)	1	2.00	0.08
	EXPOSURE (B)	1	580.60	53.79
	INTERACTION(AXB)	1	19.97	1.32
1.0 MG./KG. DITRAN	DRUG (A)	1	342.1	40.22
	EXPOSURE (B)	1	365.8	38.91
	INTERACTION(AXB)	1	297.6	32.11
0.32 MG./KG. ESERINE	DRUG (A)	1	0.92	0.01
	EXPOSURE (B)	1	189.76	23.91
	INTERACTION(AXB)	1	8.15	0.92
1.0 MG./KG. D-AMPHETAMINE	DRUG (A)	1	4.10	1.01
	EXPOSURE (B)	1	219.12	34.27
	INTERACTION(AXB)	1	2.35	0.06
3.2 MG./KG. CHLORPROMAZINE	DRUG (A)	1	1.24	0.15
	EXPOSURE (B)	1	145.17	21.21
	INTERACTION(AXB)	1	1.15	0.01
0.5 MG./KG. HEMICHOLINIUM	DRUG (A)	1	1.64	0.19
	EXPOSURE (B)	1	115.82	14.83
	INTERACTION(AXB)	1	17.90	0.67

*FOR 1 AND 20 DF, $F_{0.05} = 4.5$; $F_{0.01} = 8.10$.

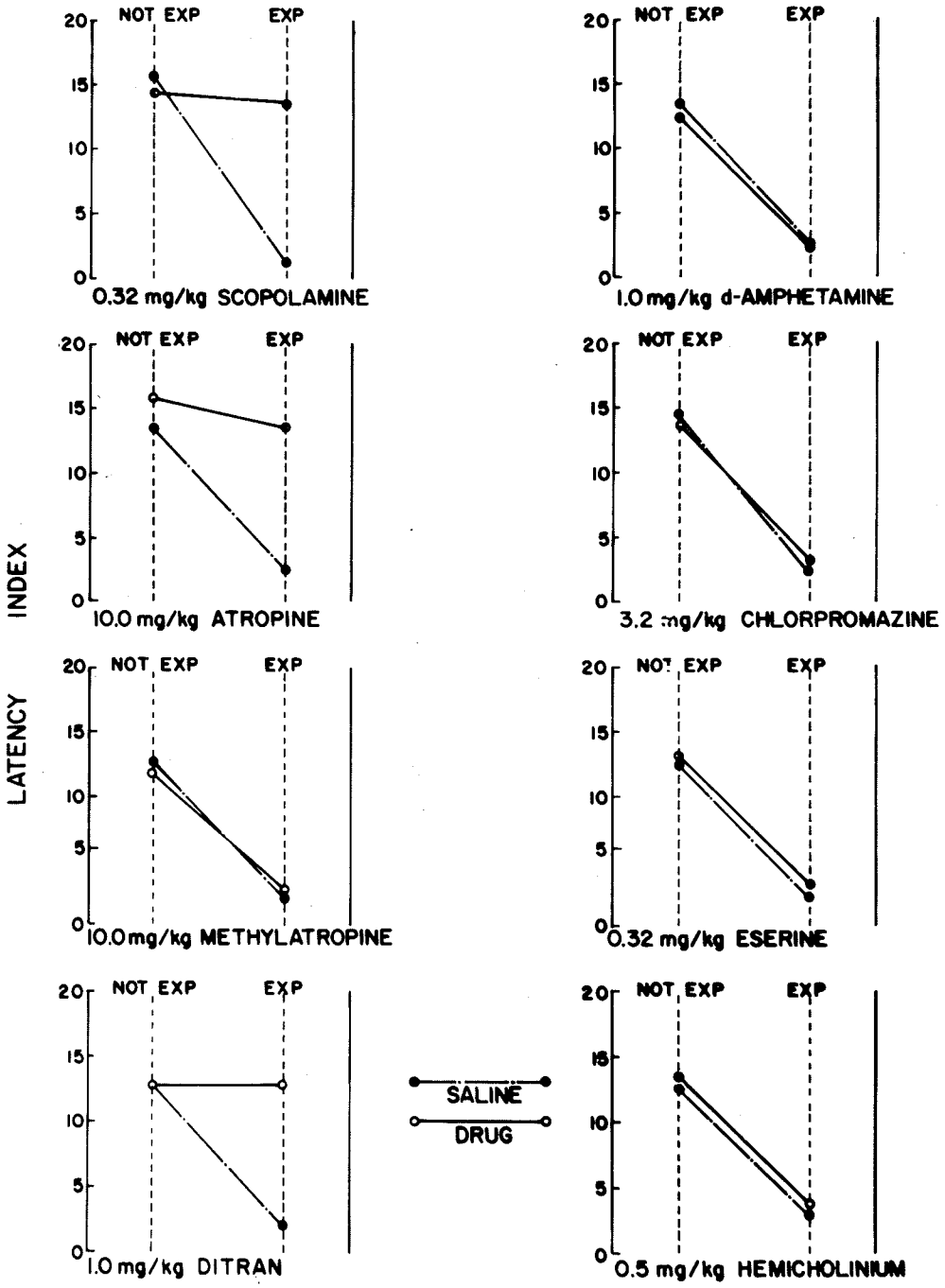

Fig. 4 Mean latency indices for each group in the initial dose evaluations. Latency Index is the latency value in 0.01 mins. divided by 10.

TABLE 8 PRESENTS A SUMMARY OF DOSE-EFFECT DATA FOR SCOPOLAMINE, ATROPINE, METHYLATROPINE AND D-AMPHETAMINE. IT CAN BE SEEN THEREFROM THAT THE LATENCY ATTENUATING EFFECT OF PRIOR EXPOSURE WAS NOT A CONTINUOUS FUNCTION OF DOSE AT THE INERVALS EMPLOYED. THE EFFECT WAS TOTALLY PRESENT AT A SPECIFIC DOSE LEVEL BELOW WHICH IT DID NOT OCCUR IN ANY MAGNITUDE AND ABOVE WHICH IT OCCURRED AT FULL EFFECT (HIGHER DOSES DID NOT INCREASE THE EFFECT); I.E., AN "ALL OR NONE" EFFECT WAS OBTAINED WITH THE DOSE INTERVALS EMPLOYED.

THE RESULTS OF THE ANTAGONISM STUDIES ARE SUMMARIZED IN TABLE 9. IN EVERY INSTANCE, ANTAGONISM OF THE DRUG-INDUCED ATTENUATION OF THE PRIOR EXPOSURE INDUCED DIMINUTION OF APPROACH LATENCY WAS ACCOMPLISHED. BOTH THE INTRAPERITONEAL AND INTRACRANIAL ROUTES RESULTED IN ANTAGONISM FOR COMBINATIONS OF SCOPOLAMINE AND ESERINE. THE EFFECT PRODUCED BY INTRACRANIALLY ADMINISTERED METHYLATROPINE WAS ANTAGONIZED BY INTRAPERITONEALLY ADMINISTERED ESERINE. TACRINE WAS EFFECTIVE IN ANTAGONIZING THE EFFECT OF EITHER SCOPOLAMINE OR DITRAN.

INTRACRANIAL INJECTIONS OF SCOPOLAMINE OR ATROPINE WERE SIMILARLY EFFECTIVE (IN RELATION TO THE INTRAPERITONEAL ROUTE) AS REGARDS INHIBITING THE LATENCY ATTENUATING EFFECTS OF PREVIOUS EXPOSURE. METHYLATROPINE IN CONTRAST TO ITS EFFECT INTRAPERITONALLY, WAS ACTIVE WHEN ADMINISTERED INTRACRANIALLY. SPECIFIC VALUES ARE PRESENTED IN TABLE 10.

TABLE 8

MEAN APPROACH LATENCY VALUES (0.01 MINS) FOR VARIOUS DOSES OF SEVERAL DRUGS

DRUG	DOSE (MG./KG.) I.P.	NOT EXPOSED SALINE	NOT EXPOSED DRUG	EXPOSED SALINE	EXPOSED DRUG	DIFFERENCE EXPOSED SALINE & DRUG
SCOPOL-	0.032	135.2	126.7	41.6	31.7	-9.9
AMINE	0.1	132.6	134.1	34.7	30.6	-4.1
	0.32*	136.6	142.9	28.2	137.0	+118.8
	1.0	130.1	131.5	34.6	133.8	+99.2
	3.2	145.2	136.6	27.4	125.7	+98.3
ATROPINE	1.0	131.2	135.0	30.0	27.7	-2.3
	3.2	127.0	136.2	27.0	29.6	-2.6
	10.0*	133.8	159.1	24.6	132.8	+108.2
	32.0	139.5	138.9	32.9	139.5	+106.6
METHYL-	0.32	140.3	138.4	26.5	32.3	+5.8
ATROPINE	1.0	137.1	135.1	34.6	30.6	-4.0
	3.2	135.5	141.8	30.9	34.2	+3.3
	10.0*	128.0	121.5	25.6	25.6	0.0
	32.0	124.6	120.7	25.8	28.9	+3.1
D-AMPHET-	0.32	139.8	132.1	34.1	27.5	-6.6
AMINE	1.0*	132.6	127.0	28.1	25.7	-2.4
	3.2	128.7	133.9	25.0	31.6	+6.6
	10.0	124.1	120.7	37.0	25.7	-11.3

*VALUES FOR THESE DOSE LEVELS WERE TAKEN FROM DATA IN TABLE 6.

TABLE 9

THE ANTAGONISTIC RELATIONSHIP BETWEEN SCOPOLAMINE OR DITRAN AND ESERINE OR TACRINE AS MEASURED BY APPROACH LATENCIES (MEAN PER GROUP IN 0.01 MINS)

AGONIST		ANTAGONIST						
	DOSE		DOSE	NOT EXPOSED		EXPOSED		
DRUG	(MG./KG.)	DRUG	(MG./KG.)	SALINE	DRUG	SALINE	DRUG	EFFECT[C]
SCOPOL-AMINE	0.32 I.P.	ESERINE	0.1 I.P.	139.1	141.6	43.2	35.5	+
SCOPOL-AMINE	0.0005[A] I.C.[B]	ESERINE	0.0001[A] I.C.[B]	144.2	133.8	27.4	38.0	+
SCOPOL-AMINE	0.32 I.P.	TACRINE	1.0 I.P.	140.2	128.9	37.1	35.9	+
METHYL-ATROPINE	0.001[A] I.C.[C]	ESERINE	0.1 I.P.	136.3	132.1	30.2	30.3	+
DITRAN	1.0 I.P.	TACRINE	1.0 I.P.	116.9	127.6	33.7	38.5	+

A. DOSAGE VALUES ARE IN TOTAL MG., NOT MG./KG.
B. I.C. = INTRACRANIAL INJECTION.
C. + = ANTAGONISM; - = NO ANTAGONISM.

TABLE 10

MEAN APPROACH LATENCY VALUES (0.01 MINS) FOLLOWING INTRACRANIAL INJECTIONS OF SCOPOLAMINE, ATROPINE AND METHYLATROPINE

DRUG	DOSE (MG.)	NOT EXPOSED		EXPOSED	
		SALINE	DRUG	SALINE	DRUG
SCOPOLAMINE	0.0005	128.9	134.1	34.2	133.2
ATROPINE	0.001	140.3	133.9	32.9	134.6
METHYLATROPINE	0.001	132.6	134.9	40.0	136.8

MOTIVATIONAL PARAMETERS

THERE APPEARED TO BE AN INTERACTION BETWEEN LENGTH OF WATER DEPRIVATION AND THE APPROACH LATENCY OF ALL ANIMALS IRRESPECTIVE OF TREATMENT. THE LATENCY VALUES WERE INVERSELY RELATED TO DEPRIVATION TIME - AS DEPRIVATION TIME INCREASED LATENCY DECREASED. IT CAN BE SEEN FROM TABLE 11, HOWEVER, THAT THE EFFECT IS COMMON TO ALL GROUPS, NOT JUST SPECIFIC TO THE DRUG TREATED SUBJECTS.

CONDENSED MILK WAS AS EFFECTIVE A REINFORCER AS WATER WHILE LABORATORY CHOW WAS INEFFECTIVE EVEN AFTER INCREASED DEPRIVATION. THE DATA RELEVANT TO THESE FINDINGS ARE PRESENTED IN TABLE 12. THERE WERE NO QUANTITATIVE DIFFERENCES IN WATER CONSUMPTION BETWEEN ANY OF THE GROUPS DURING THE 48 HOURS FROM INJECTION OF SCOPOLAMINE OR ATROPINE TO INITIATION OF DEPRIVATION. TABLE 13 PRESENTS MEAN TOTAL AMOUNT OF WATER CONSUMED BY THE VARIOUS GROUPS DURING THIS PERIOD; TABLE 14 SUMMARIZES AN ANALYSIS OF VARIANCE FOR THESE DATA.

WHEN THE DATA WERE CONSIDERED IN TERMS OF TIME INTERVALS, HOWEVER, A QUALITATIVE DISTINCTION BETWEEN DRUG AND SALINE TREATED ANIMALS BECAME EVIDENT. EXAMINATION OF THE CUMULATIVE VALUES IN TABLE 15 AND THE GRAPHIC DEPICTION OF DISCRETE VALUES IN FIGURE 5 SHOWS THAT THE WATER CONSUMPTION OF DRUGGED ANIMALS INCREASED VERY MARKEDLY FOR THE FIRST SIX HOURS FOLLOWING DOSAGE THEN DECREASED MARKEDLY FOR THE NEXT 18 HOURS. ONLY IN THE SECOND 24 HOURS DID THE CONSUMPTION VALUES OF THE DRUGGED SUBJECTS BECOME

TABLE 11

MEAN APPROACH LATENCY VALUES (0.01 MINS) FOLLOWING DOSAGE WITH SCOPOLAMINE OR ATROPINE AND VARIOUS HOURS OF WATER DEPRIVATION

DRUG	DOSE (MG./KG.)	DEPRIVATION (HOURS)	NOT EXPOSED		EXPOSED	
			SALINE	DRUG	SALINE	DRUG
SCOPOLAMINE	0.32	3.0	1309.4	1291.5	1470.8	1196.0
		6.0	1368.5	1279.4	1500.0	1149.2
		12.0	1333.7	1249.6	943.9	1317.5
		24.0	156.6	142.9	18.2	137.0
		48.0	91.6	108.0	16.2	108.6
		72.0	88.5	91.8	11.3	102.9
ATROPINE	10.0	3.0	1335.3	1206.5	1136.6	1130.0
		6.0	1363.3	1338.4	1245.2	1257.4
		12.0	1316.4	1298.3	1121.8	1338.6
		24.0	133.8	159.1	24.6	132.8

TABLE 12

MEAN APPROACH LATENCY VALUES (0.01 MINS) FOR FOOD REINFORCEMENT FOLLOWING DOSAGE WITH SCOPOLAMINE OR ATROPINE AND VARIOUS HOURS OF DEPRIVATION

DRUG	(MG./KG.)	TYPE OF FOOD	DEPRIVATION (HOURS)	NOT EXPOSED		EXPOSED	
				SALINE	DRUG	SALINE	DRUG
SCOPOLAMINE	0.32	MILK	24	132.3	133.9	23.9	130.2
			48	112.2	107.3	15.5	111.9
			72	103.9	112.1	11.8	107.2
		CHOW	24	133.1	131.8	25.3	40.3
			48	116.3	118.5	12.0	13.6
			72	106.9	62.9	19.8	11.2
ATROPINE	10.0	MILK	24	131.8	136.9	30.1	130.3
		CHOW	24	125.6	134.5	30.2	35.1

TABLE 13

MEAN VOLUME OF WATER CONSUMED (CC/SS) BY EACH EXPERIMENTAL GROUP DURING PERIOD BETWEEN DRUG DOSAGE AND INITIATION OF DEPRIVATION PERIOD

DRUG	DOSE (MG./KG.)	NOT EXPOSED		EXPOSED	
		SALINE	DRUG	SALINE	DRUG
SCOPOLAMINE	0.32	16.3	14.0	15.9	13.7
ATROPINE	10.0	18.7	16.0	19.0	16.0

TABLE 14

ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING WATER CONSUMPTION MEASURE

DOSE/DRUG	SOURCE	DF	MS	F*
0.32 MG./KG. SCOPOLAMINE	DRUG (A)	1	0	0.0
	EXPOSURE (B)	1	0	0.0
	INTERACTION (AXB)	1	19	0.05
10.0 MG./KG. ATROPINE	DRUG (A)	1	0	0.0
	EXPOSURE (B)	1	0	0.0
	INTERACTION (AXB)	1	17	0.04

* FOR 1 AND 20 DF, $F_{0.05} = 4.35$; $F_{0.01} = 8.10$

TABLE 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)

DRUG	DOSE (MG./KG.)	TIME FROM INITIAL EXPOSURE (HOURS)	NOT EXPOSED		EXPOSED	
			SALINE	DRUG	SALINE	DRUG
SCOPOLAMINE	0.32	3.0	0.3	0.8	0.0	1.1
		6.0	1.8	5.3	2.7	5.5
		12.0	6.8	6.1	6.1	6.6
		24.0	9.4	6.5	8.7	7.6
		3.0	0.0	0.1	0.1	0.3
		6.0	1.7	1.9	1.7	1.6
		12.0	3.9	4.3	3.9	4.2
		24.0	7.1	7.5	7.3	6.3
ATROPINE	10.0	3.0	0.07	0.9	0.03	1.0
		6.0	2.0	5.8	2.0	6.2
		12.0	5.9	6.0	5.9	6.3
		24.0	9.6	7.3	9.6	8.1
		3.0	0.06	0.0	0.03	0.02
		6.0	2.4	2.9	2.1	2.5
		12.0	5.6	5.6	5.7	4.8
		24.0	9.1	9.8	9.4	7.9

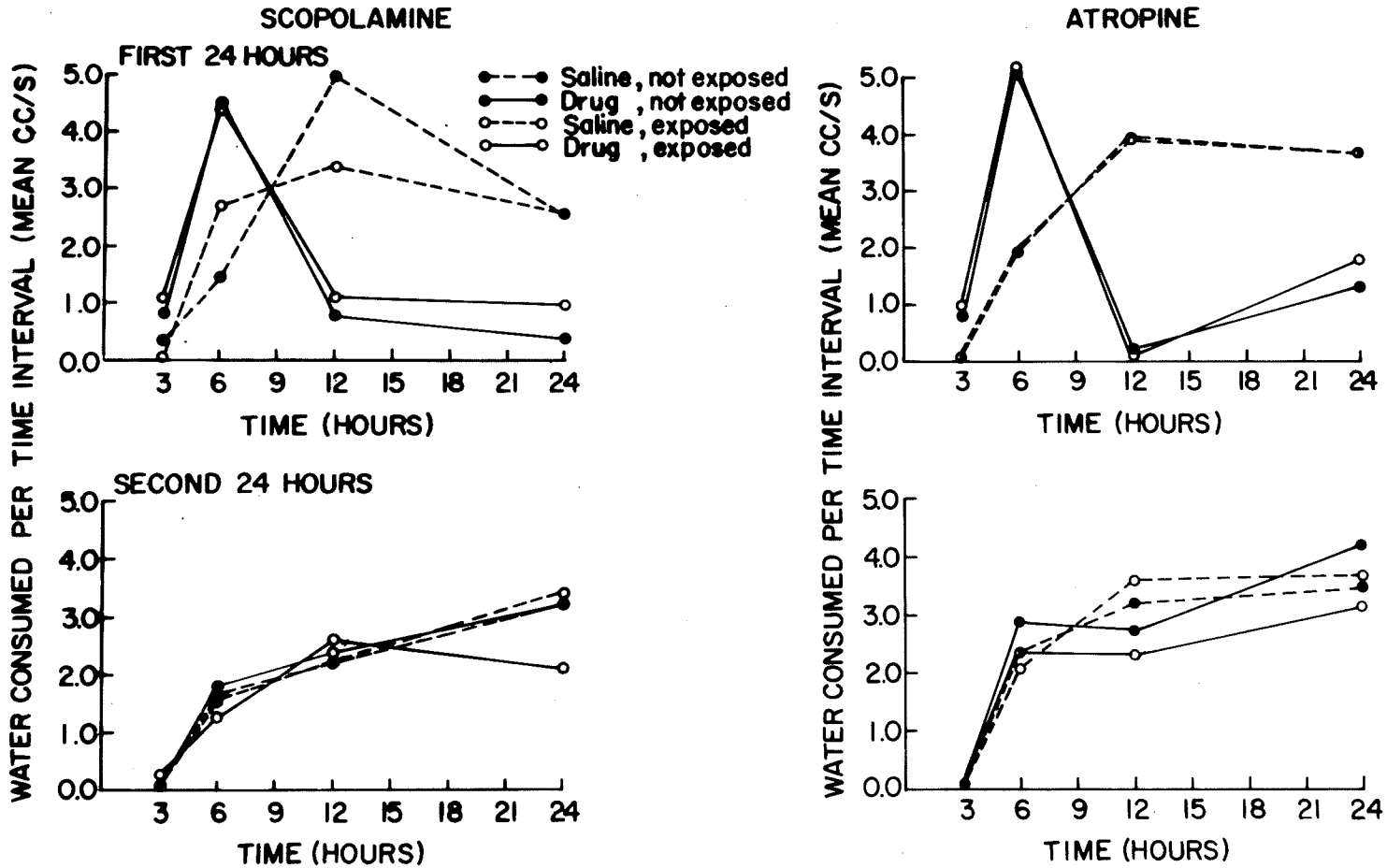

Fig. 5 Mean amount of water consumed by each experimental group (cc./subject) within various time periods following dosage with 0.32 mg./kg. Scopolamine, i.p. or 10.0 mg./kg. Atropine, i.p.

SIMILAR TO THOSE OF THE SALINE TREATED ANIMALS.

THE AMOUNT OF WATER CONSUMED, AS MEASURED BY RATE OF LICKING OF THE WATER TUBE DURING THE 15 MINUTE SECOND EXPOSURE PERIOD, WAS SIGNIFICANTLY GREATER ($P < 0.05$) FOR PREVIOUSLY EXPOSED SUBJECTS TREATED WITH SALINE RELATIVE TO NON-EXPOSED ANIMALS IN ALL EXPERIMENTS. PRIOR EXPOSED SCOPOLAMINE AND ATROPINE TREATED SUBJECTS, HOWEVER, MAINTAINED CONSUMPTION LEVELS MORE COMPARABLE TO NON-EXPOSED ANIMALS LIKEWISE DOSED (THE T-RATIO BETWEEN THE MEANS WAS NON-SIGNIFICANT IN THE INSTANCE OF BOTH DRUGS). THE DATA IN TERMS OF NUMBER OF LICKS ARE SUMMARIZED IN TABLE 16 WITH APPROPRIATE STATISTICAL ANALYSIS IN TABLE 17.

THE PRESENCE OF THE DRINKING TUBE DURING THE FIRST EXPOSURE HAD NO EFFECT ON DRUG MODIFIED APPROACH LATENCIES (TABLE 18). THE MEAN VALUES FOR BOTH ATROPINE AND SCOPOLAMINE WERE NOT SIGNIFICANTLY DIFFERENT (T-RATIO) FROM THOSE OBTAINED WITH THE USUAL PROCEDURE (TABLE 6).

STIMULUS PARAMETERS

CHAMBER ILLUMINATION MAINTAINED AT SPECIFIED WAVELENGTHS DURING EITHER ONLY THE INITIAL OR ONLY THE SECOND EXPOSURE DID NOT ALTER THE EFFECT OF SCOPOLAMINE ON APPROACH LATENCY. TABLE 19 SUMMARIZES THE RESULTS OF THESE EXPERIMENTS. NONE OF THE MEAN VALUE IN TABLE 19 WERE SIGNIFICANTLY DIFFERENT (T-RATIO) FROM THEIR COUNTERPARTS IN THE INITIAL EVALUATION OF SCOPOLAMINE (TABLE 6).

TABLE 16

MEAN NUMBER OF LICKS ON DRINKING TUBE PER 15.0 MINUTES FOLLOWING DOSAGE WITH SEVERAL DRUGS

DRUG	DOSE (MG./KG.)	NOT EXPOSED		EXPOSED		T-RATIO BETWEEN DRUG TREATED EXPOSED AND NON-EXPOSED GROUPS*
		SALINE	DRUG	SALINE	DRUG	
SCOPOL-AMINE	0.32	1600	1482	2468	1594	0.04
ATROPINE	10.0	1379	1462	2691	1394	0.04
D-AMPHET-AMINE	1.0	1338	1886	3497	2449	2.46
METHYL-ATROPINE	10.0	1677	1571	2568	1832	2.41

* FOR 10 DF, $T_{0.05} = 2.23$; $T_{0.01} = 3.17$

TABLE 17

ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING LICKING RATE MEASURE

DOSE/DRUG	SOURCE	DF	MS	F*
0.32 MG./KG. SCOPOLAMINE	DRUG (A)	1	1120938	4.60
	EXPOSURE (B)	1	1579062	5.08
	INTERACTION (AXB)	1	1011584	3.27
10.0 MG./KG. ATROPINE	DRUG (A)	1	1091763	5.01
	EXPOSURE (B)	1	1825336	4.99
	INTERACTION (AXB)	1	998321	2.26
1.0 MG./KG. D-AMPHETAMINE	DRUG (A)	1	884100	2.07
	EXPOSURE (B)	1	1763821	5.31
	INTERACTION (AXB)	1	1000101	3.10
10.0 MG./KG. METHYLATROPINE	DRUG (A)	1	962101	2.42
	EXPOSURE (B)	1	1499999	4.91
	INTERACTION (AXB)	1	1101720	3.31

* FOR 1 AND 20 DF, $F_{0.05} = 4.35$; $F_{0.01} = 8.10$

TABLE 18

MEAN APPROACH LATENCIES (0.01 MINS) FOLLOWING DOSAGE WITH SCOPOLAMINE AND ATROPINE WITH DRINKING TUBE PRESENT DURING INITIAL EXPOSURE PERIOD

DRUG	DOSE (MG./KG.) I.P.	NOT EXPOSED		EXPOSED	
		SALINE	DRUG	SALINE	DRUG
SCOPOLAMINE	0.32	131.4	139.6	29.9	126.0
ATROPINE	10.0	130.3	145.5	27.5	150.9

TABLE 19

EFFECT OF COLOURED ILLUMINATION ON MEAN APPROACH LATENCY VALUES (0.01 MINS) FOLLOWING A DOSE OF 0.32 MG./KG. SCOPOLAMINE

STIMULI VALUES (MU)	STIMULI PRESENT DURING:	NOT EXPOSED		EXPOSED	
		SALINE	DRUG	SALINE	DRUG
632.7	INITIAL EXPOSURE	135.4	134.9	27.7	133.0
	SECOND EXPOSURE	133.6	138.3	25.2	134.4
569.6	INITIAL EXPOSURE	139.2	140.3	28.8	134.0
	SECOND EXPOSURE	136.3	130.4	29.2	132.4
486.6	INITIAL EXPOSURE	138.5	137.5	33.7	133.3
	SECOND EXPOSURE	133.5	129.3	34.9	133.4

As the data in Table 20 indicate, intermittent interruption of chamber illumination only during the second exposure disrupted the effect of scopolamine on approach latency. However, all other values were similarly elevated with the exposed groups' latencies being higher than the non-exposed when the blinking light was present only during initial exposure or during both exposures, the drug effect was unaltered.

Table 20

Effect of Intermittant Illumination (3.0 Flashes per Second) on Scopolamine-Modified Approach Latency Values (0.01 Mins)

Stimuli Present During:		Not Exposed		Exposed	
		Saline	Drug	Saline	Drug
Initial Exposure	Latency	129.6	131.9	32.4	130.4
	T-ratio*	0.63	2.01	0.04	0.64
Second Exposure	Latency	213.2	231.6	160.1	167.5
	T-ratio*	7.62	8.71	9.12	10.81
Both Exposures	Latency	130.7	133.6	30.3	133.0
	T-ratio*	0.07	1.94	0.02	0.01

* Comparison between present values and those from initial evaluation of scopolamine (Table 6.). For 10 df, $T_{0.05} = 2.23$; $T_{0.01} = 3.17$.

Introduction of "white noise" only during the second exposure was also disruptive to the effect of scopolamine on approach latency. The presence of the sound only during the initial exposure or during both exposures did not alter the drug-effect. There was no observable difference in these actions

BETWEEN CONSTANT AND INTERMITTENTLY PRESENTED NOISE. DATA RELEVANT TO THOSE FINDINGS ARE PRESENTED IN TABLE 21.

RESPONSE PARAMETERS

TABLE 22 PRESENTS A SUMMARY OF THE DOSE-EFFECT DATA AS MEASURED AT VARIOUS TIMES POST-ADMINISTRATION BY THE PHOTOBEAM INTERRUPTION TECHNIQUE OF ASSESSING GENERAL ACTIVITY.

FOLLOWING A TEN MINUTE PRETREATMENT TIME, WITH THE EXCEPTION OF METHYLATROPINE AND D-AMPHETAMINE, ALL DRUGS, RELATIVE TO SALINE TREATMENT, EFFECTED INCREASES IN ACTIVITY AS DOSAGE WAS INCREASED. THE VARIABILITY ALSO TENDED TO BE GREATER AT EFFECTIVE DOSE LEVELS. METHYLATROPINE AND D-AMPHETAMINE WERE BIPHASIC IN ACTION IN THAT LOWER DOSES INCREASED ACTIVITY, HIGHER DOSES WERE INEFFECTIVE OR DECREASED ACTIVITY RELATIVE TO SALINE. SCOPOLAMINE, ATROPINE AND DITRAN WERE STILL EFFECTIVE AFTER 72 HOURS, BUT TO A LESSER EXTENT THAN AFTER TEN MINUTES. ALSO, PREVIOUSLY EXPOSED SUBJECTS TENDED TO BE LESS ACTIVE AT 72 HOURS THAN ANIMALS NAIVE TO THE CHAMBER. THESE RELATIONSHIPS ARE GRAPHICALLY REPRESENTED IN FIGURE 6.

TABLE 23 PRESENTS PHOTOBEAM INTERRUPTION VALUES FOR SEVERAL DOSES OF SCOPOLAMINE WHEN THE VALUES WERE USED AS THE MEASURE IN PLACE OF APPROACH LATENCY IN THE DRINKING TUBE PROCEDURE. IT APPEARS THAT THESE VALUES, AS WITH APPROACH LATENCY, REFLECT THE ATTENUATING EFFECT OF THE DRUG. ALSO, AS WITH DOSE-EFFECT MEASURED BY APPROACH LATENCY (TABLE 8), THE MOTOR

TABLE 21

EFFECT OF VARIOUS CONDITIONS OF "WHITE NOISE" ON SCOPOLAMINE MODIFIED APPROACH LATENCY VALUES (0.01 MINS)

"WHITE NOISE" STATE	STIMULUS PRESENT DURING		NOT EXPOSED SALINE	NOT EXPOSED DRUG	EXPOSED SALINE	EXPOSED DRUG
CONSTANT	INITIAL EXPOSURE	LATENCY	134.1	136.0	33.8	133.1
		T-RATIO*	0.01	0.0	0.05	1.62
	SECOND EXPOSURE	LATENCY	182.6	195.5	161.8	178.3
		T-RATIO*	5.43	5.81	8.76	8.93
	BOTH EXPOSURES	LATENCY	143.3	137.5	31.9	130.5
		T-RATIO*	1.01	0.03	0.02	0.68
INTERMITTENT	INITIAL EXPOSURE	LATENCY	131.7	130.7	28.2	128.1
		T-RATIO*	0.09	1.16	0.0	1.06
	SECOND EXPOSURE	LATENCY	227.9	227.6	159.7	197.3
		T-RATIO*	9.76	12.01	8.73	7.93
	BOTH EXPOSURES	LATENCY	138.1	133.9	30.3	137.1
		T-RATIO*	0.06	0.91	0.01	0.0

* COMPARISON BETWEEN PRESENT VALUES AND THOSE FROM INITIAL EVALUATION OF SCOPOLAMINE (TABLE 6). FOR 10 DF, $T_{0.05} = 2.23$; $T_{0.01} = 3.17$.

TABLE 22

MEAN AND STANDARD DEVIATION FOR NUMBER OF PHOTOBEAM INTERRUPTIONS PER 15 MINUTES FOLLOWING VARIOUS DOSES OF SEVERAL DRUGS*

DRUG	DOSE (MG./KG.)	PRETREATMENT TIME 10.0 MINUTES	72. HOURS EXPOSED	72. HOURS NOT EXPOSED
SCOPOLAMINE	0.1	126 (84.0)	126 (72.8)	139 (96.6)
	0.32	200 (54.7)	134 (43.8)	339 (125.3)
	1.0	360 (119.6)	159 (38.08)	292 (175.8)
	3.2	393 (263.2)	191 (74.16)	329 (165.5)
	SALINE	121 (38.08)	102 (27.5)	127 (31.05)
ATROPINE	1.0	133 (55.3)	118 (54.9)	158 (49.4)
	3.2	215 (68.6)	201 (131.9)	197 (81.0)
	10.0	318 (101.5)	232 (109.0)	287 (108.2)
	32.0	318 (62.9)	318 (130.8)	343 (143.5)
	SALINE	134 (29.6)	117 (55.1)	131 (28.6)
METHYLATROPINE	0.32	160 (54.6)	146 (39.1)	125 (43.9)
	1.0	146 (55.5)	139 (41.4)	129 (79.2)
	3.2	215 (74.4)	142 (28.9)	136 (23.6)
	10.0	141 (20.6)	140 (38.6)	140 (38.6)
	SALINE	153 (62.8)	119 (48.4)	141 (22.2)

TABLE 22 (CONTINUED)

DRUG	DOSE (MG./KG.)	PRETREATMENT TIME 10.0 MINUTES	72. HOURS EXPOSED	72. HOURS NOT EXPOSED
DITRAN	0.1	149 (22.0)	124 (15.2)	139 (25.9)
	0.32	260 (73.8)	207 (109.1)	211 (109.5)
	1.0	314 (124.9)	193 (119.1)	219 (108.6)
	3.2	429 (20.5)	282 (54.6)	303 (96.0)
	SALINE	148 (25.6)	107 (12.6)	141 (21.0)
D-AMPHETAMINE	0.32	141 (29.7)	106 (48.8)	143 (30.5)
	1.0	221 (13.7)	126 (28.4)	129 (17.3)
	3.2	341 (40.7)	110 (10.5)	142 (25.8)
	10.0	131 (178.6)	118 (10.5)	144 (36.6)
	SALINE	125 (55.9)	111 (6.4)	130 (22.3)
METHYLPHENIDATE	0.32	132 (52.1)	112 (6.8)	129 (12.3)
	1.0	139 (28.3)	114 (21.1)	141 (10.1)
	3.2	299 (66.6)	100 (39.9)	129 (19.4)
	10.0	390 (134.5)	107 (17.0)	141 (7.4)
	SALINE	134 (13.8)	105 (29.6)	137 (24.3)

*S.D.'S ARE IN PARENTHESIS.

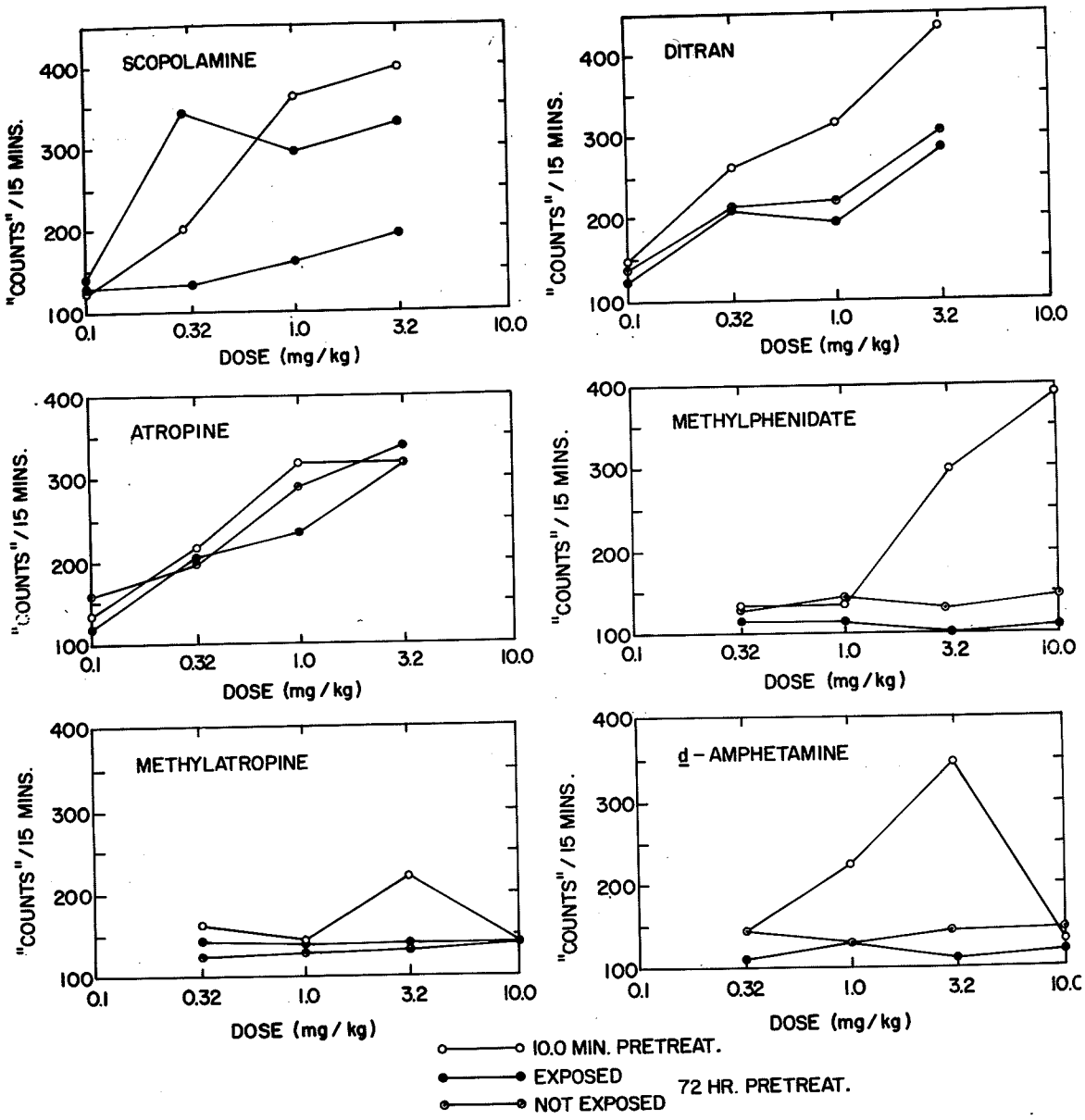

FIGURE 6 DOSE EFFECT CURVES FOR GENERAL ACTIVITY AT VARIOUS TIMES FOLLOWING SCOPOLAMINE, ATROPINE, METHYLATROPINE, DITRAN, d-AMPHETAMINE, AND METHYLPHENIDATE, ALL ADMINISTERED INTRAPERITONEALLY.

ACTIVITY VALUES SHOW AN "ALL OR NONE" EFFECT. AN ANALYSIS OF VARIANCE, SUMMARIZED IN TABLE 24, FURTHER VERIFIES THAT THE ACTIVITY MEASURE IS SENSITIVE TO THE DRUG EFFECT IN A MANNER SIMILAR TO APPROACH LATENCY.

TABLE 23

MEAN NUMBER OF PHOTOBEAM INTERRUPTIONS UNTIL DRINKING TUBE APPROACH FOR SEVERAL DOSES OF SCOPOLAMINE

DOSE (MG./KG.)	NOT EXPOSED		EXPOSED	
	SALINE	DRUG	SALINE	DRUG
0.1	29	28	27	29
0.32	34	42	8	33
1.0	32	30	6	38

TABLE 24

ANALYSIS OF VARIANCE FOR DRUG AND EXPOSURE GROUPS EMPLOYING PHOTOBEAM MOTOR ACTIVITY MEASURE

DOSE OF SCOPOLAMINE	SOURCE	DF	MS	F*
0.1	DRUG (A)	1	9	0.03
	EXPOSURE (B)	1	4862	9.21
	INTERACTION (AXB)	1	81	1.08
0.32	DRUG (A)	1	6456	11.72
	EXPOSURE (B)	1	6670	12.22
	INTERACTION (AXB)	1	3127	5.72
1.0	DRUG (A)	1	7291	12.80
	EXPOSURE (B)	1	6830	11.91
	INTERACTION (AXB)	1	2481	4.14

* FOR 1 AND 20 DF, $F_{0.05} = 4.35$; $F_{0.01} = 8.10$.

THERE APPEARED TO BE A DIRECT LINEAR RELATIONSHIP BETWEEN LEVEL OF DEPRIVATION AND ACTIVITY LEVEL - AS THE FORMER WAS INCREASED, THE LATTER INCREASED. TABLE 25 SHOWS THE EFFECT IN TERMS OF EACH OF THREE REINFORCERS.

TABLE 25

MEAN AND STANDARD DEVIATION FOR PHOTOBEAM INTERRUPTIONS AT VARIOUS DERIVATION LEVELS FOR WATER, CONDENSED MILK AND LABORATORY CHOW*

DEPRIVATION LENGTH (HOURS)	REINFORCER		
	WATER	MILK	CHOW
3.0	142	94	117
	(50.9)	(66.9)	(58.1)
6.0	169	139	153
	(18.4)	(26.4)	(31.4)
12.0	157	197	202
	(50.3)	(58.5)	(22.1)
24.0	224	225	225
	(48.3)	(75.8)	(72.7)
48.0	228	279	305
	(69.4)	(112.7)	(71.6)
72.0	266	269	309
	(86.3)	(63.6)	(51.2)

*S.D.'S ARE IN PARENTHESIS.

THE EFFECT OF INTRACRANIALLY ADMINISTERED ATROPINE AND METHYLATROPINE ON MOTOR ACTIVITY IS PRESENTED IN TABLE 26. THE DRUGS APPEARED TO MARKEDLY INCREASE ACTIVITY WITH THE HIGHER DOSE LEVELS IN MUCH THE SAME WAY THEY AFFECTED SUCH CHANGES FOLLOWING INTRAPERITONEAL INJECTION.

TABLE 26

MEAN AND STANDARD DEVIATION FOR NUMBER OF PHOTOBEAM INTERRUPTIONS PER 15 MINUTES FOLLOWING INTRACRANIAL DOSES OF ATROPINE AND METHYLATROPINE*

DOSE (MG.)	ATROPINE	DRUG	METHYLATROPINE
0.001	126		131
	(51.1)		(51.4)
0.003	178		212
	(58.4)		(56.7)
0.01	272		290
	(146.3)		(38.1)
SALINE	116		133
	(70.2)		(64.3)

* S.D.'S ARE IN PARENTHESIS.

ANCILLARY DATA

THE PRIMARY FINDINGS, OUTSIDE OF THOSE DESCRIBED ABOVE, INVOLVED THE GENERAL EFFECTS OF MANY OF THE DRUGS. THESE ARE DETAILED IN TABLE 27.

TABLE 27

SYMPTOMATOLOGICAL SUMMARY OF THE EFFECTS OF THE DRUGS EMPLOYED IN THE VARIOUS EXPERIMENTS

DRUG	DOSE (MG./KG.)	EFFECTS*
SCOPOLAMINE	0.032	SL. MYDRIASIS
	0.1	SL. MYDRIASIS
	0.32	MOD. MYDRIASIS
	1.0	MKD. MYDRIASIS
		SL. TACHYPNEA
		SL. INC. MOTOR ACTIVITY
	3.2	MKD. MYDRIASIS
		SL. TACHYPNEA
		MOD. INC. MOTOR ACTIVITY
ATROPINE	1.0	MOD. MYDRIASIS
	3.2	MKD. MYDRIASIS
	10.0	MKD. MYDRIASIS
	32.0	SL. INC. MOTOR ACTIVITY
METHYLATROPINE	1.0	MOD. MYDRIASIS
	3.2	MOD. MYDRIASIS
	10.0	MOD. MYDRIASIS
	32.0	MOD. MYDRIASIS
DITRAN	0.1	MOD. MYDRIASIS
	0.32	MOD. MYDRIASIS
		SL. TACHYPNEA
		SL. INC. MOTOR ACTIVITY
	1.0	MKD. MYDRIASIS
		MOD. TACHYPNEA
		MOD. INC. MOTOR ACTIVITY
	3.2	MKD. MYDRIASIS
		MOD. TACHYPNEA
		MOD. INC. MOTOR ACTIVITY
CHLORPROMAZINE	3.2	MKD. DEC. MOTOR ACTIVITY
		SL. DYSPNEA
		LOSS OF PINNAL, MYOTATIC REFLEXES
		MOD. PTOSIS
		MOD. HYPOTONIA
		SL. HYPOTHERMIA
		SL. INC. DEFECATION & MICTURATION

TABLE 27 (CONTINUED)

DRUG	DOSE (MG./KG.)	EFFECTS*
ESERINE	0.32	SL. TACHYPNEA MOD. FASICULATION MOD. DEC. MOTOR ACTIVITY MOD. INC. DEFECATION & MICTURATION MOD. TACTILE HYPERSENSITIVITY SL. HYPOTONIA
HEMICHOLINIUM	0.5	SL. DEC. MOTOR ACTIVITY SL. TACHYPNEA
METHYPHENIDATE	0.32	NO OBSERVABLE EFFECTS
	1.0	SL. INC. MOTOR ACTIVITY
	3.2	SL. INC. MOTOR ACTIVITY
	10.0	MOD. INC. MOTOR ACTIVITY SL. TACHYPNEA
D-AMPHETAMINE	0.32	SL. TACHYPNEA SL. PILOERECTION SL. TACTILE HYPERSENSITIVITY
	1.0	MOD. INC. MOTOR ACTIVITY SL. TACHYPNEA MOD. TACTILE HYPERSENSITIVITY
	3.2	MKD. INC. MOTOR ACTIVITY MOD. TACHYPNEA SL. TACHYCARDIA MKD. TACTILE HYPERSENSITIVITY
	10.0	MKD. INC. MOTOR ACTIVITY MOD. DEC. MOTOR ACTIVITY MOD. TACHYPNEA MOD. TACHYCARDIA SL. TACTILE HYPERSENSITIVITY STRAUB TAIL
TACRINE	1.0	NO OBSERVABLE EFFECTS

* SL. = SLIGHT
MOD. = MODERATE
MKD. = MARKED
INC. = INCREASED
DEC. = DECREASED

CHAPTER IV

DISCUSSION

PHARMACOLOGICAL CONSIDERATIONS

THE METHOD FOR MEASURING APPROACH LATENCY AS A FUNCTION OF PRIOR EXPOSURE UTILIZED IN THE PRESENT STUDIES SEEMED TO BE EQUIVALENT TO THE TECHNIQUE DESCRIBED BY CARLTON (1966B, 1968; CARLTON & VOGEL, 1966) IN THAT IT WAS SELECTIVELY SENSITIVE TO THE ACTION OF SEVERAL DRUGS KNOWN TO HAVE POTENT MUSCARINIC ANTICHOLINERGIC PROPERTIES. SPECIFICALLY, SUFFICIENT INTRAPERITONEAL DOSES OF SCOPOLAMINE, ATROPINE AND DITRAN CLEARLY AND MARKEDLY INHIBITED THE LATENCY ATTENUATING (OR, IN CARLTON'S TERMS, HABITUATION) EFFECT OF PREVIOUS EXPOSURE TO THE CHAMBER.

METHYLATROPINE WAS THE ONE MUSCARINIC ANTICHOLINERGIC DRUG TESTED THAT PROVED INEFFECTIVE IN ALTERING THE EFFECT OF PRIOR EXPOSURE ON LATENCY. THE LACK OF ACTIVITY, HOWEVER, ONLY OCCURRED WITH INTRAPERITONEAL DOSAGE. THE DRUG WAS EFFECTIVE, IDENTICALLY TO THE OTHERS, WHEN IT WAS ADMINISTERED INTRACRANIALLY, THEREBY LENDING CREDENCE TO THE AFOREMENTIONED GENERALLY ACCEPTED CONTENTION (E.G., THOMPSON & SCHUSTER, 1968) THAT IT DOES NOT EXERT A BEHAVIOURALLY REFLECTED ACTION ON CNS TISSUES BECAUSE IT DOES NOT PASS THE SO-CALLED BLOOD BRAIN BARRIER (BAKAY, 1956; MILLERN & HESS, 1958). OBVIOUSLY, INJECTING DRUGS DIRECTLY INTO

THE BRAIN DOES NOT MITIGATE THEIR ACTING PERIPHERALLY. AS FELDBERG POINTS OUT:

> THERE IS NO DOUBT THAT SUBSTANCES INJECTED INTRAVENTRICULARLY OR PERFUSED THROUGH THE CEREBRAL VENTRICLES CAN BE ABSORBED INTO THE BLOOD STREAM (1963, P. 30).

HOWEVER, SINCE METHYLATROPINE WAS BEHAVIOURALLY INACTIVE WHEN ADMINISTERED SYSTEMICALLY, IT WOULD SEEM THE ONLY CONCLUSION POSSIBLE IS THAT THE DRUG DOES, IN FACT, ACT WITHIN THE CNS WHEN PREVENTING THE PRIOR EXPOSURE INDUCED DECREASE IN LATENCY.

THE POINT IS FURTHER EMPHASIZED BY THE GENERAL ACTIVITY DATA (TABLE 26) WHICH PRESENT SIMILAR CIRCUMSTANCES; I. E., INTRACRANIALLY ADMINISTERED METHYLATROPINE INCREASED ACTIVITY IN A MANNER CHARACTERISTIC OF OTHER MUSCARINIC ANTICHOLINERGICS WHILE INTRAPERITONEAL DOSAGE WAS RELATIVELY INEFFECTIVE. INTERESTINGLY, THE 3.2 MG./KG., I.P., DOSE OF METHYLATROPINE DID INDUCE A MODERATE ACTIVITY INCREASE. A SIMILAR FINDING WAS REPORTED BY MEYERS ET AL. (1964) USING A DOSE OF 2.1 MG./KG. IN THEIR STUDY, HIGHER DOSES (UP TO 16.8 MG./KG.) WERE EITHER INEFFECTIVE OR SLIGHTLY DEPRESSED ACTIVITY. THAT EFFECT WAS NOT OBSERVED IN THE PRESENT ACTIVITY EXPERIMENTS, BUT IT HAS LONG BEEN ESTABLISHED FOR VARIOUS MUSCARINIC ANTICHOLINERGICS (MACHT, 1924).

THESE BIPHASIC ACTIONS OF SYSTEMICALLY ADMINISTERED METHYLATROPINE MAY BE A FUNCTION OF THE COMPLEX TEMPORAL PERIPHERAL-CENTRAL RELATIONSHIPS REPORTED WITH SEVERAL TROPIC ACID ESTERS (HERXHEIMER, 1958; OSTFELD, MACHNE & UNNA, 1960). FOR EXAMPLE, OSTFELD ET AL. (1960) USING HUMAN SUBJECTS, FOUND THAT

THE PERIPHERAL EFFECTS OF A GIVEN DOSE OF ATROPINE WERE MAXIMAL AT TWO HOURS, DISAPPEARING AFTER FOUR HOURS, WHEREAS ELECTROENCEPHALOGRAPHIC ACTIVITY AND BEHAVIOURAL EFFECTS WERE MAXIMAL AT FOUR HOURS DISAPPEARING AFTER TEN HOURS. ON THE ASSUMPTION THAT THESE RELATIONSHIPS VARY WITH DOSE, THE ISSUE COULD BE RESOLVED BY SYSTEMATIC MULTIPARAMETIC TIME-COURSE-DOSE EVALUATIONS OF METHYLATROPINE.

ALSO AS REPORTED BY CARLTON (1968), CHLORPROMAZINE AND D-AMPHETAMINE WERE INEFFECTIVE IN THE PRESENT STUDIES IN REGARD TO ALTERING THE INFLUENCE OF PREVIOUS EXPERIENCE ON APPROACH LATENCY. AS WAS POINTED OUT, CARLTON (1968) USED THAT FINDING TO: 1.) CONCLUDE THAT GENERAL CNS DEPRESSION OR STIMULATION IS NOT A CONTINGENT CONDITION RELEVANT TO MODIFICATION OF APPROACH LATENCY AND 2.) TO INDICATE THAT ALTERATION OF MOTOR ACTIVITY HAS NO DIRECT EFFECT ON APPROACH LATENCY. THE FACT THAT ALL DOSES OF D-AMPHETAMINE TESTED IN THE PRESENT EXPERIMENTS WERE NON-ACTIVE IN AFFECTING ANY ASPECT OF THE APPROACH LATENCY MEASURE WHILE ALSO HAVING MODERATE TO MARKED BIPHASIC EFFECTS ON MOTOR ACTIVITY, CLEARLY SUPPORTS THE LATTER CONTENTION; I.E., THE CHANGES IN APPROACH LATENCY ARE NOT A FUNCTION OF MOTOR ACTIVITY PER SE.

HOWEVER, THE FORMER CONTENTION SUFFERS FROM AN IMPORTANT SEMANTIC VAGUENESS - ONE THAT IS UNFORTUNATELY QUITE COMMON IN PSYCHOPHARMACOLOGICAL DISCOURSE. COMMENTING ON THE SAME ISSUE IN A PAPER BY COOK AND KELLEHER (1962), MARRAZZI, ADAPTING A JACKSONIAN (1888) TENET TO CONTEMPORARY PSYCHOPHARMACOLOGY, SAID:

> I SUGGEST THAT IT IS IMPROPER TO CLASSIFY A DRUG AS A STIMULANT OR A DEPRESSANT ON THE BASIS OF BEHAVIORAL ACTION. THOSE TERMS ORIGINATED IN AN ANALYSIS OF EFFECTS ON CELLS - IN THIS CASE ON CELLS IN THE NERVOUS SYSTEM - AND THE ONLY THING THAT CAN HAPPEN IS THAT THEY CAN BE EITHER STIMULATED OR DEPRESSED. IT IS NOT CORRECT TO BELIEVE THAT INHIBITION OF THE NERVOUS SYSTEM ALWAYS RESULTS IN DECREASED ACTIVITY BECAUSE THIS DYSINHIBITION OR RELEASE FROM INHIBITION RESULTS IN INCREASED ACTIVITY. LIKEWISE, EXCITATION OF THE NERVOUS SYSTEM DOES NOT ALWAYS RESULT IN INCREASED BEHAVIORAL ACTIVITY... (1962, P. 335).

IN EFFECT, THE POINT CANNOT BE DEFINITIVELY RESOLVED SINCE CARLTON DID NOT SPECIFY WHAT IS BEING STIMULATED AND/OR DEPRESSED. IN ANY INSTANCE PRESENT NOTIONS REGARDING THE SITE AND MODE OF ACTION OF CHLORPROMAZINE AND THE AMPHETAMINES ARE NOT CONCLUSIVE ENOUGH TO ALLOW SUCH SPECIFICATION (JARVIK, 1965; WEISS & LATIES, 1962).

STILL, SOME RELEVANT FACTS ARE AVAILABLE. IT WILL BE RECALLED CARLTON (1963) POSTULATED THE EXISTENCE OF AN ANTAGONISTIC ADRENERGIC ACTIVATING SYSTEM AND DEMONSTRATED THAT AMPHETAMINE IS SYNERGISTIC WITH ATROPINE (CARLTON & DIDAMO, 1961). IT COULD, THEREFORE, BE POSTULATED THAT D-AMPHETAMINE WOULD INHIBIT PRIOR EXPERIENCE INCREASED DRINKING TUBE APPROACH BEHAVIOUR. CONVERSELY, AMONG ITS MANY ACTIONS, CHLORPROMAZINE IS A POTENT α-ADRENERGIC BLOCKING AGENT (AHLQUIST, 1966; SLY & HEIMLICK, 1966; THOENE, HURLIMANN & HAEFELY, 1965). THEREFORE IT COULD CONCEIVABLY PREVENT EXPRESSION OF THE ADRENERGIC ACTIVATING SYSTEM WHICH WOULD BE BEHAVIOURLY REFLECTED BY FACILITATION OF PREVIOUS EXPOSURE INDUCED DECREASES IN APPROACH LATENCY. IN EFFECT, THEN, D-AMPHETAMINE SHOULD ACT SIMILARLY TO THE MUSCARINIC

ANTICHOLINERGICS, CHLORPROMAZINE, SIMILARLY TO WHAT WOULD BE EXPECTED FROM PARASYMPATHOMIMETIC AGENTS. PUT ANOTHER WAY, ON THE BASIS OF THEIR ESTABLISHED ACTION, D-AMPHETAMINE BY STIMULATING THE ADRENERGIC SYSTEM WOULD BE EXPECTED TO DEPRESS APPROACH LATENCY, CHLORPROMAZINE BY DEPRESSING THE ADRENERGIC SYSTEM TO STIMULATE APPROACH LATENCY. THE TERM - INOLOGICAL AMBIGUITY IS, THUS, EVIDENT.

OF COURSE, THE FAILURE OF THE DRUGS TO MANIFEST ANY EFFECT MAKES THE MATTER TOTALLY SPECULATIVE. IN FACT, THE ABSENCE OF THESE POSTULATED EFFECTS CASTS SOME DOUBT ON THE EXISTENCE OF AN ADRENERGIC COMPONENT IN THE SCHEME. THE ISSUE WOULD HAVE TO BE RESOLVED BY A DETAILED ANALYSIS OF THE ADRENERGIC MECHANISM (SUCH CONSIDERATIONS AS ITS RELATIVE α AND β COMPONENTS, THE SPECIFIC RELATIVE CONTENT OF VARIOUS CATECHOLAMINES, ETC.), HOW IT INTERACTS WITH THE CHOLINERGIC MECHANISM (ARE THEY MUTUALLY ANTAGONISTIC, BIPHASIC, ETC.) AND HOW THESE FACTORS ARE REFLECTED BEHAVIOURALLY. PRIMARY, OF COURSE, WOULD BE DOSE-EFFECT DATA ON CHLORPROMAZINE IN THE INSTANCE OF APPROACH LATENCY.

IF THE CHANGES IN THE EFFECT OF PRIOR EXPOSURE ON APPROACH LATENCY ARE DIRECTLY RELATED TO CHOLINERGIC ACTIVITY, THEN PARASYMPATHOMIMETIC DRUGS WOULD BE EXPECTED TO FACILITATE THE BEHAVIOUR JUST OPPOSITE TO THE WAY THAT MUSCARINIC ANTICHOLINERGIC SUBSTANCES INHIBIT IT. AS WAS POINTED OUT EARLIER, CARLTON (1968) OFFERED EVIDENCE TO THIS EFFECT AS A MAJOR PROPOSITION IN SUPPORT OF HIS NOTION. THE ASSESSMENT OF ESERINE DESCRIBED IN THIS REPORT

FAILED TO SHOW ANY SUCH FACILITATION. HOWEVER, SINCE THE ANTAGONISM STUDIES MOST CLEARLY INDICATED INVOLVEMENT OF ESERINE, THE FAILURE TO DEMONSTRATE ENHANCEMENT OF THE PRIOR EXPOSURE EFFECT COULD SIMPLY BE A REFLECTION OF THE INSENSITIVITY OF THE METHOD TO CHANGES OF THAT TYPE (E.G., PERHAPS THE APPROACH LATENCY VALUES FOR UNAFFECTED ANIMALS REPRESENTS A PHYSICAL MAXIMUM).

ESERINE QUITE EFFECTIVELY ANTAGONIZED THE EFFECT OF SCOPOLAMINE BY EITHER OF TWO ROUTES OF ADMINISTRATION. TACRINE, LIKEWISE, WAS AN EFFICACIOUS ANTAGONIST OF EITHER SCOPOLAMINE OR DITRAN. THESE DATA ARE HIGHLY SUGGESTIVE IN REGARD TO THE NOTION THAT CHOLINERGIC CHANGES OCCUR SIMULTANEOUSLY WITH EXTEROENVIRONMENTAL EXPERIENTIAL CONDITIONS. IN FACT, THEY DEMONSTRATE THAT VARYING THE ONGOING CHOLINERGIC ACTIVITY WILL RESULT IN PREDICTABLE CHANGES IN BEHAVIOUR. THAT, OF COURSE, IS CARLTON'S (1963) MOST BASIC CONTENTION. THE ANTAGONISM DATA, THEN, DO NOT IN ANY WAY ELABORATE ON THE NOTION, BUT RATHER, SIMPLY ENHANCE ITS PHARMACOLOGICAL CREDENCE.

HEMICHOLINIUM (H-3) IS PRESENTLY BELIEVED TO MANIFEST ITS ACTION OF INHIBITING ACETYLCHOLINE RE-SYNTHESIS BY RENDERING THE NEURAL MEMBRANE IMPERMEABLE TO CHOLINE (BURN, 1963; CHANG & RAND, 1960; ELMQUIST & QUASTEL, 1965; ECCLES, 1964; LONG, EVANS & WONG, 1967; MACINTOSH, BIRKS & SASTRY, 1956; SCHUELER, 1960). THIS IS IN CONTRAST TO MUSCARINIC ANTICHOLINERGICS WHICH ARE SAID TO ACT BY COMPETING WITH ACETYLCHOLINE AT RECEPTOR SITES (INNES & NICKERSON, 1965). HOWEVER, IN BOTH INSTANCES THE FINAL RESULT

IS THE SAME - NON-ACTIVATION OF THE POST-SYNAPTIC MEMBRANE (DURELL, GARLAND & FRIEDEL, 1969), I.E., BLOCKAGE OF TRANSMISSION. THUS, ON THE BASIS OF CARLTON'S (1963) HYPOTHESIS, THE BEHAVIOURAL RESULT FOLLOWING ADMINISTRATION OF EITHER HEMICHOLINIUM OR A MUSCARINIC ANTICHOLINERGIC AGENT COULD BE THE SAME. THE RESULTS OF THE PRESENT EXPERIMENTATION DO NOT REVEAL ANY EFFECT OF HEMICHOLINIUM ON PRIOR EXPERIENCE MODIFIED APPROACH LATENCY.

IT SHOULD BE POINTED OUT IMMEDIATELY THAT THE DATA INVOLVE ONLY ONE DOSE OF HEMICHOLINIUM - AN APPARENT VIOLATION OF SOUND PHARMACOLOGICAL PROCEDURE AS DISCUSSED EARLIER. THE DRUG, HOWEVER, HAS AN EXTREMELY LIMITED POTENCY RANGE BETWEEN LETHAL AND INACTIVE DOSE LEVELS (BARNES & ELTHERINGTON, 1965; MARSHALL & LONG, 1959; SCHUELER, 1960) AND THERE IS NO EVIDENCE OF ANY BIPHASIC ACTION (ELMQVUIST & QUASTEL, 1965; SCHUELER, 1960). IN ADDITION, BECAUSE OF ITS MODE OF ACTION, HEMICHOLINIUM WOULD BE EXPECTED TO MANIFEST ITS EFFECT ONLY IN ACETYLCHOLINE DEPLETED TISSUES. WHETHER THERE WAS SUFFICIENT PRIOR ACTIVITY TO INDUCE SUCH DEPLETION CANNOT BE DETERMINED FROM THE PRESENT EXPERIMENTS.

MORE PRECISELY, THEN, USING A DOSE OF HEMICHOLINIUM THAT WOULD HAVE A REASONABLE PROBABILITY OF SHOWING AN EFFECT, NONE WAS OBSERVED. IT WOULD THUS SEEM THAT, CONTRARY TO CARLTON'S (1963) BELIEF, DEACTIVATION OF CHOLINERGIC TRANSMISSION, IN ITSELF, IS NOT THE SIGNIFICANT PHYSIOLOGICAL SUBSTRATE IN REGARD TO MODIFYING THE INFLUENCE OF EXPERIENCE. EVIDENCE EXISTS (BOVET-NITTI, 1966) WHICH INDICATES THAT NICOTINE FACILITATES

BEHAVIOUR IN A MANNER SIMILAR TO MUSCARINIC ANTICHOLINERGIC DRUGS (AS DISCUSSED IN THE INTRODUCTION). FROM THAT, IT COULD BE POSTULATED THAT PERHAPS ACETYLCHOLINE REFLECTS A MUSCARINIC-NICOTINIC ACTION AT THE BEHAVIOURAL LEVEL SIMILAR TO THAT SEEN IN PERIPHERAL VASCULAR ACTIVITY (BURN, 1963). IN THE PRESENCE OF ATROPINE, INCREASED LEVELS OF ACETYLCHOLINE AFFECT BLOOD PRESSURE IN A MANNER SIMILAR TO THAT FOLLOWING INJECTIONS OF NICOTINE. HOWEVER, SINCE THE NICOTINIC EFFECT IS THOUGHT TO INVOLVE ADRENERGIC MECHANISMS, ITS POSTULATION DOES NOT TOTALLY COMPROMISE CARLTON'S (1963) CONCEPT OF A DUAL CHOLINERGIC-ADRENERGIC MECHANISM. THE NOTION IS COMPLICATED BY RECENT EVIDENCE SUGGESTING THAT HEMICHOLINIUM MAY HAVE NONCHOLINERGIC ACTIONS IN THAT SOME OF ITS EFFECTS ON AXONAL CONDUCTION CANNOT BE ANTAGONIZED BY CHOLINES (FRAZIER, NARAHASHI & MOORE, 1969).

CONCERNING FURTHER THE PROBLEM OF METHODOLOGICAL INSENSITIVITY MENTIONED ABOVE, THE DOSE-EFFECT DATA ALSO REVEAL POSSIBLE INADEQUACIES. THE ACTIVE DRUGS DO NOT EXPRESS GRADUATED DOSE-EFFECT RELATIONSHIPS IN THEIR ATTENUATING EFFECT ON PRIOR EXPOSURE, BUT INSTEAD SHOW TOTAL INHIBITION ONCE A SPECIFIC DOSE LEVEL (A THRESHOLD?) HAS BEEN EXCEEDED. THAT THESE DRUGS DO HAVE GRADUATED EFFECTS ON BEHAVIOUR IS EVIDENT FROM CONSIDERATION OF THE DOSE-EFFECT VALUES WHEN GENERAL ACTIVITY WAS MEASURED (FIGURE 6). FURTHERMORE, ALL BEHAVIOURS OF THE TYPE UNDER CONSIDERATION - EXTINCTION, HABITUATION OR WHATEVER - SHOW A GRADUATED COURSE OF DEVELOPMENT THAT WOULD MOST LIKELY BE

PARALLELED BY A SPATIALLY OR TEMPORALLY NON-SALTATORY PHYSIOLOGICAL MECHANISM. TO CONCEIVE OTHERWISE WOULD BE CONTRARY TO EVERY KNOWN FACT CONCERNING NEURAL ACTIVITY CORRELATES (E.G., PFAFFMANN, 1959). AGAIN, IT MUST BE CONCLUDED THAT THE MEASURE IS SIMPLY INSENSITIVE TO SMALL CHANGES.

THE PHARMACOLOGICAL MANIPULATIONS DESCRIBED HEREIN HAVE SERVED TO CLARIFY FOUR SIGNIFICANT POINTS: 1.) THE METHYLATROPINE DATA SEEM TO INDICATE THAT THE DRUG ACTIONS ASSOCIATED WITH CHANGES IN THE INFLUENCE OF PRIOR EXPOSURE ON APPROACH LATENCY DO OCCUR WITHIN THE CNS, 2.) THE DOSE-EFFECT AND ANTAGONISM DATA (ESPECIALLY THE LATTER) SUGGEST THAT THE ACTION IS SPECIFIC TO DRUGS CHARACTERIZED AS MUSCARINIC ANTICHOLINERGIC AGENTS, BUT 3.) THE ACTION - AS SUGGESTED BY THE HEMICHOLINIUM DATA - IS NOT SIMPLY A MATTER OF CHOLINERGIC BLOCKADE, AND 4.) THERE ARE REASONS TO DOUBT THE EXISTANCE OF AN ANTAGONISTIC ADRENERGIC SYSTEM.

FUTURE RESEARCH TO ELABORATE THESE CONCLUSIONS MIGHT INCLUDE STUDIES OF OTHER DRUGS REPORTED TO HAVE ANTICHOLINERGIC ACTIVITY (E.G., MORPHINE; PATON, 1957) OR DRUGS KNOWN TO INTERFERE WITH CENTRAL SYNAPTIC TRANSMISSION (E.G., DIPHENYLHYDANTOIN; WOODBURY, 1955 - THIS DRUG HAS RECENTLY BEEN REPORTED AS FACILITATING HABITUATION TO A CLICKING NOISE BY AGED RATS; GORDON, 1969). IN ADDITION, AN EVALUATION OF THE EFFECTS OF HEMICHOLINIUM IN CHOLINERGICALLY DEPLETED MICE WOULD BE OF INTEREST AS WELL AS A CONSIDERATION OF NICOTENIC AGENTS AND VARIOUS CATECHOLAMINES - BOTH IN TERMS OF DOSE-EFFECT AND ANTAGONISTIC

SYNERGISTIC RELATIONSHIPS.

MOTIVATIONAL ASPECTS

WHILE THERE IS LITTLE DOUBT THAT DRUG EFFECTS ARE MODIFIABLE BY, OR INTERACT WITH, AN ORGANISM'S APPETITIVE STATE (BROWN & RICHARDS, 1966; COLE, 1963; 1965, GYLYS, 1966; HILL, BELLEVILLE & WIKLER, 1957; HOLMES, CARTER & FUJIMOTO, 1958; MEGINNISS, 1967; SCHMIDT, 1958), THERE IS CONSIDERABLE CONFUSION AS TO THE MECHANISMS INVOLVED IN THE RELATIONSHIP. INTEREST IN THE INTERACTION WAS INTENSIFIED BY REVELATION OF THE NOW WELL-KNOWN ANOREXIC ACTIONS OF THE AMPHETAMINES (HARRIS, IVY & SEARLE, 1947).

THE CONFUSION OVER THE EFFECT OF DRUGS ON FOOD AND WATER CONSUMPTION (AND, PERHAPS EVEN MORE IMPORTANT, THE EFFECTS OF CONSUMPTION ON DRUG ACTION) STEMS PRIMARILY FROM THE FACT THAT APPETITIVE BEHAVIOUR INVOLVES NUMEROUS VARIABLES. FOR EXAMPLE, IN DISCUSSING FOOD MOTIVATION, STELLAR POINTS OUT:

> ....HUNGER AND FEEDING ARE UNDER MULTIFACTOR CONTROL. MANY SENSORY FACTORS, BOTH LEARNED AND UNLEARNED, CONTRIBUTE IN AN ADDITIVE WAY TO THE AROUSAL OF HUNGER AND TO THE DEVELOPMENT OF SATIATION; TASTE, SMELL, GASTRIC CONTRACTIONS AND GASTRIC DISTENTION TO NAME SOME MAJOR ONES. ADDED TO THESE ARE POWERFUL INFLUENCES FROM THE INTERNAL ENVIRONMENT, INCLUDING BOTH OSMOTIC AND SPECIFIC CHEMICAL CHANGES. THE SECOND MAIN POINT IS THAT ALL OF THESE FACTORS ARE INTEGRATED IN THE CENTRAL NERVOUS SYSTEM, PARTICULARLY IN THE HYPOTHALAMUS WHERE THERE ARE BOTH EXCITATORY AND INHIBITORY MECHANISMS CONTROLLING FOOD INTAKE AND HUNGER MOTIVATION (1967, PP. 105-106).

STILL ANOTHER CONFOUNDING FACTOR INVOLVES THE COMPLEX INTERACTIONS BETWEEN VARIOUS MOTIVATION STATES (E.G., BETWEEN FOOD AND WATER). THESE HAVE AN ESPECIALLY PROFOUND SIGNIFICANCE BECAUSE TYPICALLY ONE REINFORCER IS UTILIZED IN A DEPRIVATION SCHEDULE WITHOUT REGARD FOR CONCOMITANT INFLUENCES RELEVANT TO THE OTHER (BINDRA, 1968; DELL, 1958; GLICKMAN & SCHIFF, 1967; HULL, 1933; PLISKOFF & TOLLOVER, 1960; VERPLANCK & HAYES, 1953). THE POINT IS COGENTLY MADE BY VERPLANCK & HAYES:

> FOOD AND WATER INTAKE...ARE INTERDEPENDENT TO A HIGH DEGREE. EXPERIMENTAL DEPRIVATION OF ONE IS ASSOCIATED WITH A LARGE DROP IN THE INTAKE OF THE OTHER THAT MAY BE CONSIDERED A 'SELF-IMPOSED' DEPRIVATION (1953, P. 332).

YET A THIRD CONSIDERATION INVOLVES THE RELATIONSHIP BETWEEN DRUG-STIMULUS INTERACTIONS (DISCUSSED IN DETAIL BELOW) AND MOTIVATIONAL STATE. BROWN (1965), BROWN & RICHARDS (1966), AND HILL ET AL. (1957) HAVE DEMONSTRATED THAT REINFORCING INFLUENCES CAN BE MARKEDLY ALTERED BY MANIPULATIONS OF DRUG-STIMULUS VARIABLES. FOR EXAMPLE, BROWN & RICHARDS (1966) MAINTAINED "NORMAL" FOOD-REINFORCED RESPONDING IN PIGEONS TREATED WITH ANOREXIC DOSES OF VARIOUS AMPHETAMINES BY INTRODUCING "ALTRUISTIC" SOCIAL OPPORTUNITIES.

AS MIGHT BE EXPECTED, IT HAS BEEN SUGGESTED THAT DRUG-MOTIVATIONAL INTERACTIONS COULD BE ASSESSED BY EMPLOYING MULTIPARAMETRIC ANALYSES. SEVERAL YEARS AGO MILLER OFFERED THE NOTION THAT:

> In studying the effects of drugs on motivation it is desirable to use a number of techniques that are as diverse as possible in order to avoid misleading generalizations from effects that are specific to the particular indicator used...I believe that it is ...desirable that they are...diverse in that they do not depend on the same response and, hence, can assure us against being misled by effects that are specific to that response (1956, p. 318).

Such approaches were generally unfruitful, serving only to further emphasize the confounding influences already elaborated (Miller & Barry, 1960). The difficulties with the approach were summarized by Dews and Morse:

> The dependence of hunger on number of hours of deprivation was studied using a variety of 'measures of hunger'...Thirst was similarly measured...The functional dependencies found differed radically according to which method of measurement was used, and so did the effects of amphetamine. No method is given for combining these contradicting results to obtain a clear 'measure' of the effect of amphetamine on hunger or thirst per se...It should be emphasized that the measures are in conflict only in so far as they are regarded as measures of hypothetical unitary variables hunger or thirst; otherwise they simply give valuable information on an interesting situation (1961, pp. 164-165).

The data from the studies described in this report concerning the influence of deprivation level on drug-affected modifications of previous experience indicate a very distinct interaction both quantitatively and qualitatively. Just as was seen with drug doses, increasing deprivation also reached a specified level (always 24 hours) before prior exposure changed approach latencies were significantly influenced, and the drug effect revealed. But, unlike dose levels, once influenced, the

VALUES ASSUMED AN INVERSE RELATIONSHIP (I.E., AS DEPRIVATION INCREASED, LATENCY WAS DECREASED).[3] THE FACT THAT THE DRUGS HAVE NO OBSERVABLE INFLUENCE BELOW THE OPTIMAL DEPRIVATION LEVEL INDICATES A DIRECT AND DEFINITE RELATIONSHIP BETWEEN THE EFFICACY OF THE DRUGS AND THE MOTIVATIONAL STATE OF THE ANIMAL. AGAIN, AS WITH THE DOSE-EFFECT FINDINGS, THE ABRUPT ONSET OF DEPRIVATION INFLUENCES MAY REFLECT METHODOLOGICAL INSENSITIVITY BECAUSE THE GENERAL ACTIVITY DATA REVEALED A GRADUATED RELATIONSHIP BETWEEN MAGNITUDE OF DEPRIVATION AND LEVEL OF BEHAVIOUR (TABLE 25).

ALSO OF SIGNIFICANCE WAS THE OBSERVATION THAT THE ANTI-CHOLINERGIC DRUGS MANIFESTED THEIR ATTENUATION OF PRIOR EXPOSURE ONLY WITH THE LIQUID REINFORCERS WATER AND MILK. AT NO LEVEL OF DEPRIVATION UP TO THREE DAYS (FAR IN EXCESS OF WHAT IS USUALLY NECESSARY FOR FOOD TO BECOME REINFORCING - FERSTER & SKINNER, 1957) DID DRY CHOW RESULT IN APPROACH LATENCIES TYPICAL OF THOSE OBSERVED WITH WATER. PERHAPS THAT IS NOT TO BE UNEXPECTED SINCE IT HAS BEEN PREVIOUSLY DEMONSTRATED THAT THE VOLUME OF FOOD CONSUMED DOES NOT CONTINUE TO INCREASE WITH PERIODS OF DEPRIVATION OVER 24 HOURS - IN FACT, IT MAY ACTUALLY DECREASE (MILLER, 1956). OTHER REPORTS (MOSS, 1924; WARDEN, 1931) HAVE IMPLIED THAT UNCONDITIONED APPROACH RESPONSES TO FOOD REACHED A MAXIMUM AFTER 72 HOURS

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[3] IT IS INTERESTING TO NOTICE THAT SOME OF THE VALUES DO GO BELOW THE MORE TYPICAL LEVELS THUS INDICATING THAT THE EARLIER SPECULATED PHYSICAL MAXIMUM IS NOT A POSSIBLE REASON FOR ESERINE'S INACTIVITY.

DEPRIVATION AND THEN DECREASED. CONVERSELY, THE MILLER (1956) STUDY SHOWED THAT CONDITIONED RESPONSES CONTINGENT ON FOOD REINFORCEMENT CONTINUE TO INCREASE WITH INCREASING DEPRIVATION. EXPRESSED SLIGHTLY DIFFERENT, DEPRIVATION MAY AFFECT A DECLINE IN THE UNCONDITIONED OR CONSUMMATORY BEHAVIOURS AND AN INCREASE IN THE CONDITIONED OR APPETITIVE COMPONENTS (TINBERGEN, 1951). WITH THAT ASSUMPTION, IT COULD BE CONCLUDED THAT THE APPROACH BEHAVIOUR OBSERVED IN THESE STUDIES IS AN UNCONDITIONED CONSUMMATORY ACT I.E., NOT A LEARNED RESPONSE. THE LACK OF ANY APPARENT INFLUENCE BY THE DRINKING TUBE'S BEING PRESENT DURING THE INITIAL EXPOSURE FURTHER VERIFIES THIS CONTENTION (TABLE 18).

IN THE DRY CHOW STUDIES, THE DIFFERENCE BETWEEN PRIOR EXPOSURE AND NON-EXPOSURE WAS MAINTAINED AND THERE WAS, AS INDICATED ABOVE, A DEFINITE DIMINUTION OF ALL VALUES AS DEPRIVATION WAS INCREASED. IN EFFECT, THE PATTERN OF VALUES WAS IDENTICAL TO THOSE OBTAINED WITH NON-ACTIVE DRUGS WHEN WATER REINFORCEMENT WAS EMPLOYED. THUS, THE DRUG EFFECT WAS TOTALLY REVERSED BY QUALITATIVELY CHANGING THE MOTIVATION CONDITIONS.

DEFINITION OF THE MECHANISMS INVOLVED IN THE INTERACTION WOULD NECESSITATE A SYSTEMATIC EVALUATION OF INGESTIONAL INFLUENCES (E.G., "DRY-MOUTH" DUE TO ANTISALIAGOGUE EFFECTS, DECREASED GUT MOTILITY DUE TO ANTISPASMODIC EFFECTS, ETC.), INTRAMODALITY RELATIONSHIPS (E.G., MAINTENANCE OF WATER INTAKE IN RELATION TO DRY CHOW), AND DRUG-BEHAVIOUR INTERACTIONS (E.G., COULD ENVIRONMENTAL CONDITIONS, SAY SOCIAL, BE CREATED IN WHICH THE DRUG EFFECT

WOULD OCCUR WITH DRY CHOW?) HOWEVER, ONE EVIDENT POSSIBILITY CAN BE DERIVED FROM THE CONSIDERATION OF AN ESTABLISHED EFFECT OF CHOLINERGIC SUBSTANCES ON CONSUMMATION. GROSSMAN, (1960, 1962, 1964) AND OTHERS (E.G., CIRCERO & MYERS, 1968; COURY, 1967; EPSTEIN, 1960; FISHER & COURY, 1962; KHAVARI, HEEBINK & TRAUPMAN, 1968; MILLER, 1965; MYERS & CICERO, 1968) HAVE FOUND THAT CHOLINERGIC AGENTS, APPLIED DIRECTLY TO DISCRETE BRAIN AREAS, INITIATE DRINKING BEHAVIOUR WHILE ADRENERGIC COMPOUNDS INSTIGATE THE EATING OF FOOD. IT WOULD FOLLOW, THEN, THAT BLOCKING OF THE CHOLINERGIC SYSTEM BY INJECTION OF AN ANTICHOLINERGIC DRUG WOULD DECREASE DRINKING (LEVITT & FISHER, 1966; WEISS & STRONGMAN, 1969) WHICH, IN THE PRESENT STUDIES WOULD BE REFLECTED AS AN INCREASED APPROACH LATENCY ON THE PART OF PRIOR EXPOSED ANIMALS. HAMILTON AND GROSSMAN (1969) HAVE SHOWN THAT DIRECT INJECTIONS OF ANTICHOLINERGIC AGENTS INTO VARIOUS AREAS OF CAT'S BRAINS AFFECTED ACQUISTION OF AVOIDANCE BEHAVIOUR IN THE SAME MANNER AS SYSTEMIC TREATMENTS. IT WOULD BE OF INTEREST TO TEST ANIMALS IN THE PRESENT PARADIGM FOLLOWING APPLICATION OF RELEVANT AUTONOMIC AGENTS TO APPROPRIATE CONSUMMATORY-ASSOCIATED BRAIN AREAS.

ONE POTENTIAL DIFFICULTY WITH THIS INTERPRETATION CONCERNS THE DURATION OF ACTION OF THE DRUGS INVOLVED. THE GENERAL ACTIVITY DATA IN TABLE 24 AND FIGURE 6 SHOW THAT ATROPINE, SCOPOLAMINE, AND DITRAN DID MAINTAIN AN EFFECT FOR AT LEAST THE 72 HOURS THAT WOULD BE NECESSARY. IN ADDITION, BROWN (1967) OFFERS DATA WHICH INDICATED THAT ATROPINE AFFECTED INCREASES IN WATER REINFORCED

LEVER PRESSING BY MONKEYS FOR MORE THAN 36 HOURS POST-ADMINISTRATION.

CONVERSELY, AD-LIBITUM WATER CONSUMPTION BY MICE DOSED WITH SCOPOLAMINE OR ATROPINE, AS DESCRIBED HEREIN, REVEALED NO DIFFERENCES FROM SALINE-TREATED ANIMALS AFTER THE FIRST 24 HOURS (TABLE 15, FIGURE 5). DRUG-TREATED PRIOR-EXPOSED SUBJECTS DID CONSUME LESS WATER DURING THE SECOND EXPOSURE PERIOD (ATTAINING LEVELS NOT SIGNIFICANTLY DIFFERENT FROM NON-PRIOR EXPOSED ANIMALS) BUT, OF COURSE, THEY ALSO TOOK LONGER TO INITIATE DRINKING. COMPARATIVE SATIATION CURVES WOULD BE OF VALUE TO CLARIFICATION OF THIS POINT.

NONETHELESS, THE FACT REMAINS THAT THESE FINDINGS SERIOUSLY LIMIT ANY GENERALITIES CONCERNING ANTICHOLINERGIC MODIFICATION OF PRIOR EXPERIENCE BY IMPLICATING THE ANIMAL'S NUTRITIONAL CONDITION IN THE EXPRESSION OF THE DRUG'S ACTION. IT IS THUS NOT FEASIBLE TO CONSIDER A GENERAL ACTIVATING-DEACTIVATING SYSTEM ONLY IN TERMS OF RELATIVE ADRENERGIC-CHOLINERGIC ACTIVITY.

THE DRUG-STIMULUS INTERACTION PROBLEM

EXPERIMENTAL VERIFICATION OF THE FACT THAT ENVIRONMENTAL CONTINGENCIES CAN ALTER THE EFFECT OF A DRUG LONG PROCEEDED ITS DELINEATION AS A PRIMARY PROBLEM FOR PSYCHOPHARMACOLOGICAL CONSIDERATION. IN 1940, GUNN AND GURD REPORTED THAT THE EFFECTS OF THE AMPHETAMINES WERE MARKEDLY ENHANCED IN MICE MAINTAINED UNDER CONDITIONS OF SOCIAL AGGREGATION AS OPPOSED TO THOSE KEPT

ISOLATED. THE FINDING HAS BEEN EXTENSIVELY REPLICATED (SEE REVIEW BY THIESSEN, 1964), SHOWN TO BE ANTAGONIZABLE BY CNS DEPRESSANT DRUGS (LASAGNA & MCCANN, 1957), REPRODUCABLE IN OTHER SPECIES (ZALIS & KAPLAN, 1966), AND SUBJECTED TO DETAILED PARAMETRIC EVALUATION (E.G., CHERNOV, FURNESS, PARTYKA & PLUMMER, 1966; HARDINGE & PETERSON, 1964; MOORE, SAWDY & SCHAUL, 1965; SWINYARD, CLARK, MIYAHARA & WOLF, 1961; WELCH & WELCH, 1966).

NONETHELESS, A THEORETICAL STRUCTURE RELEVANT TO THE FINDINGS WAS NOT PROVIDED UNTIL 1956 BY SIDMAN WHO CALLED SUCH RELATIONSHIPS DRUG-BEHAVIOUR INTERACTIONS. HE DELIMITED THE NOTION QUITE CLEARLY:

> IN RECENT YEARS...IT HAS BECOME EVIDENT THAT A HITHERTO-NEGLECTED SET OF VARIABLES CONTRIBUTES POWERFULLY TO THE UNCERTAIN CONSEQUENCES OF DRUG ADMINISTRATION. THESE VARIABLES, BROADLY DESCRIBED, ARE THE RELATIONS BETWEEN BEHAVIOR AND ITS CONTROLLING ENVIRONMENT. DRUG EFFECTS ARE DEPENDENT NOT ONLY ON THE PHYSIOLOGICAL STATE OF THE ORGANISM, BUT ALSO ON THE ENVIRONMENTAL CONTINGENCIES THAT ARE MAINTAINING ITS BEHAVIOR AT THE TIME (1956, P. 282).

BROWN UTILIZED THE CONCEPT IN AN ANALYSIS OF DRUG EFFECTS ON VISION AND BROADENED ITS EXPLANATORY UTILITY. HE POINTED OUT:

> THE RELATIONSHIP BETWEEN THE BEHAVIOR OF AN ORGANISM AND THE STIMULUS CONDITIONS UNDER WHICH IT OCCURS CAN INTERACT WITH DRUGS FROM EITHER OR BOTH ASPECTS. THAT IS, IT CAN AFFECT RESPONDING, HAVE <u>ITS</u> EFFECT MODIFIED BY STIMULUS CIRCUMSTANCES, OR BOTH. THE FORMER IS THE MOST OBVIOUS AND COMMONLY MEASURED VARIABLE IN DRUG EXPERIMENTATION, THE SECOND IS SOMEWHAT LESS OBVIOUS AND EMPHASIZED BUT MORE SIGNIFICANT...(1967, P. 295).

THOMPSON AND SCHUSTER, ALSO RECOGNIZING THE SIGNIFICANCE OF DRUG-BEHAVIOUR INTERACTIONS, SAY:

> ANALYZING THE MECHANISMS BY WHICH DRUGS AFFECT BEHAVIOR WOULD BE IMMEASURABLY EASIER IF ORGANISMS COULD BE ISOLATED FROM THEIR ENVIRONMENTS. HOWEVER, IN THE WORLD OF INTACT BEHAVING ANIMALS, THE ORGANISM AND ITS ENVIRONMENT ARE INSEPARABLY INTERDEPENDENT; AND IT IS INEVITABLE THAT THE EFFECTS OF DRUGS ADMINISTERED TO INTACT ANIMALS WILL BE MODIFIED BY ENVIRONMENTAL CONDITIONS. ALTHOUGH THE IMPORTANCE OF ENVIRONMENTAL INFLUENCES SHOULD BE OBVIOUS, INADEQUATE CONSIDERATION OF SUCH FACTORS IS ONE OF THE COMMONEST WEAKNESSES OF DRUG-BEHAVIOR RESEARCH (1968, P. 158).

THE IMPORTANCE OF THE CONCEPT CANNOT BE OVERSTRESSED. ANY DRUG EFFECT ON BEHAVIOUR - INCLUDING PLACEBO EFFECTS (BEECHER, 1955; FRANKENHAEUSER, JARPE, SVAN & WRANGSJO, 1963) - CAN ONLY BE FULLY INTERPRETED IN THE CONTEXT OF DRUG-BEHAVIOUR INTERACTION CONSIDERATIONS. UNFORTUNATELY THE CONCEPT, WHEN HEEDED AT ALL, IS USUALLY CONSIDERED ONLY FROM A METHODOLOGICAL PERSPECTIVE. CONCERNING THAT POINT, GOLLUB AND BRADY SAY:

> SUCH REFERENCE HAS USUALLY SERVED TO INDICATE THAT 'PARADOXICAL' DRUG EFFECTS MAY NOT BE QUITE SO PUZZLING WHEN ENVIRONMENTAL CONDITIONS AND OTHER CRITICAL EXPERIMENTAL DETAILS ARE CAREFULLY SPECIFIED AND CONSIDERED. THE IMPORTANCE OF THE DRUG-BEHAVIOR INTERACTION CONCEPT, HOWEVER, GOES BEYOND SIMPLY ACCOUNTING FOR INCONSISTANCIES IN THE PSYCHOPHARMACOLOGICAL LITERATURE. FIRST IT WOULD SEEM TO LIMIT THE EXTENT TO WHICH DRUG EFFECTS ARE SPECIFIABLE UNDER THE RUBRIC OF SUCH BROAD PHARMACOLOGICAL CLASSES AS 'STIMULANTS', 'DEPRESSANTS', 'TRANQUILIZERS', AND THE LIKE, DESPITE THE APPARENT JUSTIFICATION FOR SUCH CLASSIFICATIONS ON CLINICAL OR EVEN PHYSIOLOGICAL GROUNDS. SECOND, A CONSIDERED EVALUATION OF THE DRUG-BEHAVIOR INTERACTION CONCEPT WOULD SEEM TO RAISE SERIOUS QUESTIONS CONCERNING THE

> EFFICACY OF PSYCHOPHARMACOLOGICAL APPROACHES WHICH EMPHASIZE A SEARCH FOR DRUGS EXPECTED TO HAVE SELECTED EFFECTS UPON SUCH INADEQUATELY SPECIFIED PSYCHOLOGICAL PROCESSES AS 'FEAR', 'ANXIETY', 'CONFLICT', AND THE LIKE (1965, P. 252).

THE LAST POINT WOULD CERTAINLY INCLUDE THE NOTION OF "HABITUATION" BEING SELECTIVELY INHIBITED BY ANTICHOLINERGIC DRUGS.

IN REGARD TO BOTH VISUAL AND AUDITORY STIMULUS MODALITIES, THE EXPERIMENTS DESCRIBED IN THE PRESENT STUDY REVEALED A MEASURABLE INFLUENCE ONLY WHEN INTERMITTENT STIMULATION WAS UTILIZED. THAT WOULD BE EXPECTED SINCE BOTH FLICKERING LIGHT AND SOUND STIMULATION ARE SENSITIVE BEHAVIOURAL INDICATORS (GOTTLIEB & SIMMER, 1969; HARRISON & ABELSON, 1959; HENDRICKS, 1966; TARAVELLA, CLARK, PAUTLER & SCHWARTZ, 1957) INCLUDING THE REVELATION OF DRUG EFFECTS THEREON (PAUTLER & CLARK, 1961; TURNER, 1965). IN ADDITION, FLICKERING ILLUMINATION HAS BEEN FOUND TO BE RESISTANT TO HABITUATION. PIERON (1965) AND PAVLOV (1927) REPORTED THAT ORIENTING REFLEXES COULD BE MAINTAINED LONGER UNDER CONDITIONS OF INTERMITTENT STIMULATION.

FLICKERING STIMULI PRESENTED ONLY DURING THE SECOND EXPOSURE WERE APPARENTLY DISRUPTING IN THAT THEY NEGATED THE USUAL EFFECT OF SCOPOLAMINE - IN FACT, THE LATENCIES FOR ALL GROUPS WERE ELEVATED. A DIFFERENCE BETWEEN PRIOR EXPOSED AND NON-EXPOSED ANIMALS WAS MAINTAINED, BUT NOT BETWEEN PRIOR EXPOSED DRUG AND SALINE TREATED SUBJECTS - THE DIFFERENCE THAT IS TAKEN AS THE INDICATOR OF DRUG ACTION. THUS A RATHER OBVIOUS AND DEFINITE DRUG-BEHAVIOUR INTERACTION WAS REVEALED. THE CONDITIONS

OF THE FIRST EXPOSURE, HOWEVER, WERE APPARENTLY NOT SO SPECIFIC THAT ABSENCE OF FLICKER PRESENT THEREIN IMPAIRED PERFORMANCE DURING THE SECOND EXPOSURE. IT WOULD THUS SEEM THAT PRESENCE AND ABSENCE OF STIMULATION ARE ALSO QUALITATIVELY DISTINCT (HARRISON & ABELSON, 1959) - AN INTERESTING NOTION FOR FUTURE EXPERIMENTATION.

EVEN MORE SIGNIFICANTLY, WHEN THE INTERMITTENT STIMULATION WAS PRESENT DURING BOTH EXPOSURES, THE DRUG EFFECT OCCURRED IN A TYPICAL MANNER. FROM THAT, THEN, IT WOULD SEEM THAT SPECIFIED STIMULUS CONDITIONS DURING INITIAL EXPOSURE CAN INDEED INFLUENCE THE CONSEQUENCE OF THE SECOND EXPOSURE. AGAIN, A DRUG-BEHAVIOUR INTERACTION.

THAT THE ANTICHOLINERGIC EFFECT CAN BE MODIFIED BY MANIPULATION OF ENVIRONMENTAL ASPECTS IS INCOMPATIBLE WITH CARLTON'S (1963) HYPOTHESIS IN THE SENSE THAT EXOGENOUS STIMULATION ALTERS THE EFFICACY OF THE ORGANISM'S BIOCHEMICAL STATE - I.E., THE DATA SUGGEST THAT THE CHOLINERGICALLY MEDIATED BEHAVIOUR WILL NOT INEVITABLY EXPRESS ITSELF ONCE AN OPTIMAL QUANTITY OF ACETYLCHOLINE IS PRESENT AT THE RELEVANT RECEPTOR SITE. THERE IS NO TOTALLY PREDICTABLE UNITARY RELATIONSHIP SIMPLY BECAUSE OTHER FACTORS, NOT THE LEAST OF WHICH ARE EXTEROCEPTIVE CONDITIONS, WILL INFLUENCE THE BEHAVIOURAL EXPRESSION OF THE BIOCHEMICAL ACTIVITY. IT REMAINS FOR FUTURE RESEARCH TO SPECIFY THOSE CONDITIONS.

THE SUPERIORITY OF GENERAL MOTOR ACTIVITY AS A MEASURE OF THE INFLUENCE OF PREVIOUS EXPERIENCE

THE TERMINOLOGY USED TO DESIGNATE MEASURE OF THE APPARENTLY RANDOM MOVEMENT OF AN ANIMAL ABOUT A SPACE IS OBJECTIVELY VAGUE AND AMBIGIOUS. IN AN ATTEMPT AT CLARITY, MUNN OFFERS A DESCRIPTION AND DEFINITION THAT HAS THE VIRTUE OF FUNCTIONAL UTILITY IF NOT OBJECTIVE ACCURACY:

> THE RAT, IN COMMON WITH OTHER ANIMALS, DISPLAYS A VARIETY OF ACTIVITIES WHICH APPEAR TO DEPEND MORE UPON INTERNAL PHYSIOLOGICAL CONDITIONS THAN UPON THE STIMULATING PROPERTIES OF THE EXTERNAL ENVIRONMENT...MUCH OF THIS INTERNALLY REGULATED BEHAVIOR IS...WITHOUT THE KIND OF SPECIFIC DIRECTION THAT WE OBSERVE WHEN AN ANIMAL RUNS TOWARD FOOD, TOWARD WATER, OR TOWARD A SEXUAL PARTNER. WHAT THE ANIMAL DOES IS RUN AROUND IN ITS CAGE OR RUN IN A REVOLVING DRUM (1959, P. 52).

HE THEN GOES ON TO SAY:

> TWO TERMS HAVE BEEN USED TO DESIGNATE THIS... ACTIVITY. ONE OF THESE IS <u>SPONTANEOUS ACTIVITY</u>, AND THE OTHER, <u>GENERAL ACTIVITY</u>. THE FIRST TERM INVOLVES THE ASSUMPTION THAT NO EXTERNAL STIMULATION, OR AT LEAST NO EXPERIMENTALLY VARIED EXTERNAL STIMULATION IS RESPONSIBLE FOR ELICITING OR REGULATING THE BEHAVIOR. IT HAS ALSO BEEN USED TO MEAN THAT THE STIMULUS FOR THE ACTIVITY IS UNKNOWN. THE SECOND TERM MAKES NO ASSUMPTIONS ABOUT STIMULATION AND BEING JUST AS DESCRIPTIVE AS THE FIRST, IT IS TO BE PREFERRED (1950, P. 52).

IN EFFECT, THEN, THE TERM GENERAL ACTIVITY IS SIMPLY DESCRIPTIVE OF WHATEVER METHOD OF MEASUREMENT IS EMPLOYED. THOSE MEASURES ARE NUMEROUS AND ALMOST AS OLD AS ANIMAL PSYCHOLOGY ITSELF. THE FIRST TECHNIQUE SO DESCRIBED WAS THE ACTIVITY OR

RUNNING WHEEL FOR RATS (SLONAKER, 1908; STEWART, 1898). SINCE THEN THERE HAVE BEEN REPORTS CONCERNING VARIOUS STABILIMETRIC OR "JIGGLE" CAGES - EITHER TAMBOUR MOUNTED (RICHTER, 1927) OR CANTILEVER SUSPENDED (CHAPPEL, GRANT, ARCHIBLAD & PAQUETTE, 1957), TILT-OR TURN-TABLES (GRIFFITH & FARRIS, 1942), ELECTRICAL SHORTING BY CONTACT WITH METAL PLATES (KNOLL, 1961), INTERRUPTION OF A PHOTOBEAM - THE SO-CALLED "LIGHT BOX" (SPENCER, 1929; SIEGEL & HAND, 1950), PEDOMETERS (LIDDELL, 1925; CURTIS, 1937), ELECTRICAL FLUX INDUCTION (GLOW & CHAMBERS, 1960) AND DISRUPTION OF ULTRASONIC SOUND WAVES (PEACOCK, HODGE & THOMAS, 1966) TO MENTION A FEW. DETAILED REVIEWS OF THE METHODS HAVE BEEN COMPILED BY REED (1947) AND HALL (1961).

GENERAL ACTIVITY MEASUREMENTS HAVE FOUND WIDESPREAD UTILITY IN THE MEASUREMENT OF DRUG EFFECTS (E.G., CHAPPEL ET AL. 1957; DAVIS, 1957; DEWS, 1953; EVERETT, 1961; KNOLL, 1961; LIPMAN ET AL. 1963), EVEN TO THE EXTENT OF ATTEMPTING TO ESTABLISH THE ONTOGENETIC DEVELOPMENTAL RATE OF THE ADRENERGIC-CHOLINERGIC ACTIVATION SYSTEMS (CAMPBELL, LYTLE & FIBIGER, 1969). NOT UNEXPECTEDLY, THERE HAS BEEN SOME CONFUSION IN REGARD TO THE ACTION OF A GIVEN DRUG. TO TAKE MORPHINE AS AN EXAMPLE, SOME STUDIES HAVE REPORTED THAT IT DECREASED ACTIVITY (COLLINS, 1965; HILL, PESCOR, BELLEVILLE & WIKLER, 1957; SIMON & EDDY, 1935), OTHERS THAT IT INCREASED ACTIVITY (BEACH, 1957; JOEL & ETTINGER, 1926; MACHT & MORA, 1920). THERE IS NO EVIDENCE TO SUGGEST THAT THE TECHNIQUES THEMSELVES (ALLOWING FOR PHARMACOLOGICAL AND SPECIES-SPECIFIC

DIFFERENCES) WOULD PRODUCE DIFFERENT RESULTS. ON THE CONTRARY, ISSAC AND ROOT (1956) USED A VARIETY OF METHODS, INCLUDING OBSERVER RATINGS, PHOTOBEAM INTERRUPTION, AND TWO STABLIOMETRIC DEVICES, TO ASSESS THE EFFECT OF X-RADIATION ON THE ACTIVITY OF MONKEYS. THEY FOUND VERY HIGH INTERCORRELATIONS (RELIABILITY COEFFICIENTS BETWEEN +0.79 AND +0.99) AMONG ALL THE MEASURES. SIMILAR FINDINGS IN REGARD TO THE EFFECT OF MORPHINE ON RAT ACTIVITY HAVE BEEN REPORTED BY BROWN AND MEGINNISS (IN PRESS) USING PHOTOBEAM INTERRUPTION, A STABLIOMETRIC CAGE, AN ACTIVITY WHEEL, AN ULTRASONIC DEVICE, AND LEVER PRESSING.

HOWEVER, THE LATTER STUDY ALSO REVEALED A PROFOUND DIFFERENCE IN REGARD TO MOTIVATIONAL CONTINGENCIES, I.E., MORPHINE DECREASED OR INCREASED ACTIVITY DEPENDENT ON WHETHER THE BEHAVIOUR WAS CONTINGENT UPON POSITIVE OR NEGATIVE REINFORCEMENT. THE NON-EXPERIMENTALLY REINFORCED SITUATION UNIVERSALLY REVEALED DECREASED ACTIVITY CHARACTERISTIC OF POSITIVE REINFORCEMENT. IT HAS BEEN SUGGESTED THAT CURIOSITY OR EXPLORATORY BEHAVIOUR (BERLYNE, 1966) AND ACTIVITY ITSELF (HUNDT & PREMACK, 1963) ARE POSITIVELY REINFORCING.

THE FACT REMAINS THAT, WHATEVER THEIR CONTINGENCIES, GENERAL ACTIVITY MEASURES ARE EXTREMELY SENSITIVE, REPLICABLE, AND MEANINGFUL TECHNIQUES FOR ASSESSING DRUG ACTION. THE RESULTS OF THE STUDIES REPORTED HEREIN VERIFY THIS CONTENTION. IN EVERY INSTANCE, THE GENERAL ACTIVITY MEASURE PRODUCED DATA THAT ALLOWED CONCLUSIONS IDENTICAL TO THOSE OBTAINED FROM THE APPROACH LATENCY

DATA. IN THE INSTANCE OF DOSE-EFFECTS, GENERAL ACTIVITY WAS MORE SENSITIVE THAN APPROACH LATENCY TO THE EFFECT OF LOWER DOSES, AND, IN THE INSTANCE OF DEPRIVATION LEVELS, MORE SENSITIVE TO SHORTER DEPRIVATION TIMES. MOST SIGNIFICANTLY, THE TECHNIQUE WAS ENTIRELY REVEALING OF THE INFLUENCES OR PRIOR EXPERIENCE WITHIN A LESS COMPLEX METHODOLOGICAL CIRCUMSTANCE. IN FACT, USE OF THE ACTIVITY MEASURE IN PLACE OF APPROACH LATENCY WITHIN THE SAME PARADIGM RESULTED IN AN "ALL-OR-NONE" EFFECT IDENTICAL TO THAT OBTAINED WITH APPROACH LATENCY. IN CONTRAST, WATTERS AND BLOCK (1969) REPORTED THAT SCOPOLAMINE (1.0 MG./KG.) INCREASED GENERAL ACTIVITY BUT DID NOT AFFECT THE COURSE OF HABITUATION. IT IS POSSIBLE THAT THE TIME SPANS INVOLVED IN THE PRESENT STUDIES MAY HAVE BEEN SO SLIGHT AS TO PRECLUDE FULL EXPRESSION OF THE ACTIVITY EFFECT. THE POINT COULD BE CLARIFIED BY TIME-DISTRIBUTION STUDIES OF GENERAL ACTIVITY. IT WOULD SEEM, THOUGH, THAT GENERAL ACTIVITY OFFERS A MORE SENSITIVE AND VERSATILE METHOD FOR ASSESSING THE BEHAVIOUR RELEVANT TO CARLTON'S (1963) HYPOTHESIS.

SOME CONCLUSIONS AND AN ALTERNATIVE HYPOTHESIS

USING THE EFFECT OF VARIOUS DRUGS ON EXPERIENCE MODIFIED APPROACH LATENCIES AND GENERAL ACTIVITY AS BEHAVIOURAL MEASURES, IT HAS BEEN ASCERTAINED THAT:

1.) DRUGS THAT ABOLISH PRIOR EXPOSURE INDUCED DECREASES IN APPROACH LATENCY SEEM TO DO SO IN CONJUNCTION WITH ACTIONS WITHIN THE CNS. ATTENUATION OF PREVIOUS EXPERIENCE INFLUENCES

WAS AN ACTION SPECIFIC TO MUSCARINIC ANTICHOLINERGIC DRUGS, BUT DID NOT SEEM TO BE SIMPLY DUE TO ATTENUATION OF CHOLINERGIC ACTIVITY.

2.) THE DRUG EFFECT COULD BE MODIFIED BY MANIPULATION OF THE ANIMAL'S NUTRITIONAL CONTINGENCIES (SUCH AS LEVEL OF DEPRIVATION AND/OR QUALITY OF REINFORCEMENT). THE MODIFICATION APPEARED TO BE RELATED TO THE CONSUMMATORY ASPECT OF BEHAVIOUR.

3.) IN FACT, THE DRUG EFFECT COULD ALSO BE MODIFIED BY ENVIRONMENTAL CHANGES OF A SENSORY NATURE. THE EFFECTIVENESS OF THE DRUGS WAS HIGHLY DEPENDENT ON THE ENVIRONMENTAL CIRCUMSTANCES UNDER WHICH THE ANIMAL'S PERFORMANCE WAS ASSESSED.

4.) AND, IT WOULD SEEM THAT GENERAL ACTIVITY IS AS ACCURATE AN INDICATOR OF THE ABOVE DESCRIBED EFFECTS AS THE APPROACH LATENCY MEASURE. THE TECHNIQUE IS METHODOLOGICALLY SIMPLER AND MORE SENSITIVE TO TREATMENTS.

WITHOUT QUESTION, THE RESULTS OF THESE STUDIES VERY SERIOUSLY COMPROMISE CARLTON'S (1963) HYPOTHESIS. THEY ILLUSTRATE THE OBVIOUS DIFFICULTY IN CARLTON'S ATTEMPT TO DESCRIBE A SIMPLISTIC UNITARY RELATIONSHIP BETWEEN THE ACTIVITY OF TWO BIOCHEMICAL SYSTEMS AND A SPECIFIC INSTANCE OF BEHAVIOUR. AS WAS POINTED OUT PREVIOUSLY, THE NOTION WAS COMPROMISED FROM THE INSTANT OF ITS INCEPTION BECAUSE IT WAS BASED UPON FALLACIOUS PRESUMPTIONS. THE DATA FROM THE PRESENT STUDIES HAVE MORE THAN AMPLY HIGHLIGHTED THE SHORTCOMINGS OF THE ATTEMPT TO BIOCHEMICALLY LOCALIZE A SPECIFIC BEHAVIOUR.

SUPERFICIALLY, THE NOTION APPEARED VIABLE BECAUSE OF ITS SECOND SHORTCOMING - LACK OF METHODOLOGICAL VERSATILITY OR INABILITY TO MANIPULATE AND ACCOUNT FOR MANY OF THE PARAMETRIC CONTINGENCIES. WHAT SEEMED TO BE DESIRABLE PARSIMONY WAS, IN FACT, ABSENCE OF A BROAD ANALYTICAL BASIS. THIS WAS ESPECIALLY EVIDENT IN RELATION TO LACK OF CONSIDERATION FOR THE MOTIVATIONAL CONTINGENCIES AND THEIR PROFOUND INTERACTION WITH THE DRUG EFFECTS. MORE GENERALLY, EMPLOYMENT OF THE GENERAL ACTIVITY MEASURE REVEALED THE RELATIVE INSENSITIVITY OF APPROACH LATENCY AS A MEASURE OF THE INFLUENCE OF PRIOR EXPERIENCE.

IF ALL FACTORS ARE TAKEN INTO CONSIDERATION - WHEN THE TOTAL ORGANISM IS CONSIDERED IN A TOTAL ENVIRONMENT (THEREBY NOT NECESSITATING ANY SEVERE CONCEPTUALIZATION OF DRUG ACTION OR STRICT DEFINITION OF BEHAVIOUR), IT BECOMES POSSIBLE TO OFFER A HYPOTHETICAL CONSTRUCT WHICH COVERS THE CIRCUMSTANCES REVEALED BY THE EXPERIMENTS REPORTED HEREIN. IN GENERAL TERMS, THE FOLLOWING SCHEME MAY BE PROPOSED:

NEURAL ACTIVITY	X	INTERNAL STATE	X	EXTROENVIRONMENTAL CONDITIONS
HUMORAL		NUTRITIONAL		REINFORCEMENT
ELECTRO-CHEMICAL		GLANDULAR		EXTEROCEPTIVE STIMULI
		ANATOMICAL "ACTIVITY" LEVEL		

= BEHAVIOUR

AND, APPLYING THE GENERAL CONSTRUCT TO THE CIRCUMSTANCES OF THE PRESENT EXPERIMENTS:

DEPRESSED MUSCARINIC ACTION OF ACETYLCHOLINE	X	DEPRIVATION OF WATER (OPERATIONAL DEFINITION OF "THIRST")	X	DRINKING TUBE IN DEFINED EXTEROCEPTIVE CIRCUMSTANCES (A CHAMBER, PREVIOUS EXPOSURE, ETC.)

= SUPPRESSED APPROACH TO DRINKING TUBE.

THE MULTIPLICATION SIGN IS USED TO EMPHASIZE THE INTERACTION BETWEEN THE VARIOUS CONDITIONS. THAT IS, IT SUGGESTS THAT IF ANY ONE OF THE FACTORS WERE ABSENT, THE BEHAVIOURAL RESULT WOULD NOT OCCUR; ZERO TIMES ANY VALUE IS ZERO. OF COURSE, SOME OF THE FACTORS ARE, OF PRESENT NECESSITY, VAGUELY DEFINED SINCE MUCH MORE PARAMETRIC SPECIFICATION IS NEEDED. EMPLOYMENT OF THE GENERAL ACTIVITY MEASURE WILL ALLOW SUCH SPECIFICATION TO PROCEED MORE EFFICACIOUSLY AND THE ALTERNATE HYPOTHESIS OFFERS A CONCEPTUAL FRAMEWORK WITHIN WHICH SYSTEMATIC DEFINITION CAN PROCEED. EQUALLY IMPORTANT THE ABOVE HYPOTHESIS IS INDEPENDENT OF ANY NOTION ATTEMPTING TO DEFINE BEHAVIOUR IN TERMS OF A LOCALIZED PHYSIOLOGICAL MECHANISM WHILE AT THE SAME TIME GIVING THE PHYSIOLOGICAL ASPECTS FULL CONSIDERATION. THE CONSTRUCT SIMPLY STATES THE CONDITIONS UNDER WHICH A PARTICULAR INSTANCE OF BEHAVIOUR MAY OCCUR. THE CIRCUMSTANCES ARE MADE COMPATIBLE WITH THE IDEAL SO APTLY EXPRESSED BY BANNISTER:

> ....IT IS NOT USEFUL TO TALK OF PHYSIOLOGICAL EVENTS OR PSYCHOLOGICAL EVENTS BUT ONLY OF PHYSIOLOGICAL AND PSYCHOLOGICAL MODES OF CONSTRUING EVENTS...THUS IT DOES NOT MAKE SENSE TO ASK QUESTIONS LIKE, 'ARE PHYSIOLOGICAL AND PSYCHOLOGICAL EVENTS RELATED?' ONLY QUESTIONS SUCH AS, 'CAN PHYSIOLOGICAL AND

> PSYCHOLOGICAL CONSTRUCTS BE, FOR PURPOSES OF SCIENTIFIC EXPLANATION, USEFULLY RELATED?' ARE APPROPRIATE (1968, P. 229).

IT IS TO BE HOPED THAT UTILIZATION OF SUCH CONCEPTIONS WILL ALLOW PSYCHOCHEMICAL RESEARCH TO MOVE FROM THE PREPARADIGMATIC STAGE (MANDELL & SPOONER, 1968) INTO A POSITION OF DEVELOPING MEANINGFUL CONSTRUCTS WHICH CAN RELATE TO BEHAVIOURAL ANALYSIS.

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