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THE EFFECTS OF MESCALINE ANALOGUES ON THE OPERANT BEHAVIOUR OF RATS

by

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FOREWORD

As a modern science, psychopharmacology is still in its infancy despite the fact that the race has been exposing itself to drugs since antiquity. In the past decade we have seen the new field of psychopharmacology develop at an unprecedented rate, from very small beginnings. The pharmacologists are pressed by urgent practical needs to discover new and better drugs for use in psychiatry. They are also pressed to seek new theoretical foundations for an understanding of the higher functions of the central nervous system. In these tasks they are not self sufficient. Psychopharmacology can hardly go forward faster than the rate of progress in the related fields of psychology, neurophysiology, neurology, neuroanatomy and biochemistry.

SECTION I

THE 'PSYCHO' IN PSYCHOPHARMACOLOGY

CONTEMPORARY PSYCHOLOGY

There are two sides to contemporary, experimental psychology. One takes behaviour to indicate intraorganismic occurrences, and may be symbolized S-O-R. The other takes behaviour as a direct consequence of response- environmental contingencies. It may be symbolized S^d-R-S^r.

According to the first tradition, a quality or purpose is assigned to behaviour to bring 'what the organism is behaving for' into the effective present, or the organism is said to behave in a given way because it 'intends to achieve', or 'expects to have', a given effect. The teleological problem is, of course, not solved until we have answered certain questions: What gives the action its purpose or what leads an organism to expect its behaviour to have an effect? The answers to such questions are eventually to be found in past instances in which similar behaviour has been effective. This is the position taken by the S^d-R-S^r tradition.

The S^d-R-S^r psychologist, in their search for the environmental determinants of behaviour, often employ operant conditioning techniques. To some, the use of these techniques constitutes the experimental analysis of behaviour but it is no more than an experimental analysis. Its

advantage lies in the control the experimenter has over the consequences of a response. The behaviours evoked by mazes, puzzle boxes, memory drums etc. are shaped without specific programming of contingencies. The rat in a maze is exposed to a set of conditions for which it possesses no adequate behaviour. Responses occur - the rat explores the maze and eventually some responses are reinforced in a way that leads to a terminal performance. The data is usually plotted in the form of a learning curve from which we may predict, within limits, how another organism will behave in similar circumstances. The curve, however, tells us little about the process of conditioning and extinction that can be revealed in an operant analysis. It is merely a crude overall effect of adventitious contingencies, and it often tells us more about the apparatus or procedure than about the organism.

The psychologist's primary contribution to psychopharmacology lies in the development of a behavioural analysis in the laboratory. The ultimate test of reliability or reproducibility for any such technique is not to be found in the method but in the degree of control achieved, at test which operant conditioning usually passes easily.

The operant analysis, which recognizes the individuality of organisms is particularly valuable when contact is made with other disciplines. Furthermore, the S^d-R-S^r psychologist, by avoiding hypothetical constructs as 'explanations' of behaviour, leaves the internal mechanism controlling behaviour in the hands of biochemists and physiologists. By correlating environmental input with behavioural output the S^d-R-S^r psychologist leaves the way open for a translation of these events into physiological or biochemical processes.

INTERDISCIPLINARY RESEARCH

The universal common interest of the biological sciences is behaviour, the single characteristic which best defines and differentiates the living animal. When the biochemist, pharmacologist, physiologist or anthropologist employs behaviour as a dependent variable then he is contributing to interdisciplinary research. These disciplines all represent different levels of analysis of the behavioural output but theoretically even cultural variables should be able to be defined in biochemical terms.

From the viewpoint of the S^d-R-S^r psychologist, the effects of a drug are examined in terms of the relevant environmental variables responsible for the behaviour and by the differential effect of the drug on the various behavioural processes. The cause of the behaviour, for the psychologist, is in environmental variables that produce it and a drug can alter behaviour only by weakening, strengthening or modifying one or more of the environmental variables maintaining or otherwise determining the occurrence of that behaviour.

From the viewpoint of the pharmacologist, the effects of a drug are examined in terms of the relevant physiological processes responsible for the behaviour and by the differential effect of the drug on these processes. Both analyses are perfectly compatible since the environmental influences have physiological concomitants and the different viewpoints only represent different levels of analysis - both, however, fall within the realm of psychopharmacology.

OPERANT TECHNIQUES

Operant condition involves manipulating and recording the behaviour of an organism within a controlled experimental environment. The organism is free to behave in any way, but by arranging for certain events to be dependent upon a particular behavioural pattern it has been shown that the probability of this behaviour can be increased. The behaviour pattern selected for manipulation is normally a response that can be detected by automatic equipment. This apparatus sets a criterion for the response so that its occurrence is defined by the equipment and is not a subjective estimation by the experimenter. The apparatus also arranges for certain events to occur as a consequence of these responses. A common consequence of a response is the presentation of a reinforcement. Reinforcement is defined empirically. When reinforcements follow a response they increase the likelihood that the organism will behave in the same way again. Thus food can be a reinforcement if an organism has been deprived. Normally, the response is a lever press although many other responses have been employed. The independent variables which govern this arbitrary piece of behaviour are examined in detail and it is assumed that, although there are undoubtedly differences in complexity,

no new principles (with the exception of respondent conditioning[+]) are involved in the control of other forms of behaviour.

Normally, reinforcements do not follow every lever press but their occurrence is contingent upon some pre-determined conditions. These conditions are referred to as the reinforcement schedule. For example, reinforcement may only be delivered after a fixed number of responses (fixed-ratio schedule) or after a fixed period of time has elapsed (fixed-interval schedule). It is possible to program negative as well as positive reinforcement schedules. By definition, an event is a negative reinforcement if its termination reinforces behaviour (and therefore leads to an increase in the probability that the organism will behave the same way again). Negative reinforcement may be delivered according to a punishment, escape or an avoidance schedule. If a neutral stimulus (e.g. light) is repeatedly paired with a negative reinforcement it can be shown that termination of the former will reinforce behaviour. The previously neutral stimulus is then a conditioned negative reinforcer. The schedule employed in the present investigation is a discriminated continuous avoidance schedule. The consequence of a response on this schedule can be escape from a conditioned negative reinforcer.

[+] These two cases exhaust the possibilities: an organism is conditioned when a reinforcer (i) accompanies another stimulus or (ii) follows upon the organisms own behaviour.

THE STEADY STATE METHODOLOGY

One consequence of the increased control over behaviour, as a result of operant techniques, has been the development of a new methodology in psychology - the steady-state methodology.

Steady state behaviour is behaviour whose characteristics do not change over long periods of time. When an animal is exposed to a reinforcement schedule there is a characteristic acquisition period during which the behaviour is rapidly changing. After prolonged training, however, it becomes apparent that this transitional state is no longer being recorded; the animal's behaviour is in equilibrium with the independent variables of the schedule. The dependent variable is then said to be under stimulus control and it becomes possible to predict, with great accuracy, the behaviour which will occur during any experimental session. It is this highly predictable nature of steady states that makes them particularly useful for examining the effects of any further independent variables which are introduced into the experimental situation. The effects of additional independent variables can be seen clearly against the stable behavioural baseline.

In the past the effects of drugs on behaviour have normally been assessed by comparing the performance of groups of

subjects without the drug with that of other groups after drug administration. A statistical analysis of the differences in performance between the groups is then carried out. This estimates the probability that such a difference could have resulted from chance factors (such as individual differences between subjects) other than the drug itself. With steady state methodology, group analysis is not necessary since each animal acts as its own control. If a stable level of performance exists prior to drug administration then any changes in behaviour following drug administration may be attributed to the drug if, on a subsequent day, the former steady state can once more be achieved. This recovery of the initial state eliminates the possibility that the behavioural changes were simply a sequence effect. The immediate virtue of the steady state as a substitute for the control group is the elimination of inter subject variability. This enormously increases the sensitivity of the behavioural measurements. Variables that might have been dismissed as having little or no effect, when group comparisons are made, may prove to be extremely powerful when evaluated against a stable individual baseline. The steady state approach eliminates the use of statistics in behavioural analysis. Sidman (149)

in fact has attacked statistical analysis on the grounds that if a phenomena cannot be demonstrated within the behaviour of a single organism then it does not have any psychological meaning. He points out that behaviour is, in the final analysis, characteristic of the single organism, not of groups. In this context, it should be noted that statistics, as they exist today, were evolved to deal with discrete events. They are not applicable to any time sequence (e.g. E.E.G. recordings or lever pressing) where any change does not constitute a discrete event, and may be highly dependent upon an immediately preceding event.

With reference to the steady state methodology, three important topics must be discussed: sample size, reliability and generality of results. The first is often considered to fall within the realm of statistical theory - this is not true. The sample size required in any psychological experiment should be empirically determined. It is dependent upon the degree of control in the experimental situation and the behavioural stability which is necessary to demonstrate the effects of the manipulated variable.

As a criterion of reliability or generality, inter subject replication is a more powerful tool than inter group replication. Inter group replication provides an indicator of reliability in so far as it demonstrates that changes in control

tendency for a group can be repeated. With respect to generality, however, inter group replication does not answer the question of how many individuals the data actually represents. With inter subject replication, on the other hand, each additional experiment increases the representativeness of the findings. Indeed, replication of an experiment with two subjects establishes greater generality for the data among the individuals of a population than does replication with two groups of subjects whose individual data have been combined.

Operant techniques and the Steady-State methodology are entirely independent and many experimenters have used the technique without the methodology or the methodology without the technique. The author is of the opinion that, when used together, they form a powerful tool in experimental psychology and a very useful approach to psychopharmacology.

REVIEW OF THE LITERATURE

As a consequence of the large variety of behavioural techniques and drugs employed in psychopharmacological investigations any survey of the literature must be highly selective. This review will be limited to a discussion of experimental results that are more or less relevant to the present investigation and involve the use of amphetamine, chlorpromazine or psychotomimetic drugs.

The toxicity of amphetamine is markedly enhanced by experimental procedures involving stress. Factors such as grouping of animals, temperature, size of cage, noise and shock have all been effective in reproducing this phenomena (33, 34, 87, 178). Chlorpromazine has been shown to antagonize this enhanced toxicity (24, 79, 109, 121, 126, 167) whereas pentobarbital, meprobamate and benzactyzine have all been reported to be devoid of any protective action (24, 109). The ability of CPZ and related drugs to reduce the responsiveness of the animal to stress-producing stimuli, probably by their influence as afferent collaterals entering the reticular formation (18) may explain these results, rather than a direct action of CPZ on the lethal actions of amphetamine.

Thiopropazate, perphenazine, prochlorperazine and promethazine have all been reported to be effective in protecting again the lethal actions of mescaline. In this study (127) CPZ, promazine and reserpine

were relatively ineffective, but no information is available as to whether the animals were grouped or isolated following the mescaline injections.

There have been numerous studies of the effects of CPZ and amphetamine on Spontaneous Motor Activity (14, 79, 92, 116, 167, 169). CPZ appears to reduce S.M.A. whereas amphetamine has the opposite effect. This increase in S.M.A. caused by amphetamine is antagonized by CPZ given either before (104) or after (67) the former, but the reduction in S.M.A. following CPZ appears to be resistant to any reversal by amphetamine (67).

Amphetamine and CPZ cause a dose-dependent reduction of food and water intake (3, 150) although the CPZ effect may well be non-specific since this drug has been reported to have a general suppressing action on all behaviours maintained by both positive and negative reinforcement (58, 123, 181). A selective inhibition of either positively or negatively reinforced behaviour, by CPZ, has been suggested (123, 181) but any such comparisons are open to alternative explanations. A direct comparison of the effects of a drug on positive and negative reinforcement schedules would require an equilibration of the magnitude of the positive and negative reward (related to deprivation and shock threshold) as well as frequency of reinforcement - such an experiment has not yet been designed!

In spite of the anorexic properties of amphetamine it will increase the rate of responding even when the reinforcement is food or water (20, 52, 136, 146). Larger doses, however, cause a marked

reduction in behavioural output and a peculiar behavioural pattern often called (134) 'amphetamine stereotyped behaviour' (A.S.B.).

The effects of amphetamine on behaviour maintained by multiple schedules of reinforcement have been investigated by Weissman (181), Cook and Kelleher (43), Kelleher and Morse (102) and Clark and Steele (40). The general result of these studies suggest that the amphetamine 'excitation' is highly dependent on the pre-drug rate of responding. Low rates of responding (e.g. during S^{Δ} periods) are increased whereas high rates (e.g. during FR periods) are decreased by the same dose. Clark and Steele describe the effects of high doses of amphetamine (2 mg/kg - 4 mg/kg) as producing 'a moderate rate of responding characterized by burst of two or three responses separated by larger inter-response times ..... during which animals were hyperactive, although not responding to the lever.' This disruption appears to occur at doses which have been reported, by other authors, to produce A.S.B. (134).

Amphetamine also substantially increases the output of behaviour maintained by positive reinforcement if electrical stimulation of the brain, rather than food or water, is used as the reward (88, 160, 161, 163). Increases in the rate of free operant avoidance behaviour under amphetamine have been obtained by Sidman (148), Verhave (177), Teitelbaum and Derks (171) and Heise and Boff (84). This is a general effect since increase in avoidance rates using noise (83) or cold (179) as the aversive stimuli have also been reported. Kelleher and Morse (102)

have demonstrated that higher doses cause a decrease in rate similar to the effects on behaviour maintained by positive reinforcement. Once again, this was observed at doses which are normally associated with A.S.B. (134).

Verhave (177) made the interesting observation that no increase in response rate can be detected against very low rates of responding. This has been confirmed by other experimenters (51).

In order to account for the many actions of amphetamine Dews (52) has put forward the general statement that small doses of amphetamine decrease the frequency of long inter-response times while large doses also decrease the frequency of short inter-response times. This does not account for the findings of Verhave (177) where no increase in rate was detected. Stein (162) has suggested that moderate or optimum doses of amphetamine can be said to have a facilitating effect on behaviour if account is taken for the following, (i) amphetamine depresses food and water intake; (ii) some minimum tendency to respond is required; (iii) the facilitating effect will be less conspicuous when the tendency to respond is great. Furthermore, he suggests that the facilitation caused by amphetamine is a result of a reduction in reward thresholds, and presents some convincing evidence by demonstrating that currents, which will not maintain behaviour on saline days, are effective after amphetamine, in an I.C.S.S. experiment. By an independent line of reasoning, Weiss and Laties (180) have concluded that moderate doses of amphetamine

'might be said to generate responding at probabilities of reinforcement that ordinarily are not great enough to maintain responding.' This statement incorporates the idea of a reduced reward threshold, a minimum probability of reinforcement being necessary, and presumably the decrease in behaviour having a high probability is a direct result of the increase in behaviour having a low probability of occurrence.

The effects of CPZ on avoidance behaviour have been described by Courvoisier et al (47), Cook and Weidley (42), Neilsen et al (121) and many others. They all found that CPZ causes an abolition of the conditioned response (CR) while the unconditioned response (UCR) remains intact. The dosage, which is dependent upon the test used and route of administration, varied from an effective dose (ED_{50}) 10.5 mg/kg by mouth for pole climbing avoidance (42) to 4 mg/kg (i.p.) for shuttle box ED_{50} (121) using rats as experimental subjects. Strictly speaking, the term unconditioned response is inappropriate in this context (pole climbing is not a UCR to shock) and the CPZ effect is better described as blocking an avoidance response but not an escape response. More sophisticated analyses of CPZ interaction with avoidance schedules has been made by Morpurgo (119), Maffii (114), Bovet and Gatti (16, 68, 69) and Clark and Steele (39) but these will be discussed at some length later.

A blockade of the CAR is not confined to the action of 'tranquillizers' and has been demonstrated in the case of psychotomimetic drugs, CNS stimulants, monoamine oxidase inhibitors, serotonin

and cholinergic drugs (42, 71, 170). The effects of psychotomimetic drugs on avoidance behaviour have been described by numerous authors (36, 42, 46, 71, 80, 97, 114, 154, 155, 156, 157, 168). The dosage of hallucinogenic drugs which blocks the avoidance response also normally affects the escape response. Both mescaline (17) and LSD (62) have been reported to produce a period of no-responding on positive reinforcement schedules involving ratio requirements and a gradual decline in response rate on interval schedules.

The ability of a drug to block a conditional avoidance response may be related to its affect on the aversive qualities of the conditioned stimulus. This reasoning has encouraged many experimental investigations (19, 21, 22, 86, 89, 90, 91) of drug effects on the 'conditioned emotional response' (CER).

The CER was first described by Estes and Skinner (55). After several pairings of a previously neutral stimulus (e.g. light) with an aversive stimulus (e.g. shock) the neutral stimulus acquires the ability to suppress behaviour maintained by positive reinforcement. The behavioural suppression is accompanied by all the physiological signs of 'anxiety' (132). Many drugs have been examined for their ability to enhance or abolish this conditioned suppression. Brady (19, 21, 22) has reported that amphetamine enhances and reserpine abolishes conditioned suppressions. He employed a partial suppression effect as a baseline whereas, to the authors knowledge, all other experimenters have used complete or almost complete suppression.

The amphetamine effect reported by Brady remains therefore, unconfirmed but many subsequent experiments have demonstrated that the complete suppression is virtually unaffected by the drug. Brady's result with amphetamine is consistent with Steinis observations that the drug decreases reinforcement thresholds - in this case it is negative reinforcement.

Reserpine and CPZ have been tested many times (13, 89, 103, 111, 135) and it would appear that, contrary to the report by Brady, these drugs do not affect the CER. The observation that CPZ does not abolish complete suppression suggests that factors other than its action on afferent collaterals to the reticular formation (18) or decrease in 'anxiety' are responsible for its CAR blockade.

LSD has been reported to reduce suppression in a dose-related manner when a 50-60 cps tone was used but failed to produce any such reduction when the CS was a 523 cps tone (86). This experiment highlights the importance of investigating the effect of these drugs on auditory or visual discrimination since a disruption of avoidance or a reduction in conditioned suppression could easily be due to a failure in discrimination.

It would be impossible to make any general statments about drugs and discrimination since the results are highly dependent upon the nature of the discrimination (colour, size, shape, pattern, temperal, visual, auditory etc.) and the experimental design employed. For

example, in one experimental situation a drug may cause an animal to take shock which in turn disrupts a learned discrimination, whereas the same drug, in a non-shock situation, may have no effect on this same discrimination. Furthermore, any claim to support a positive relation of drug-response effects to the visual condition under which they occur, must eliminate the possibility of direct or indirect drug effects on the response measured. The results of the discrimination experiment to be described will, therefore, only be discussed within the context of the experimental design which is employed, and no attempt will be made to relate these to the findings of other experimenters.

A BEHAVIOURAL DEFINITION OF A HALLUCINOGENIC DRUG

Barrios (9) defined a hallucination as 'a highly vivid image which is incongruous with the present sensory environment.' A better definition which covers auditory as well as visual hallucinations, is 'an experience having the character of sense perception but without relevant or adequate sensory stimulation' (54).

Whatever the word hallucination may or may not mean, one thing must be true if it is to be of any relevance to a behavioural scientist - it must evidence itself in observable behaviour. To hold that hallucinations have an independent, noncorporeal existence, either in themselves or as a cause of behaviour, puts the matter into metaphysics. To hold that hallucinations exist corporeally but have no effect on behaviour, both contradicts the asserted importance of hallucinations as a factor contributing to psychotic behaviour and makes them irrelevant to the science. To hold that a hallucination is a hypothetical construct is to agree, apart from the debatable merits of such a construction, that behaviour is the initial datum of reference.

Normally, the evidence for hallucinating at the human level is in the form of verbal behaviour. A subject who has taken LSD may report his visual experiences as evidence of his hallucinations. If the experimenter takes this data as refertially introspective, then he becomes the captive of his subjects verbal reinforcement history and must accept his subject's perceptual lexicon. On the other hand, he

may accept the verbal behaviour as a response and determine the extent to which this response is compatible with the stimulus situation and personality, or reinforcement history of the subject.

When treating verbal responses in this manner, he is accepting that languages is not privileged data exempted from the controls necessary when examining any other behaviour, as did the language analyses of Kantor (100,101) and Skinner (151).

The defining characteristic of an hallucinogenic drug is the extent to which the subjects responses, verbal or otherwise, are inconsistent with the physical environment. The drug may be characterized by the subject reporting that he sees a non-existent cup of tea or equally well by drinking it! It is unfortunate that, at the human level, so much emphasis has been placed on the verbal report as defining characteristic of hallucinations and no adequate incompatibility tests have been devised to recognize the drugs in a non-verbal situation. At the animal level no verbal response is available, so we must rely on a non-verbal characterisation of the drug.

STUDIES OF HALLUCINOGENIC DRUGS USING ANIMAL TESTS

Early attempts by Noteboom (121) and De Jong (98) to recognize hallucinogenic drugs using animal tests, relied on the production of 'experimental catatonia'. A number of β phenylethylamine derivatives were investigated but unfortunately very large drug doses were necessary in order to obtain this effect and one cannot exclude the possibility that peripheral effects may account for many of their results. Some of their findings have, however, been confirmed by other authors using more sensitive techniques. In particular, their report that replacement of the 4-methoxy group by hydroxy, in mescaline, abolishes activity has been investigated by Smythies and Levy (153) using the Winter and Flataker test. They were able to confirm the De Jong finding and further demonstrate that activity was decreased by removing the 5-Methoxy group and increased by substituting a benzyloxy group in the 4-position.

The effects of β phenylethylamine derivatives on Shuttle-box avoidance behaviour (CAR) in the rat has been studied by Smythies and Sykes (154, 155, 156, 157). It was shown that mescaline at 25.0 mg/kg produced a biphasic effect on reaction time manifested by a CAR inhibition followed by excitation. Mescaline at 12.5 mg/kg caused only a decrease in reaction time. 3,4,5 trimethoxyphenylethylamine was completely inactive and N,N-dimethyl mescaline produced effects unrelated to the mescaline profile.

Knoll et al (105) have attempted to distinguish between

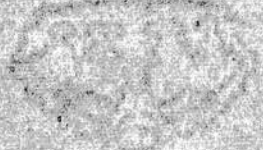
amphetamine-like activity and psychotomimetic activity in a series of methamphetamine derivatives. To do this, it was necessary to employ a combination of techniques including behavioural effects in cats and avoidance, mobility and anti-tetrabenazine or anti-reserpine properties of the drugs in rats. They concluded that side-chain substitutions in methamphetamine derivatives had little or no effect on the properties of the drug, but ring substitution, particularly in the para-position, could greatly increase the psychotomimetic properties, as measured by their tests. Ortho-substitution, on the other hand, resulted in a strong stimulant drug with anti-reserpine or anti-tetrabenazine properties similar to methamphetamine. It would be valuable if these interesting observations could be confirmed and behavioural techniques developed which would enable amphetamine-like compounds to be distinguished from psychotomimetics using a single experimental procedure. It would also be desireable to increase the sensitivity of the behavioural measures since Knoll reports that 200.0 mg/kg Mescaline was the ED95 for blockade of hot-plate avoidance - at this dosage peripheral effects must be taken into consideration (154).

Other attempts to use animal tests as indices of hallucinogenic activity in man have included hypothermia in rabbits, anti-analgetic action in mice and hyper-activity in rats (95, 96, 113). More recently, Corne et al have employed drug-induced head-twitches in mice as a possible index (44). It would appear that most of these techniques are either non-specific or involve a response which would be difficult to quantify.

THE PRESENT INVESTIGATION

The present investigation is concerned with ascertaining the features of the hallucinogenic molecule, which are necessary for its unique effect. This may be the first step in explaining its mode of action. It is clear that the fundamental pre-requisite for any such programme is the ability to reliably detect and quantify hallucinogenic activity using animal tests. In the present state of evolution of the biological sciences such a test can only be determined empirically. If it is possible to show that a particular behavioural change is unique for known hallucinogenic drugs then, with the normal scientific reservations which govern any animal experimentation, this may be used to investigate the mode of action of these drugs and examine unknown comppunds for possible hallucinogenic activity. The usefulness of any such test must ultimately depend on its success when measured by the results obtained from human experimentation.

SECTION II



THE 'PHARMACOLOGY' IN PSYCHOPHARMACOLOGY

THE CATECHOLAMINES

Our knowledge of the way the various tranquillizers, anti-depressants and hallucinogens act is incomplete, but an effort will be made to present what is known or presumed about the pharmacology of these substances.

The brain is certainly involved in carbohydrate, protein and lipid metabolism but, important as these activities are, it appears that specific amines, and their enzymes dominate the picture of psychoactive pharmacology. It is these biogenic amines that act as synaptic transmitters, and it is at or near the synapse that the psychopharmaceuticals exert their differential effect on the higher nervous functions.

The presumed neurohumoral transmitters are predominantly amines although this is not invariably true. They may be sub-divided into a number of classes: the catecholamines like noradrenaline, indole amines like seretonin and a number of others including γaminobuteric acid, glutamic acid and histamine. In addition, acetylcholine is a well proven C.N.S. transmitter which does not have an amine structure.

There is now much indirect evidence which suggests that the catecholamines, in particular noradrenaline, act as transmitters in the C.N.S. They have been shown to exist within neurones in the C.N.S. and in close proximity to enzymes which are involved in their synthesis and metabolism. Furthermore, it is now clear that NA is concentrated in the terminal regions of the neurones where its concentration may

be several hundred times greater than elsewhere in the same nerve cell (94). Although the amine appears to be stored only in the 'small, granulated vesicles' (129) there is considerable pharmacological and biochemical evidence that these stores do not constitute a single homogenous pool. This might be explained by different types of binding of NA within the vesicles, unequal distribution of vesicles leading to different availability to drugs or the existence of an axoplasmic 'pool' (48, 93, 107, 117, 131, 172).

A schematic model of the adrenergic synapse which is most compatible with the existing evidence, is shown on Fig. 1. The functional pool, from which the amine is readily released, exhibits a rapid rate of NA turnover and is in equilibrium with an essentially nonfunctional storage pool in which the amine is tightly bound. The level of NA in the functional pool is maintained by transfer from the storage pool which serves as a reservoir and also by reuptake of NA from the synaptic cleft.

The enzyme systems responsible for the synthesis and metabolism of NA are now well understood (Fig. 1). The first step is the conversion of the dietary amino acid L-tyrosine to L-dopa. This reaction takes place in the presence of tyrosine 3-hydroxylase (TH)

+ The enzyme will not convert metahydroxytyrosine to Dopa but will convert phenylethylamine to parahydroxytyrosine. It appears then that the meta hydroxy group prevents the entry of an additional para hydroxy group.

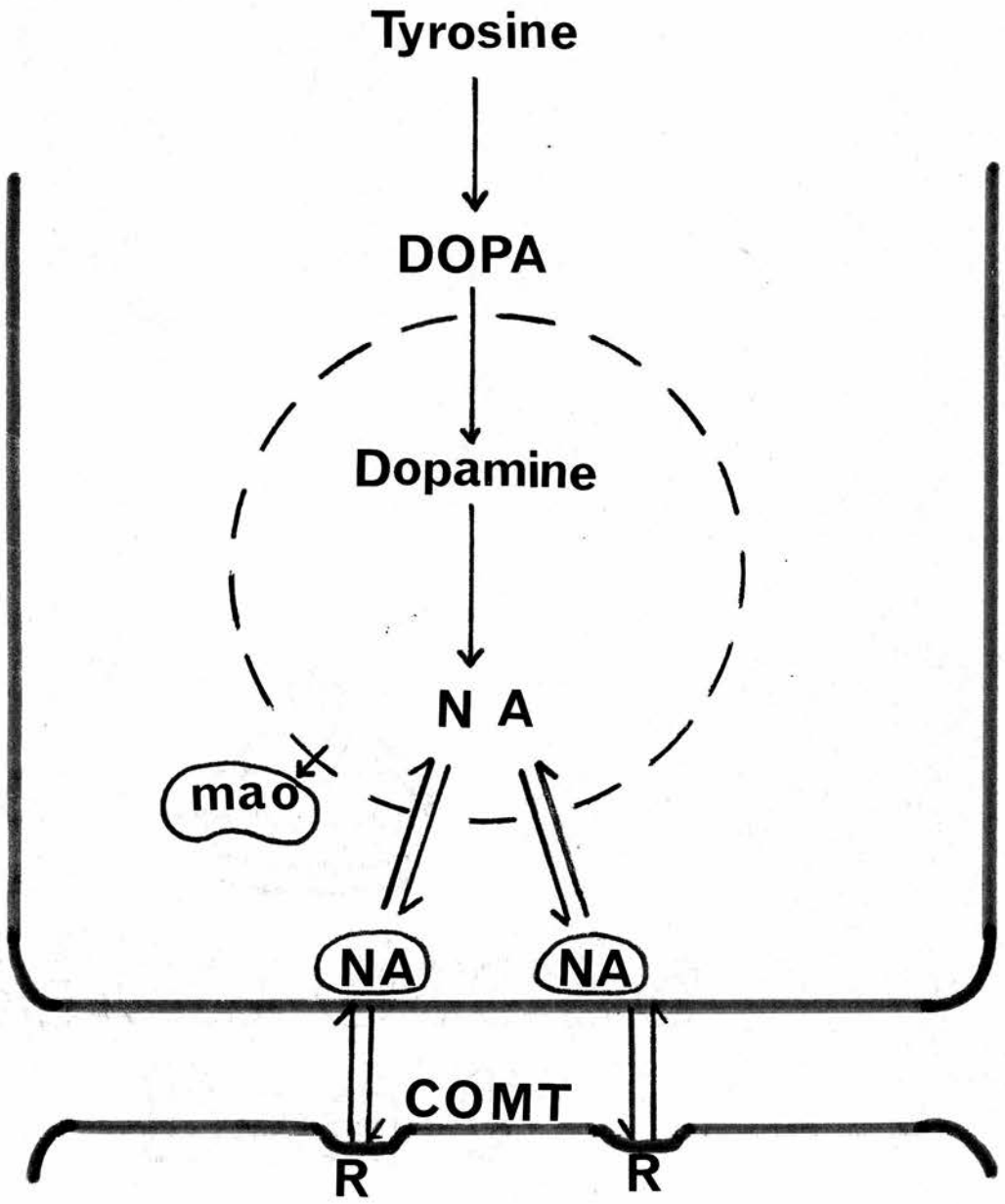


FIG. 1: Schematic Diagram of Adrenergic Synapse.

and is the rate limiting step in the synthesis of NA. A number of amino acids have been shown to be potent inhibitors of TH activity by competing with the substrate. The most potent inhibitors are 3-halogenated derivatives of α methyltyrosine. It has been noted by Udenfriend (173) that catechol compounds, including NA, can also inhibit the enzyme by competing with the pteridine cofactor (dihydrobiopterin) which has been shown to activate adrenergic tyrosine hydroxylase. This latter inhibitory process may constitute a feedback mechanism for the regulation of NA synthesis.

The second stage in the synthesis of NA is the decarboxylation of L-dopa to form 3,4 dihydroxyphenylethylamine (Dopamine) in a reaction catalysed by the enzyme aromatic-L-amino acid decarboxylase. This enzyme is also responsible for the decarboxylation of 5-hydroxytryptophan, L-histidine, α methyl dopa and other amino acids.

This synthetic step can be inhibited by L-α methyl dopa and L-α methyl-m-tyrosine but not by the D-isomers (158). It is important to note, when employing these agents in pharmacological manipulations, that they are not specific inhibitors of this reaction but affect a wide range of enzyme systems (158).

Dopamine is converted to NA by a further hydroxylation. The enzyme involved is dopamine β-hydroxylase and the reaction requires the presence of oxygen and ascorbic acid. Dopamine-β-hydroxylase is probably a copper enzyme, the function of ascorbate being to reduce the cupric ions to cuprous, which are reoxidized during the

β hydroxylation. The enzyme is non-specific and accepts a variety of amines including phenylethylamine, tyramine, (+) amphetamine, (+) p-OH-amphetamine and mescaline (74).

Competative inhibition by amino acetophenone analogues of A and NA (adrenalone and arterenone) has been deomonstrated in vivo (78). As one would expect from the nature of the enzyme, chelating agents such as E.D.T.A. and Disulfiram (reduced to diethyldithiocarbamate) are also powerful inhibitors. It is important to note that, with the possible exception of Disulfiram, the inhibitors of neither decarboxylase nor dopamine-β-hydroxylase reduce endogenous levels of catecholamines appreciably as a consequence of inhibition of synthesis (159). Several agents, such as α methyl-m-tyrosine, reduce tissue NA content but this has been shown to be due to the displacement of the catechol by a 'false transmitter' (27, 70, 174).

The β-hydroxylation of dopamine probably takes place within the storage pool where the newly formed NA may form a complex with ATP (94). The active form of NA is released from the sympathetic nerves on stimulation and an efficient process for the removal of the transmitter must be available. Two enzyme systems, mono amine oxidase (MAO) and catechol-O-methyl transferase (COMT) are obvious candidates for this role.

MAO which catalyses the oxidative deamination of catecholamines remains poorly characterized, largely because of the difficulty in

in obtaining soluble preparations of this enzyme from mitrochondrial particles. It does not appear to be concerned with the removal of the transmitter (since sympathetic nerve stimulation is not enhanced by MAO inhibition) but is probably responsible for the regulation of the intraneuronal concentration of NA (94). Inhibitors of MAO fall into two classes. In general the non-hydrazine type are more specific than the hydrazine inhibitors which interfere with a variety of enzymes systems other than MAO. A high degree of MAO inhibition is necessary for an increase in endogenous monoamines and this effect is dependent on the species, the tissue, the amine, the mode of administration as well as the chemistry of the inhibitor. It seems, that the concept of a monoamine oxidase is still badly defined and the current classifications of amine oxidases are obsolete. Blaschko (11) has shown that the histaminase of pig kidney is a 'diamine oxidase' and the histaminase in pig plasma is a 'monoamine oxidase'. Plasma amine oxidases have been shown to exist in a number of mammalian species (12) and have been implicated in the metabolism of exogenous amines (11) - in particular mescaline.

COMT catalyses the transfer of methyl groups from S-adenosyl methionine to the 3-hydroxy position of catacholamines. Hepatic COMT appears to play an important role in the metabolism of circulating NA (29) however, <u>in vitro</u> experiments (94) suggest that it only plays a minor role in the inactivation of NA released by nerve stimulation.

The discovery of dopacetamide, an inhibitor of COMT with a low toxicity, should soon lead to a better understanding of the exact function of the enzyme *in vivo* (28).

It is now becoming generally accepted that the removal of NA from active receptor sites is carried out by a non-metabolic process. The findings that tissue innervated by sympathetic nerves lose their ability to take up NA when denervated and that cocaine, which inhibits the active uptake of NA (184) causes a marked potentiation of the effects of nerve stimulation, suggest that the system is an important process in the inactivation of the amine.

NA, released from the sympathetic nerve presumably reacts with an active receptor site on the postsynaptic membrane. There is still much debate concerning the nature of adrenergic receptor sites. Recently, on the occasion of the Second Symposium on Catacholamines, Moran (118) has reviewed the situation and is of the opinion that "Ahlquist's original classification of *alpha* and *beta* receptors has been strengthened by events in the past 17 years, especially by the discovery of DCl and subsequent *beta* adrenergic blocking drugs." He concludes that "at present, the broad classification of two main adrenergic receptor sites is the simplest and most convenient" and that "most physiological effects of sympathomimetic drugs can be placed in one of these two broad categories." There has been some speculation about the nature of the α and β sites on the basis of the

chemical properties of the catecholamines. However, in the absence of more direct experimentation, the simple adrenergic receptor proposed by Moran would appear to be the most acceptable working model.

REVIEW OF THE LITERATURE

Muscholl (120) has suggested that it is useful to divide sympathomimetic amines into three classes on the basis of their effects following denervation or cocaine. Using the nictitating membrane of the cat, Fleckenstein and Burn (59) distinguished between (a) amines which have no effect following denervation, (b) those that are only slightly affected and (c) those whose actions are enhanced by this procedure. The amines in group (a) which contain either one or only one phenolic hydroxyl group and lack of β-hydroxy group were assumed to act indirectly since their action was dependent upon the presence of the transmitter at the nerve ending. Group (b) amines, which have no more than one phenolic hydroxy group but all have a β-hydroxy group, appear to act both directly and indirectly. The group (c) amines, catecholamines, probably act directly on the post-synaptic receptor site. Burn and Rand (35) observed that, after reserpine pretreatment, the presser action of the group (a) amines was abolished.

Amphetamine, in this classification, is an indirectly acting sympathomimetic amine (group (a)) and presumably acts by releasing NA. This is supported by a number of experiments by Scheckel and Boff (140) who have correlated behavioural excitation on a continuous avoidance schedule with the selective release of NA. The duration of the stimulant effects of αMMT was shown to coincide with the release of NA. Also behavioural stimulation produced by TBZ, RO4-1284 or reserpine,

in animals pretreated with MAOI, followed the same time course as the depression produced by these drugs when given alone. The behavioural depression had previously been shown to be related to the decrease in brain amines. In the iproniazid pretreated animals, biochemical studies revealed that there was a marked reduction in NA concentrations but only a slight or no fall in the 5 HT levels. Iproniazid could not reverse TBZ depression in rats pretreated with α MMT indicating that, when NA concentrations were reduced, the subsequent administration of Iproniazid and TBZ could not release NA in sufficient quantities to produce stimulation. The selective release of NA by small doses of TBZ caused behavioural stimulation if imipramine is given to prevent the reuptake of the released NA. There was a close temporal relation between NA release and behavioural stimulation, which could be blocked by first depleting the amine with α MMT.

However, Van Rossum et al (139) have demonstrated that reserpine pretreatment did not appreciably affect the excitating response to amphetamine in mice but the action of cocaine was completely abolished. They concluded; 'These results strongly indicate that cocaine has an indirect arterenergic mechanism of action presumably by releasing catecholamines from their stores. On the other hand, its seems to be proven that amphetamine has a direct artenergic mechanism of action.' These authors also report that large substituents on the nitrogen atom of amphetamine abolished the direct stimulant action of the drug since the effect could be blocked by pretreatment with reserpine. The results are somewhat confounded by their use of reserpine as an amine-depleting agent since this drug does not block the biosynthesis

of NA nor inhibit uptake into the nerve terminal (26). These two processes may continue to supply the functional pool with NA, enabling normal or even ehhanced sympathetic output (45).

Quinton and Halliwell (133) have carried out a complex series of pharmacological manipulations in order to examine the mode of action of the amphetamine excitating response in rats. They found that amphetamine excitation was enhanced by pretreatment with reserpine (18 hours before) and this ehhanced excitation could be abolished by α MeDopa (but not RO4-4602, a powerful decarboxylase inhibitor) given two hours prior to the amphetamine injection. Furthermore, the blockade of reserpine induced enhancement of amphetamine excitation could be reversed by DL DOPA given approximately one hour after amphetamine. In the absence of either, reserpine pretreatment or reserpine and α MeDopa pretreatment, the DL dopa had no effect on amphetamine excitation. If the α MeDopa was given just before the reserpine or a MAOI just after it, then the reserpine induced enhancement of amphetamine excitation could not be observed. Their results suggest that although reserpine itself cannot block amphetamine excitation the combined amine depleting actions of reserpine and α MeDopa can. Tetrabenazine (TBZ) by itself can abolish the amphetamine excitation, and DOPA given after the amphetamine can only cause an excitation if α MeDopa has been given previously. They report that the amphetamine action can be accentuated by imipramine and prolonged by MAOIs.

Although these results support the general hypothesis that amphetamine excitation is dependent upon available NA, it is possible that α MeDopa, which can be converted into a 'false transmitter', only interferes with a direct action of amphetamine.

Weissman et al (182) have used the amphetamine induced excitation on a non-discriminated avoidance schedules and investigated the effects of inhibition of NA synthesis on this response. They demonstrated that α MeT pretreatment abolishes the amphetamine excitation and this blockade can be overcome by prior administration of MAOI or imipramine. Both MAOIs and imipramine probably restore NA levels to the critical level necessary for amphetamine action. This evidence strongly supports an indirect action for amphetamine.

The issue becomes more complicated with the finding that D.M.I. pretreatment or reserpine (133, 164) plus D.M.I. pretreatment potentiate amphetamine action (165) but again, there has been no block of NA synthesis and this may be sufficient to maintain the amphetamine excitation and prolong the action by preventing reuptake. Sulser (164) has shown that D.M.I. pretreatment resulted in a striking and subtained elevation in the body levels of d-amphetamine. This suggests that D.M.I. inhibits the metabolism of amphetamine in vivo leading to a greater direct action of the drug. However, Dingell et al (53) have confirmed this increase in brain amphetamine level following D.M.I. but have further demonstrated that, even in the presence of this enhanced concentration, the stimulatory actions of the drug could be

prevented by tyrosine hydroxylase inhibition. It would appear then that α-methyl tyrosine, in contrast to reserpine or α-methyl-meta-tyrosine in doses which deplete brain NA (166, 182), is capable of blocking amphetamine excitation. This suggests that the mechanisms of stimulation of amphetamine is dependent upon the availability of newly synthesized noradrenaline.

Axelrod (6) has examined the metabolism of amphetamine in dogs. Within 48 hours of an intraperitoneal injection of the d-isomer, 30% was excreted in the urine unchanged, 11% as free p-OH amphetamine and 9% as conjugated p-OH amphetamine. Plasma levels were low and rate of removal from plasma was only 8%/hr. suggesting extensive localisation in the tissue. Although this was true for both dogs and rats he found that guinea pigs and rabbits excreted only small amounts of amphetamine or the p-OH metabolite. In virto studies (7) suggest that deamination may be an important mechanism in the guinea pig and rabbit.

Goldstein et al (77) noted that the metabolism of amphetamine isomers was similar, but that only (+) amphetamine was a substrate for dopamine-β-hydroxylase in vitro. Using tritriated amphetamine, Goldstein and Anagoste (75) found that in the rat the (+) isomer accumulated, in all organs, to a greater extent than the (-) form. Only amphetamine was found in the brain, amphetamine and p-OH amphetamine in the liver and amphetamine, p-OH amphetamine and p-OH norephedrine

(3-hydroxy, β-OH amphetamine) in the heart. Pretreatment with a powrful dopamine β hydroxylase inhibitor (disulfiram) prevented the formation of pOH norephedrine (76). Whereas amphetamine is an *in vitro* substrate for dopamine β-hydroxylase it would not appear to be so *in vivo* since no norephedrine was detected in any organ. Goldstein et al (75) have suggested that amphetamine must first be para-hydroxylated (mainly in the liver) before hydroxylation is possible. It has been demonstrated by Kopin et al (106) that β -hydroxylation probably occurs in sympathetic nerve endings and more specifically (130) in the granulated vesicles.

The pharmacology of the phenothiazines and hallucinogens is not known, but a number of theories are held concerning possible mechanisms of action. Much experimentation will be necessary before any of them could finally be accepted. One assumption is that phenothiazines prevent the transition from resting to higher levels of activity within the neurone by impeding electron transport. Some investigators consider that phenothiazine activity is centred at the cell membrane, selectively enhancing permeability. These drugs are electron donors and they may prime the Na-K pump shifting cellular activities toward normal, thereby quietening the manic and activating the catatonic.

Since the phenothiazines have a carbon-nitrogen group on the side chain just like NA, competitive inhibition at the synapse is another possibility. Sulser (165) has suggested that CPZs main

action is a blockade of adrenergic post synaptic sites whereas imipramine like drugs block the reuptake of NA through the pre-synaptic membrane and have only weak adrenergic blocking properties at post synaptic sites. Furthermore, the metabolic conversion of tertiary amines to the corresponding secondary amines increases NA potentiation (blockade of amine transparent mechanism) and decreases sympatholytic properties (blockade of post synaptic sites).

Very little indeed is known about the pharmacology of the psychotomimetic drugs. LSD is a strong seretonin antagonist; however this is not its mechanism of producing hallucinations since Brom-LSD is a better seretonin antagonist, it crosses the blood-brain barrier, and yet has not psychotomimetic properties. Although a simple explanation of LSD action by the antagonism of brain seretonin is no longer tenable some close relationship between LSD and indole amine receptor sites, may still exist. More subtle interactions involving the binding, release and competition with seretonin may still play an important role.

There is other evidence linking LSD to receptors for seretonin in brain. For example, when brain monoamines were depleted following pretreatment with reserpine, the effects of LSD was markedly enhanced and prolonged in both rat and man (5, 60). MAOIs which raise amine levels in brain have been reported to diminish the effects of LSD in man (137).

It has been noted that the half life of the drug as human plasma

correlated with the peak effect (1) and maximum increase in seretonin levels were associated with the termination of the acute behavioural effects (61). As yet, this latter finding remains unexplained.

The chemical structure of mescaline suggests that it may belong to the same pharmacologic group as NA and related sympathomimetic amines. In vitro studies (49) have shown that mescaline can be demethylated to 3,4 dimethoxy-5-hydroxyphenethylamine and 3,5dimethoxy-4-hydroxyphenethylamine. The major metabolite, however, is 3,4,5 trimethoxyphenylacetic acid and this deamination could be inhibited by iproniazid, semicarbazide and by nicotinamide and TPN. Lesser inhibition was observed with n-octanol. Slotta and Muller (152) were unable to detect the presence of 3,4,5 trimethoxyphenylacetic acid in human urine although later experimenters have found that 18% of the administered mescaline does occur as the acid derivative (64) - the remaining recovered maternal being unchanged mescaline (23%). Charalampous et al (35) have confirmed the presence of mescaline and the acid metabolite in humans. They also report finding small amounts of N-acetyl-β- (3,4 dimethoxy-5-hydroxyphenyl)ethylamine and N-acetylmescaline.

The acid metabolite (35, 152) and 3,4 dimethoxyphenethylamine (64) have both been reported to be inactive in human studies. Furthermore, the 2,3,4 trimethoxy derivative had little or no effect in normal subjects but reacted more strongly on the schizophrenic than mescaline (152). Peretz et al (125) found that α methyl mescaline (3,4,5 trimethoxyamphetamine) was about twice as active

as mescaline in humans. This has been confirmed by Shulgin (144) who also reported that 2,4,5 trimethoxyamphetamine was seventeen times more active than mescaline and the 2,3,4 was inactive in human subjects, (144).

Friedhoff and Van Winkle (65, 66) claimed that tritriated dopamine given to schizophrenics was converted to 3,4-dimethoxy phenylacetic acid which was detected in the urine. There is, however, no confirmating evidence that it is actually DMPE which is present in schizophrenic urine but it is possible than some schizophrenics are excreting a substance not found in normal subjects. This appears as a pink spot on the chromatogram but has not been positively identified as methoxylated derivative of β - phenylethylamine. Barbeau et al (8), using Friedhoff and Van Winkle's chromatographic method, have shown that a pink spot occurs in the urine of 80 per cent of patients suffering from Parkinson's disease. Many studies, however, have failed to detect the pink spot compound at all and the position has recently been reviewed by Boulton et al (15). Their studies, using a mass spectrograph, indicate that 'pink spot' is, in fact para-tyramine and is more prominent in Parkinson's disease than schizophrenia. This, in itself, is an interesting finding but since these authors used a different extraction procedure from that employed by Friedhoff and Van Winkle the contraversial issue has not yet been satisfactorally concluded.

SECTION III

ANALYSIS OF THE SCHEDULE

THE SCHEDULE

Avoidance procedures have figured prominently in studies of psychopharmacological agents and have been of particular value in characterizing some of the pharmacological properties of the earlier tranquillizers and clearly differentiate them from C.N.S. depressants (42).

Heise and Boff (84) have compared avoidance procedures with food-reinforced schedules and conclude that the former are more appropriate in drug interaction studies because there is greater inter- and intra-session stability and they allow an examination of behavioural depression unconfounded by 'anti-appetite' effects.

In general, the avoidance procedures can be separated into two classes: discrete avoidance and continuous avoidance. The discrete avoidance procedure involves presentation of a stimulus (C.S.) for a fixed period of time before the delivery of a shock (U.S.). A response during the C.S. terminates the C.S. and avoids shock. If the conditioned avoidance response (C.A.R.) does not occur, the U.S. is presented and an escape response will terminate the U.S. In a typical continuous avoidance procedure shocks of brief duration are delivered at regular shock-shock intervals unless the animal responds; each response postpones the shock for a specified response-shock interval. The delivery of a shock is the only exteroceptive stimulus change in this procedure

whereas a C.S. is always involved in the discrete avoidance procedure.

The schedule employed in the present investigations was a combination of both discrete and continuous avoidance procedures - a discriminated continuous avoidance task. A stimulus light was introduced into the continuous avoidance procedure to signal the occurrence of shock. The effect of this preaversive stimulus is to create an area within the schedule (light on) where there is a high probability of a response and a second are (light off) where few responses occur. Thus the schedule is sensitive to both stimulant and depressant drugs.

On the discriminated avoidance schedule employed in the present investigation an animal receives a shock every 10 seconds (S_2-S_2 interval) unless it makes a lever press. A response on the lever at any time postpones shock for 30 second (R-S_2 interval). During the last ten seconds of this response-shock interval a discriminative stimulus light is turned on inside the experimental chamber and remains on until the next lever press occurs. When an animal has been exposed to this schedule for a long period of time, the majority of its responses occur in the presence of the preaversive stimulus - thus efficiently avoiding shock.

This schedule is similar to that used by two Italian experimenters, Bovet and Gatti (16, 68, 69). They carried out a fairly comprehensive study of a large variety of drugs over wide

dose ranges and developed behavioural profiles which enabled them to distinguish between drugs from different pharmacological categories. The response output of the animal was classified according to where it occurred in the schedule cycle. The parameters used were an $R-S_2$ interval of 30 seconds, and $R-S_1$ interval of 18 seconds and an S_2-S_2 interval of 30 seconds. Two electronic counters recorded the number of times the rat pressed the lever during the 12 seconds after the light appeared and the number of responses made during the 12 second period after delivery of shock. Three response categories were then distinguished, the number of 'conditioned responses', the number of 'unconditioned responses' and the number of 'non-motivated responses.' It is not clear to the author why any response occurring within 12 seconds of shock should be classified as an 'unconditioned response' since the first response after shock terminates the stimulus light and there is no justification for describing a response up to 12 seconds following this as an 'unconditioned response' thus implying that it is functionally related to the shock. An alternative method of dealing with the data, without prejudging the issue, is to make a distinction between interresponse times less than three seconds (burst responses) and those greater than three seconds but less than twenty seconds (premature responses) and then examine the data for a possible relationship between the occurrence of shock and burst responding.

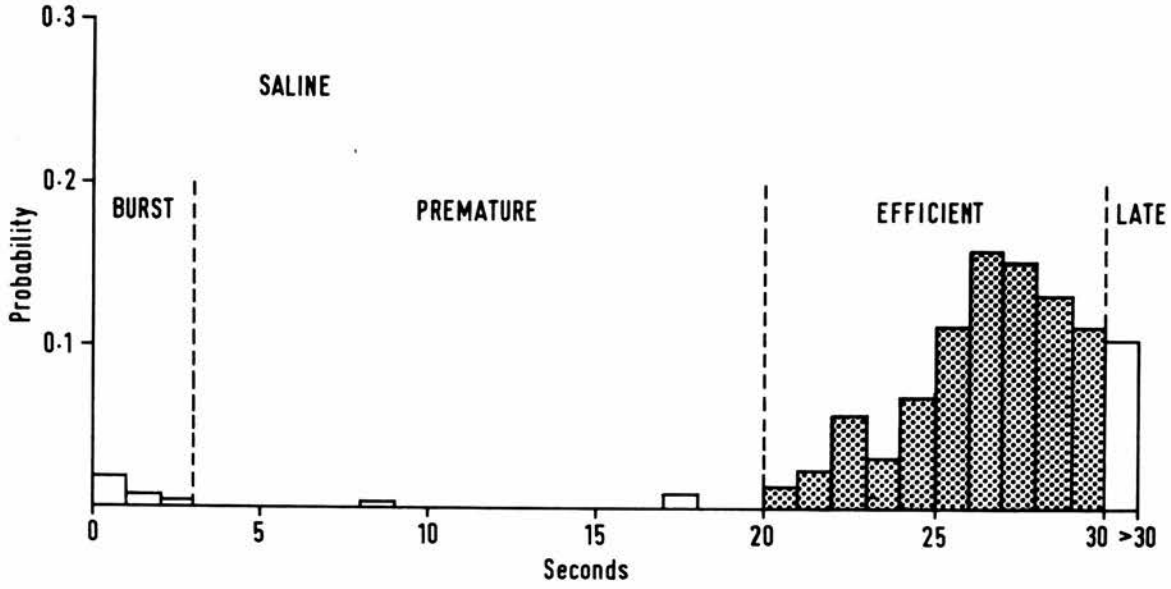


FIG. 2: Classification of inter-response times on discriminated continuous avoidance schedule.

Since every response on a continuous avoidance schedule postpones shock the term premature response (P) has been substituted for 'non motivated' response. In experimental psychology the term 'unconditioned response' is normally reserved for a response which is elicited by a stimulus without previous conditioning. Thus the knee-jerk in the patellar-tendom reflex is an 'unconditioned response' since it is elicited by a tap on the knee without previous learning. Rats do not normally press levers when they are shocked! The response category which Bovet and Gatti have called 'unconditioned responses' has been renamed late responses (L) and includes only the first response which is emitted following shock. Furthermore, since responses at any time in the schedule cycle are products of the reinforcement contingencies, and thus can be called conditioned, the response category 'conditioned response' has been renamed efficient response (E). The new response classification is shown in Fig. 2 Bovet and Gatti express the cumulative reaction time as a percentage of the total experimental duration (%RT).

With these minor changes in definition and nomenclature, the Bovet-Gatti classification has been employed in the present investigations. Fig. 3 shows typical behavioural profiles induced by chlorpromazine, reserpine and amytriptiline (or amphetamine) taken from Bovet and Gatti (68). They have also tested Imipramine, perphenazine, triflumethazine, chlorprothizene, scopolamine, benactyzine, nicotine and methaminodiazepoxide.

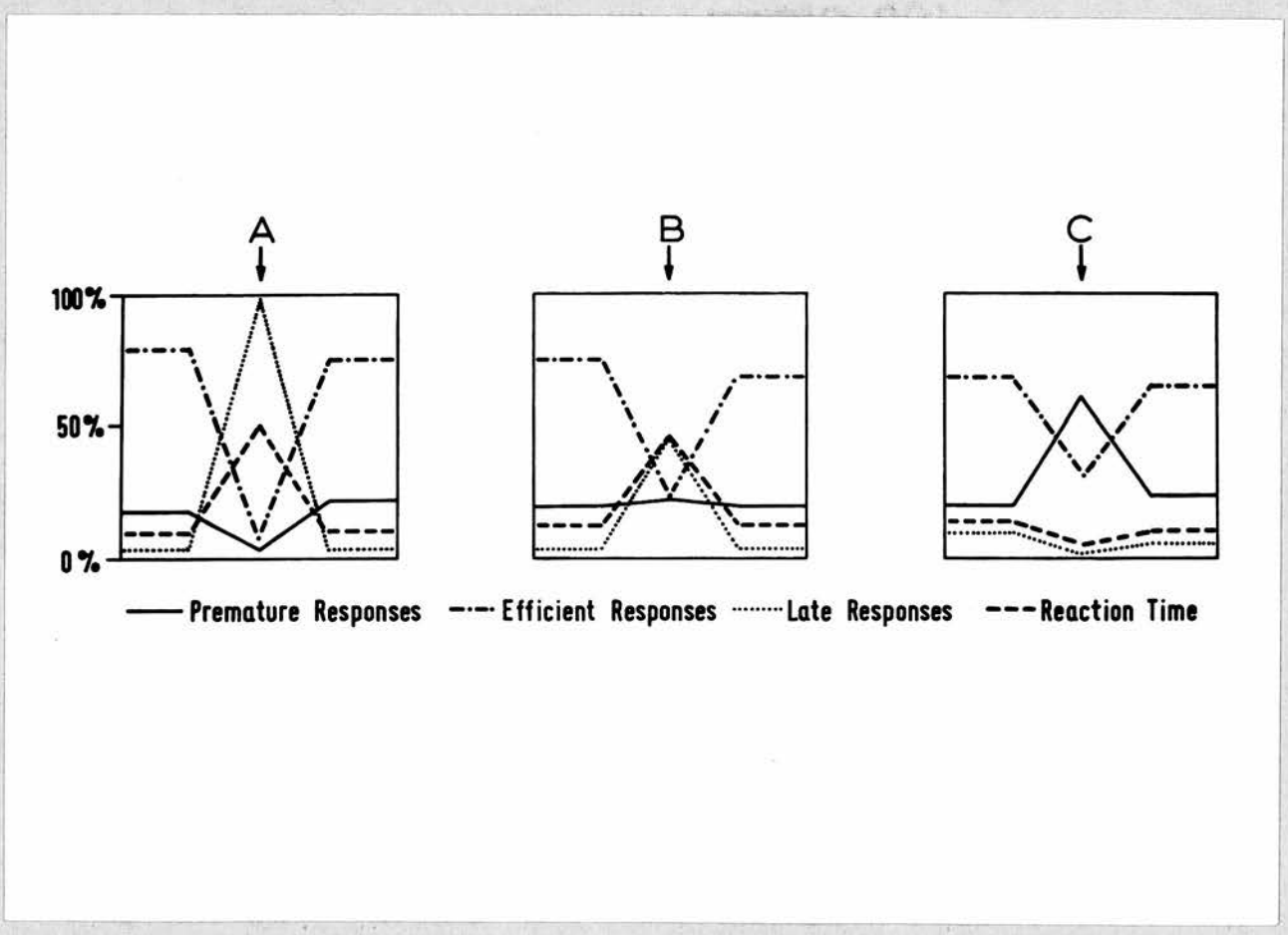


FIG. 3: Behavioural profiles for Chlorpromazine (A), Reserpine (B) and Amytriptiline (C) after Bovet and Gatti (68).

During these drug investigations they found that the behavioural parameters, described above, varied in a manner which was characteristic of the drug in question.

It is clear that these studies form a very useful basis for any psychopharmacological investigation which employs a discriminated continuous avoidance schedule as a behavioural baseline.

DATA PROCESSING

The data from all the behavioural and drug experiments to be described was collected in the form of cumulative records and the time between consecutive responses. These inter-response times (I.R.T.s) were recorded in sequence by a printing counter and subsequently analysed by digital computer. It will be convenient to discuss the entire functions of the computer program (Appendix A) at this point since this standard program was employed throughout.

First Order Functions

The Program: I Corrected all I.R.T.s for errors due to the printing time of the counter.

II Summated all corrected I.R.T.s until their sum was equal to one hundred minutes, to the nearest I.R.T., and neglected all others. Thus the experimental duration was kept constant.

III All corrected I.R.T.s falling within the first one hundred minutes of the experiment were classified into four categories (see Fig. 3)

(a) Burst Responses:- All responses occurring within three seconds from previous response (I.R.T. $<$ 3 seconds)

(b)/

(b) Premature Responses:- All other responses occurring before the onset of the stimulus light

(3 seconds $\leqslant$ I.R.T. $<$ 20 seconds)

(c) Efficient Responses:- All responses emitted during the conditioned stimulus but before shock

(20 seconds $\leqslant$ I.R.T. $<$ 30 seconds)

(d) Late Responses:- All responses emitted during the stimulus light but after shock

(30 seconds $\leqslant$ I.R.T.).

IV The frequency and probability of these four response categories was calculated.

e.g. Probability of Efficient Response = $\frac{\text{Frequency of Efficient Response}}{\text{Total number of I.R.T.s}}$

V The frequency of the efficient responses during each second of the ten second stimulus period was calculated and these frequencies expressed as probabilities

e.g. Probability of 25 seconds $>$ I.R.T. $\geqslant$ 24 seconds =

$$\frac{\text{Frequency 25 seconds} > \text{I.R.T.} \geqslant 24 \text{ seconds}}{\text{Total I.R.T.s}}$$

VI The Inter Response Time per opportunity statistic (IRT/OP) was computed for each second of the 10 second stimulus period. This estimates the probability of a response in a certain time interval on the condition that the animal reaches the initial boundary of the

interval and hence has an opportunity for a response in the interval. It is clear that the number of opportunities for a given band of I.R.T.s equals the number of I.R.T.s in the sample than are longer than the lower limit of this band (Anger, 1963).

e.g. IRT/OP for 25 seconds $>$ I.R.T. $\geqslant$ 24 seconds =

$$\frac{\text{Frequency 25 seconds} > \text{I.R.T.} \geqslant 24 \text{ seconds}}{\text{Frequency I.R.T.} \geqslant 24 \text{ seconds}}$$

VII The percentage reaction time was calculated in the same manner as Bovet and Gatti

$$\% \text{ RT} = \frac{((\text{I.R.T.} \geqslant 20 \text{ seconds}) - (20 \text{ seconds})) \times 100}{\text{Experimental Duration in seconds}}$$

All first-order data can be found in appendix B.

Second Order Functions[+]

This section of the program deals with the four response categories classified by the First Order Analysis: Burst Responses (B), Premature Responses (P), Efficient Responses (E) and Late Responses (L).

[+] The program in appendix A calculates sequential dependencies up to 3rd order condition probabilities but this information will not be referred to in the present investigations since it was soon found that the sample size which one can obtain from drug experiments using rats is not sufficiently large to make meaningful deductions from this data.

Consider the sequence of I.R.T.s:-

25.4, 25.6, 30.1, 00.2, 00.1, 19.0, 27.6, 30.3

These would be classified:-

E E L B B P E L

The program then calculated the frequency of a B response being followed by a B. The frequency of B being followed by a P etc. For the data above f(B.B) = 1. That is, the frequency of all overlapping binary combinations was calculated and expressed in a frequency matrix in Appendix C.

These frequencies were then transformed into probabilities by dividing each frequency by the total frequency of all binary combinations. This data is also expressed as a matrix in Appendix C For example, p(B.B) = 1/7 = .143.

A conditional probability matrix was also calculated (Appendix C). For example the conditioned probability of the binary combinations (B.B) is equal to the frequency of (B.B) divided by the frequency of (B). For the data above

e.g. $cp(B.B) = \frac{1}{2} = 0.5$

That is, the conditional probability of any binary combination is the frequency of that combination divided by the frequency of the first member of the combination. This data is more meaningful

than the probability data since it takes into account the occurrence of the first event and relates the second event to this occurrence.

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EXPERIMENT 1: AN ANALYSIS OF THE CONTROLLING VARIABLES

An adequate description of the behaviour generated by continuous avoidance schedules must include an identification of reinforcement for the avoidance response. Anger (4) and Wertheim (182) investigated the nature of the controlling variables in non-discriminated avoidance behaviour, and suggest that the decrease in aversiveness of temporal stimuli at long post-response times (P.R.T.s) is the primary source of reinforcement. Sidman (147) has reported that prolonged training on a discriminated continuous avoidance schedule facilitates the formation of an independent time discrimination, thus implicating CATS (conditioned aversive temporal stimuli) as one source of reinforcement on the discriminated schedule. The relative importance of the 'temporal discrimination' and the warning stimulus as controlling variables has been studied by Ulrich et al (175). They reported that with a constant response-shock interval, response rate increased as the interval between the response and the onset of the warning stimulus was shortened, and hence concluded that the termination of the pre-shock signal was the primary source of reinforcement on the discriminated schedule. Since the schedule manipulations, carried out by Ulrich et al, did not include any conditions where there was an opportunity for the termination of long P.R.T.s (and hence reinforcement) prior to the onset of the pre-aversive stimulus, and the results only indicate that avoidance behaviour can be maintained in the absence of

CATS and do not reflect directly on the relative importance of each source of reinforcement on the original schedule.

It has been shown that the avoidance response may be maintained (i) by the substitution of short P.R.T.s in place of longer P.R.T.s without any exteroceptive warning stimulus, and (ii) by the termination of a pre-aversive stimulus in the absence of CATS. The present report describes the significance of both sources of reinforcement on the continuous discriminated avoidance schedule.

Method

Subjects:

Six male Lister hooded rats, approximately 100 days old at the start of the experiment, served as subjects.

Apparatus:

The apparatus was a standard one-lever rat chamber (GS-E3125C) fitted with a shock grid, house light and stimulus lights. All programming and recording equipment was contained in a separate room.

Procedure:

Ss were exposed to daily 2¾ hour sessions of discriminated avoidance. A brief shock of 0.6 ma. and 0.5 seconds duration occurred every 10 seconds (Ss_2 - S_2) unless the lever was pressed. A response on the lever at any time postponed the next shock for 30 seconds (R-S_2). After 20 seconds of the response-shock interval had elapsed the stimulus lights (S_1) were turned on inside the experimental chamber and remained on until the next lever-press was emitted. These experimental

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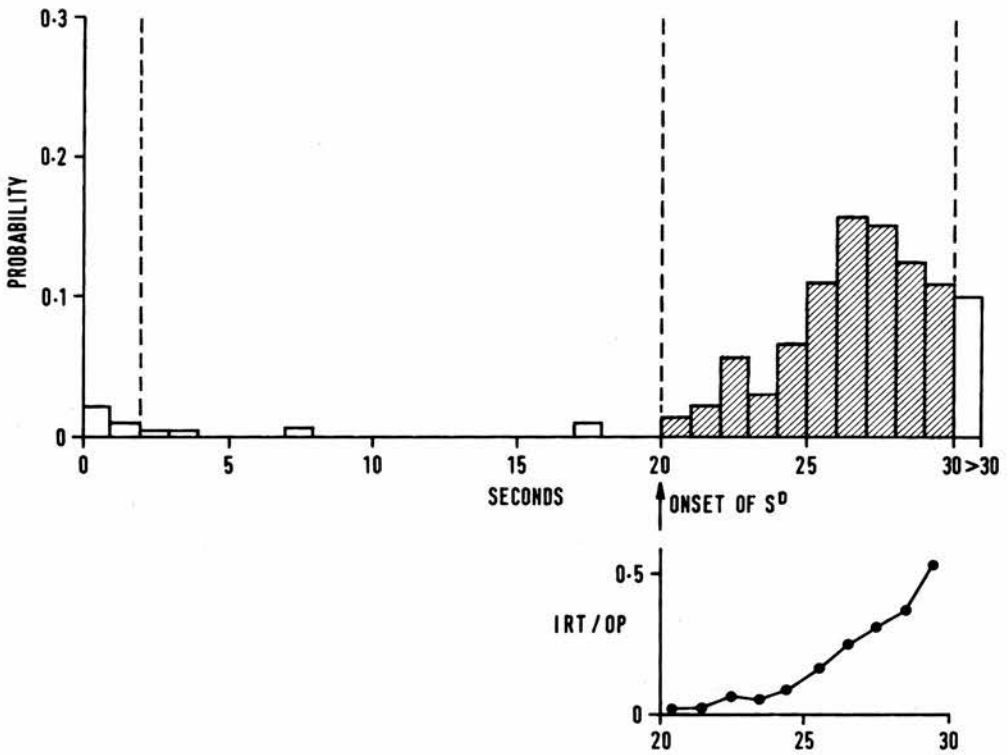

FIG. 4A: Inter-response time distribution on 75th avoidance session for R1.

contingencies were introduced on the first day of training and were in operation for 75 consecutive experimental sessions prior to the schedule manipulation. All results presented or discussed are taken from the last 2 hours of the experimental session. Inter-response times were recorded in sequence by a printing counter and subsequent analysis was carried out by digital computer.

Results and Discussion

Early avoidance is characterized by a high probability of a response being emitted prior to the onset of the pre-aversive stimulus. With prolonged training there is a progressive decline in this behaviour, accompanied by an increase in the probability of a response occurring in the presence of S_1 (Sidman, 147; Ulrich et al, 175). A third phase in the development of avoidance behaviour is shown in Fig. 4, which is taken from the 75th avoidance session of animals R1 and R2[+] (Appendix B Nos. 1 - 2). There is no further increase in the probability of responses being emitted during SL but the inter-response time distribution becomes skewed towards the latter half of the 'warning' stimulus. Both the I.R.T. distribution and the IRT/OP statistic (Anger, 1963) reflect the development of a differential response to 'temporal' cues within the pre-aversive stimulus.

[+]The I.R.T. distributions of these two animals represent the maximum variation between animals found at this stage in training.

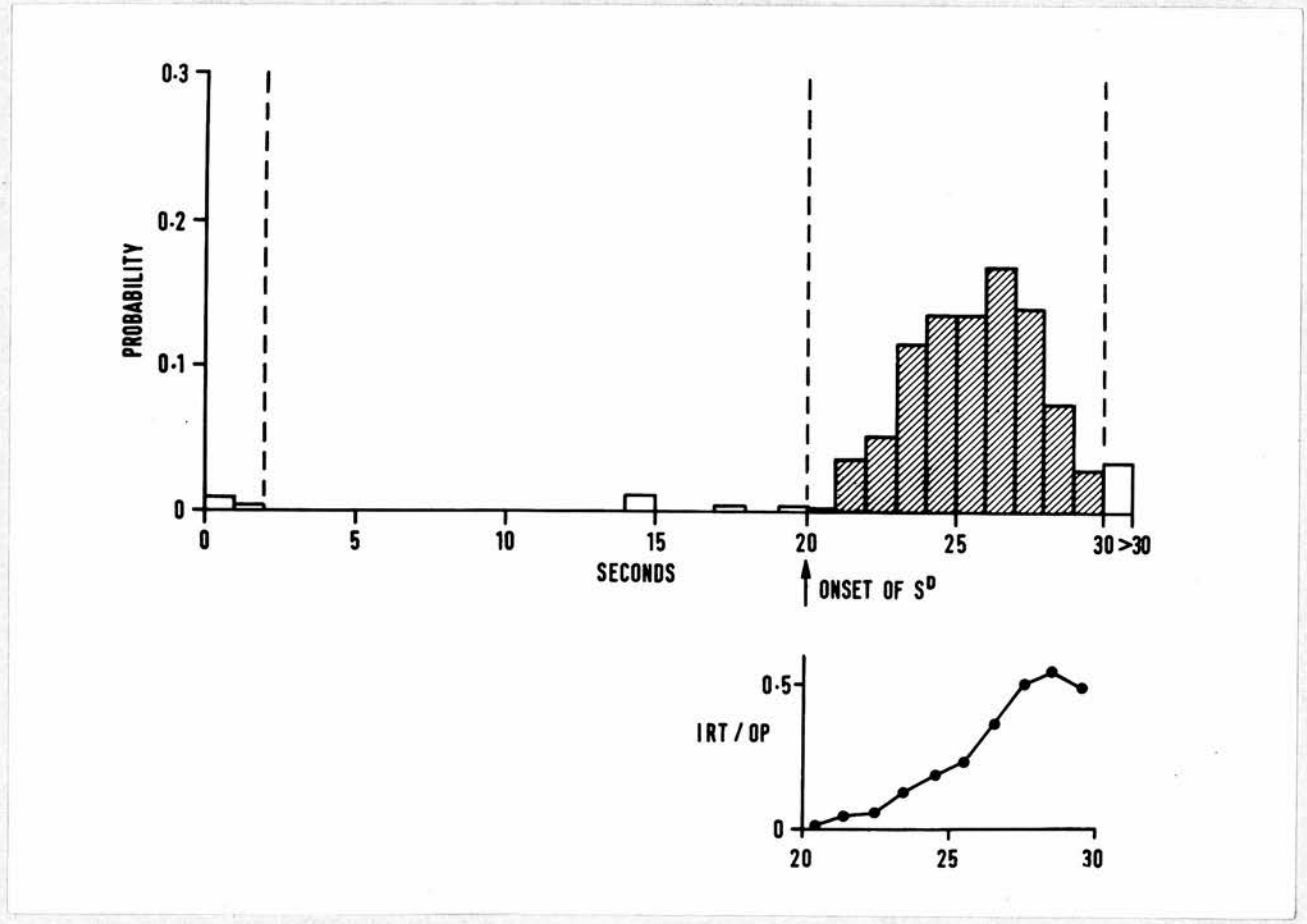

FIG 4B: Inter-response time distribution on 75th avoidance session for R2.

It appears then, that early in acquisition, the light is a conditioned aversive stimulus by virtue of repeated light-shock pairings. Responses which are emitted prior to the onset of the pre-shock signal, avoid this conditioned aversive stimulus, and are thus reinforced. Consequently, the number of light-shock pairings is reduced and the aversive properties of the stimulus light diminish. Kamin et al (99) using a conditioned suppression technique, have been able to monitor this decrease in the aversive properties of warning stimulus which develops during the course of avoidance training. In the second phase of avoidance behaviour, the signal, as a conditioned aversive stimulus, is too weak to support avoidance but sufficiently strong to support escape. The reinforcement which maintains the avoidance behaviour described in Fig. 4 is probably not the termination of the 'warning' signal per se, but rather escape from a compound stimulus situation, involving both the pre-aversive stimulus and conditioned aversive temporal stimuli. That is, the variables which control a non-discriminated avoidance schedule are operating within the light period and are under control of the pre-shock signal! The CATS associated with long post-S_1 onset times (PS_1T) would be very aversive by virtue of their close proximity to shock. The 'temporal' stimuli at short PS_1T would be less aversive and the CATS at short P.R.T. would be least aversive. The greater the PS_1T preceding the response (up to shock) the greater the reinforcement of responses following long PS_1Ts. It is clear that this 'temporal discrimination' is entirely dependent upon the presence of S_1 and is distinct from that proposed by Sidman (147).

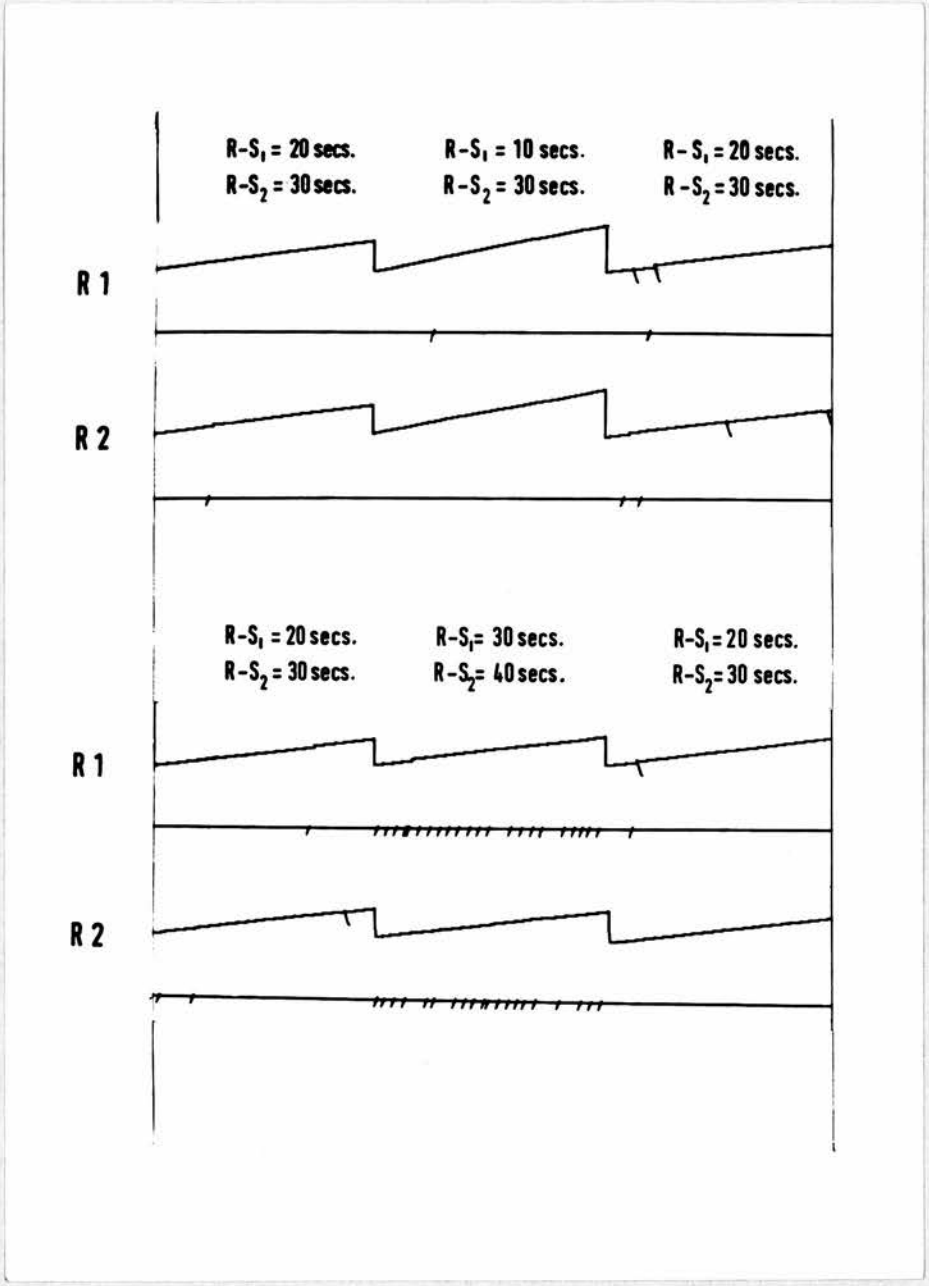

FIG. 5: Cumulative records showing the effects of different $R-S_1$ intervals on the avoidance response rate of R1 and R2. The records are taken from the first day on which the schedule parameters were varied. Deflections on the cumulative records signify shock and those on the event marker signify responses prior to the onset of the stimulus light.

On session 76 of the avoidance training, the R-S_1 interval was altered for 10 minute periods and the parameters were changed in a different sequence for each of the two animals, R_1 and R_2. Fig. 5 is a series of cumulative records taken from session 76. Deflections on the event-marker record indicate responses which occurred prior to the onset of S_1. When R-S_1 was decreased from 20 seconds to 10 seconds and R-S_2 was kept constant, the response rate of both subjects increased. This agrees with the findings of Ulrich et al (175). However, when the R-S_1 interval was increased to 30 seconds and S_1 - S_2 interval kept at 10 seconds, there was no change in the response rate. The majority of responses were emitted between 20 and 30 seconds. Since these occurred before the onset of the pre-shock signal, it would appear that they are reinforced by the substitution of short P.R.T.s for long P.R.T.s, thus implicating conditioned aversive temporal stimuli as one source of reinforcements on the original schedule. The R-S_1 manipulations described in Fig. 5 were carried out on the following three daily sessions. By session 79, the increase in rate associated with the decrease in R-S_1, still persisted but responding prior to S_1, when R-S_1 was increased, had extinguished. This suggests that escape from S_1 is the most important source of reinforcement on the discriminated schedule. It is relevant that the response distribution within the pre-shock signal, when R-S_1 was decreased, still tended to be skewed.

It would appear, then, from these investigations, that the primary source of reinforcement on the discriminated continuous avoidance

schedule, is escape from the conditioned aversive temporal stimuli which are at present at long PS_1T.

Summary

Having examined the reinforcement contingencies which are in operation on the continuous discriminated avoidance schedule it will now be useful to review the suitability of this schedule for psychopharmacological investigations.

I Avoidance schedules generate greater inter- and intra-session stability than positive reinforcement schedules (84) and are thus more compatible with a Steady-State Methodology (149).

II Avoidance schedules allow an examination of drug induced behavioural depression unconfounded by 'anti appetite' effects (84).

III The programming and data analysis can be entirely automatic thus reducing experimental error.

IV Continuous avoidance schedules are more sensitive to drug action than discrete avoidance schedules (84).

V The extensive studies of Bovet and Gatti form a useful basis for any drug manipulations using this schedule (16, 68, 69).

VI The schedule generates periods of high and low response probability and is thus suitable for examining stimulant as well as depressant drugs.

VII The schedule involves both a visual and temporal discrimination so that drug effects may be examined on behaviour controlled by both

external and internal stimuli (110).

VIII The schedule is capable of detecting any 'biphasic effect' on reaction time such as that reported to occur when hallucinogenic drugs were administered to animals on discrete avoidance schedules (154, 155, 156, 157).

SECTION IV

THE EFFECTS OF DRUGS ON THE SCHEDULE

BEHAVIOURAL STABILITY

No stability criteria were employed but it is clear from Appendix B Nos. 1 - 6, that all animals had reached a high level of performance (> 80% efficient) after 75 avoidance sessions. An earlier study+ had shown that an even higher level of performance was possible (> 95% efficient) using higher shock intensities (1.5 ma.) and a shorter $S_1 - S_2$ interval (5 seconds). Increasing the $S_1 - S_2$ interval to ten seconds and decreasing the shock intensity to 0.5 ma. aided the development of the temporal distribution within the stimulus light and made the schedule more sensitive to drug action.

The level of performance remained stable throughout the experiments. Data in Appendix B Nos. 1 - 12 compares the performance of all the animals at least six months later, with the performance on the 75th avoidance session.

Saline injections were administered to all animals on the day before and the day after every drug administration during experiments 2, 3, 4, 5, 6 and 7. No effect of saline injections could be detected except for a slight disturbance on the day following high doses of amphetamine. (This also occurred in the absence of the injection). In the remaining experiments, with the exception of pretreatment studies, where fluid volume might have been important, all saline injections were neglected. This negligence appears to be justified by the absence of

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+ This experiment drew attention to the importance of the response distribution within the $S_1 - S_2$ interval which was then increased from five to ten seconds for all subsequent experiments.

any saline effect and the importance of maintaining the health of the animals by minimizing the number of intraperitoneal injections.

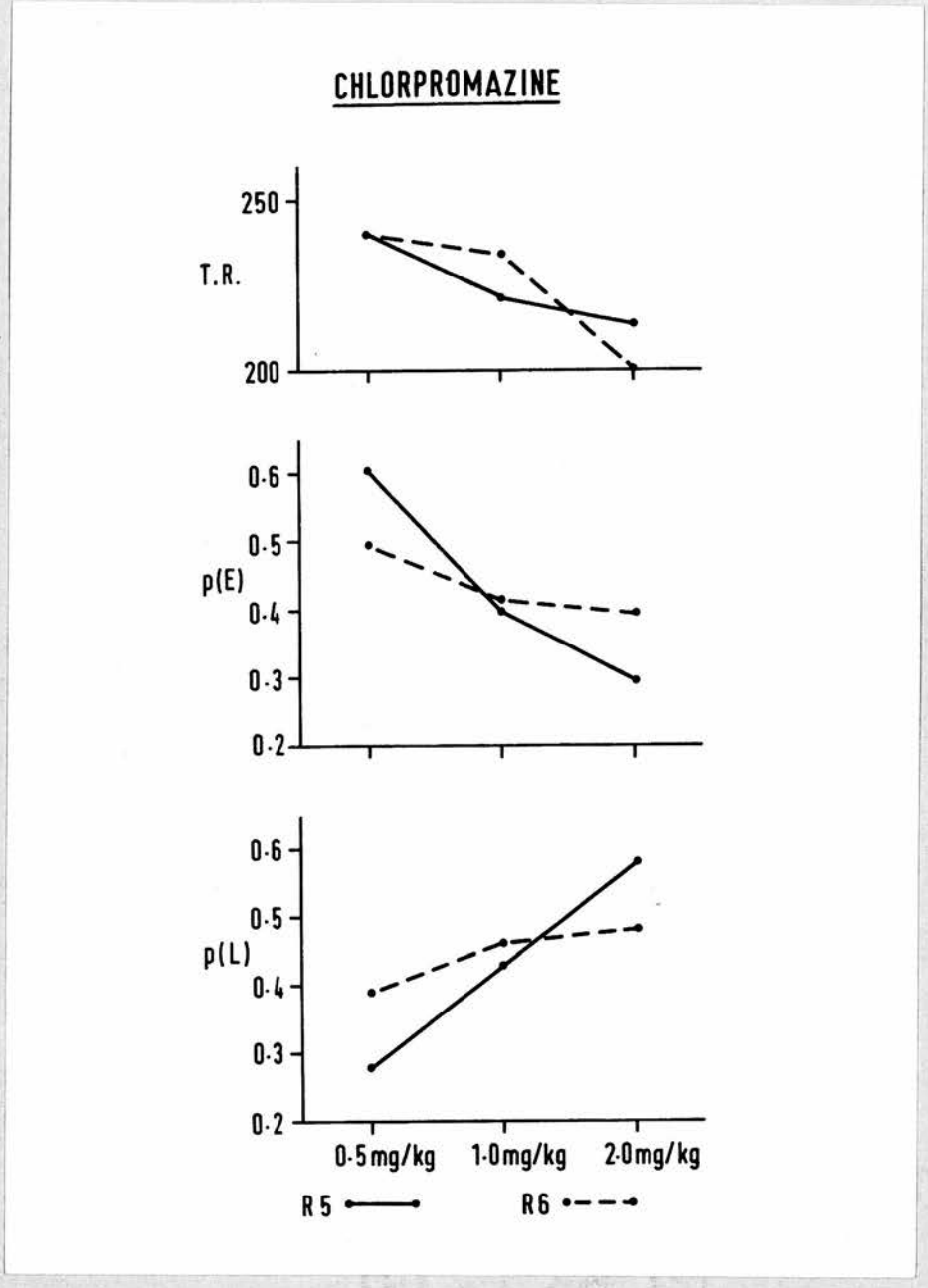

FIG. 6: The effects of increasing dosage of Chlorpromazine on three parameters of the avoidance schedule.

T.R. = Total responses
p(E) = Probability of efficient response
p(L) = Probability of late response.

EXPERIMENT 2: THE EFFECTS OF CHLORPROMAZINE ON THE AVOIDANCE SCHEDULE

Method

Subjects and Apparatus:

Two of the trained Lister hooded rats (R_5 and R_6) served as subjects. The apparatus was similar to that described in the previous experiment.

Procedure:

Throughout the experiment each subject was tested at the same time every day for $2\frac{3}{4}$ hours. The experimental session can be subdivided into a 15 minute 'warm up' period, a 30 minute pre-injection or control period and a two hour test period. Each S served as his own control and was injected with 0.5 ccs (i.p.) of a physiological saline solution on the pre- and post-drug days. Drugs were given after the pre-injection period and the subject was immediately placed in the Skinner box for the two hour test period.

Each S received three doses of CPZ (0.5 mg/kg, 1.0 mg/kg and 2.0 mg/kg) in a total fluid volume of 0.5 ccs (i.p.) Each animal was subjected to a different drug sequence with two weeks elapsing between each drug administration.

The data was collected in the form of sequential I.R.T.s and analysed by the standard computer program (Appendix A).

Results and Discussion

In all cases no disruption of behaviour was detected during

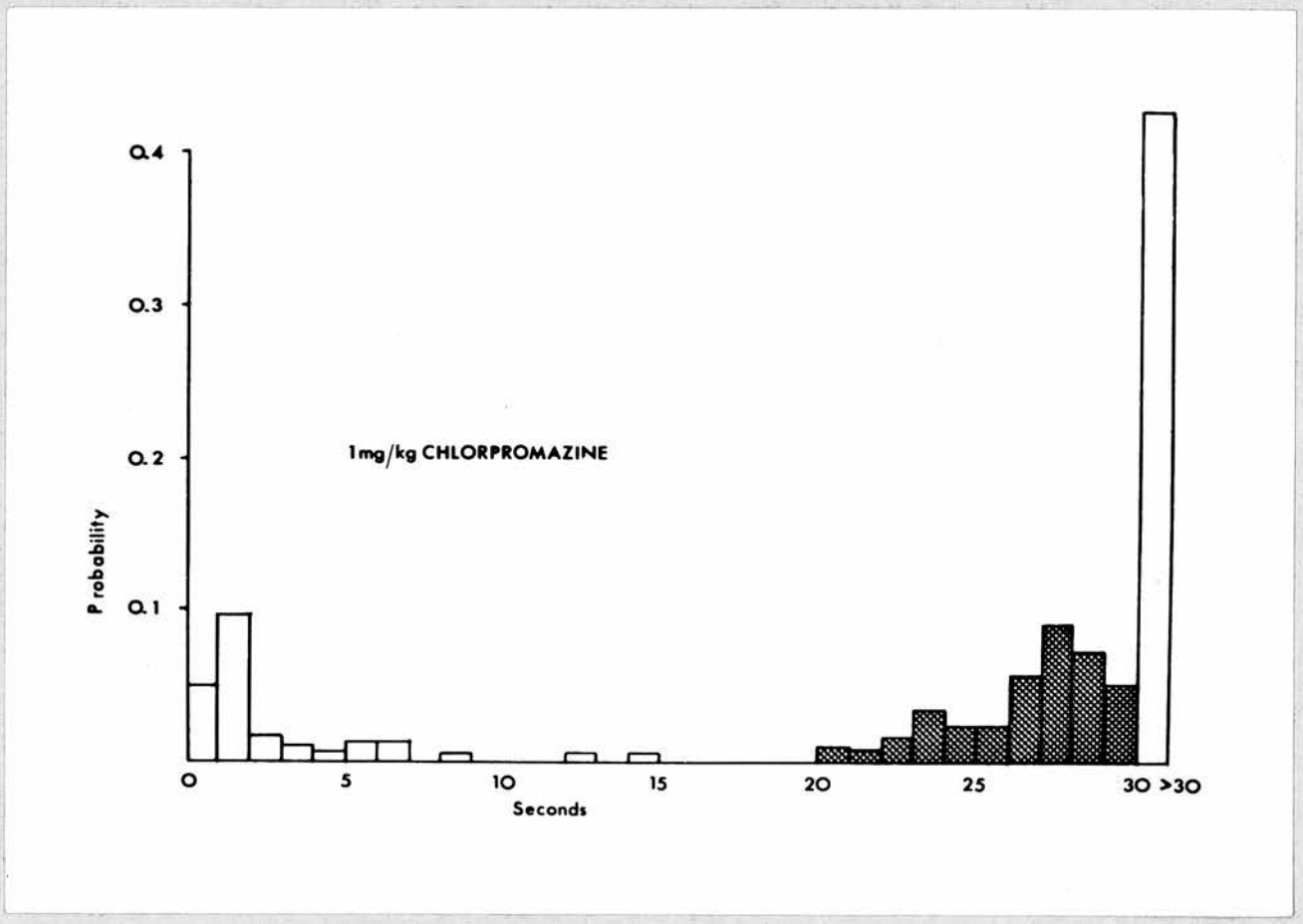

FIG. 7: Inter-response time distribution showing the effects of 1.0 mg/kg Chlorpromazine. (Subject R5).

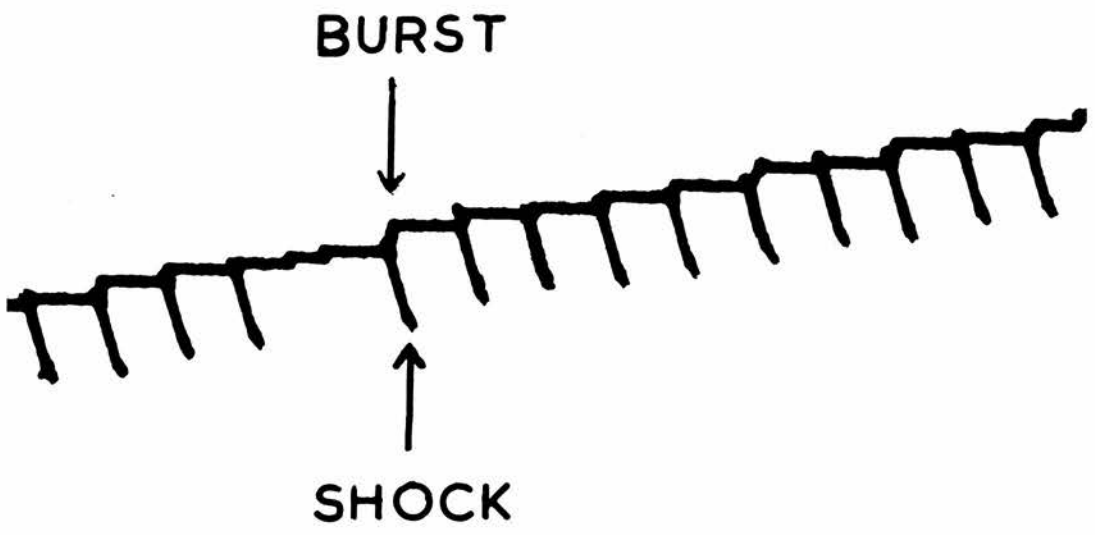

FIG. 8: Cumulative record showing the occurrence of burst responding following shock after treatment with Chlorpromazine.

the saline control days nor the pre-injection period prior to drug administration. Fig. 6 shows the effects of increasing dosage of CPZ on the behaviour of both animals (Appendix B Nos. 13-18). Concurrent with the decrease in total response rate (TR) and the probability of an efficient response (p(E)) there is an increase in the probability of a late response (p(L)). Fig. 7 is a typical I.R.T. distribution following CPZ (Appendix B No. 14). It is clear that there is an increase in the probability of a response being emitted before the onset of the stimulus light (premature and burst responses). Bovet and Gatti (68), however, have reported a decrease in premature responses (they call this category 'non-motivated' responses) under CPZ. There appears to be a simple explanation for this discrepancy. Under CPZ the animals tend to 'ignore' the warning stimulus and thus receive shock. From the sequential print out of I.R.T.s it was clear that a shock was often followed by a number of very short latency responses (Fig. 8). Since Bovet and Gatti classified all responses occurring within twelve seconds of shock as 'unconditioned responses' then they would detect no increase in 'non motivated' response. Burst responses, as defined earlier, would be classified in the 'unconditioned response' category. When I.R.T.s < 3 seconds are ignored on Fig. 7 then the probability pre-light responses are not affected by the drug. Furthermore, it is very probable that the animals used by Bovet and Gatti were not trained to the same level of performance and made a high percentage of 'non motivated' responses on control days. Measurements from their published data (68) suggest that

that this was indeed the case. The acquisition data reported in Experiment 1 andthe observations of Maffi (114) suggest that these 'non motivated' responses can be considered as secondary avoidance responses. That is, they avoid the stimulus light which is a strong conditioned negative reinforcer during acquisition (Kamin (99)). Maffi (114) has demonstrated that CPZ blocks both the primary and secondary avoidance response. It would appear then that where there is a high probability of 'non motivated' responses the effect of CPZ would be to cause a substantial reduction in this response category as reported by Bovet and Gatti (Fig. 2). On the other hand, where there is only a low probability of a premature response being emitted, as in the present experiment, one would expect little or no change in this category.

Figs. 9, 10, 11 show the complete second-order probability distributions for all three doses of CPZ. All probabilities which occupy less than 5% of the total distribution are neglected on the figures (Appendix C Nos. 1 - 3). The equivalent data for the second animal is in Appendix C Nos. 4 - 6. As the dose of CPZ increases from 0.5 mg/kg to 2.0 mg/kg there is a progressive increase in p(L.L) and of course p(E.E) decreases. The characteristic burst following shocks p(L.B) shown in Fig. 8 is present at all dose levels. An increase in p(L.B) could easily be due to increased frequency of shock. i.e. Increase in p(L) causes increase in p(B) and therefore increase in p(L.B). An examination of the conditional probabilities, however, reveals that this is not the whole story. The relationship between late and burst

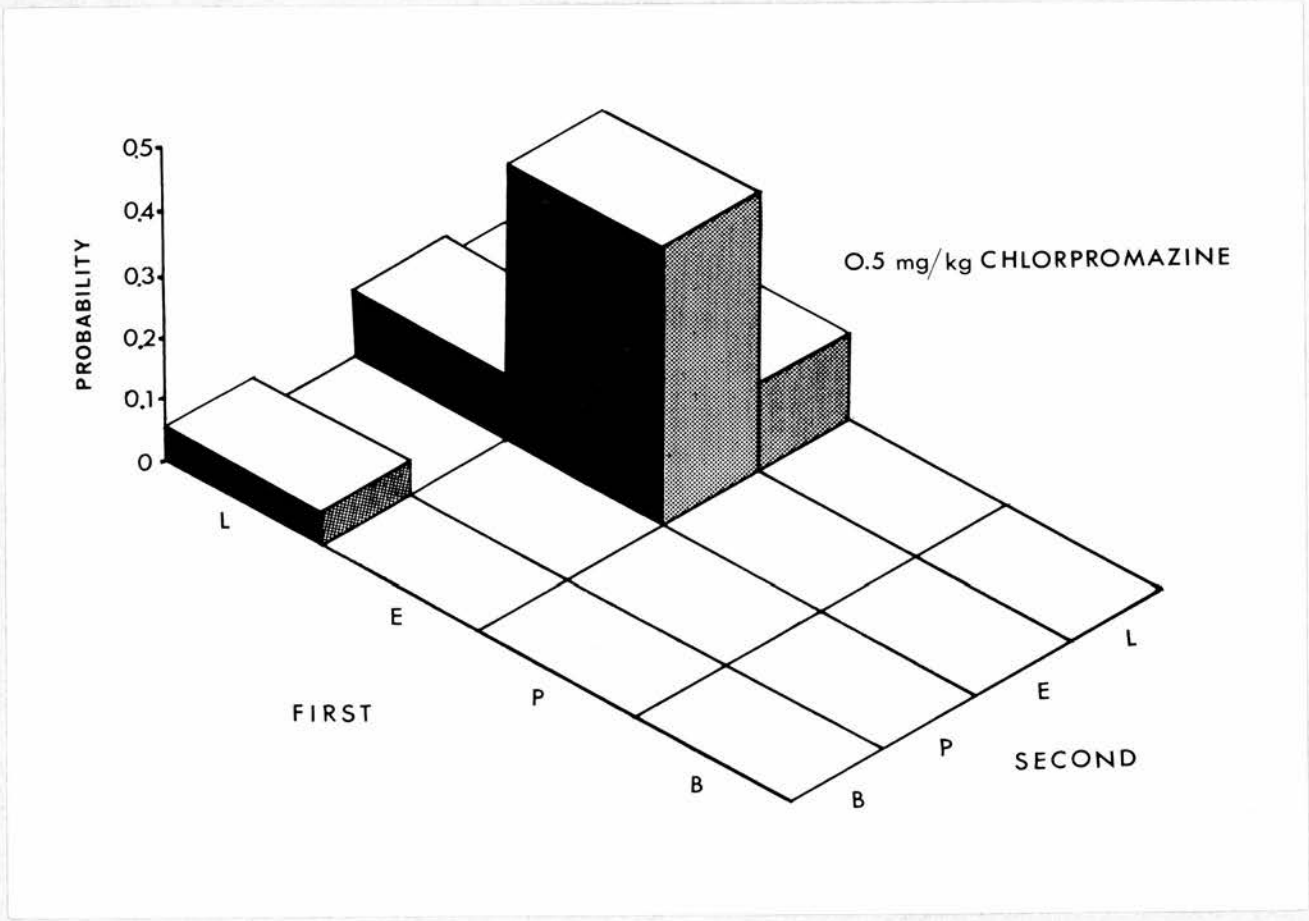

FIG. 9: Histogram showing the second order probability distribution following 0.5 mg/kg Chlorpromazine. All probabilities less than 0.05 are neglected from the figure. (Subject R5).

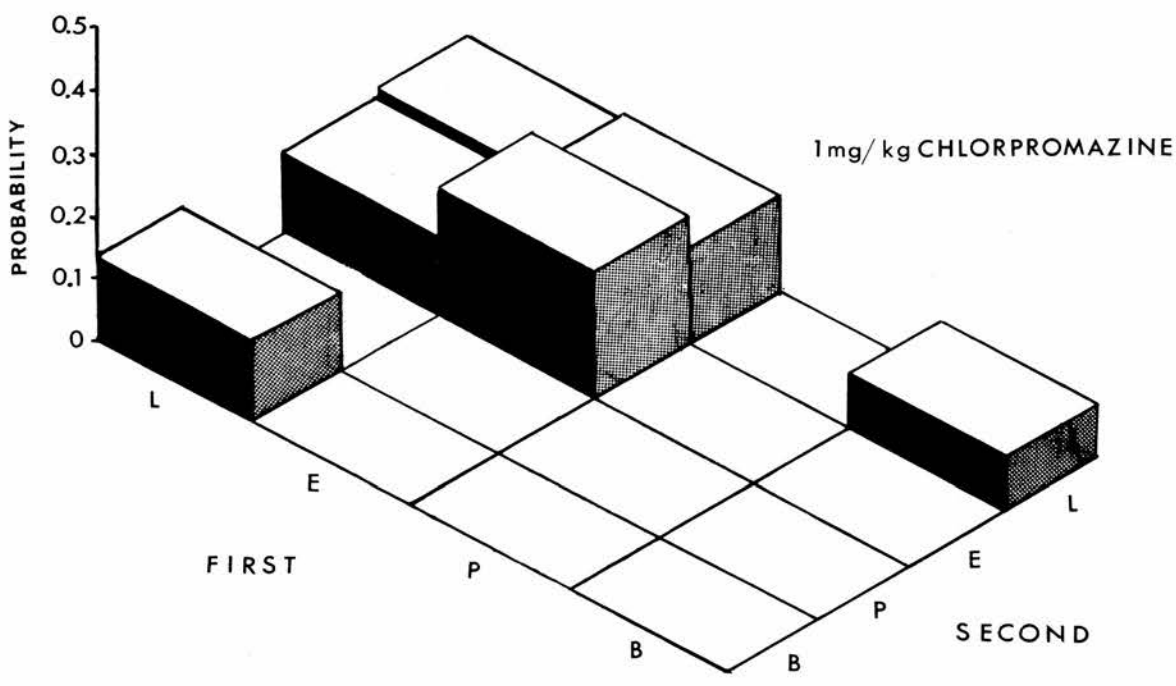

FIG. 10: Histogram showing the second order probability distribution following 1.0 mg/kg Chlorpromazine. All probabilities less than 0.05 are neglected from the figure. (Subject R5).

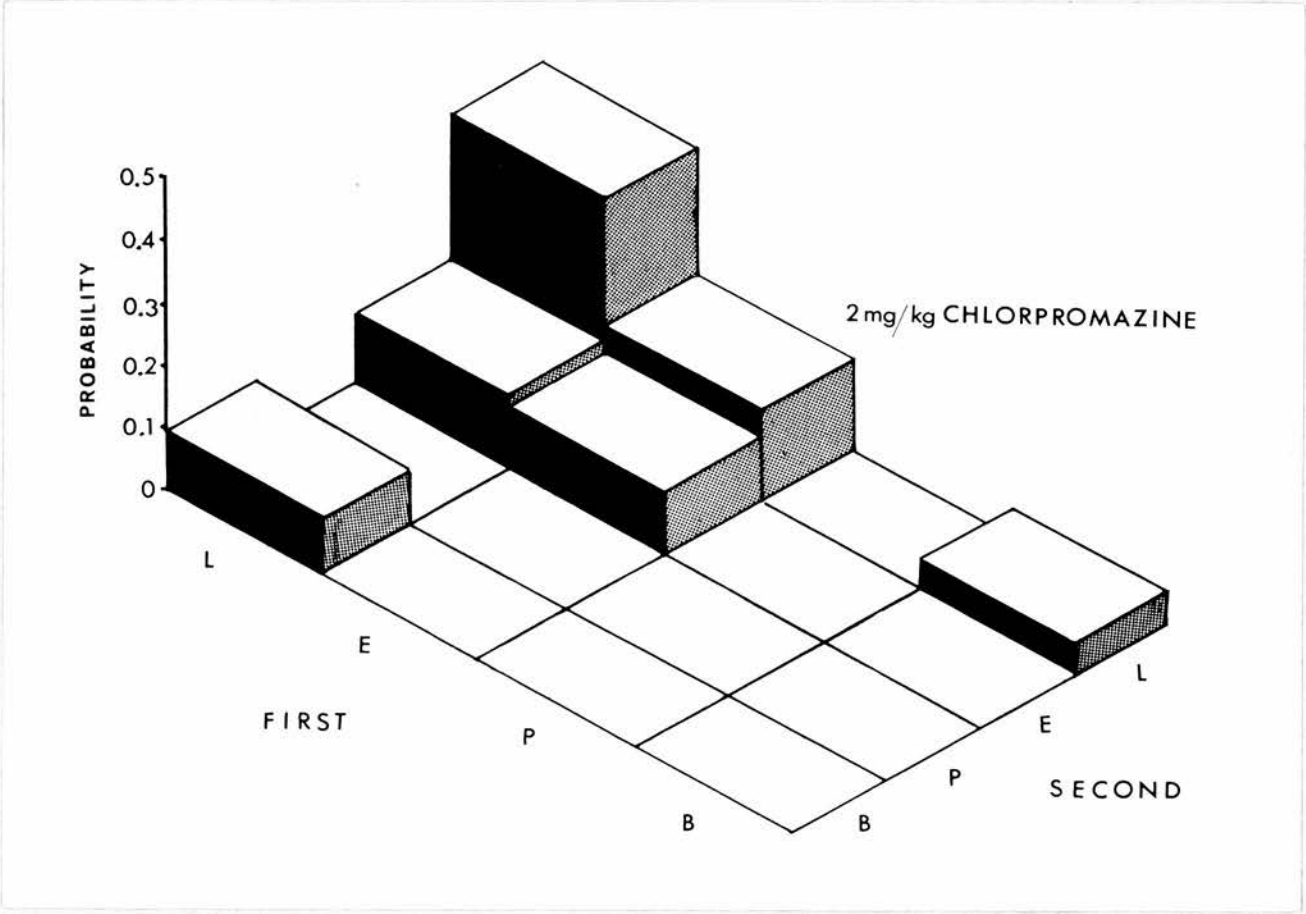

FIG. 11: Histogram showing the second order probability distribution following 2.0 mg/kg Chlorpromazine. All probabilities less than 0.05 are neglected from the figure. (Subject R5).

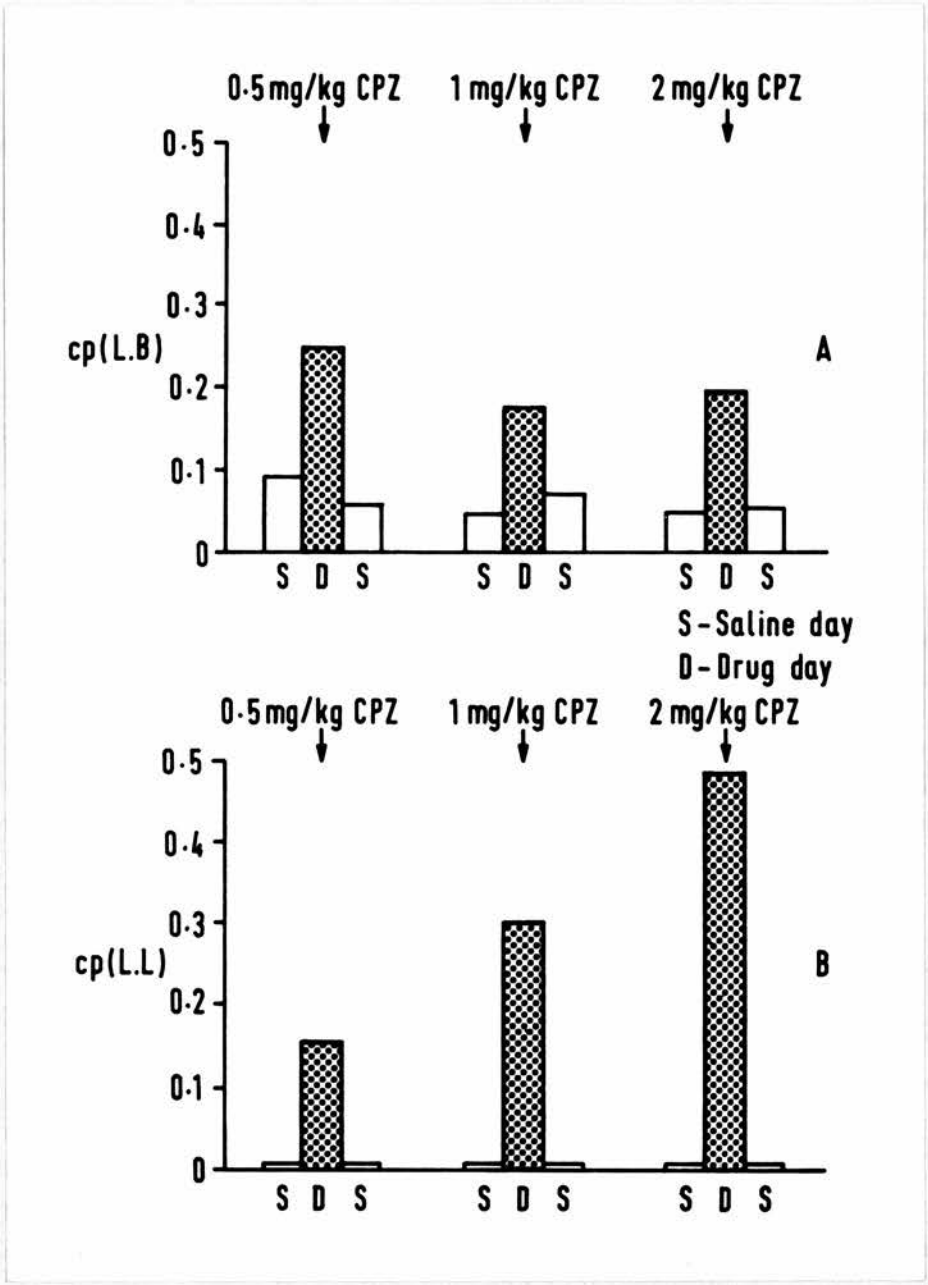

FIG. 12: Conditional probability of a burst response (A) or a late response (B) following a late response under three doses of Chlorpromazine. (Subject R6).

responses, where the frequency of late responses is taken into consideration, (conditional probabilities) is shown in Fig. 12. At all dose levels there is a higher conditional probability of a burst response following a late response (cp(L.B)) than on control days. The values (0.1 to 0.3) are much lower than that reported by Clark and Steele (0.98) using a non-discriminated avoidance schedule (39). This is probably related to the fact that there is immediate feedback (light goes off) on the discriminated schedule indicating that a response has been effective.

The present experiment does not throw any light on the reason for the increase in cp(L.B) under CPZ. At least two hypotheses are possible (a) CPZ per se decreases shock threshold (b) CPZ leads to the animal receiving more shock and therefore shock threshold is decreases (sensitization). It should be possible to distinguish between these two alternatives by delivery of a fixed number of 'free shocks' (not related to schedule) to the same animal during extinction with or without CPZ.

Fig. 12 shows a clear dose dependent increase in cp (L.L). This indicates that, as the dose of CPZ increases, there is an increase in the frequency of runs of late responses (see Fig. 8).

Conclusions

When account is taken of the slightly different response classification employed in the present investigation then the effects of CPZ on the discriminated avoidance shhedule are similar to those reported by Bovet and Gatti.

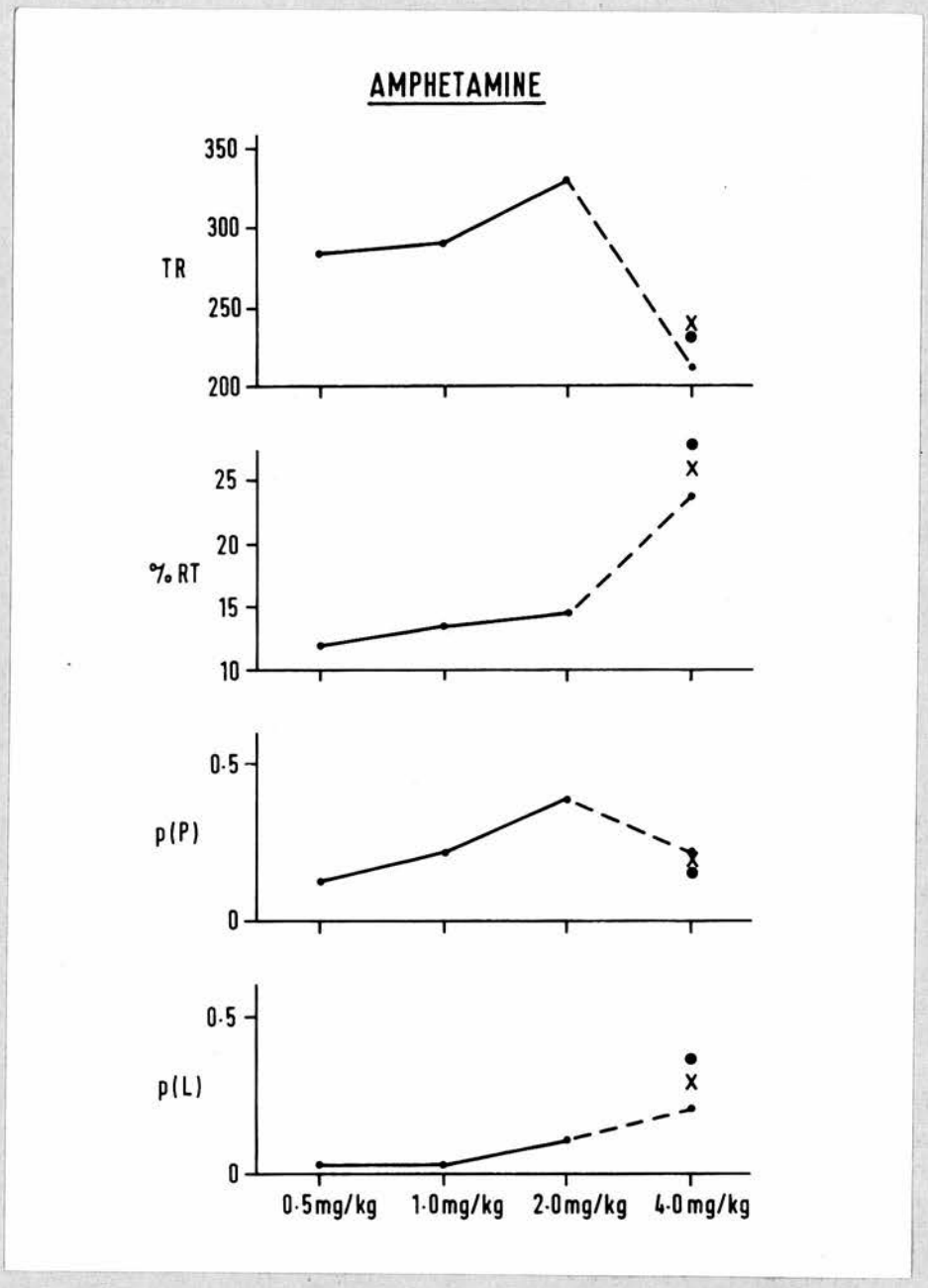

FIG. 13: The effects of increasing dosage of Amphetamine on four parameters of the avoidance schedule.

T.R. = Total responses
%RT = Percentage reaction time
p(P) = Probability of premature response
p(L) = Probability of late response.

EXPERIMENT 3: THE EFFECTS OF AMPHETAMINE ON THE AVOIDANCE SCHEDULE

Method

Subjects and Apparatus:

Two of the trained Lister Hooded rats (R1 and R4) served as subjects. The apparatus was similar to that described before.

Procedure:

The session length and injection procedure were similar to that described in the previous experiment. Each S served as his own control and received 0.5 ccs (i.p.) of physiological saline on the pre-and post-drug days. Four doses of amphetamine 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg and 4.0 mg/kg were studied. R1 was given all doses in the following order - 2.0 mg/kg, 0.5 mg/kg, 1.0 mg/kg and 4.0 mg/kg. R4 received 4.0 mg/kg on two separate occasions. The drugs were dissolved in 0.5 cc saline and two weeks elapsed between each administration.

The data was collected in the form of sequential I.R.T.s and analysed by the standard computer program.

Results and Discussion

Fig. 13 shows the effects of increasing dosage on the performance of R1 (Appendix B Nos. 19-22). As the dose of amphetamine increased from 0.5 mg/kg to 2.0 mg/kg there was a corresponding increase in the total number of responses, the probability of a premature response,

and the percentage reaction time. The increase in the probability of premature responding agrees well with the general hypothesis of Weiss and Laties (180) that amphetamine 'generates responding at probabilities that ordinarily are not great enough to maintain responding.' This was also reflected in the form of the response distribution within the pre-aversive stimulus (Fig. 14). There was a marked skew in the distribution towards the onset of the stimulus light. On control days, few responses occurred early in the stimulus period since the conditioned aversive temporal stimuli at these short post S_1 times were not sufficient to maintain responding (see Experiment 1). Under amphetamine, however, it would appear that the reinforcement threshold has been reduced (162) and the stimulus light is a strong negative reinforcer. It is relevant that Brady (19) has shown that amphetamine enhances conditioned suppression. This supports the general hypothesis that amphetamine increases the aversive properties of a stimulus by reducing the reinforcement threshold.

The increase in response rate under amphetamine should, therefore, not be considered as a 'motor stimulation' per se but as a direct result of increased 'motivation', or more explicitly decreased reinforcement threshold. It is possible that premature responses occurred as a result of a loss in stimulus control. That is, the animal could no longer 'discriminate' between the light-on period and the light-off period. This will be considered in a subsequent experiment.

The behavioural effects of 4.0 mg/kg amphetamine for R1 and

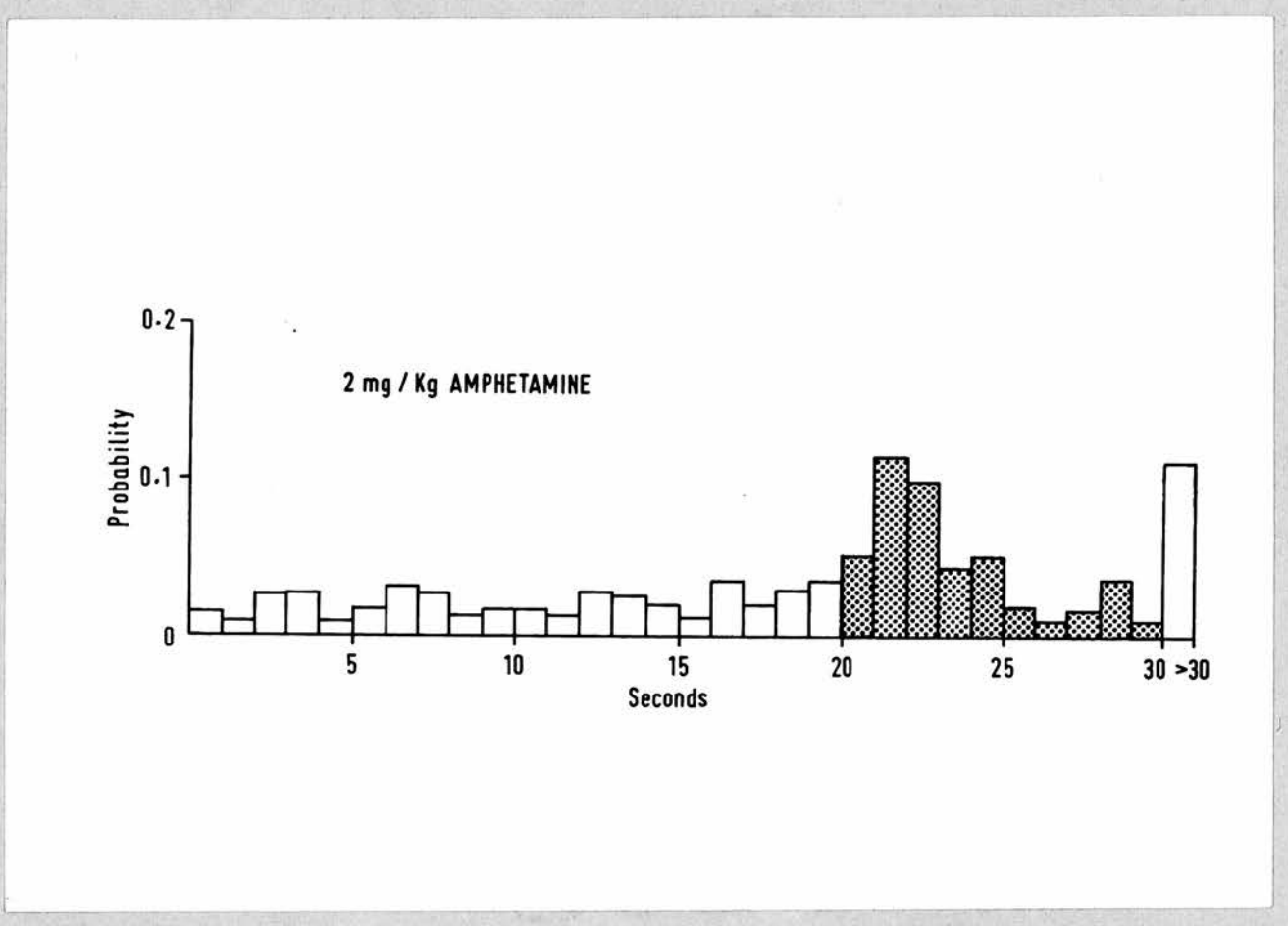

FIG. 14: Inter-response time distribution showing the effects of 2.0 mg/kg Amphetamine. (Subject R1).

and R4 are shown in Fig. 13. It is clear that the effects of this high dose of amphetamine were not in line with the general trend. Although there is a further increase in the probability of late responses; the total response rate and probability of a premature response both decreased. Observation of the animals suggest this was not due to any motor deficit. The animals were hyperactive although not responding on the lever. Increased salivation was also apparent. The behaviour was similar to that observed by Clarke and Steele (40) using high doses of amphetamine on a positive reinforcement schedule. The animals often received many shocks before emitting a lever press (long I.R.T.s) as well as the typical short I.R.T.s which occurred with lower doses of the drug.

If the animal did not respond early in the stimulus period then, normally, it would not respond at all until a shock, or series of shocks, had been delivered. Therefore, I.R.T. distributions (Appendix B Nos. 22 - 24) for the high dose of amphetamine still exhibit a marked skew towards the onset of the stimulus light.

Fig. 15 presents the second order probabilities for R1 at the low doses of amphetamine (Appendix C Nos. 7 - 9). There is a clear trend in the data. The stimulation of amphetamine is reflected in the increasing p(P.P) with the increasing dosage. It is important to note that the increased p(P) and p(P.P) occur in their absence of any significant increase in p(L). This excludes the possibility that the increase in premature responding under amphetamine can be considered as avoidance responses of the stimulus light which has become a stronger

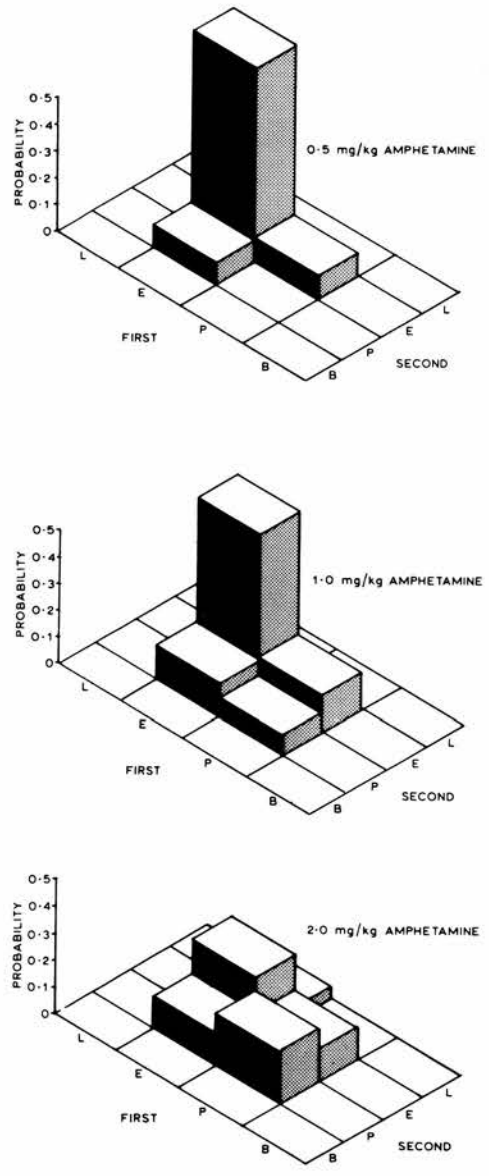

FIG. 15: Histograms showing the second order probability distributions following three doses of Amphetamine. All probabilities less than 0.05 are neglected from the figure. (Subject R1).

conditioned negative reinforcer by virtue of increased light-shock pairings.

Conclusions

The effects of low doses of amphetamine on the discriminated continuous avoidance schedule are similar to those described by Bovet and Gatti and can easily be distinguished from the effects of CPZ. High doses of amphetamine cause an unusual behaviour pattern which resembles the low dosage effect only in the marked skew in the response distribution within the 'warning stimulus'.

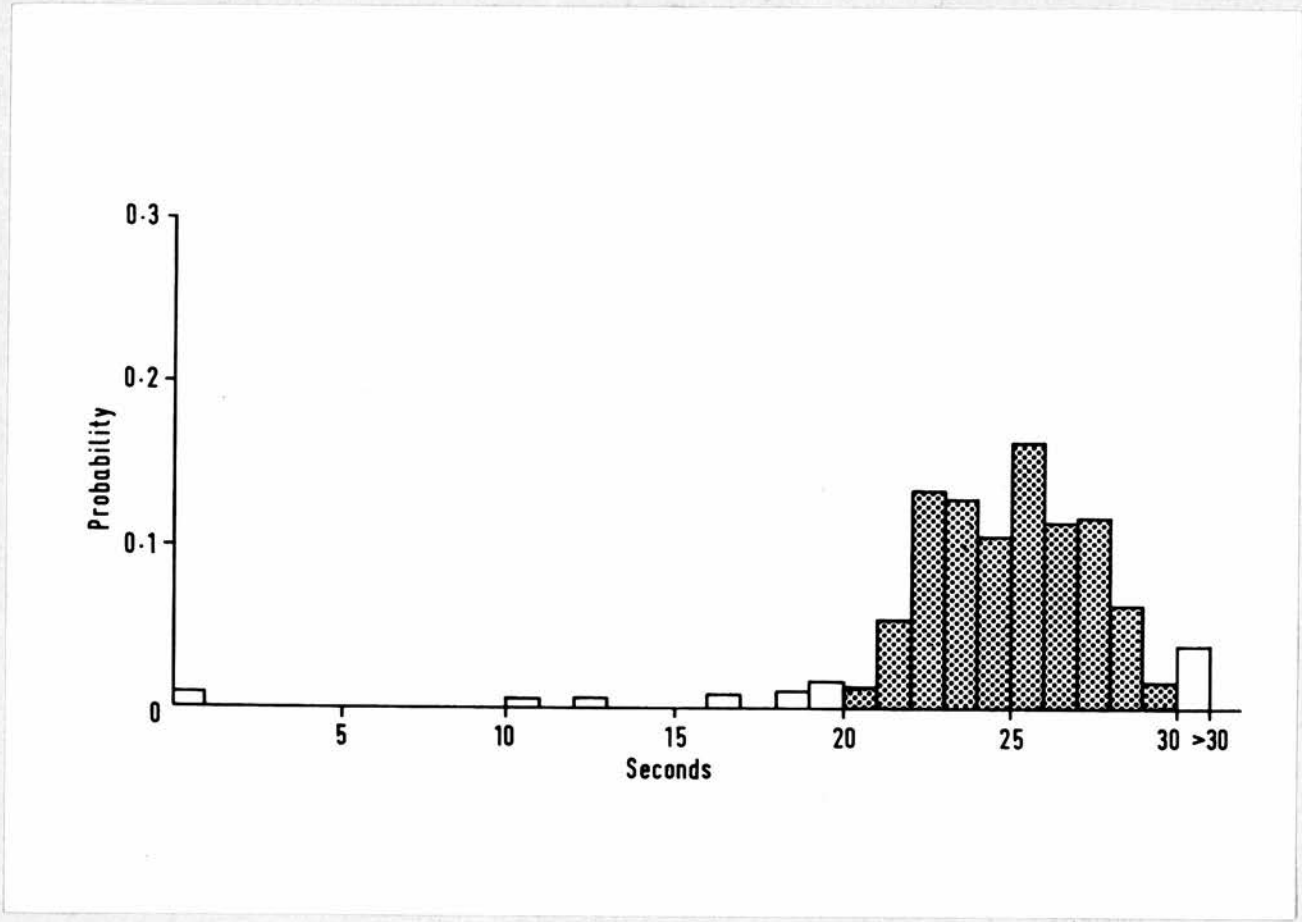

FIG. 16: Inter-response time distribution showing the effect of 12.5 mg/kg Mescaline.

EXPERIMENT 4: THE EFFECTS OF HALLUCINOGENS ON THE AVOIDANCE SCHEDULE

Method

Subjects and Apparatus:

Five of the trained Lister hooded rats (R1, R2, R3, R4 and R5) served as subjects. The standard programming and recording equipment were employed.

Procedure:

The experimental design and drug administration procedure have already been described in the previous experiments. Animals R1, R2 and R3 each received 12.5 mg/kg, 17.5 mg/kg and 25.0 mg/kg mescaline, in a random order. Subject R4 was given 0.25 mg/kg, 0.5 mg/kg and 1.0 mg/kg LSD and R5 received 25.0 mg/kg mescaline, 1.0 mg/kg LSD and 10.0 mg/kg N,N Dimethyltryptamine. These three drugs cover a wide range of structural differences within the psychotomimetic classification.

As before, all drugs were given intraperitoneally in 0.5 ccs saline and two weeks were allowed to elapse between each drug administration. The data was analysed by the standard program.

Results and Discussion

Fig. 16 shows a typical I.R.T. distribution following 12.5 mg/kg mescaline. The only observable effect of this dose was a disturbance of the I.R.T. distribution within the stimulus period (cf. Fig. 4). The p(P) and p(L) remained unchanged. The net result therefore, was a decrease in the % RT. Using a shuttle-box avoidance

procedure, Smythies and Sykes (154) have reported a similar decrease in reaction time following 12.5 mg/kg mescaline. Measurements from their published data (156) reveal that, in some cases, they obtained $\Sigma (D-\bar{S})$ scores for four animals, with greater than 16 seconds reduction in reaction time. Thus, since the average $(D-\bar{S})$ score was approximately 4 seconds, it follows that on saline control days, their animals must have allowed at least four seconds, of the five second CS, to elapse before crossing to the other side of the shuttle-box. It would appear then, that the experimental procedure they employed, (80-85% avoidance criterion and prolonged 'warm up' period) facilitated the development of a 'temporal discrimination', similar to the present experiment, and it is the disruption of this process that causes the decrease in reaction time observed at low doses of mescaline.

It is not surprising that a disturbance of the response distribution within the C.S. is the first detectable behavioural change since Laties and Weiss (110) have shown that behaviour controlled by internal stimuli (temporal discrimination) is less resistant to drug effects than behaviour controlled by external stimuli (visual discrimination).

There was no marked skew in the response distribution towards the onset of the C.S. as was the case for amphetamine. This was true for all doses of the drug (Appendix B Nos. 25 - 33). The 'stimulant' action of mescaline is therefore much less than that for amphetamine and not sufficient to cause an increase in p(P) at 12.5 mg/kg. This is also true for a low dose (0.25 mg/kg) of LSD.

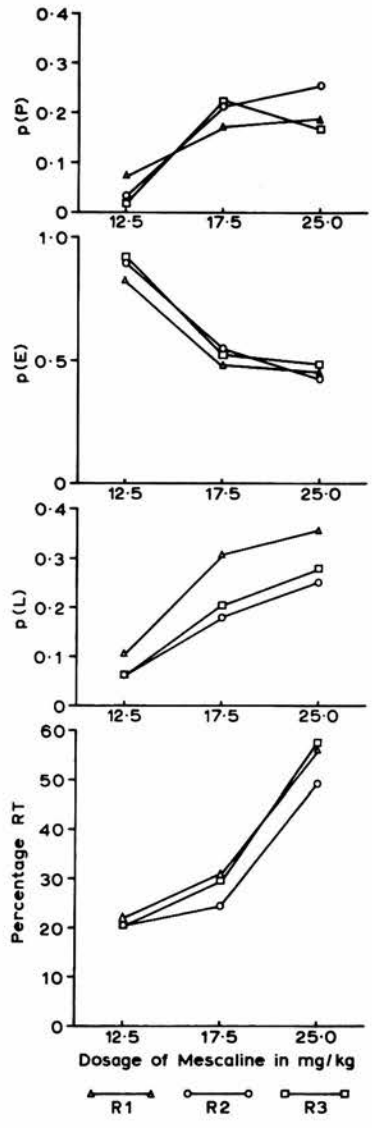

FIG. 17: The effects of increasing dosage of Mescaline on four parameters of the avoidance schedule.

p(P) = Probability of premature response
p(E) = Probability of efficient response
p(L) = Probability of late response
%RT = Percentage reaction time.

Using low doses of LSD, Taeschler et al (168) found a similar decrease in latency of jumping a rod in an avoidance situation - in this case performance was improved. Jerard (97) had also reported an improved performance with small doses of LSD, in a non-discriminated avoidance situation. Both these authors used a decrease in the probability of shock as an index of improved performance and the efficiency of the behaviour was not considered. Thus, even amphetamine at low doses, which causes a decrease in shock received, would be considered to improve performance even though the high rate was inefficient in terms of the number of responses necessary for successful avoidance.

Although no significant improvement was detected against the high pre-drug performance levels in the present pxperiment, the results suggest that a reduction in shock probability could be observed against a less efficient behavioural baseline. It was noted in Experiment 1 that the temporal distribution within the CS period was equivalent to a non-discriminated avoidance schedule. Since 12.5 mg/kg mescaline caused a shift in this response distribution towards shorter I.R.T.s then it would almost certainly have the same effect on a non-discriminated schedule causing less efficient behaviour, but a reduction in the number of shocks received. Although Jerard does not report the exact shock frequency on control days it appears to be in the order of 130 shocks in a two hour session. Even the slight forward skew in the response distribution observed after 12.5 mg/kg mescaline should be sufficient to reduce this shock frequency.

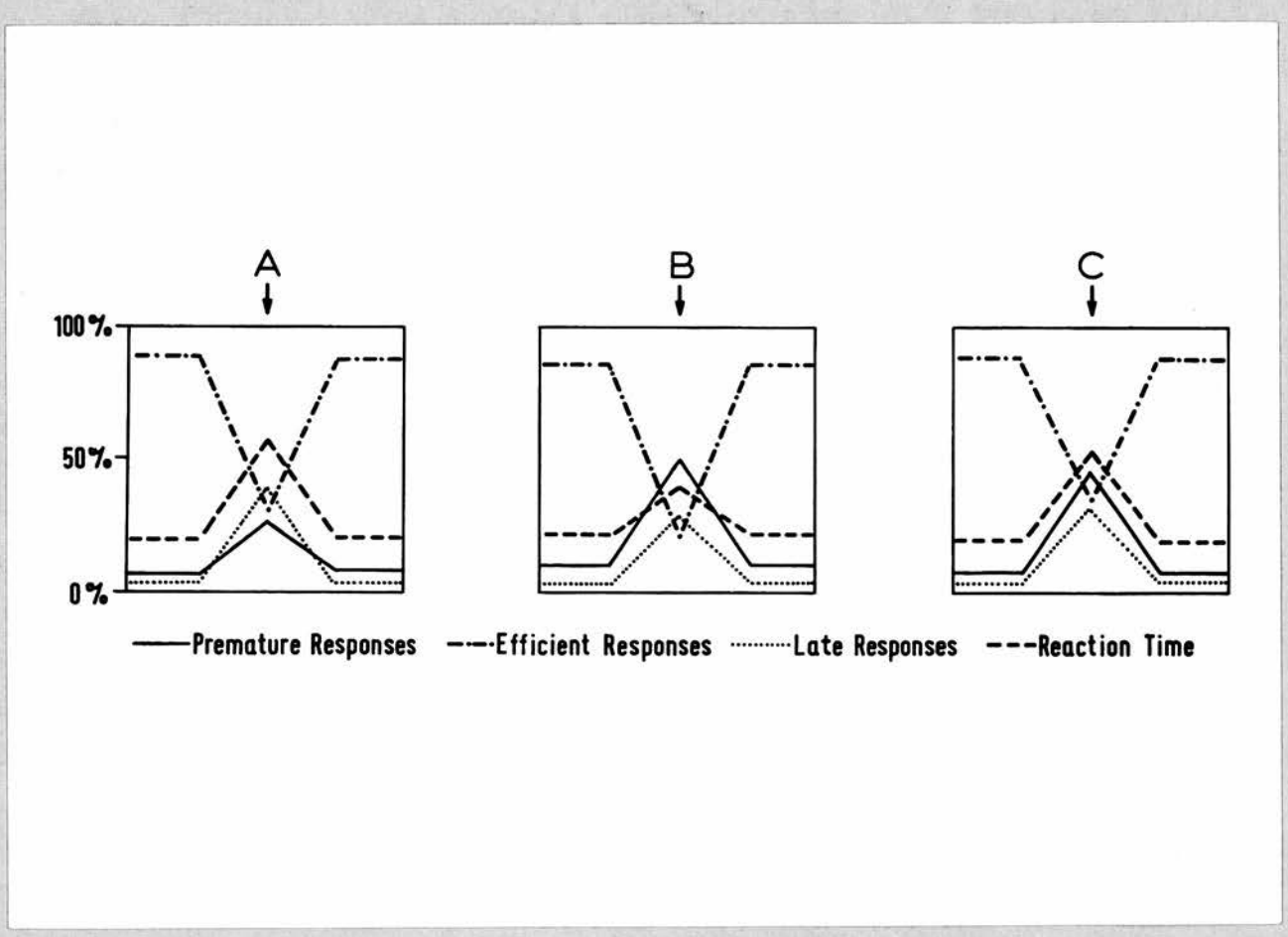

FIG. 18: Behavioural profiles for 25.0 mg/kg Mescaline (A), 0.5 mg/kg L.S.D. (B) and 10.0 mg/kg N,N-Dimethyltryptamine.

The effects of increasing dosage on four of the behavioural parameters can be seen in Fig. 17. Mescaline caused a dose dependent increase in p(P), p(L) and % RT. The impaired performance at high doses of hallucinogens has been reported by many authors (97, 154) and does not appear to be due to any motor defect at these doses. Both Smythies and Sykes (154) and Jerard (97) have stressed these 'central-stimulating' and 'central-depressing' actions of hallucinogenic drugs depending on dose level.

The high dose mescaline effect is presented in the form of a Bovet and Gatti behavioural profile in Fig. 18 (Appendix B No. 37). The effects of 0.5 mg/kg LSD (Appendix B No. 38) and 10 mg/kg N,N DMT (Appendix B No. 39) are also shown.

It would appear that high doses of hallucinogenic drugs cause an increase in p(P), p(L) and % RT, whereas low doses only decrease % RT on this behavioural test. This is quite different from the amphetamine increase in p(P) which was not associated with an increase in p(L). At high doses of amphetamine, when an increase in p(L) did occur, there was always a marked skew in the I.R.T. distribution towards the onset of the stimulus light. The response distribution within the stimulus period following a high dose of hallucinogen, was similar to that observed following low doses of these drugs.

The second order distributions for all animals receiving three doses of mescaline are shown in Figs. 19, 20, 21. Although there was some individual difference, the general trend was similar for

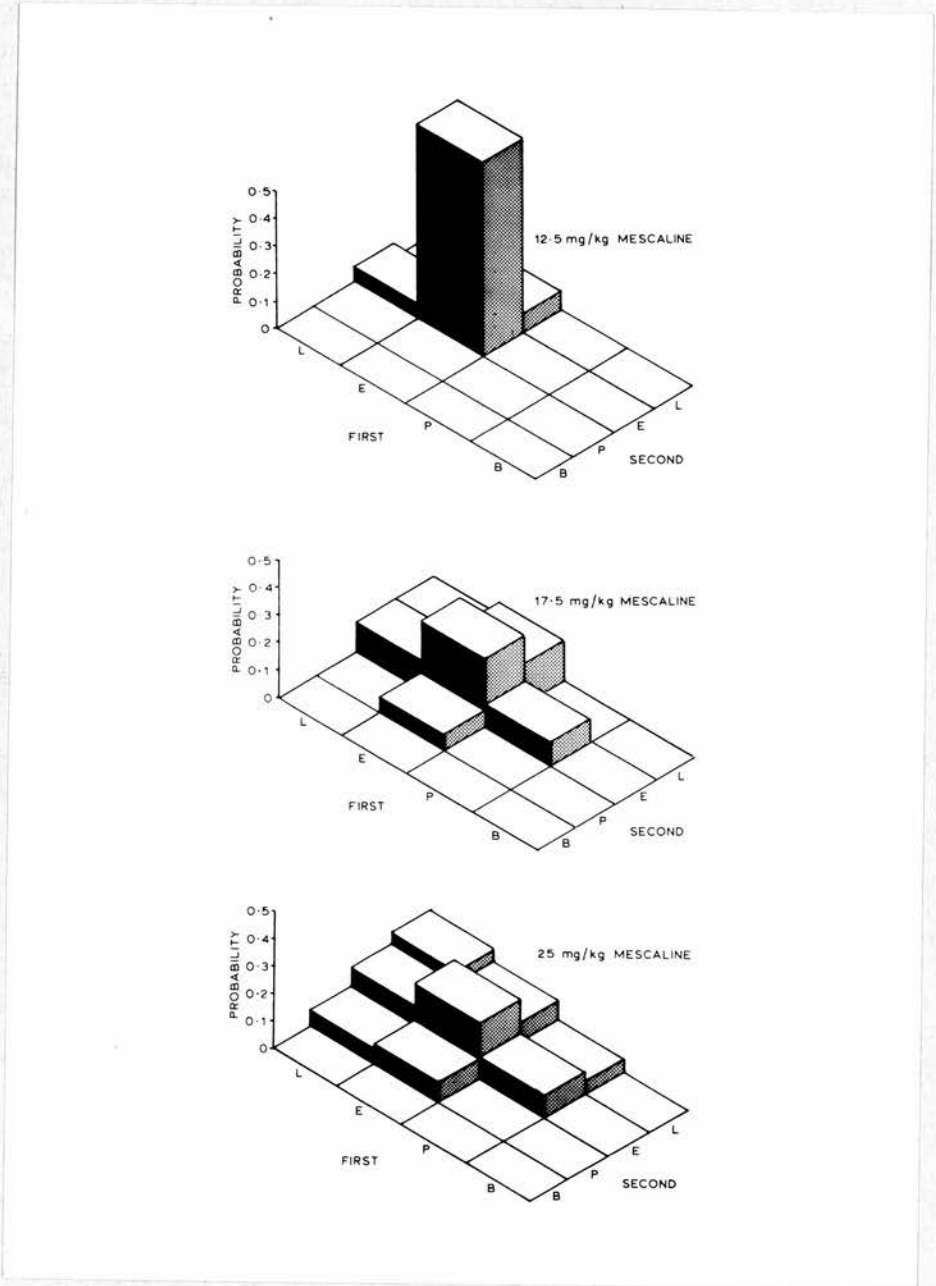

FIG. 19: Histograms showing the second order probability distributions following three doses of Mescaline. All probabilities less than 0.05 are neglected from the figure. (Subject R1).

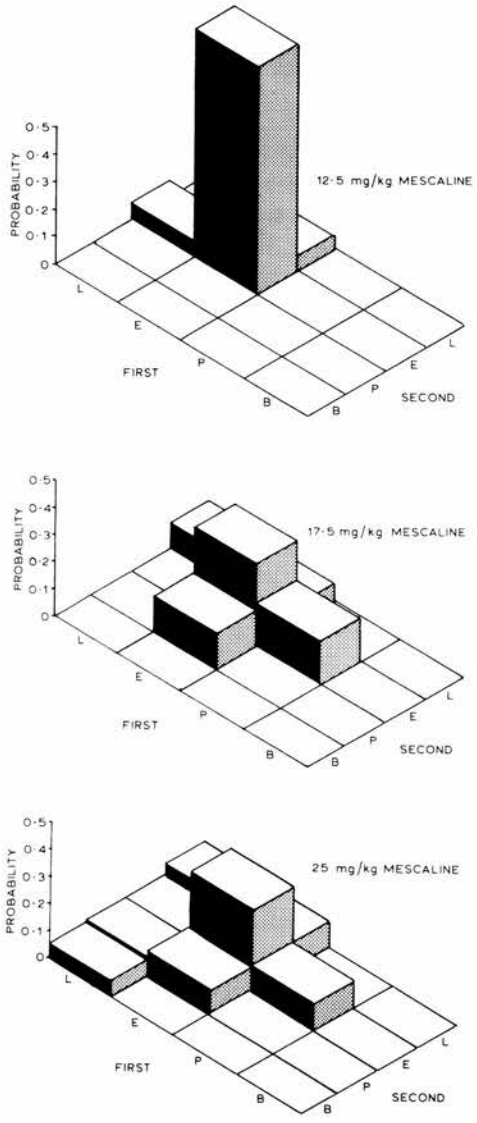

FIG. 20: Histograms showing the second order probability distributions following three doses of Mescaline. All probabilities less than 0.05 are neglected from the figure. (Subject R2).

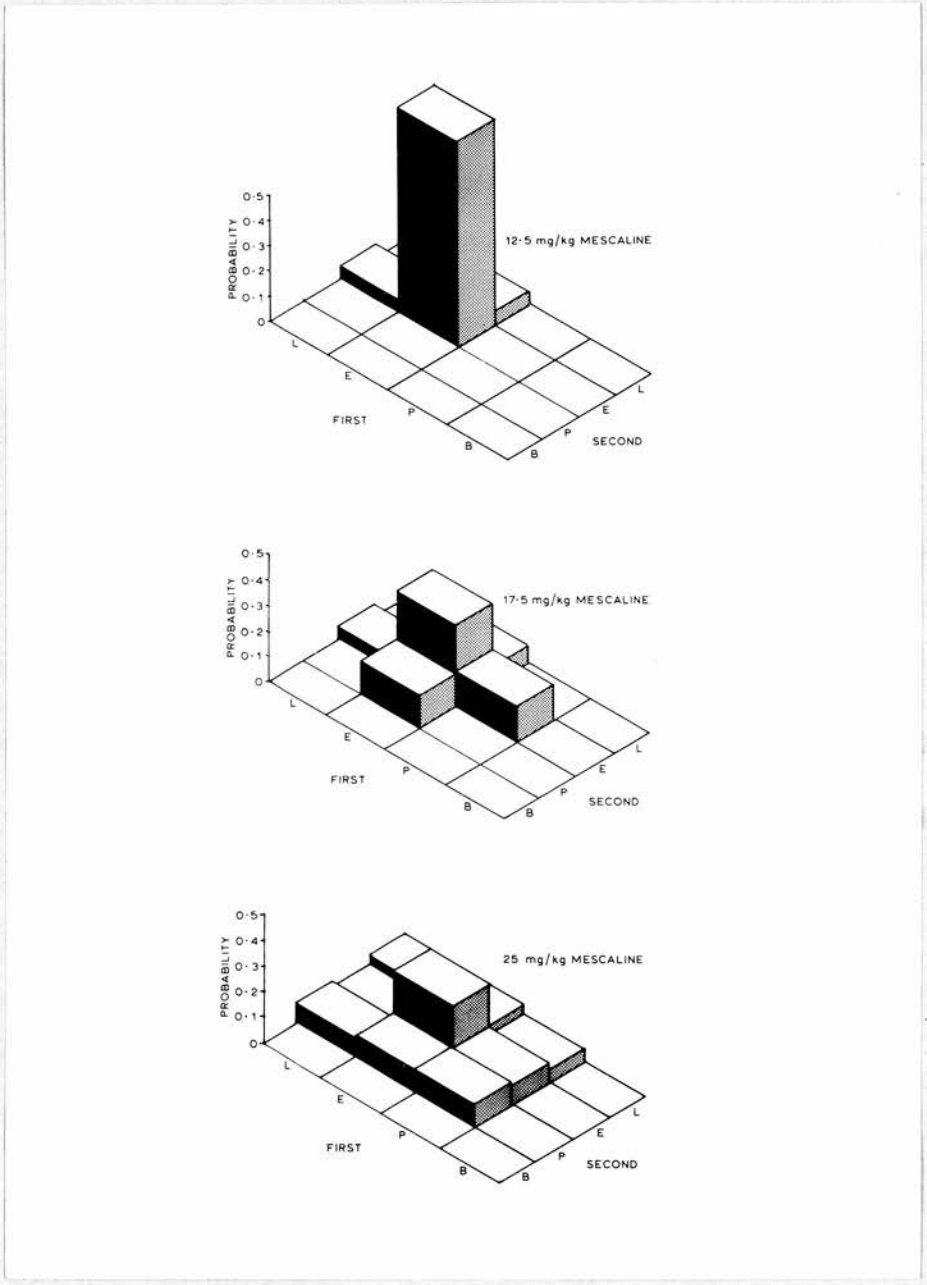

FIG. 21: Histograms showing the second order probability distributions following three doses of Mescaline. All probabilities less than 0.05 are neglected from the figure. (Subject R3).

for all animals. The p(P.P) was very low and never occurred in the absence of a comparable increase in p(L.L). Premature responses under mescaline do not therefore occur in runs to the same extent as that observed with amphetamine. Unlike CPZ, the p(L.B) was very low at all dose levels.

Conclusions

The typical behaviour profile for a high dose of a psychotomimetic drug is (a) an increase in p(L); (b) an increase in p(P); (c) an increase in % RT; (d) a decrease in p(E); (e) a disruption of the I.R.T. distribution within the stimulus light. This last effect occurs, at low doses of hallucinogens, without any increase in p(L) and is reflected in a decrease in % RT.

The 'stimulant' action of amphetamine, which is characterized by (I) increase in response rate, (II) marked skew in response distribution within CS and (III) increase in p(P) at doses which do not increase p(L), can be clearly distinguished from the effects of hallucinogenic drugs.

The behavioural changes following CPZ are quite different. At no dose investigated was their any significant increase in premature responding and the I.R.T. distribution during the stimulus light was not affected.

None of the drugs studied by Bovet and Gatti gave behavioural profiles which could be confused with the effects of the psychotomimetic drugs.

SECTION V

THE FUNCTIONAL ANALYSIS OF DRUG ACTION

INTRODUCTION

From the viewpoint of a functional analysis of behaviour a drug alters behaviour by modifying the control of the independent variables of the schedule which controls that behaviour. It was clear from experiment 1 that the major controlling variable on the discriminated avoidance schedule was the stimulus light. We can distinguish between two aspects of the stimulus; the stimulus control or visual discrimination and the aversive properties of the stimulus. These are not independent properties of the stimulus since the light can have no aversive properties unless it 'can be discriminated' by the animal. Two experiments, however, were carried out to investigate the effects of CPZ, amphetamine and mescaline on these two aspects of the visual stimulus which controlled the standard avoidance schedule.

EXPERIMENT 5: THE EFFECTS OF DRUGS ON VISUAL DISCRIMINATION

Method

Subjects and Apparatus:

Two male Lister hooded rats (R7 and R8) served as subjects. The experimental chamber was a modified two-lever Behaviour Apparatus Skinner Box fitted with a house light, two cue lights, a buzzer and shock grids. The shock grids of the standard Behaviour Apparatus box were turned through 90°, so that they ran parallel to the sides of the chamber. This was necessary since it was soon found that the animals could avoid shock by standing on one bar of the grid, rather than pressing the lever. In the new position, bar-press avoidance developed in preference to any other avoidance behaviour. The intensity of the house light, cue lights and shock source were altered until they approximated that of the Grason-Stadler chamber. A $4\frac{1}{2}$ volt house buzzer was used as an auditory stimulus.

Procedure:

Both animals were exposed to the standard discriminated continuous avoidance schedule, with a R-S_2 interval of 30 seconds and a S_2-S_2 interval of 10 seconds, for daily, two hour avoidance sessions. The warning stimulus (S_1) in the present experiment, however, was a buzzer, instead of the two cue lights, and a response on either lever was effective in postponing shock. These experimental conditions were in operation for thirty days. At the end of this

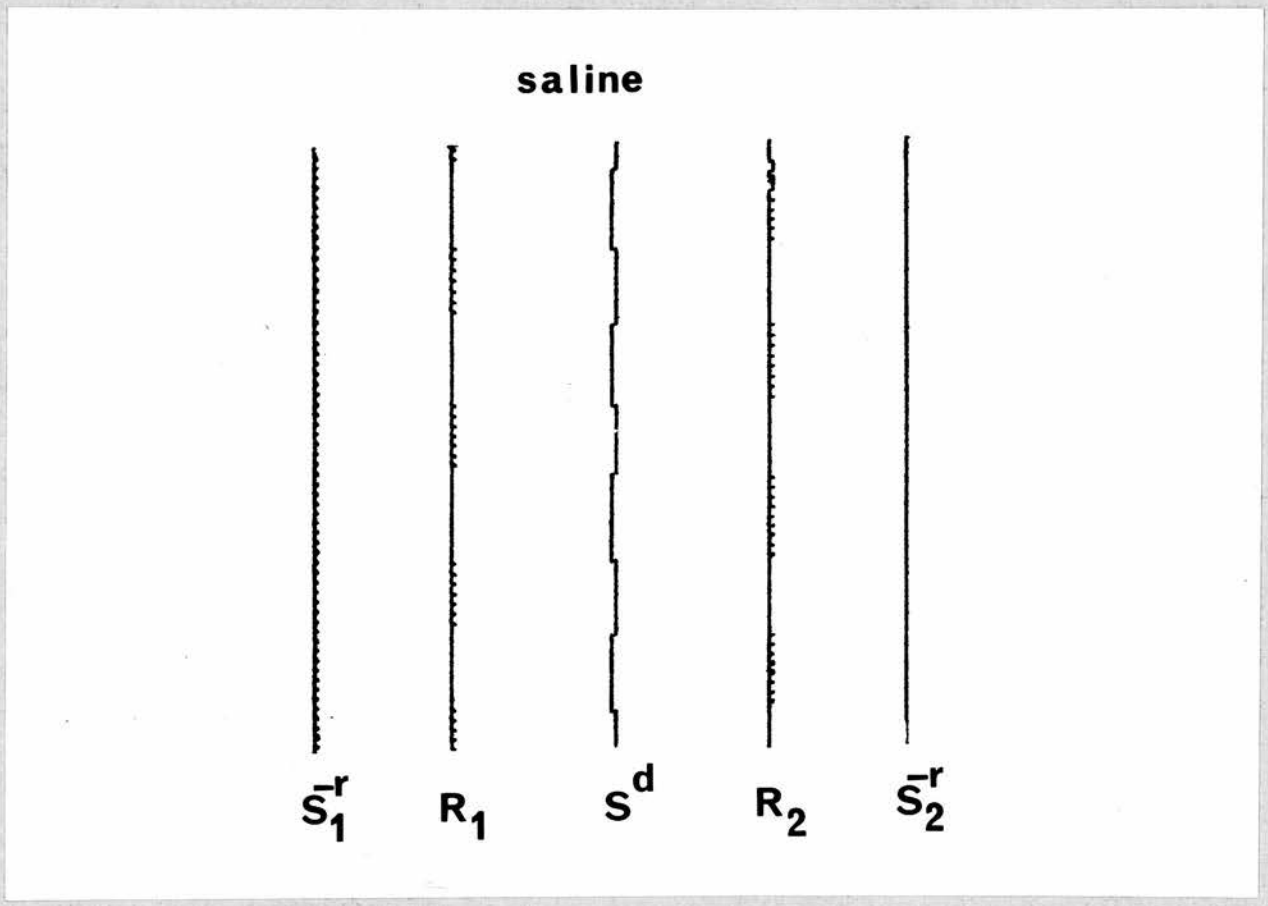

FIG. 22: Kymograph record showing the effects of Saline on a two lever discriminated continuous avoidance schedule. (Subject R7).

S_1^{-r} = Warning buzzer

R_1 = Responses on first lever

S^d = Discriminative stimulus light

R_2 = Responses on second lever

S_2^{-r} = Shock.

time both animals had attained a high level of avoidance behaviour.

On day thirty-one of avoidance training, the cue lights (S^d) were turned on inside the experimental chamber. In the presence of S^d only a response on one lever (R_1) was effective in avoiding shock. When the animals were efficiently avoiding on this lever the cue lights were turned off and only a response on the other lever (R_2) postponed shock. This switching procedure was in operation over the following twenty days with 'S^d on' and 'S^d off' periods becoming progessively shorter. At the end of this period rat R7 was under the control of S^d but the behaviour of R8 became completely disorganized and eventually this animal had to be discarded from the experiment.

The behaviour of R7 was monitored by a five channel pen recorder and a series of counters which recorded the number of shocks, number of responses on R1 and number of responses on R2. The presentation of S^d was under manual control and S^d was never turned on or off in the presence of the buzzer. The final S^d interval was approximately three minutes and a typical record of the steady-state performance of R7 under these conditions is shown in Fig. 22. The pen marked S^d was deflected to the right in the presence of the cue lights and to the left in their absence. S_2^{-r} marked the occurrence of shock and S_1^r was deflected in the presence of the buzzer. Bar presses on the levers were recorded on R1

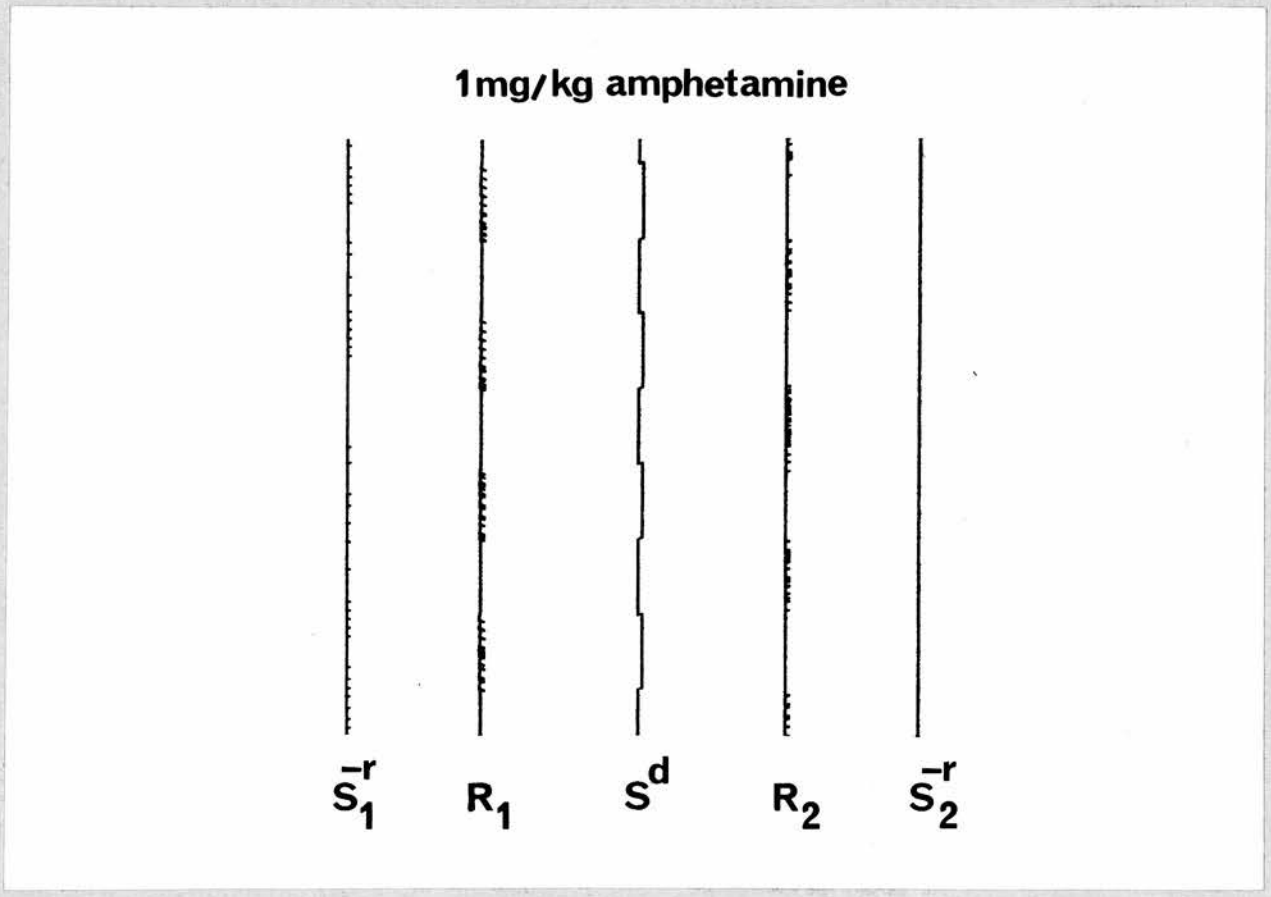

FIG. 23: Kymograph record showing the effects of 1.0 mg/kg Amphetamine on a two lever discriminated continuous avoidance schedule. (Subject R7).

and R2. There was a very high level of performance on saline control days. Few responses were emitted in the absence of the warning stimulus (see regular S_1^{-r}) and very few shocks were delivered.

The animal received 1.0 mg/kg amphetamine, 17.5 mg/kg mescaline, 2.0 mg/kg CPZ, 25.0 mg/kg mescaline, 1.0 mg/kg CPZ and 4.0 mg/kg amphetamine in that order. Two weeks elapsed between each drug administration and physiological saline control injections were given on the pre- and post-drug days. Drugs and saline injections (0.5 ccs fluid) were given after a one hour 'warm up' period and the animal replaced in test chamber for a one hour test period. The complete drug and average saline data are in Appendix D Nos. 1-7.

Results and Discussion

Fig. 23 shows the effects of 1.0 mg/kg amphetamine (Appendix D No. 2). This dose of the drug caused a high rate of responding on both levers but the responses were still well under the control of S^d. There was a high percentage of premature responses reflected in the figure by a decrease in the frequency of S_1^{-r}. When the buzzer was allowed to come on, a response was emitted almost immediately.

The typical effects of CPZ are shown in Fig. 24. Total response rate was decreased following both doses of this drug and the frequency of shock increased. At 1.0 mg/kg there was no escape failure (E_F) but at 2.0 mg/kg the animal often received two or three

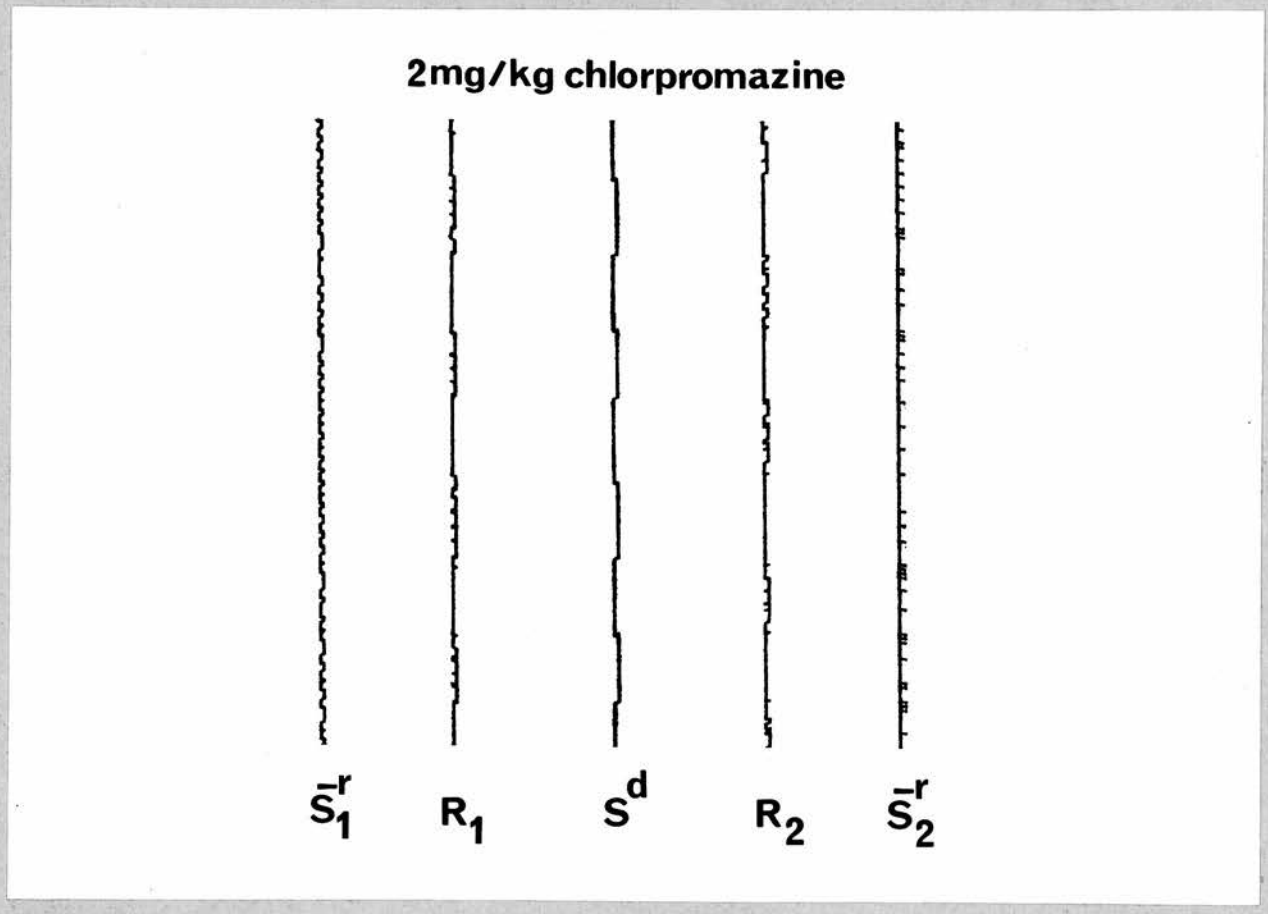

FIG. 24: Kymograph record showing the effects of 2.0 mg/kg Chlorpromazine on a two lever discriminated continuous avoidance schedule. (Subject R7).

shocks before an escape response was emitted. Bar holding was prevalent at both doses of the drug (prolonged deflection of R1 or R2). There was a loss in 'discrimination' especially after 2.0 mg/kg of CPZ but the errors almost always occurred at the S^d switch over. Thus, in Appendix D, a distinction is made between errors immediately following the change in the cue lights (C_E) and other discrimination errors (D_E).

The effects of 25.0 mg/kg mescaline are shown in Fig. 25. As with CPZ, there was an increase in shocks at both doses although escape failure was more prominent following the higher dose of the drug. The record is characterized by both bar holding and discrete pressing with an increase in both premature and late responding. The loss in visual discrimination was marked at the 25.0 mg/kg level and this was not confined to periods when shock was being delivered (see upper section of Fig. 25). A very similar record was obtained for 4.0 mg/kg amphetamine (Appendix D No. 7).

The drug effects on the basic avoidance schedule in the present experiment are very similar to those obtained with the standard schedule described in the previous experiments. One notable exception is the increase in response rate following mescaline and the high dose of amphetamine. This is probably related to the buzzer being a more effective warning stimulus than the lights.

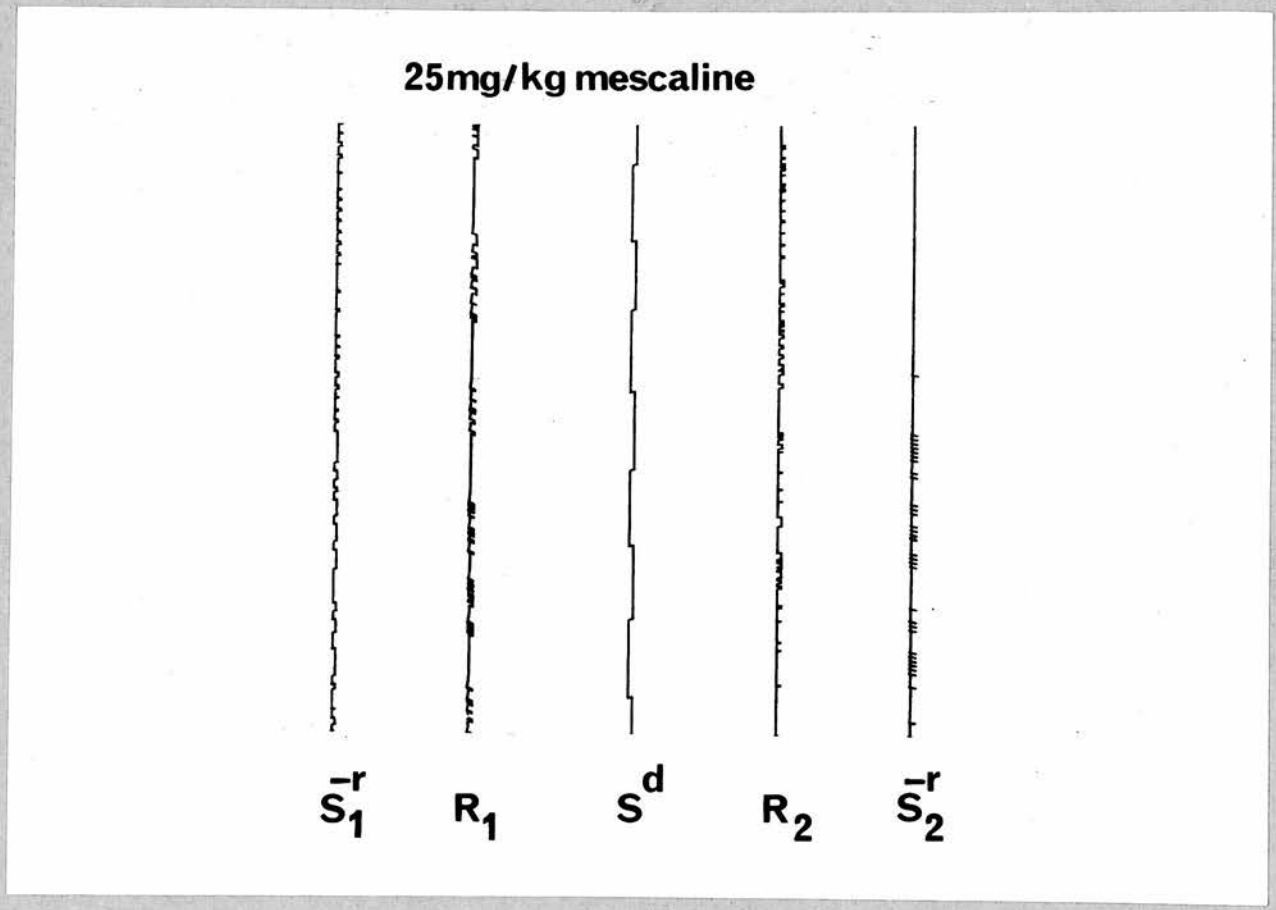

FIG. 25: Kymograph record showing the effects of 25.0 mg/kg Mescaline on a two lever discriminated continuous avoidance schedule. (Subject R7).

A discussion of the results of the present experiment will be witheld until the next experiment has been described.

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EXPERIMENT 6: THE EFFECTS OF DRUGS ON CONDITIONED INFLATION

The conditioned suppression effect was first described by Estes and Skinner (55). They carried out a series of experiments in which they demonstrated that repeated presentations of a tone, terminated by an electric shock, had the effect of suppressing bar-pressing behaviour which was maintained by food reinforcement. Sidman (149) has demonstrated that the same procedure was an avoidance schedule. Both conditioned suppression and conditioned inflation are accompanied by the behavioural and physiological+ signs of stress.

If a drug decreases the aversive properties of stimulus then one would expect a loss of the conditioned suppression or inflation which normally accompanies the presence of this stimulus. Thus, a condition suppression or inflation experiment allows an investigation of the effects of drugs on the aversive properties of the stimulus lights which control the standard avoidance schedule. The conditioned inflation technique is more relevant to the present

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+The author has assisted in an experiment demonstrating conditioned suppression and conditioned inflation in human subjects. Records of skin resistance reported a marked decrease in the presence of the conditioned stimulus and all subjects reported feeling very anxious in the presence of the warning stimulus (132).

investigation since it permits an examination of the negative reinforcement properties of a stimulus in an avoidance situation.

Method

Subjects and Apparatus:

Two male Lister hooded rats (R9 and R10) served as subjects. The experimental chamber was a one-lever Behaviour Apparatus Skinner Box with the modifications described in the previous experiment.

Procedure:

Both animals were exposed to a non-discriminated avoidance schedule with a R-S_1 interval of 30 seconds and a S_2 - S_2 interval of 10 seconds. When these experimental contingencies had been in operation for twenty-seven consecutive daily, two hour sessions, both animals had reached a high level of performance. During the next ten experimental sessions a conditioned inflation procedure was brought into operation. Following a one hour 'warm up' period, the stimulus lights were turned on for the last three minutes of every ten minute period, in the remaining hour of the experimental session. Each of the six stimulus periods was immediately followed by a brief unavoidable electric shock (0.5 m.a., 0.5 sec.). At the end of sixty stimulus-shock pairings both animals showed a consistent increase in response rate in the presence of the warning stimulus.

Each animal received 1.0 mg/kg amphetamine, 17.5 mg/kg mescaline, 2.0 mg/kg CPZ, 12.5 mg/kg mescaline, 1.0 mg/kg CPZ, 25.0 mg/kg mescaline

and 4.0 mg/kg amphetamine in that order. Two weeks elapsed between each drug administration and physiological saline control injections were given on the pre- and post-drug days. Drugs and saline injections (0.5 ccs fluid) were given after the one hour 'warm up' period and the animal replaced in the test chamber for a one hour test period. Two counters recorded the number of lever presses emitted during the three minutes just before stimulus light and the three minutes stimulus period. An inflation ratio was then calculated.

$$\text{Degree of Inflation} = \frac{\text{no. of responses during 3 minutes C.S.}}{\text{no. during 3 minutes prior to C.S.}}$$

Results and Discussion

Both animals had a fairly consistent increase in response rate on the saline control days. The average inflation ratio and range for each animal is shown in Appendix D No. 8 and 9. Following both 1.0 mg/kg amphetamine and 12.5 mg/kg mescaline there was a small but consistent increase in the inflation ratio. At higher doses of these drugs (4.0 mg/kg amphetamine, 17.5 mg/kg mescaline and 25.0 mg/kg mescaline) the inflation ratio was markedly reduced. A decrease in the inflation ratio was also observed following both 1.0 mg/kg and 2.0 mg/kg CPZ. This result is particularly interesting since CPZ has been shown to have no effect on conditioned suppression (13, 89, 103, 131, 135).

Morpurgo (119) has investigated the action of CPZ on an active and passive avoidance situation. He found that CPZ, in a dose which had no effect on visual discrimination, caused a marked increase in active avoidance failures but had no effect on passive avoidance failures. He suggested that the drug suppresses the avoidance response by delaying locomotor initiation. This conclusion would also explain the apparent discrepancy between the effects of CPZ on conditioned inflation and suppression. The former would be reduced since it requires an active response by the animal, whereas no response is required in the case of conditioned suppression. The hypothesis would explain why discrimination errors, in the previous experiment, only occurred at changeover times. The increased bar holding, under CPZ, may also be related to this delay in locomotor initiation.

The effects of 1.0 mg/kg amphetamine on conditioned inflation support the observations of Brady (19) on conditioned suppression. Amphetamine increases the aversive properties of a conditioned negative reinforcer. This would also appear to be true for 12.5 mg/kg mescaline which also enhanced conditioned inflation. At higher doses of mescaline and amphetamine there was a decrease in conditioned inflation but the results of the previous experiment suggest that this was probably due to a failure in visual discrimination.

Since similar stimulus lights have been employed in the discrimination and condition inflation experiments as those used

in the standard continuous avoidance schedule the following deductions can be made.

(I) The increase in shocks under CPZ are probably not related to any loss of visual discrimination but may be due to a delay in locomotor initiation. This conclusion has also been arrived at by Posluns, (128).

(II) The increase in premature responses and the marked skew in the I.R.T. distribution within the stimulus light, under low doses of amphetamine, is probably related to an increase in the aversive properties of the stimulus light.

(III) The slight skew in the I.R.T. distribution following 12.5 mg/kg mescaline may reflect a similar process.

(IV) Increased premature and late responding at high doses of amphetamine or mescaline are due to a failure in visual discrimination.

It is clear that there is a close similarity between the actions of amphetamine and mescaline on all the behavioural parameters studied in the preceding experiments. Both drugs caused a disruption of the temporal distribution within the stimulus light at low doses, and a loss of visual discrimination at higher doses. It should also be noted that both drugs are closely related structurally and many authors (162, 141) have reported the strong stimulant action of small doses of β-phenylethylamine in animals pretreated with iproniazid. Some authorities believe that amphetamine in high doses, is a true hallucinogen. Connell (41), who has made a detailed study

of amphetamine 'toxicity' concluded: 'Amphetamine can be considered a true hallucinogen, since it will produce a psychoses with hallucinations after a single large dose.' He also noted that 'the most important finding in the present study was the absence of disorientation as a sign of intoxication. Thus, one of the main psychiatric criteria in the diagnosis of a toxic state was lacking.' He went on to make the constructive suggestion that 'proper investigation of this problem may reconcile the well-known fact that schizophrenic symptoms are intensified by amphetamine, with the fact that paranoid symptoms on as yet unknown basis develop after ingestion of this drug in persons who are not schizophrenic and appear not to develop schizophrenia.'

As far as the present investigations are concerned, however, any drug having a strong stimulant action will be considered to be an amphetamine-like compound and will be distinguished from those with a 'pure hallucinogenic profile'. This seems to be a reasonable position since, although amphetamine may or may not be hallucinogenic in high doses, there is no doubt that the main effect of the drug is stimulation.

SECTION VI

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON THE MESCALINE MOLECULE

INTRODUCTION

The effect induced by a drug is the resultant of an interaction between the molecules of that drug and the molecules of which the organism is composed. The higher the specificity required in the structure of the drug molecule, the more probable it becomes that the effect is based on an interaction of these molecules with certain specific molecules in the biological object. These specific molecules are often called the receptor for the drug.

There has been much speculation about the nature of receptor sites but there is no doubt that if the forces at work are of physiochemical origin, as is generally supposed, and the physiochemical properties of a compound are the direct result of its chemical structure, then there must be a relationship between structure and biological activity. Structure, in this context, is not confined to the physical structure, as in the lock-key model for drug-receptor interaction, but includes the charge distribution and the location of the active groups on a molecule.

The present investigation is an attempt to determine the structural requirements of the mescaline molecule. This information should throw some light on the nature of the receptor site on which the drug is acting.

EXPERIMENT 7: THE INFLUENCE OF THE METHOXY GROUP CONFIGURATION

Method

Subjects and Apparatus:

Nineteen male Lister hooded rats were used in this study. Three of the subjects (R1, R2 and R3) had previously been trained on the discriminated continuous avoidance schedule.

Two modified Levine shuttle-boxes and a Standard Grason-Stadler Skinner box were used. These experimental chambers were enclosed in ventilated and sound-proofed chests and all experimental contingencies were controlled by a system of relays and timers in an adjacent room. Two behavioural schedules were used in this experiment; discrete trial avoidance in the shuttle box and the standard continuous avoidance schedule in the Skinner box.

Procedure:

The Shuttle box procedure was similar to that used by Smythies et al (154). The animal was required to cross from one side of the shuttle box to the other in response to a conditioned stimulus. The C.S. (a buzzer) sounded for five seconds, at the end of which time the unconditioned stimulus (electric shock of I.0ma) was presented if the animal had failed to terminate the C.S. by a cross. A two hour experimental session consisted of seven runs of twenty trials each, the runs being separated by a time interval of five minutes.

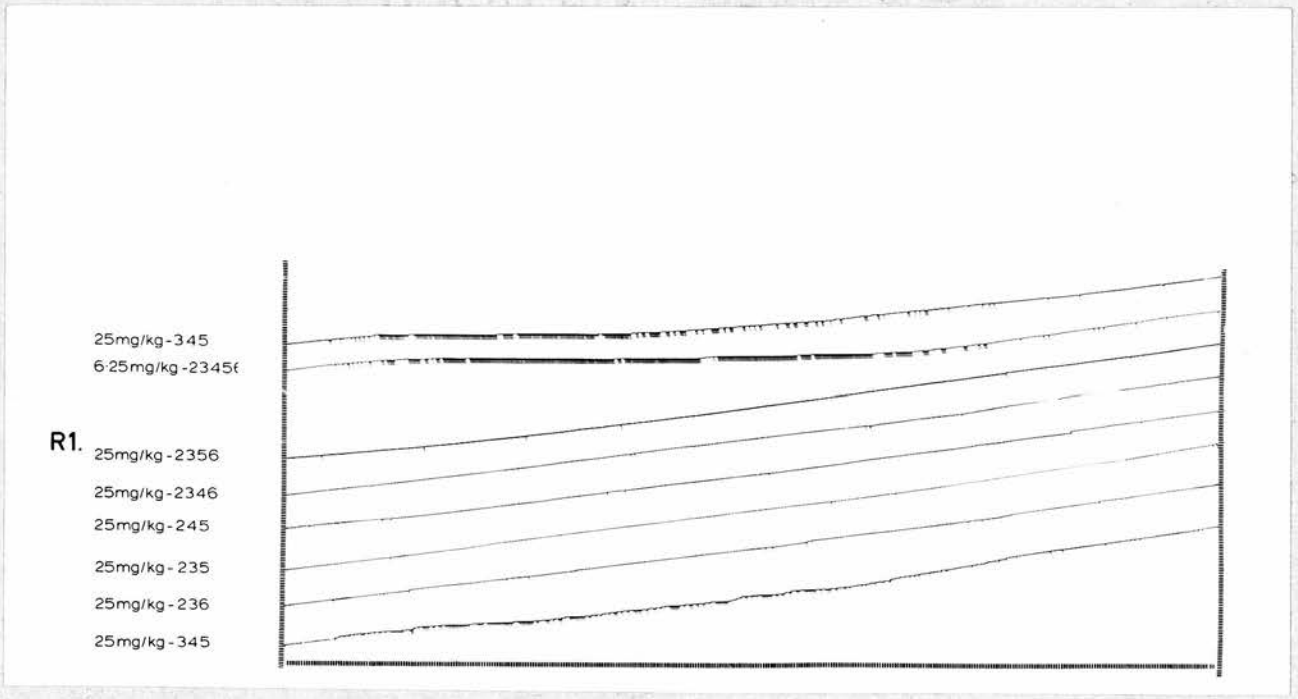


FIG. 26: Cumulative records showing the effects of position and number of methoxy group substitution on the avoidance behaviour of Subject R1.

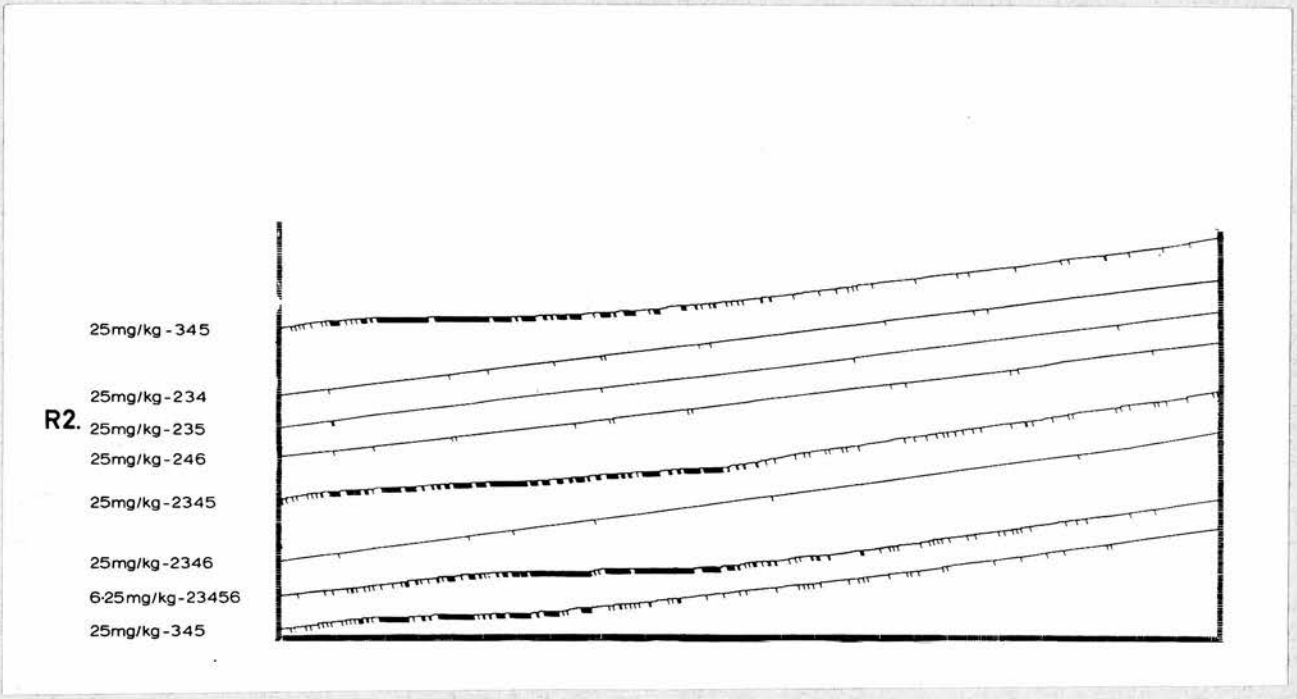


FIG. 27: Cumulative records showing the effects of position and number of methoxy group substitution on the avoidance behaviour of Subject R2.

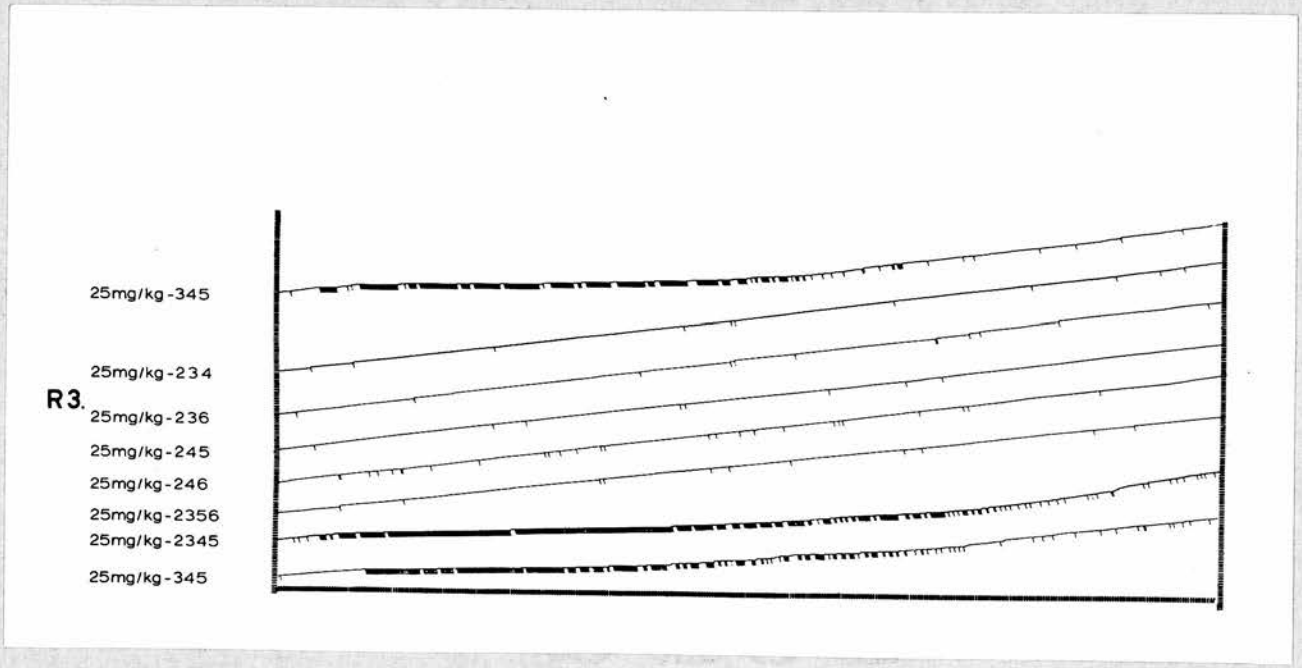


FIG. 28: Cumulative records showing the effects of position and number of methoxy group substitution on the avoidance behaviour of Subject R3.

Sixteen animals were trained to an 85% avoidance criterion on this schedule. On treatment days, intra peritoneal injections of either drug or saline were given after 40 trials: i.e. two runs of 20 trials. The seven sets of twenty trials then continued as on training days. Drug results are expressed as $(D-\bar{S})$ scores (the difference between the drug score and the mean of the pre- and post-drug saline scores). All nineteen possible ring methoxylated combinations on the β-phenethylamine molecule were tested.

Initially the response to 25.0 mg/kg mescaline was determined for each animal. Then the series of ring-methoxylated β-phenylethylamine was tested at two dose levels, 12.5 mg/kg and 25.0 mg/kg. Penta methoxy-β-phenylethylamine, which was found to be very active, was also tested at 3.1 mg/kg and 6.2 mg/kg. Four animals received each dose level of a given drug according to a random design, and two weeks were allowed to elapse between every drug treatment.

The three trained avoidance animals were given 25.0 mg/kg mescaline and then each was subjected to a different drug sequence with fourteen days between each drug administration. The experiment was designed so that each drug result was replicated on two different animals. Finally, each subject received a further 25.0 mg/kg mescaline. As before, drug and saline injections (0.5 ccs fluid) were given after the pre-injection period and saline control records were taken on the pre- and post-drug days.

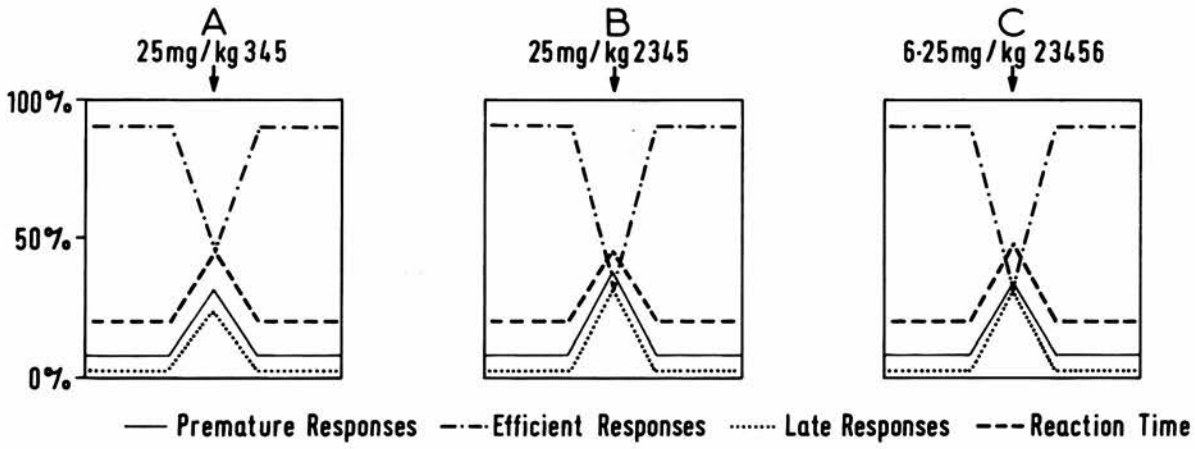


FIG. 29: Behavioural profiles for the three active compounds.
A - 3,4,5 Trimethoxy phenylethylamine.
B - 2,3,4,5 Tetramethoxy phenylethylamine.
C - 2,3,4,5,6 Pentamethoxy phenylethylamine.
(Subject R2).

Results

In all cases no disruption of behaviour was detected during the saline control days nor the pre-injection period prior to drug administration. The cumulative records on Figs. 26, 27 and 28 show the behavioural effects of the drugs on the continuous avoidance animals. A comparison of the effects of 25.0 mg/kg mescaline given before and after the drug sequence reveals that any tolerance which had developed over the experimental days was negligible. In all cases, no dose greater than 25.0 mg/kg was tested since it has been suggested that higher doses may have neuro-muscular effects (154). The results of the mono and di methoxy substituting are not shown since they were all inactive.+

The three active compounds; 3,4,5 trimethoxy, 2,3,4,5 tetramethoxy and 2,3,4,5,6 pentamethoxy phenylethylamine all inhibit bar pressing. Animal R2, received all the active drugs and allows a direct comparison of their relative potencies. The behavioural profiles for this animal (Fig. 29) revealed that the active compounds had behavioural effects similar to mescaline. Pentamethoxy was by far the most potent; 6.25 mg/kg of this drug had a more pronounced effect than 25.0 mg/kg mescaline. The 2,3,4,5 tetramethoxy compound was also more active than mescaline.

+This includes 3,4 dimethoxyphenylethylamine, the so-called 'pink spot' compound, which has previously been shown to be inactive in both human subjects (64) and animals (5).

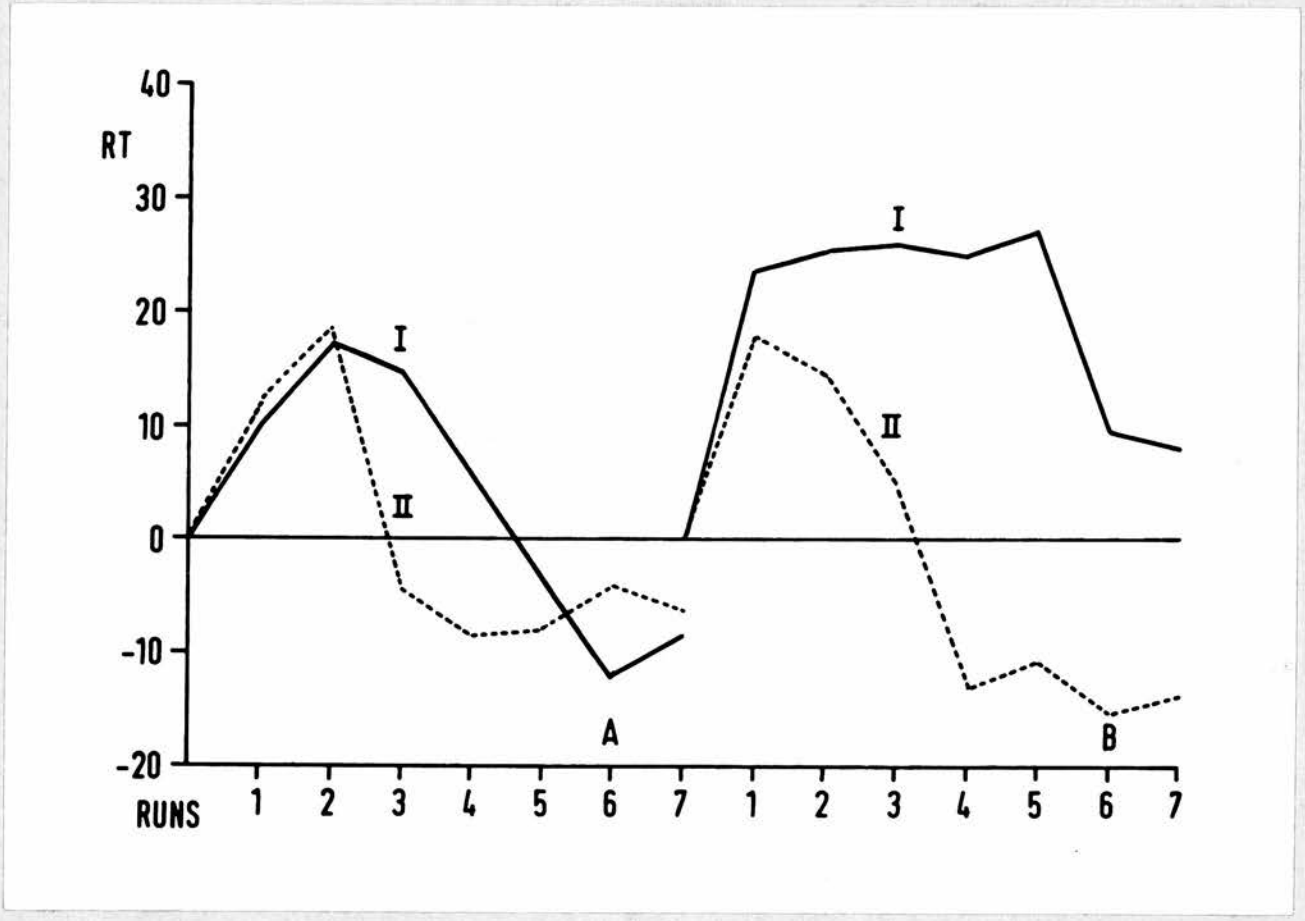


FIG. 30: Comparison of effects of Mescaline and 2,3,4,5 Tetramethoxy phenylethylamine. Abscissa: Blocks of runs of 20 trials each. The interval between runs represents 13 min. in each case (run 8 min., 5 min. time out). Ordinate: Mean change in reaction time in seconds (D-S). Each point represents 80 readings (20 trials x 4 animals) averaged. A - 12.5 mg/kg. B - 25.0 mg/kg.
I - in each case is the averaged drug response and
II - in each case is the averaged response to 25.0 mg/kg Mescaline for the same 4 animals.

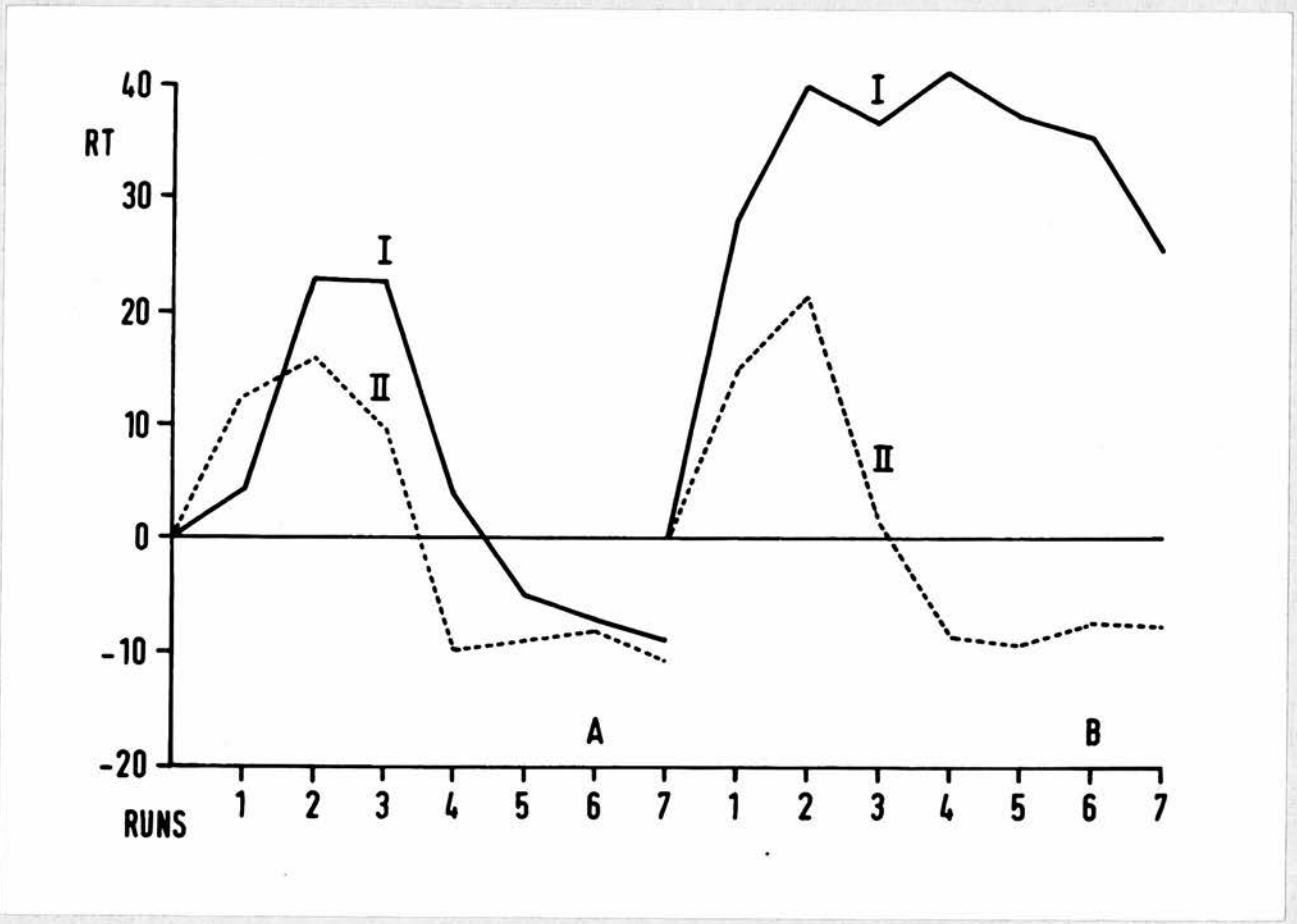


FIG. 31: Comparison of effects of Mescaline and 2,3,4,5,6 Pentamethoxy phenylethylamine. A - 3.1 mg/kg. B - 6.25 mg/kg. I - in each case is the averaged drug response and II - in each case is the averaged response to 25.0 mg/kg Mescaline for the same 4 animals.

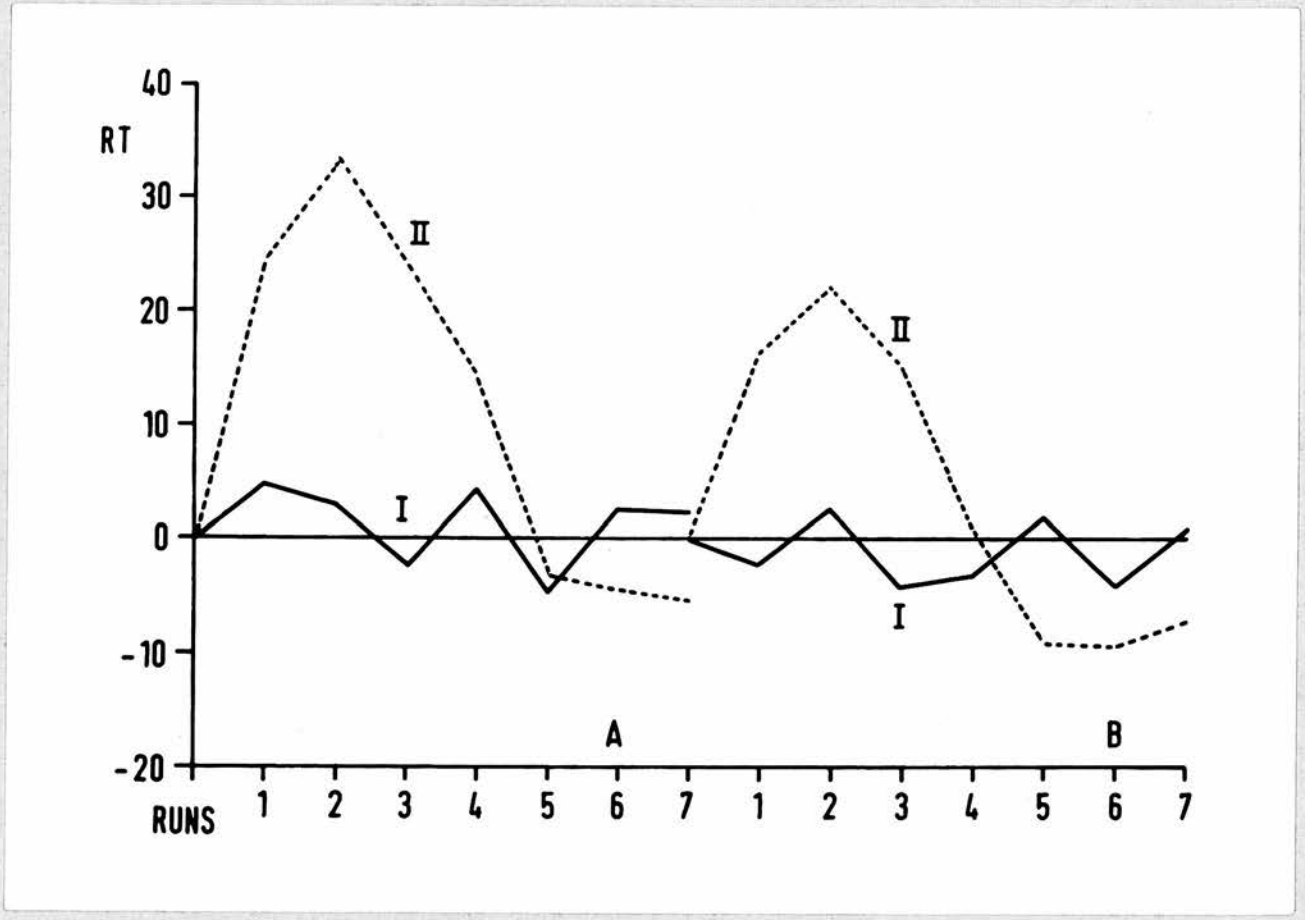


FIG. 32: Comparison of effects of Mescaline and 2,3,5,6 Tetramethoxy phenylethylamine. A - 12.5 mg/kg B - 25 mg/kg. I - in each case is the averaged drug response and II - in each case is the averaged response to 25.0 mg/kg Mescaline for the same 4 animals.

Very similar results were obtained using the Shuttle box procedure (Figs. 30, 31, 32). Each figure shows two doses of the active drugs compared with the 25.0 mg/kg mescaline response for the four animals involved. A biphasic curve for 2,3,4,5 tetramethoxy phenylethylamine was obtained with 12.5 mg/kg and a pure inhibitory effect was found at 25.0 mg/kg. (Fig. 30). Only 3.125 mg/kg of penta-methoxy was required to give the biphasic response (Fig. 31). Fig. 32 shows a typical inactive drug, 2,3,5,6 tetramethoxy phenylethylamine. At no dose studied was a biphasic response observed for any compounds other than the 2,3,4,5 tetramethoxy, the penta methoxy and mescaline itself.

Discussion

It would appear from these results that the 3,4,5 configuration is necessary for 'psychotomimetic activity' in β-phenylethylamines. The effect of adding extra methoxy groups is to increase the activity, provided that the 3,4,5 configuration is maintained. One extra methoxy group produces a moderate increase in activity; two a marked increase.

How can these findings be explained? The first obvious suggestion is that the hallucinogenic properties of these compounds may be related to their resistance to attack by amine oxidase. That is, those which are quickly metabolized are not hallucinogens and the compounds which are not broken down by amine oxidase, are hallucinogens.

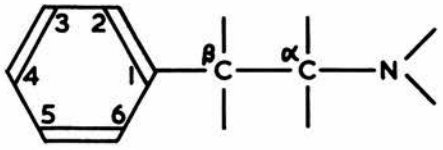
Data has been published by Clark et al (38) on the relation-ship between methoxy group configuration and the susceptibility to

oxidation of these compounds by 'tyramine oxidase' and 'mescaline oxidase'. These studies were carried out in vitro using a rabbit-liver preparation with and without semicarbazide. The results indicated that all the compounds in this series with both 2 and 6 positions substituted and all compounds with more than three methoxy groups were not substrates for either 'tyramine' or 'mescaline' oxidases. Furthermore, in the presence of semicarbazide, mescaline was no longer a substrate for this enzyme system. If amine oxidase susceptibility was the major factor governing the hallucinogenic activity of this series of compounds, then 2,6 dimethoxy phenylethylamine should be hallucinogenic; this is not the case. However, amine oxidase activity may explain why the pentamethoxy compound and the 2,3,4,5 tetramethoxy compound are more potent hallucinogens than mescaline. That is, if we assume that the 3,4,5 configuration is necessary for the psychotomimetic activity, but having these, the potency of the drug depends on its resistance to amine oxidase then mescaline would be relatively inactive. The 2,3,4,5 tetramethoxy compound should be more active since it contains the four methoxy groups necessary for protection and the 2,3,4,5,6 should be most active since it contains, not only the four protective methoxy groups, but also has the additional protection of the 2 and 6 positions being filled.

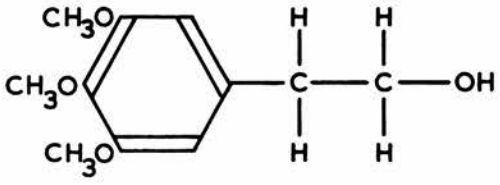
An alternative, and perhaps more parsimonious explanation of the results can be found by an examination of the lipid solubilities of these compounds. Both the tetramethoxy and the pentamethoxy

compounds are more lipid soluble[+] than mescaline (Appendix E). If the lipid solubility was the whole story then we would expect the 2,3,4,6 compound to be a potent hallucinogen. But once again, if we accept that the 3,4,5 configuration is necessary for the compound to be hallucinogenic then the increase in potency with additional methoxy groups correlates well with the increase in lipid solubility.

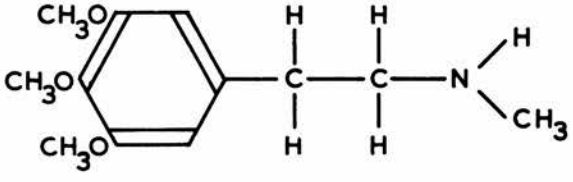
[+]The relative lipid solubilities were estimated from lipid solvent (chlorform) - water partition coefficients. (Appendix E).



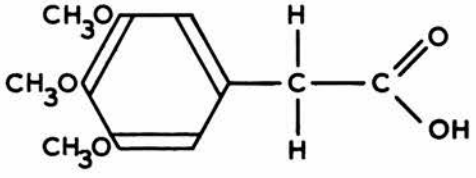
Basic Structure.



Alcohol Derivative.



N-methyl Derivative.



Acid Derivative.

FIG. 33: Three inactive derivatives of Mescaline.

EXPERIMENT 8: THE EFFECTS OF SIDE-CHAIN MANIPULATIONS

Method

Subjects and Apparatus:

Three of the trained avoidance animals (R1, R2 and R3) served as subjects. The apparatus was the standard Grason-Stadler test chamber and programming equipment.

Procedure:

Three side-chain derivatives of the mescaline molecule were tested (Fig. 33). Each animal received 25.0 mg/kg of all the drugs in 0.5 ccs saline, at two week intervals.

Results and Discussion:

N-methyl and both acid and alcohol derivatives of mescaline were inactive when given in a dose of 25.0 mg/kg (Appendix B Nos. 44-52). Friedhoff and Goldstein (63) have claimed that the aldehyde or alcohol derivative could be the active metabolite of mescaline and found the latter to be active in the rabbit when injected intravenously. It is possible that the route of administration or the species difference may account for the different findings of the present investigation. However, this seems unlikely since both α methyl mescaline (125) and pentamethoxy β phenylethylamine are active and yet they are immune to attack by amine oxidase. It would appear then, that aldehyde or alcohol formation is not necessary for psychotomimetic activity. Also, the rate of onset of the mescaline effect, suggests that a metabolite is not involved.

It is interesting that even a small substitution on the nitrogen atom abolishes the psychotomimetic action of mescaline. This same substitution in the NA molecule, changes a probable neurotransmitter into what is now believed to be primarily on a hormone with no transmitter function (112). If this is so, then the primary amine configuration is required for successful interaction with the α receptor site. Perhaps, it is this requirement which governs the structure of the mescaline molecule. It should be possible to support this speculation by examining the effects of α sympatholytics on the mescaline response.

A side chain manipulation, of particular interest, is the substitution of an α methyl group. Since this change in the molecule makes the compound immune to amine oxidase then it allows an examination of the ring-methoxy group configuration, required for psychotomimetic potency, unconfounded by amine oxidase activity.

EXPERIMENT 9: THE INFLUENCE OF THE METHOXY GROUP CONFIGURATION ON THE α METHYL MESCALINE MOLECULE

α methyl mescaline is 3,4,5 trimethoxy amphetamine. This compound has already been shown (125, 145) to be twice as active as mescaline in human studies. Shulgin (144) has examined three trimethoxylated amphetamines (345, 245, 234) in human subjects and noted that repositioning of a meta-methoxy group to an ortho-location in α methyl mescaline augmented the hallucinogenic effect. Since all these studies were carried out using human subjects, they present an opportunity for further validating the animal tests by attempting to replicate the results. Only eleven of the nineteen possible ring-methoxylated amphetamines were available. These were 234, 246, 345 and 245 Trimethoxyamphetamine; 23, 35, 25 and 34 Dimethoxyamphetamine as well as the three mono substituted derivatives. All these compounds were tested.

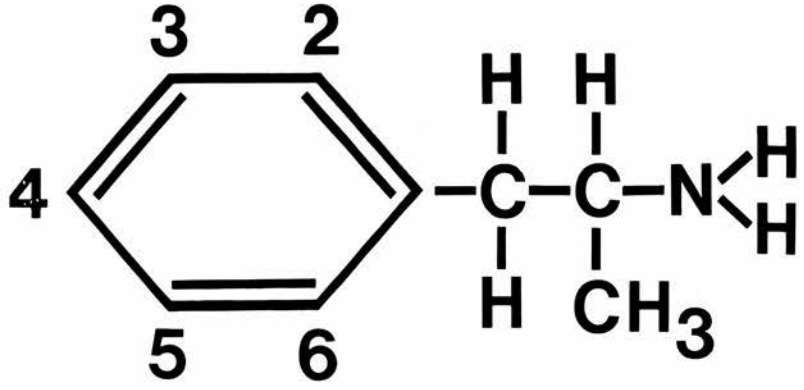
Method

Subjects and Apparatus :

Three of the trained Lister hooded rats (R2, R4 and R5) served as subjects. The standard Grason-Stadler test chamber and programming equipment was employed.

Procedure:

Due to the wide differences in potency of these compounds,



2	3	4	5	6	Potency Relative to Mescaline
X	X	X			<< M
X		X		X	< M
	X	X	X		> M
X		X	X		>> M

FIG. 34: The effect of position and number of ring methoxy group substitution on the potency of four methoxylated amphetamines.

a systematic study was not possible and the drug dosage was altered throughout the experiment. The final level of each active drug was examined in at least two animals. All drugs were administered in 0.5 ccs saline after the preinjection period and the animals returned to the experimental chamber for the two hour test period. Two weeks elapsed between each administration. The I.R.T.s were collected and analysed by the standard computer program.

Results and Discussion

The Trimethoxyamphetamines:

Shulgin had observed that 2,4,5 trimethoxyamphetamine was seventeen times more active than mescaline. The 3,4,5 he found to be twice as potent as mescaline and the 2,3,4 was inactive. This correlation between methoxy group configuration and hallucinogenic activity is mirrored in the results of the animal experiments (Fig. 34) although, as one would expect, there are differences in the quantitative relationship. All compounds, had some activity at 25.0 mg/kg and gave hallucinogenic profiles on the avoidance schedule (Appendix B Nos. 53-69). 2,4,5 trimethoxyamphetamine, not tested by Shulgin, was less active than mescaline. This finding conflicts with Shulgin's suggestion than metamethoxy repositioning to an ortho-location results in increased potency. In fact, the results of the methoxylated phenylethylamine and amphetamine series taken together elude any simple explanation in terms of molecular structure. Whereas, the 3,4,5 substituted compound is the most active in the phenylethylamine

series, the 2,4,5 is more potent than the 3,4,5 in the amphetamine series.

At least two hypotheses could be put forward to explain these differences: (1) The α methyl group on the amphetamine molecule renders the compounds immune to amine oxidase and the 'true' relationship between methoxy group configuration and hallucinogenic potency is revealed. In the phenylethylamine series the results are confounded by the relative protective action of different methoxy group combinations on the susceptibility of the molecule to amine oxidase. (II) The methyl group on the amphetamine molecule has stereochemical properties. Thus, the steric interaction of the methyl group changes the configuration of the molecule by distorting the π electron cloud which encapsulates the aromatic ring. Any change, however, in the electron distribution should result in a shift in the U.V. spectrum of the molecule. A comparison of the U.V. spectra of 2,4,5 trimethoxyamphetamine and 2,4,5 trimethoxyphenylethylamine is shown in Appendix F. No change in the wave length of the absorbed energy could be detected, suggesting that the electron configuration on the ring was very similar for both molecules.

Some additional information which helps to explain the differences in the two series was given by the results of the dimethoxylated and monomethoxylated compounds.

The Dimethoxyamphetamines:

Of the four dimethoxy compounds tested (23, 35, 25 and 34) only the 34 dimethoxy compound was active at the doses tested

(Appendix B No.s 61-73). At only 6.2 mg/kg, this compound gave a hallucinogenic profile whereas the other three analogues gave a slight amphetamine-like stimulation at this dose. When the dose was increased to 12.5 mg/kg, the 23, 35 and 25 dimethoxy derivations resulted in a marked amphetamine stimulation and the 34 compound caused a high dose hallucinogenic profile.

The Monomethoxyamphetamines:

These three compounds were the most interesting of all the drugs studied. Metamethoxyamphetamine gave a very marked amphetamine-like profile at only, 3.1 mg/kg. At this dosage ortho-methoxy amphetamine was inactive but an amphetamine-like action was observed at 6.2 mg/kg. Para-methoxy amphetamine, on the other hand, proved to be the most potent 'hallucinogen' in the series. At 3.1 mg/kg it produced a typical low dose hallucinogenic profile but at 6.2 mg/kg it disrupted bar pressing behaviour completely and induced a syndrome of bizarre behaviour in both the rats tested, at this dose. Although the rat could walk about normally and appeared to be able to eat and drink normally, it frequently walked backwards (a typical mescaline effect), had exaggerated startle repose in the absence of external stimuli and would frequently engage in bizarre behaviour reminiscent of shadow boxing, rearing and pawing the air. If placed on a table it would walk apparently normally towards the edge and fall off. This could be repeated many times. In both cases the avoidance experiment was terminated since shock was being delivered every 10 seconds and

these highly trained animals were very valuable. However, both animals died. In one case the unusual behaviour pattern peristed for a week before death, in the other case the animal died after one day of abnormal behaviour.+

It would appear that the basic requirement for psychotomimetic potency in the amphetamine series is the presence of a 4 methoxy group. Substitutions in other positions produced stimulant drugs similar to amphetamine. The relative stimulant properties of mono-methoxylated amphetamines has been investigated by Van der Shoot et al (141). They report that metamethoxy substitution leads to a greater increase in the spontaneous motor activity of mice, than either ortho- or para- substitution. The para compound is more active than the ortho. These results are supported by the present experiment if account is taken of the slight stimulant action of low doses of hallucinogens. Benington et al (10) have reported that 25.0 mg/kg of the para-methoxy compound is lethal in cats after producing a marked rage reaction. The long lasting effects of this drug suggest that it may be related to the potent hallucinogen STP. Both molecules have an amphetamine skeleton but STP has a methyl group in the 4 position. It is relevant that Knoll (104) has suggested that halogenation of the para position may result in a psychotomimetic derivative of

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+It was decided to investigate this drug at an intermediate dose but subsequent deaths made this impossible. These additional deaths resulted from para-methoxy phenylethylamine in animals pretreated with MAOI.

methamphetamine. Further investigation of different substitutions in the 4 position would appear to be the next step in the present research program.

It is interesting now to note that every potent hallucinogen in both the phenylethylamine and amphetamine series is substituted in the 4 position. The results suggest that 4 methoxy phenylethylamine and 34 dimethoxyphenylethylamine may be hallucinogenic in subjects pretreated with an amine oxidase inhibitor.

The superior potency of the mono-methoxylated derivates of amphetamine over the dimethoxy analogues may be related to their greater lipid-solubility (Appendix E).

EXPERIMENT 10 THE BEHAVIOURAL EFFECTS OF 4 METHOXY AND 34 DIMETHOXY PHENYLETHYLAMINE IN ANIMALS PRETREATED WITH IPRONIAZID

Method

Subjects and Apparatus:

Two of the trained Lister hooded rats (R1 and R2) served as subjects. The standard Grason-Stadler programming and recording equipment was in operation.

Procedure:

Animal R1 received 6.2 mg/kg paramethoxy phenylethylamine three hours after 50.0 mg/kg Iproniazid (i.p.). Subject R2 was injected with 6.2 mg/kg 3,4 Dimethoxy and 6.2 mg/kg 2,3 Dimethoxy phenylethylamine in two separate occasions following a similar dose of Iproniazid three hours previously.+ Saline injections equivalent to the total fluid volume of Iproniazid plus drug were given on the pre- and post-drug days. Three weeks were allowed to elapse between each drug administration to the same animal.

Results and Discussion

6.2 mg/kg of 4-methoxy phenylethylamine, which has previously been shown to be inactive at 25.0 mg/kg, had a very toxic effect in the pretreated animal (R1), All bar pressing behaviour stopped and the rat lay on its side, twitching slightly and unable to move. This increase in toxicity of 4-methoxy phenylethylamine following MAOI has also been reported in cats where an intense rage reaction and hyper-

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+This dose has been shown to have no behavioural effect at this dose see Experiment 11.

thermia were produced (10).

Both 34 and 23 dimethoxy phenylethylamine have been previously shown to be inactive at 25.0 mg/kg (Experiment 7). Following the MAOI, however, 34 dimethoxy gave a typical hallucinogenic profile whereas the 23 substituted compound had a slight stimulant effect. The amine oxidase inhibitor appears to bring the behavioural effects of substituted phenylethylamines into line with the results of the amphetamine series. It would be interesting to investigate the order of potency of the trimethoxylated phenylethylamines after amine oxidase inhibition since the differences found in the two series are probably due to their relative resistances to amine oxidase.

Ernst (56) has investigated the action of some methoxylated β-phenylethylamines in cats. These were (a) 4-methoxyphenylethylamine (b) 34 Dimethoxyphenylethylamine (c) 345 Trimethoxyphenylethylamine (d) 35 Dimethoxyphenylethylamine (e) 23 Dimethoxyphenylethylamine (f) 3 hydroxy-4-methoxy phenylethylamine (g) 3 methoxy-4-hydroxy phenylethylamine (h) 35 Dimethoxy-4-hydroxy phenylethylamine and (k) 3 hydroxy phenylethylamine. He reports that, in the absence of Iproniazid, only 4 MPE, 34 DMPE and 345 TMPE were capable of producing a Hypokinetic Rigid Syndrome (HRS) and catatonia. The effects could be obtained with a lower dose and persisted much longer following 345 TMPE than either 4 MPE or 34 DMPE. The compounds 35 DMPE and 23 DMPE did not produce either catatonia or HRS. Following Iproniazid, 3-hydroxy-4-methoxy PE also produced catatonia and HRS whereas all

other hydroxylated compounds tested failed to do this. He suggested that after iproniazid the hydroxylated compounds were methoxylated by COMT in the liver. Since this methoxylation is specific to the 3 position, then the metabolites of 3-methoxy-4-hydroxy PE and 35-Dimethoxy-4-hydroxy PE were still unable to cross the blood-brain barrier since a hydroxy group was still present on the ring. He made the interesting observation that following iproniazid, 3-hydroxy PE had a stimulant effect. This compound could be metabolized to 3-methoxy-PE which has been shown to have a strong stimulant action in the present investigations.

Ernst has arrived at a similar conclusion to that of the present investigator. Methoxylation in the para position appears to be necessary for the production of HRS and catatonia in cats and the hallucinogenic profile in rats. However, he found that the duration of the HRS was positively correlated with the number of places in the phenol-ring occupied by methoxy groups adjacent to the para position. The results of the present investigations suggest that this is not the case and the superior potency of the trimethoxylated derivatives over the mono and di substituted compounds is probably due to their increased resistance to amine oxidase. In the presence of an amine oxidase inhibitor, or in the amphetamine series where there is a high resistance to amine oxidase, then the mono and di substituted compounds are in fact more potent than the trimethoxylated derivatives. This increase in potency with fewer methoxy groups may be related to the increased lipid solubility of these compounds.

SECTION VII

PRETREATMENT STUDIES+

+ Some of these experiments were carried out prior to the investigation of the methoxylated amphetamines.

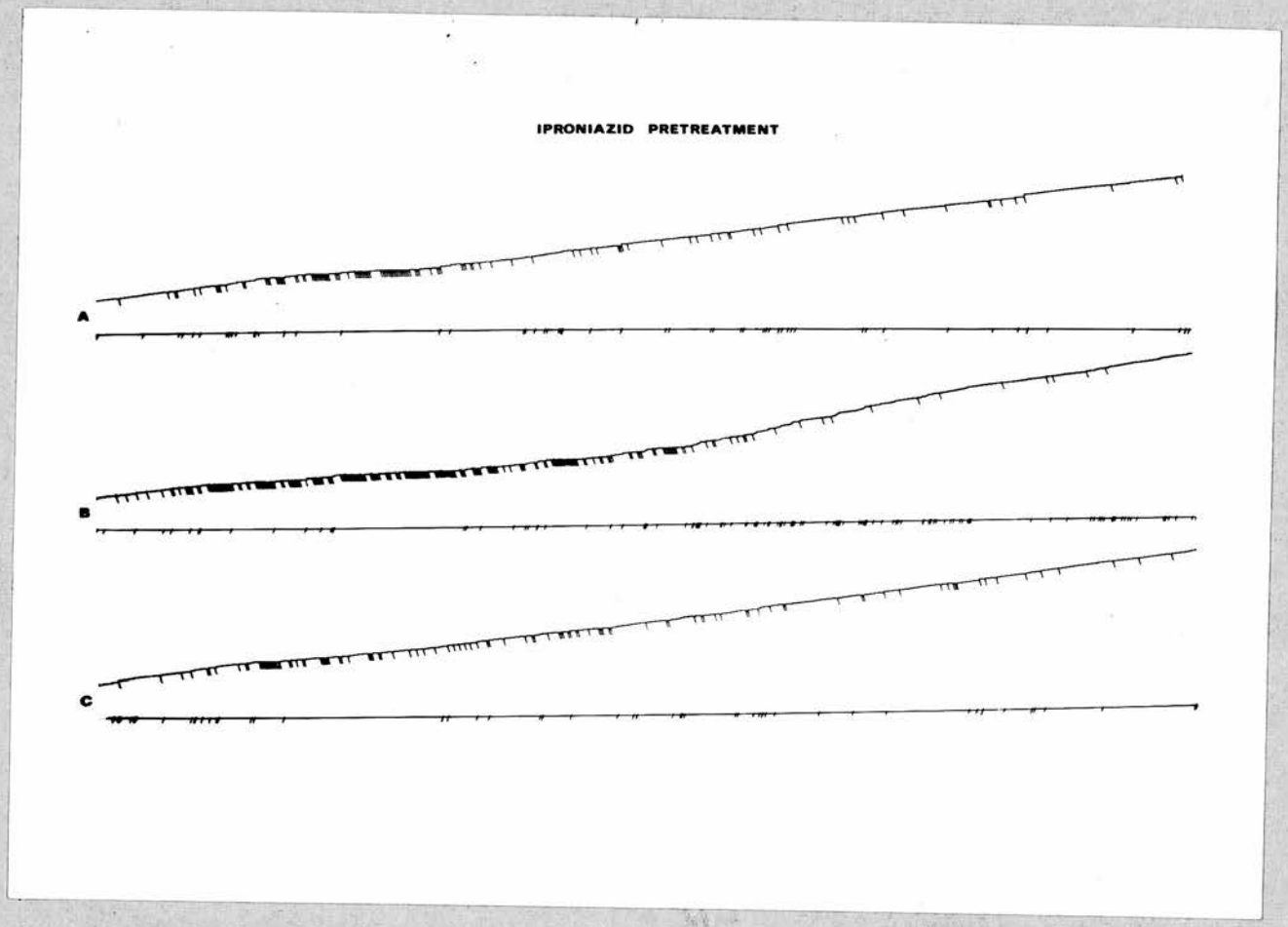

FIG. 35: Cumulative records showing the effect of Iproniazid pretreatment on the response to 17.5 mg/kg Mescaline.
A - 17.5 mg/kg Mescaline.
B - 17.5 mg/kg Mescaline after 50.0 mg/kg Iproniazid.
C - 17.5 mg/kg Mescaline.
(Subject R4).

EXPERIMENT 11: THE EFFECTS OF PRETREATMENT WITH IPRONIAZID ON THE MESCALINE RESPONSE

Method

Subjects and Apparatus:

Three of the trained male Lister hooded rats (R4, R5 and R6) served as subjects. The programming and recording equipment has already been described.

Procedure:

Each subject served as his own control and was injected with a physiological saline solution (0.5 ccs) on the pre- and post-drug days. With the exception of pre-treatment days, all drugs were given after the pre-injection period and the subject was immediately placed in the Skinner box for the two hour test period. A pilot study revealed that 100.0 mg/kg iproniazid had some behavioural effects on the avoidance schedule so the pretreatment dosage was halved to 50.0 mg/kg. At this dose level there was no behavioural effect at any time after injection. Initially the response of each animal to 17.5 mg/kg mescaline was determined. Fourteen days later each animal received 50.0 mg/kg Iproniazid (i.p.) three hours before 17.5 mg/kg mescaline. As a further control 17.5 mg/kg mescaline was given again after four weeks.

Results and Discussion

Figure 35 shows the influence of iproniazid pretreatment on the action of this dose of mescaline. (A deflection of the recorder

	R4	R5	R6
17.5 mg/kg Mescaline	113	123	97
50.0 mg/kg Iproniazid + 17.5 mg/kg Mescaline	198	229	164
17.5 mg/kg Mescaline	104	111	124

TABLE 1 The effect of iproniazid pretreatment on the shock frequency following 17.5 mg/kg mescaline.

pen marks a shock and the baseline event marker shows the occurrence of burst and premature responses.) An increase in the mescaline response was verified for all animals (Table 1).

This finding does not support the theory of Harley-Mason et al (82) that mescaline acts through a metabolite and suggests that the free amine level is the critical factor. An alternative hypothesis is that increased levels of endogenous monoamines, in some way, facilitates the hallucinogenic activity of mescaline. A number of experiments are suggested by the later hypothesis. If endogenous amine levels are involved then pretreatment with amine depleters, such as tetrabenazine (TBZ) or reserpine, should decrease hallucinogenic activity and specific MAOIs (possibly N-octanol) should enhance hallucinogenic activity. A reversal of the mescaline effect by pretreatment with TBZ would avoid any interpretation of the results as due to summated effects of two independent processes. That is, since both mescaline and TBZ block the conditioned avoidance response then any reversal of the mescaline effect would be in the opposite direction from both manipulations. Furthermore, since pharmacological agents are available which selectively interfere with the synthesis of particular amines then it might be possible to further delineate the precise action of mescaline.

EXPERIMENT 12: THE EFFECTS OF PRETREATMENT WITH TBZ AND α MT ON THE MESCALINE RESPONSE

Method

Subjects and Apparatus:

Two of the trained male Lister hooded rats (R1 and R3) served as subjects. The standard experimental chambers and programming equipment were employed.

Procedure:

Each animal's response to 17.5 mg/kg mescaline had been measured in a previous experiment (Experiment 4). The effects of pretreatment with 4.0 mg/kg TBZ and 32.0 mg/kg α MT on this response were determined for each animal. The TBZ was administered in 0.5 mls. of 0.01 normal HCl and αMT in 0.5 mls. of a cellulose suspension. On pretreatment days TBZ was given 4¾ hours before the animal was placed in the experimental chamber; the α MT pretreatment time was 2¼ hours. After the normal 'warm up' and 'preinjection' periods both animals were given 17.5 mg/kg mescaline in 0.5 ccs saline. During the pre- and post-drug days the drug vehicles were administered at the pretreatment times and 0.5 ccs saline following the pre-injection period.

Four weeks were allowed to elapse between each pretreatment experiment and the effects of 17.5 mg/kg mescaline were redetermined one month after the last drug administration.

Results and Discussion

No behavioural effect of the drug vehicles could be detected on the pre- or post-drug days and no disturbance of lever pressing was observed during the pre-injection period on pretreatment days.

Biochemical studies, by Weissman (182) have shown that, following αMT the rat brain concentration of NA and D are markedly reduced but 5HT levels are unaffected. TBZ, on the other hand, causes a reduction in all amine levels. However, neither TBZ nor αMT had a marked effect on the mescaline response. Both drugs, especially αMT, caused a slight increase in the mescaline effect (Appendix B Nos. 91-96).

As with iproniazid pretreatment, the results are open to alternative explanations since TBZ, αMT and mescaline all cause behavioural suppression and any increase in the mescaline response following pretreatment may be due to additive effects of the treatment and pretreatment drugs. The results suggest, however, that a gross reduction in amine concentration or a selective reduction in NA levels do not appreciably decrease the mescaline response but may, in fact, increase the effect. It follows that the iproniazid augmentation of mescaline described in the previous experiment is probably due to an increase in the mescaline levels rather than the endogenous amine levels. Unlike amphetamine, it would appear that mescaline does not act by a release of free NA.

EXPERIMENT 13: THE EFFECTS OF PRETREATMENT WITH ∝MT ON THE BEHAVIOURAL STIMULATION CAUSED BY META-METHOXY AMPHETAMINE.

Method

Subjects and Apparatus:

One male Lister hooded rat (R3), who had previously been trained on the standard avoidance schedule, was the experimental subject. The apparatus was similar to that described before.

Procedure:

Initially, the behavioural stimulation of 3.1 mg/kg metamethoxy amphetamine was determined for this animal. Two weeks later a pretreatment study was carried out in which 32.0 mg/kg ∝MT was given 3 hours before 3.1 mg/kg of the methoxyamphetamine. The controls were similar to those described in the previous experiment. One month after this pretreatment, the behavioural effects of the amphetamine analogue were determined once again.

Results and Discussion

Appendix B Nos. 84-86 shows the effects of ∝MT on the behavioural stimulation induced by 3-methoxy amphetamine. This blockade of stimulation by pretreatment with ∝MT is similar to the antiamphetamine effects of tyrosine hydroxylase inhibition described by Weissman et al (182). The results imply that, like amphetamine, metamethoxy amphetamine acts by a release of NA rather than a direct

action on the NA receptor.

Van Rossum (138) has investigated the stimulant action of α MmT in mice. The delayed action of the drug, compared with amphetamine, suggested that it was not α MmT itself, but a metabolite that was responsible for the stimulation. He suggested that 3-methoxy amphetamine was the active metabolite but was unable to block its stimulant action by reserpine. This is not surprising since reserpine does not interfere with NA synthesis and does not block the stimulant action of amphetamine (132). In the present experiment, where NA synthesis was reduced, 3-methoxy amphetamine was unable to induce its normal behavioural excitation. It would appear, then, that the stimulant action of α MmT is due to decarboxylation to metahydroxy amphetamine and subsequent O-methylation to metamethoxy amphetamine. Since O-methylation is specific for the meta position decarboxylated α MT is not a substrate. Decarboxylation of α MeDopa gives 34 dioxyamphetamine which may be converted to 3 methoxy, 4 hydroxy amphetamine. Since methoxylation is predominantly in the liver this metabolite could not reach the brain. Thus, the stimulant action of α MmT, but not α MT nor α MeDopa, is probably due to the formation of 3-methoxy amphetamine which acts by releasing NA.

EXPERIMENT 14: PRETREATMENT WITH A CLOSE MESCALINE CONGENER

Method

Subjects and Apparatus:

Two of the trained Lister hooded rats (R1 and R2) served as subjects. The apparatus was similar to that described before.

Procedure:

Each subject was initially treated with 17.5 mg/kg mescaline. Fourteen days later these animals were given 25.0 mg/kg 2,4,5 trimethoxy phenylethylamine in 0.5 ccs saline followed after 15 minutes by 17.5 mg/kg 3,4,5 trimethoxyphenylethylamine (mescaline) in 0.5 ccs saline. The pretreatment compound has already been shown to be inactive at this dose (Experiment 7). Saline control runs using 1.0 ccs saline were carried out on the pre- and post-drug days.

Results and Discussion

Saline injection had no effect on behaviour, but the effect of the pretreatment was to decrease the mescaline response (Appendix B Nos 87 - 90).

The antagonism between these two closely related compounds would suggest that the 2,4,5 TMPE is capable of occupying the mescaline receptor-site, though itself having no central effect. A structive-activity relationship study of this competative inhibition should throw some light on the specificity of the mescaline receptor site.

EXPERIMENT 15: THE EFFECTS OF PRETREATMENT WITH IMIPRAMINE ON THE MESCALINE RESPONSE

Method

Subject and Apparatus:

Two of the trained male Lister hooded rats (R2 and R6) served as subjects. The apparatus has been described previously.

Procedure:

Each subject received 25.0 mg/kg mescaline two weeks before and one month after the pretreatment study. A single large dose of imipramine (40.0 mg/kg) in 0.5 ccs saline was given six hours before 25.0 mg/kg mescaline (0.5 ccs fluid) during the pretreatment day. Both animals received a saline injection equivalent to the total fluid volume (1.0 ccs) on the pre- and post-drug days. All injections were intraperitoneal.

Results

Saline injections had no effect on behaviour. Imipramine (40.0 mg/kg) had an initial sedative effect but this was not observed 6 hours after the injection. Following pretreatment with imipramine the subsequent mescaline injection did not produce its normal behavioural disruption (Appendix B Nos. 97-102) but was almost inactive. The animals appeared normal and a typical saline record was obtained in both cases. Six hours were left between treatment and pretreatment administrations since it has been suggested that it is a metabolite of

imipramine which is responsible for the activity of this drug (23, 37).

Imipramine and desmethylimipramine are thought to have only weak α sympatholytic properties and their main action is probably a blockade of reuptake on the pre-synaptic membrane. Since this latter process is now considered to be the main pathway for removing NA from the synapse (94), then any blockade of reuptake should be the most effective way of increasing active NA concentrations. Under these conditions of high NA concentrations, mescaline may be inactive because (a) it cannot compete with NA for active receptor sites (b) its action depends on the active uptake process or (c) an unknown action of imipramine is responsible.

If the first hypothesis is correct, then one would expect that drugs,which are thought to block the post-synaptic receptor site, should decrease the mescaline response. CPZ has strong α sympatholytic properties and it has been reported to (a) reverse the inhibition of synaptic conduction in the transcallosal system (115); (b) protect mice against lethal doses of mescaline (127) and (c) block the effects of mescaline in 24 out of 25 human subjects (50).

EXPERIMENT 16: MESCALINE AND AMPHETAMINE: TOLERANCE AND CROSS-TOLERANCE

Method

Subjects and Apparatus:

The subject was a male Lister hooded rat (R1) that had previously been extensively trained on the avoidance schedule. The standard Grason-Stadler apparatus was employed.

Procedure:

The animal received three doses of 25.0 mg/kg mescaline in 0.5 ccs fluid on three separate days. A saline control day was run on the day before and the day after each drug administration and on the day following the last control day the subject was given 2.0 mg/kg amphetamine. One month later this procedure was repeated with the drugs reversed. Saline days alternated with 2.0 mg/kg amphetamine and the sequence was followed by a dose of 25.0 mg/kg mescaline.

The experimental paradigm can be written:

A B C D
Saline, Drug 1, Saline, Drug 1, Saline, Drug 1, Saline, Drug 2.

where drugs 1 and 2 were either 25.0 mg/kg mescaline or 2.0 mg/kg amphetamine. The letters above the drug days refer to the data shown in Figs. 36 and 37. All drug and saline injections consisted of 0.5 ccs of fluid given intraperitoneally.

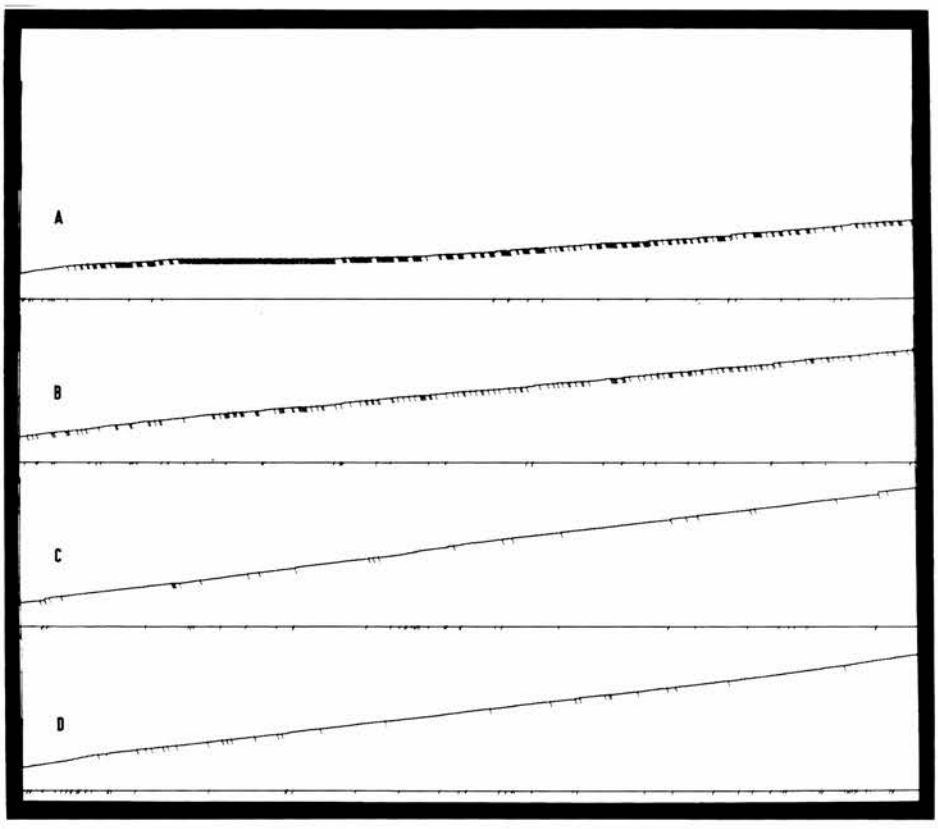

FIG. 36: Cumulative records showing the developement of tolerance to Mescaline and cross-tolerance to Amphetamine. (Subject R1)
A, B and C - 25.0 mg/kg Mescaline.
D - 2.0 mg/kg Amphetamine.
(See text.)

Results

The development of tolerance to mescaline can be seen clearly on Fig. 36 A, B and C. The rate of responding increased and the number of shocks (deflections of cumulative recorder pen) decreased over the three days. Fig. 37 D shows the mescaline response obtained after three days of amphetamine. A comparison of Fig. 37 D and Fig. 36 A reveals that the amphetamine treatment markedly decreased the mescaline response.

Fig. 37 A, B and C are cumulative records showing responding over the three amphetamine days. The even marker, below each cumulative record, deflected when a premature or burst response occurred. As tolerance to amphetamine developed the total response rate and the number of premature and burst responses all decreased. A similar reduction in the amphetamine effect was observed following the three doses of mescaline (cf. Fig. 37 A and Fig. 36 D).

Since no disturbance of behaviour was observed on the control days it can be concluded that (a) tolerance develops to mescaline (b) tolerance develops to amphetamine (c) when tolerance has developed to mescaline there is a marked cross-tolerance to amphetamine and (d) when tolerance has developed to amphetamine then there is a marked cross-tolerance to mescaline. These results underline the similarity between the actions of amphetamine and mescaline outlined in Section V.

Any attempt to explain the findings would be premature since little is known about the metabolic pathways involved in the

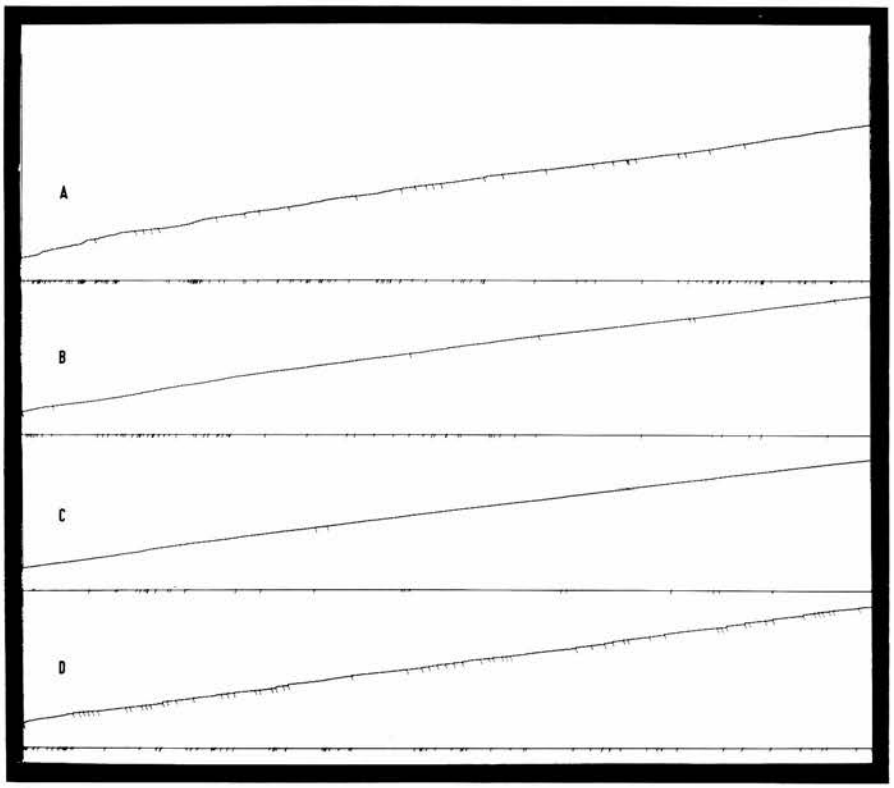

FIG. 37: Cumulative records showing the developement of tolerance to Amphetamine and cross-tolerance to Mescaline. (Subject R1)
A, B and C - 2.0 mg/kg Amphetamine.
D - 25.0 mg/kg Mescaline.
(See text.)

degredation of either amphetamine or mescaline. Some studies by Axelrod, however, suggest that the parahydroxylation of amphetamine and the deamination of mescaline may be the major metabolic pathways in the rat. If the stimulant action of amphetamine is dependent upon a release of NA perhaps a common pathway in NA and mescaline metabolism is a critical factor.

FACTS AND SPECULATIONS

There is some evidence that the effects of high doses of amphetamine are not due to NA release. Herman (85) has noted that whereas αMT can inhibit the behavioural stimulation caused by low doses of amphetamine, it has no effect on A.S.B. induced by high doses of the drug. Furthermore, when NA concentrations are increased by concomitant treatment with reserpine, nialamide and pyragallol, the A.S.B. is abolished and only an excitation is observed. This suggests that amphetamine may have a mixed action (120). Although low doses release NA, higher doses may compete with the catecholamine for the active receptor sites. Muscholl (120) has pointed out that these 'amines with mixed actions represent a gradual transition from group a to group c rather than a distinct third group. Thus mescaline could also be a mixed amine with a slight indirect action at low doses, resulting in behavioural excitation, and the major effect of the drug may be direct. This direct mode of action of mescaline is supported by the structural requirements of the drug and the results of the pretreatment studies. It is relevant that it has recently been reported that the presence of a meta or para hydroxy group on the phenol ring appears to be of greater significance (and the presence of a β hydroxy group of less significance) for enhancing the direct action of an amine, than was previously supposed (120). Hence, paramethoxylation of amphetamine or β-phenylethylamine, may decrease

the indirect action of these drugs and facilitate a direct mode of action. This would explain why this small structural change can convert predominantly stimulant drugs into compounds with 'psychotomimetic properties'.

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BIBLIOGRAPHY

1. AGHAJANIAN, G.K. and BING, O.H.L. (1964) Clin. Pharmacol. Therap., 5, 611.

2. ALLES, G.A. (1957) Neuropharmacology (Transactions of 4th Conference). New York: Josiah Macy, Jr. Foundation.

3. ANDERSSON, B. and LARSSON, S. (1957) Acta Physiol. Scand., 38, 22.

4. ANGER, D. (1963) J. Exp. Anal. Behav., 6, 477.

5. APPEL, J.B. and FREEDMAN, D.X. (1964) Biochem. Pharmacol., 13, 861.

6. AXELROD, J. (1954) J. Pharmacol. Exptl. Therap., 110, 315.

7. AXELROD, J. (1955) J. Biol. Chem., 214, 753.

8. BARBEAU, A., de GROOT, J.A., JOLY, J.G., TREMBLAY, A.R. and DONALDSON, J. (1963) J. Rev. Canad. Biol., 22, 469.

9. BARRIOS, A.A. (1965) Intern. J. Neuropsychiat., 1, 574.

10. BENINGTON, F., MORIN, R.D. and CLARK, L.C. Jr. (1964) Alabama J. Med. Sci., 4, 417.

11. BLASCHKO, H. (1961) Proceedings of the First International Pharmacological Meeting, 6, 289.

12. BLASCHKO, H., FERRO-LUZZI, G. and HAWES, R. (1958) Biochem. Pharmacol., 1, 101.

13. BOREN, J.J. (1961) Psychopharmacologia, 2, 416.

14. BORSY, J., CSANYI, E. and LAZAR, I. (1960) Arch. Intern. Pharmacodyn., 124, 180.

15. BOULTON, A.A., POLLITT, R.J. and MAJER, J.R. (1967) Nature, 215, 132.

16. BOVET, D. and GATTI, G.L. (1963) Pharmacology of Conditioning, Learning and Retentioning - Proceedings of the 2nd International Pharmacological Meeting. Prague.

17. BRADLEY, R.J. (1967) Unpublished Ph.D. thesis: Edinburgh University.

18. BRADLEY, P.B. and KEY, B.J. (1959) Brit. J. Pharmacol., 14, 340.

19. BRADY, J.V. (1956) Science, 123, 1033.

20. BRADY, J.V. (1956) Ann. N.Y. Acad. Sci., 64, 632.

21. BRADY, J.V. (1959) Psychopharmacology: Problems in Evaluation. National Academy of Sciences - National Research Council.

22. BRADY, J.V. and ROSS, S. (1960) Drugs and Behaviour. New York: John Wiley and Sons.

23. BRODIE, B.B. (1964) The Scientific Bases of Drug Therapy in Psychiatry. (Proceedings of a symposium at St. Bartholomew's Hospital, London) New York: Pergamon.

24. BURN, J.H. and HOBBS, R. (1958) Arch. Intern. Pharmacodyn., 113, 290.

25. BURN, J.H. and RAND, M.J. (1958) J. Physiol., 144, 314.

26. CARLSSON, A. (1966) Pharmacological Reviews, 18, 541.

27. CARLSSON, A. and LINDQUIST, M. (1962) Acta Physiol. Scand., 54, 87.

28. CARLSSON, A., LINDQUIST, S., FILA-HROMADKO, S. and CORRODI, H. (1962) Helv. chim. acta, 45, 270.

29. CARLSSON, A. and WALDECK, B. (1963) Acta Pharmacol.toxicol., 20, 47.

30. CARLSSON, A. and WALDECK, B. (1965) Acta Pharmacol. toxicol., 22, 293.

31. CARLTON, P.L. (1961) Psychopharmacologia, 2, 364.

32. CHALMERS, R.K. and ERICKSON, C.K. (1964) Psychopharmacologia, 6, 31.

33. CHANCE, M.R.A. (1946) J. Pharmacol. Exptl. Therap., 87, 214.

34. CHANCE, M.R.A. (1947) J. Pharmacol. Exptl. Therap., 89, 289.

35. CHARALAMPOUS, K.D., WALKER, K.E. and KINROSS-WRIGHT, J. (1966) Psychopharmacologia, 9, 48.

36. CHOROVER, S.L. (1961) Unpublished Ph.D. thesis: New York University.

37. CHRISTIANSEN, J., GRAM, L.F., KOFOD, B and RAFAELSEN, O.J. (1967) Psychopharmacologia , 11, 255.

38. CLARK, L.C., Jr., BENINGTON, F. and MORIN, R.D. (1965) Journal of Medicinal Chemistry, 8 , 353.

39. CLARK, F.C. and STEELE, B.J. (1963) Psychopharmacologia, 4, 221.

40. CLARK, F.C. and STEELE, B.J. (1966) Psychopharmacologia, 9, 157.

41. CONNELL, P.H. (1958) Amphetamine Psychoses. London: Oxford University Press.

42. COOK, L. and WEIDLEY, E. (1957) Ann. N.Y. Acad. Sci., 66, 740.

43. COOK, L. and KELLEHER, R.T. (1962) Ann. N.Y. Acad. Sci., 96, 315.

44. CORNE, S.J. and PICKERING, R.W. (1967) Psychopharmacologia, 11, 65.

45. COSTA, E., GESSA, G.L., KUNTZMAN, R. and BRODIE, B.B. (1962) Proceedings of the First International Pharmacological Meeting. Oxford: Pergamon Press.

46. COURVOISIER, S. and JULOU, L. (1956) XX Intern. Physiol. Congr., 197.

47. COURVOISIER, S., FOURNEL, J., DUCROT, R., KOLSKY, M. and KOETSCHET, P. (1953) Arch. Intern. Pharmacodyn., 92, 305.

48. CROUT, J.R., MUSKUS, A.J. and TRENDELENBURG, U. (1962) Brit. J. Pharmacol. , 18, 600.

49. DALY, J., AXELROD, J., and WITKOP, B. (1962) Ann. N.Y. Acad. Sci., 96, 37.

50. DENBER, H.C.B. (1959) Biological Psychiatry. New York: Grune and Stratton, Inc.

51. DEWS, P.B. (1955) J. Pharmacol. Exptl. Therap., 155, 380.

52. DEWS, P.B. (1958) J. Pharmacol. Exptl. Therap., 122, 137.

53. DINGELL, J.V., OWENS, M.L., NORVICH, M.R. and SULSER, F. (1967) Life Sci., 6, 1155.

54. DREVER, J. (1952) A dictionary of Psychology. Penguin Books Ltd., Harmondsworth, Middlesex.

55. ESTES, W.K. and SKINNER, B.F. (1941) J. Exp. Psychol., 29, 390.

56. ERNST, A.M. (1965) Psychopharmacologia, 7, 383.

57. ERNST, A.M. (1965) Psychopharmacologia, 7, 391.

58. FERSTER, C.B. and SKINNER, B.F. (1957) Schedules of Reinforcement. New York: Appleton-Century-Crofts.

59. FLECKENSTEIN, A. and BURN, J.H. (1953) Brit. J. Pharmacol., 8, 69.

60. FREEDMAN, D.X. (1963) Am. J. Psychiat., 119, 843.

61. FREEDMAN, D.X. and AGHAJANIAN, G.K. (1966) Lloydia, 29, 309.

62. FREEDMAN, D.X., APPEL, J.B., HARTMAN, F.R. and MOLLIVER, M.E. (1964) J. Pharmacol. Exptl. Therap., 143, 309.

63. FRIEDHOFF, A.J. and GOLDSTEIN, M. (1962) Ann. N.Y. Acad. Sci., 96, 51.

64. FRIEDHOFF, A.J. and HOLLISTER, L.E. (1966) Biochem. Pharmacol., 15, 269.

65. FRIEDHOFF, A.J. and VAN WINKLE, E. (1962) Nature, 194, 897.

66. FRIEDHOOF, A.J. and VAN WINKLE, E. (1965) Am. J. Psychiat., 121, 1054.

67. FROMMEL, E. and FLEURY, C. (1961) Med. Hyg., 19, 52.

68. GATTI, G.L. (1964) Neuropsychopharmacology, 3, 514.

69. GATTI, G.L. and BOVET, D. (1963) Psychopharmacological Methods. Oxford: Pergamon Press.

70. GESSA, G.L., COSTA, E., KUNTZMAN, R. and BRODIE, B.B. (1962) Life Sci., 1, 353.

71. GESSNER, P.K. and PAGE, J.H. (1962) Amer. J. Physiol., 203, 167.

72. GIACHETTI, A. and SHORE, P.A. (1966) Biochem. Pharmacol., 15, 607.

73. GILL, J.R., MASON, D.T. and BARTTER, F.C. (1967) J. Pharm. Exptl. Therap., 155, 288.

74. GOLDSTEIN, M. (1966) Pharmacological Reviews, 18, 77.

75. GOLDSTEIN, M. and ANAGNOSTE, B. (1965) Biochemical Biophysical Acta, 107, 166.

76. GOLDSTEIN, M., ANAGNOSTE, B. and EDGAR, L. (1964) Life Sci., 3, 763.

77. GOLDSTEIN, M. and McKEREGHAN, M.R. and LAUBER, E. (1964) Biochemical Biophysical Acta, 89, 191.

78. GOLDSTEIN, M., MUSACCHIO, J.M., KENIN, M.C., CONTRERA, J.R. and RICE, M.D. (1962) Biochem. Pharmacol., 11, 809.

79. GRAY, W.D., OSTERBERG, A.C., RAUH, C.F. and HILL, R.T. (1960) Arch. Intern. Pharmacodyn., 125, 101.

80. HAMILTON, C.L. (1960) Arch. Gen. Psychiat., 2, 104.

81. HANSON, L.C.F. (1966) Psychopharmacologia, 9, 78.

82. HARLEY-MASON, J., LAIRD, A.H. and SYMYTIES, J.R. (1958) Contin. Neurol., 18, 152.

83. HARRISON, J.M. and ABELSON, R.M. (1959) J. Exp. Anal. Behav., 2, 23.

84. HEISE, G.A. and BOFF, E. (1962) Psychopharmacologia, 3, 264.

85. HERMAN, Z.S. (1967) Psychopharmacologia, 11, 136.

86. HILL, H.E., BELL, E.C. and WIKLER, A. (1967) Arch. Intern. Pharmacodyn., 165.

87. HOHN, R. and LASAGUA, L. (1960) Psychopharmacologia, 1, 210.

88. HOROVITZ, Z.P., SHOW, M. and CARLTON, P.L. (1962) Psychopharmacologia, 3, 455.

89. HUNT, H.F. (1956) Ann. N.Y. Acad. Sci., 65, 258.

90. HUNT, H.F. (1957) Ann. N.Y. Acad. Sci., 67, 712.

91. HUNT, H.F. (1959) Psychopharmacology: Problems in Evaluation. National Academy of Sciences - National Research Council.

92. IRWIN, S., SLABOK, M., DEBIASE, P.L. and GOVIER, W.M. (1959) Arch. Intern. Pharmacodyn., 118, 358.

93. IVERSON, L.L. (1963) Brit. J. Pharmacol., 21, 523.

94. IVERSON, L.L. (1967) Nature, 214, 8.

95. JACOB, J. and LAFILLE, C. (1963) Arch. Intern. Pharmacodyn., 145, 528.

96. JACOB, J., LOISEAU, G., ECHINARD-GARIN, P. and BARTHELEMY, C. (1962) Med. Exp., 7, 296.

97. JERRARD, L.E. (1963) Psychopharmacologia, 5, 39.

98. JONG, H. de (1945) Experimental Catatonia. Baltimore: Williams and Wilkins.

99. KAMIN, L.J., BRIMER, C.J. and BIACK, A.H. (1963) J. Comp. Physiol. Psychol., 56, 497.

100. KANTOR, J.R. (1936) An objective psychology of grammer. Bloomington, Indiana: Indiana University Press.

101. KANTOR, J.R. (1945) Psychology and Logic. Bloomington, Indiana: Principia Press.

102. KELLEHER, R.T. and MORSE, W.H. (1964) Federation Proceedings, 23, 808.

103. KINNARD, W.J., ACETO, M.D.G. and BUCKLEY, J.P. (1962) Psychopharmacologia, 3, 227.

104. KNOLL, J. (1961) Arch. Intern. Pharmacodyn., 130, 141.

105. KNOLL, J., VIZI, E.S. and ECSERI, Z. (1966) Arch. Intern. Pharmacodyn., 159, 442.

106. KOPIN, I.J., FISCHER, J.E., MUSACCHIO, J. and HORST, W.D. (1964) Proc. Nat. Acad. Sci., 52, 716.

107. KOPIN, I.J., HERTTING, G. and GORDON, E.K. (1962) J. Pharmacol., 138, 34.

108. LAPIN, I.P. and SHCHELKUNOV, E.L. (1963) Second International Pharmacological Meeting. Oxford: Pergamon.

109. LASAGNA, L. and McCANN, W.P. (1957) Science, 125, 1241.

110. LATIES, V.G. and WEISS, B. (1966) J. Pharmacol. Exptl. Therap., 152, 388.

111. LAUENER, H. (1963) Pyshopharmacologia , 4, 311.

112. LEWIS, J.J. (1965) Introduction to Pharmacology. Edinburgh: Livingstone.

113. LIPMAN, V.C., SHURRAGER, P.S. and ABOOD, L.G. (1961) Arch. Intern. Pharmacodyn., 2, 722.

114. MAFFII, G. (1959) J. Pharm. Pharmacol., 11, 129.

115. MARRAZZI, A.S. (1957) Ann. N.Y. Acad. Sci., 66, 496.

116. MIRSKY, J.H., WHITE, H.D. and O'DELL, T.B. (1959) J. Pharmacol. Exptl. Therap., 125, 122.

117. MONTANARI, R., COSTA, E., BEAVEN, N.A. and BRODIE, B.B. (1964) Life Sci., 3, 769.

118. MORAN, N.C. (1966) Pharmacological Reviews, 18, 503.

119. MORPURGO, C. (1965) Psychopharmacologia, 8, 91.

120. MUSCHOLL, E. (1966) Pharmacological Reviews, 18, 551.

121. NIELSEN, I.M. and NEUHOLD, K. (1959) Acta Pharmacol. Toxicol., 15, 335.

122. NOTEBOOM, L. (1934) Proc. Roy. Acad. Sci., 37, 562.

123. OLDS, J. (1959) Neuropsychopharmacology. Amsterdam: Elsevier.

124. OWEN, J.E. (1963) J. Pharm. Sci., 52, 684.

125. PERETZ, D., SMYTHIES, J.R. and GIBSON, W.C. (1955) J. Ment. Sci., 101, 317.

126. PIALA, J.J., HIGH, J.P., HASSERT, G.L. Jr., BURKE, J.C. and CRAVER, B.N. (1959) J. Pharmacol. Exptl. Therap., 127, 55.

127. PLOTNIKOFF, N.P. and WASHINGTON, H. (1958) Proc. Soc. Exptl. Biol. Med., 98, 660.

128. POSLUNS, D. (1962) Psychopharmacologia, 3, 361.

129. POTTER, L.T. (1966) Pharmacological Reviews, 18, 439.

130. POTTER, L.T. and AXELROD, J. (1963) J. Pharmacol. Exptl. Therap., 142, 299.

131. POTTER, L.T., AXELROD, J. and KOPIN, I.J. (1962) Biochem. Pharmacol., 11, 254.

132. QUINN, J. Unpublished M.D. thesis: The Queens University of Belfast.

133. QUINTON, R.M. and HALLIWELL, G. (1963) Nature, 200, 178.

134. RANDRUP, A., MUNKVAD, I. and UDSEN, P. (1963) Acta Pharmacol. Toxicol., 20, 145.

135. RAY, O.S. (1964) Psychopharmacologia, 5, 136.

136. RAY, O.S. and BIVENS, L.W. (1966) Psychopharmacologia, 10, 32.

137. RESNICK, O., KRUS, D.M. and RASKIN, M. (1965) Life Sci., 4, 1433.

138. ROSSUM, J.M. Van (1963) Psychopharmacologia, 4, 271.

139. ROSSUM, J.M. Van, SCHOOT, J.B. Van and HURKMANS, J.A. Th. M. (1962) Experientia, 18, 229.

140. SCHECKEL, C.L. and BOFF, E. (1964) Arch. Intern. Pharmacodyn., 152, 479.

141. SCHOOT, J.B. Van der, ARIENS, E.J., ROSSUM, J.M. Van, and HURKMANS, J.A.Th.M. (1961) Arzneimittel-Forsch, 12, 902.

142. SHORE, P.A. (1966) Pharmacological Reviews , 18, 561.

143. SHULGIN, A.T. (1963) Experientia, 19, 127.

144. SHULGIN, A.T. (1964) Experientia, 20, 1.

145. SHULGIN, A.T., BUNNELL, S. and SARGENT III, T. (1961) Nature, 189, 1011.

146. SIDMAN, M. (1955) Science, 122, 925.

147. SIDMAN, M. (1955) J. Comp. Physiol. Psychol., 48, 444.

148. SIDMAN, M. (1956) Ann. N.Y. Acad. Sci., 65, 282.

149. SIDMAN, M. (1961) Tactics of Scientific Research. New York: Basic Books Inc.

150. SIEGEL, P.S., and STERLING, T.D. (1959) J. Comp. Physiol. Psychol., 52, 179.

151. SKINNER, B.F. (1957) Verbal Behaviour. London: Methuen & Co., Ltd.

152. SLOTTA, K.H. and MULLER, J. (1936) Z. physiol. Chem. 238, 14.

153. SMYTHIES, J.R. and LEVY, C.K. (1960) J. Ment Sci., 106, 531.

154. SMYTHIES, J.R. and SYKES, E.A. (1964) Psychopharmacologia 6, 163.

155. SMYTHIES, J.R. and SYKES, E.A. (1965) Neuropsychopharmacology, 4, 356.

156. SMYTHIES, J.R. and SYKES, E.A. (1966) Psychopharmacologia, 8, 324.

157. SMYTHIES, J.R. and SYKES, E.A. and LORD, C.P. (1966) Psychopharmacologia, 9, 434.

158. SOURKES, T.L. (1966) Pharmacological Reviews, 18, 53.

159. SPECTOR, S. (1966) Pharmacological Reviews, 18, 599.

160. STEIN, L. (1962) Recent Advances in Biological Psychiatry. New York: Plenum.

161. STEIN, L. (1962) Psychosomatic Medicine. Philadelphia: Lea and Feiber.

162. STEIN, L. (1964) Animal Behaviour and Drug Action. London: J. and A. Churchill.

163. STEIN, L. and SEIFTER, J. (1961) Possible Mode of Antidepressive Action of Imipramine. Science, 134, 286.

164. SULSER, F. (1966) Life Sci., 5, 2005.

165. SULSER, F. (1967) The Antidepressant Drugs: A workshop manual published by the National Institute of Mental Health.

166. SULSER, F., D'ENCARNACAO, P., OWENS, M.L. and DINGELL, J.V. The Pharmacologist, 8, 214.

167. SWINYARD, E.A., WOLF, H.H., FINK, G.B. and GOODMAN, L.S. (1959) J. Pharmacol. Exptl. Therap., 126, 312.

168. TAESCHLER, M., WEIDMANN, H. and CERLETTI, A. (1960) Helv. physiol. pharmacol. Acta, 18, 43.

169. TEDESCHI, D.H., TEDESCHI, R.E., COOK, L., MATTIS, P.A. and FELLOWS, E.J. (1959) Arch. Intern. Pharmacodyn., 122, 129.

170. TEDESCHI, R.E., TEDESCHI, D.H. and FELLOWS, E.J. (1962) Psychosomatic Medicine (First Hohnemann Symposium).

171. TEITELBAUM, P. and DERKS, P. (1958) J. Comp. physiol. Psychol., 51, 801.

172. TRENDELENBERG, U. (1961) J. Pharmacol. Exptl. Therap., 134, 8.

173. UDENFRIEND, S. (1966) Pharmacological Reviews, 18, 43.

174. UDENFRIEND, S. and ZALTZMAN-NIRENBERG, P. (1962) J. Pharmacol. Exptl. Therap., 138, 194.

175. ULRICH, R.E., HOLZ, W.C. and AZRIN, N.H. (1964) J. Exp. Anal. Behav., 7, 129.

176. VACCA, L., FUJIMORI, M., BUDDE, R.G., MARRAZZI, A.S. (1967) The Pharmacologist, 9, 188.

177. VERHAVE, T. (1958) J. Exp. Anal. Behav., 1, 207.

178. WEISS, B. and LATIES, V.G. (1959) Fed. Proc., 18, 457.

179. WEISS, B. and LATIES, V.G. (1963) J. Pharmacol. Exptl. Therap., 140, 1.

180. WEISS, B. and LATIES, V.S. (1964) Fed. Proc., 23, 801.

181. WEISSMAN, A. (1959) J. Exp. Anal. Behav., 2, 271.

182. WEISSMAN, A., KOE, B.K. and TENEN, S.S. (1966) J. Pharm. Exptl. Therap., 151, 339.

183. WERTHEIM, G.A. (1965) J. Exp. Anal. Behav., 8, 9.

184. WHITBY, L.G., AXELROD, J. and HERTTING, G. (1960) Nature, 187, 604.

APPENDIX A

THE COMPUTER PROGRAM

```
***A
JOB
MRC  003/00000001/  V S JOHNSTON PSYCHIATRY  UTOPIA
OUTPUT
0 LINE PRINTER  1500 LINES
EXECUTION  15 MINUTES
COMPILER AA
begin
integer i,j,k,p,x,y,z,m,r,q,a,c
real g,s,t,d
integer array  num(-2:3,-2:3,-2:3),no(-2:3,-2:3),n(-2:3),prob(-2:10)
cycle i=0,1,3
cycle j=0,1,3
  cycle k=0,1,3
  num(i,j,k) = 0
  no(i,j) = 0
  n(i) = 0
repeat
repeat
repeat
cycle p=1,1,10
prob(p)=0
repeat
s=0
t=0
m=0
x=-2
y=-2
1: read (g)
-> 2 if g=-1
c=int(g*0.1)
a=int(g*0.1) - 19
z=0  if  c<3
z=1  if  2<c<20
z=2  if 19<c<30
z=3  if c>29
m=a if 1 ≤ a ≤ 10
m=0 if 1>a>10
s=s+(c-20)  if c>19
t=t+c
num(x,y,z) = num(x,y,z) + 1
no(y,z) = no(y,z) + 1
n(z) = n(z) + 1
prob (m) = prob (m) + 1
m=0
x=y
y=z
```

```
-> 2 if t > 6000
-> 1
2:caption ANIMAL
newlines (3)
caption DATA # TAPE # CODE
newlines (3)
caption DATE
newline
newpage
r=0
cycle  i=0,1,3
r=r+n(i)
repeat
newline
spaces(20)
caption  THIRD # ORDER
newlines (3)
cycle  i=0,1,3
newlines(3)
if i=0  then caption sequence # of # three # starts # with # a # burst
if i=1  then caption sequence # of # three # starts # with # a # premature
if i=2  then caption sequence # of # three # starts # with # a # efficient
if i=3  then caption sequence # of # three # starts # with # a # late
newlines(2)
spaces(11)
caption third#response# is#a########burst######premature####efficient###late
newlines(2)
spaces(10)
caption frequencies
cycle j=0,1,3
newline
if j=0 then caption second#response#is#a#####burst
if j=1 then caption second#response#is#a#premature
if j=2 then caption second#response#is#a#efficient
if j=3 then caption second#response#is#a######late
spaces(4)
cycle k=0,1,3
print (num(i,j,k),4,3)
spaces(4)
repeat
repeat
newlines(2)
spaces(10)
caption probabilities
cycle j=0,1,3
newline
if j=0 then caption second#response#is#a#####burst
if j=1 then caption second#response#is#a#premature
```

```
if j=2 then caption second$response$is$a$efficient
if j=3 then caption second$response$is$a$$$$$$late
spaces(4)
cycle k=0,1,3
print((1/r)*(num(i,j,k)),4,3)
spaces(4)
repeat
repeat
newlines(2)
spaces(10)
caption conditional$probabilities
cycle j=0,1,3
newline
if j=0 then caption second$response$is$a$$$$$burst
ifj=1  then caption second$response$is$a$premature
if j=2 then caption second$response$is$a$efficient
if j=3  then caption second$response$is$a$$$$$$late
spaces(4)
cycle k=0,1,3
d=no(i,j)
-> 3 if d=0
d=1/d
3: print((d)*(num(i,j,k)),4,3)
spaces(4)
repeat
repeat
repeat
newlines (3)
spaces(20)
caption second$order
newlines(3)
spaces(10)
caption second$response$is$a$$$$$$$burst$$$$$premature$$$$efficient$$late
newlines(2)
spaces(10)
caption frequencies
cycle i=0,1,3
newline
if i=0 then caption first$response$is$a$$$$$$burst
if i=1 then caption first$response$is$a$$premature
if i=2 then caption first$response$is$a$$efficient
if i=3 then caption first$response$is$a$$$$$$$late
spaces(4)
cycle j=0,1,3
print(no(i,j),4,3)
spaces(4)
repeat
repeat
```

```
newlines(2)
spaces(10)
caption probabilities
cycle i=0,1,3
newline
if i=0 then caption first$response$is$a$$$$$$burst
if i=1  then caption first$response$is$a$$premature
if i=2 then caption first$response$is$a$$efficient
if i=3 then caption first$response$is$a$$$$$$$late
spaces (4)
cycle j=0,1,3
print((1/r)*(no(i,j)),4,3)
spaces(4)
repeat
repeat
newlines(2)
spaces(10)
caption conditional $probabilities
cycle i=0,1,3
newline
if i=0 then caption first$response$is$a$$$$$$burst
if i=1 then caption first$response$is$a$$premature
if i=2 then caption first $response$is$a$$efficient
if i=3 then caption first$response$is$a$$$$$$$late
spaces(4)
cycle j=0,1,3
d=n(i)
-> 4 if d=0
d=1/d
4:print((d)*(no(i,j)),4,3)
spaces(4)
repeat
repeat
newpage
spaces(20)
caption first$order
newlines(3)
q=0
cycle i=0,1,3
newline
if i=0 then caption frequency$$ $of$$$$$burst
if i=1 then caption frequency$$$of$premature
if i=2 then caption frequency$$$of$efficient
if i=3 then caption frequency$$$of$$$$$$late
spaces(4)
print(n(i),4,3)
if i=3 then q=n(i)
repeat
```

```
cycle i=0,1,3
newline
if i=0 then caption probability$of$$$$$burst
ifi=1  then caption probability$of$premature
if i=2 then caption probability$of$efficient
if i=3 then caption probability$of$$$$$$late
spaces(4)
print((1/r)*(n(i)),4,3)
repeat
newlines(3)
caption total
print (r,5,0)
newlines (6)
caption distribution$within$preaversive$stimulus$in$categories$of$second
newlines(2)
spaces(15)
cycle p=1,1,10
print(p,2,0)
spaces(6)
repeat
newline
caption frequency$$$
cycle p=1,1,10
print(prob(p),5,0)
spaces(3)
repeat
newline
caption probability$
cycle p=1,1,10
print((1/r)*(prob(p)),4,3)
repeat
newlines(3)
spaces(15)
cycle p=10,-1,1
print (p,2,0)
spaces(6)
repeat
newline
caption irt/op$$$$$$
cycle p=10,-1,1
q=q+prob(p)
print((1/q)*(prob(p)),4,3)
repeat
newlines(6)
caption percentage$reaction$time
spaces(4)
print((100/t)*(s),0,5)
end of program
```

APPENDIX B

FIRST ORDER DATA

SUBJECT R1 APPENDIX B

TREATMENT 75th AVOIDANCE SESSION NO. 1

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.030
FREQUENCY OF PREMATURE	4.0	PROBABILITY OF PREMATURE	0.017
FREQUENCY OF EFFICIENT	198.0	PROBABILITY OF EFFICIENT	0.850
FREQUENCY OF LATE	24.0	PROBABILITY OF LATE	0.103

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	5	13	7	16	26	37	35	30	26
PROB.	0.013	0.021	0.056	0.030	0.069	0.112	0.159	0.150	0.129	0.11
IRT/OP	0.014	0.023	0.061	0.035	0.082	0.146	0.243	0.304	0.375	0.52

TOTAL RESPONSES 233.0 PERCENTAGE REACTION TIME 25.4

SUBJECT R2 APPENDIX B

TREATMENT 75th AVOIDANCE SESSION NO. 2

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.024
FREQUENCY OF PREMATURE	10.0	PROBABILITY OF PREMATURE	0.040
FREQUENCY OF EFFICIENT	225.0	PROBABILITY OF EFFICIENT	0.900
FREQUENCY OF LATE	9.0	PROBABILITY OF LATE	0.036

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	9	14	29	34	34	43	35	19	7
PROB.	0.004	0.040	0.062	0.129	0.151	0.151	0.191	0.156	0.084	0.031
IRT/OP	0.004	0.039	0.063	0.138	0.188	0.231	0.381	0.500	0.543	0.438

TOTAL RESPONSES 250.0 PERCENTAGE REACTION TIME 21.8

SUBJECT R3 APPENDIX B

TREATMENT 75th AVOIDANCE SESSION NO. 3

FREQUENCY OF BURST	5.0	PROBABILITY OF BURST	0.020
FREQUENCY OF PREMATURE	10.0	PROBABILITY OF PREMATURE	0.040
FREQUENCY OF EFFICIENT	216.0	PROBABILITY OF EFFICIENT	0.864
FREQUENCY OF LATE	19.0	PROBABILITY OF LATE	0.076

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	9	11	25	24	30	36	36	22	17
PROB.	0.024	0.036	0.044	0.100	0.096	0.120	0.144	0.144	0.088	0.068
IRT/OP	0.026	0.039	0.050	0.120	0.130	0.188	0.277	0.383	0.379	0.472

TOTAL RESPONSES 250.0 PERCENTAGE REACTION TIME 23.9

SUBJECT R4 APPENDIX B

TREATMENT 75th AVOIDANCE SESSION NO. 4

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.025
FREQUENCY OF PREMATURE	12.0	PROBABILITY OF PREMATURE	0.051
FREQUENCY OF EFFICIENT	198.0	PROBABILITY OF EFFICIENT	0.835
FREQUENCY OF LATE	21.0	PROBABILITY OF LATE	0.089

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	10	15	21	24	25	36	31	20	12
PROB.	0.017	0.042	0.063	0.089	0.101	0.105	0.152	0.131	0.084	0.051
IRT/OP	0.018	0.047	0.073	0.110	0.142	0.172	0.300	0.369	0.377	0.364

TOTAL RESPONSES 237.0 PERCENTAGE REACTION TIME 24.0

SUBJECT R5 APPENDIX B

TREATMENT 75th AVOIDANCE SESSION NO. 5

FREQUENCY OF BURST	2.0	PROBABILITY OF BURST	0.008
FREQUENCY OF PREMATURE	15.0	PROBABILITY OF PREMATURE	0.062
FREQUENCY OF EFFICIENT	207.0	PROBABILITY OF EFFICIENT	0.855
FREQUENCY OF LATE	18.0	PROBABILITY OF LATE	0.074

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	7	11	19	22	33	40	31	26	15
PROB.	0.012	0.029	0.045	0.079	0.091	0.136	0.165	0.128	0.107	0.062
IRT/OP	0.013	0.032	0.051	0.093	0.119	0.202	0.308	0.344	0.441	0.455

TOTAL RESPONSES 242.0 PERCENTAGE REACTION TIME 24.2

SUBJECT R6 APPENDIX B

TREATMENT 75th AVOIDANCE SESSION NO. 6

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.029
FREQUENCY OF PREMATURE	13.0	PROBABILITY OF PREMATURE	0.054
FREQUENCY OF EFFICIENT	200.0	PROBABILITY OF EFFICIENT	0.833
FREQUENCY OF LATE	20.0	PROBABILITY OF LATE	0.083

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	12	10	10	21	30	34	33	27	17
PROB.	0.025	0.050	0.042	0.042	0.088	0.124	0.142	0.138	0.133	0.071
IRT/OP	0.027	0.056	0.050	0.052	0.113	0.186	0.260	0.340	0.422	0.459

TOTAL RESPONSES 240.0 PERCENTAGE REACTION TIME 24.6

SUBJECT R1 APPENDIX B

TREATMENT Approx. 300th AVOIDANCE SESSION NO. 7

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.029
FREQUENCY OF PREMATURE	9.0	PROBABILITY OF PREMATURE	0.038
FREQUENCY OF EFFICIENT	201.0	PROBABILITY OF EFFICIENT	0.845
FREQUENCY OF LATE	21.0	PROBABILITY OF LATE	0.088

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	12	10	17	18	26	34	32	26	20
PROB.	0.025	0.050	0.042	0.071	0.076	0.109	0.143	0.134	0.109	0.084
IRT/OP	0.027	0.055	0.049	0.088	0.102	0.164	0.256	0.323	0.388	0.488

TOTAL RESPONSES 238.0 PERCENTAGE REACTION TIME 24.1

SUBJECT R2 APPENDIX B

TREATMENT approx. 300th AVOIDANCE SESSION NO. 8

FREQUENCY OF BURST	1.0	PROBABILITY OF BURST	0.004
FREQUENCY OF PREMATURE	18.0	PROBABILITY OF PREMATURE	0.073
FREQUENCY OF EFFICIENT	211.0	PROBABILITY OF EFFICIENT	0.861
FREQUENCY OF LATE	15.0	PROBABILITY OF LATE	0.061

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	6	16	22	30	36	39	24	24	11
PROB.	0.012	0.024	0.065	0.090	0.122	0.147	0.159	0.098	0.098	0.045
IRT/OP	0.013	0.027	0.074	0.109	0.168	0.242	0.345	0.324	0.480	0.423

TOTAL RESPONSES 245.0 PERCENTAGE REACTION TIME 21.0

SUBJECT R3 APPENDIX B

TREATMENT approx. 300th AVOIDANCE SESSION NO. 9

FREQUENCY OF BURST	1.0	PROBABILITY OF BURST	0.004
FREQUENCY OF PREMATURE	14.0	PROBABILITY OF PREMATURE	0.057
FREQUENCY OF EFFICIENT	209.0	PROBABILITY OF EFFICIENT	0.857
FREQUENCY OF LATE	20.0	PROBABILITY OF LATE	0.082

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	9	13	17	22	29	40	32	20	21
PROBL	0.025	0.037	0.053	0.070	0.090	0.119	0.164	0.131	0.082	0.086
IRT/OP	0.026	0.040	0.061	0.085	0.120	0.179	0.301	0.344	0.328	0.512

TOTAL RESPONSES 244.0 PERCENTAGE REACTION TIME 24.3

SUBJECT R4 APPENDIX B

TREATMENT approx. 300th AVOIDANCE SESSION NO. 10

FREQUENCY OF BURST	4.0	PROBABILITY OF BURST	0.017
FREQUENCY OF PREMATURE	4.0	PROBABILITY OF PREMATURE	0.017
FREQUENCY OF EFFICIENT	209.0	PROBABILITY OF EFFICIENT	0.871
FREQUENCY OF LATE	23.0	PROBABILITY OF LATE	0.096

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	7	9	19	23	24	38	39	26	20
PROB.	0.017	0.029	0.038	0.079	0.096	0.100	0.158	0.163	0.108	0.083
IRT/OP	0.017	0.031	0.041	0.090	0.199	0.141	0.260	0.361	0.377	0.465

TOTAL RESPONSES 240.0 PERCENTAGE REACTION TIME 24.7

SUBJECT R5 APPENDIX B

TREATMENT approx. 300th AVOIDANCE SESSION NO. 11

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.025
FREQUENCY OF PREMATURE	13.0	PROBABILITY OF PREMATURE	0.055
FREQUENCY OF EFFICIENT	201.0	PROBABILITY OF EFFICIENT	0.845
FREQUENCY OF LATE	18.0	PROBABILITY OF LATE	0.076

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	6	7	12	17	38	34	39	26	16
PROB.	0.025	0.027	0.029	0.050	0.071	0.160	0.143	0.164	0.109	0.067
IRT/OP	0.027	0.028	0.034	0.060	0.090	0.222	0.256	0.394	0.433	0.471

TOTAL RESPONSES 238.0 PERCENTAGE REACTION TIME 24.9

SUBJECT R6 APPENDIX B

TREATMENT approx. 300th AVOIDANCE SESSION NO. 12

FREQUENCY OF BURST	4.0	PROBABILITY OF BURST	0.017
FREQUENCY OF PREMATURE	14.0	PROBABILITY OF PREMATURE	0.059
FREQUENCY OF EFFICIENT	195.0	PROBABILITY OF EFFICIENT	0.826
FREQUENCY OF LATE	23.0	PROBABILITY OF LATE	0.097

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	0	7	5	17	21	36	38	30	31	10
PROB.	0.000	0.030	0.021	0.072	0.089	0.153	0.161	0.127	0.131	0.042
IRT/OP	0.000	0.032	0.024	0.083	0.111	0.214	0.288	0.319	0.484	0.303

TOTAL RESPONSES 236.0 PERCENTAGE REACTION TIME 23.9

SUBJECT R5 APPENDIX B

TREATMENT 0.5 mg/kg Chlorpromazine NO. 13

FREQUENCY OF BURST	19.0	PROBABILITY OF BURST	0.079
FREQUENCY OF PREMATURE	11.0	PROBABILITY OF PREMATURE	0.046
FREQUENCY OF EFFICIENT	144.0	PROBABILITY OF EFFICIENT	0.600
FREQUENCY OF LATE	66.0	PROBABILITY OF LATE	0.275

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	0	3	10	8	13	21	23	25	25	16
PROB.	0.000	0.012	0.042	0.033	0.054	0.087	0.096	0.104	0.104	0.067
IRT/OP	0.000	0.014	0.048	0.041	0.069	0.119	0.148	0.189	0.234	0.195

TOTAL RESPONSES 240.0 PERCENTAGE REACTION TIME 28.0

SUBJECT R5 APPENDIX B

TREATMENT 1.0 mg/kg Chlorpromazine NO. 14

FREQUENCY OF BURST	29.0	PROBABILITY OF BURST	0.131
FREQUENCY OF PREMATURE	12.0	PROBABILITY OF PREMATURE	0.054
FREQUENCY OF EFFICIENT	86.0	PROBABILITY OF EFFICIENT	0.389
FREQUENCY OF LATE	94.0	PROBABILITY OF LATE	0.425

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	2	4	8	5	5	13	19	15	12
PROB.	0.014	0.009	0.018	0.036	0.023	0.023	0.059	0.086	0.068	0.054
IRT/OP	0.017	0.011	0.023	0.047	0.031	0.032	0.085	0.136	0.124	0.113

TOTAL RESPONSES 221.0 PERCENTAGE REACTION TIME 38.3

SUBJECT R5 APPENDIX B

TREATMENT 2.0 mg/kg Chlorpromazine NO. 15

FREQUENCY OF BURST	19.0	PROBABILITY OF BURST	0.089
FREQUENCY OF PREMATURE	11.0	PROBABILITY OF PREMATURE	0.052
FREQUENCY OF EFFICIENT	60.0	PROBABILITY OF EFFICIENT	0.282
FREQUENCY OF LATE	123.0	PROBABILITY OF LATE	0.577

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	1	5	4	4	9	9	8	6	13
PROB.	0.005	0.005	0.023	0.019	0.019	0.042	0.042	0.038	0.028	0.061
IRT/OP	0.005	0.005	0.028	0.023	0.023	0.054	0.057	0.053	0.042	0.096

TOTAL RESPONSES 213.0 PERCENTAGE REACTION TIME 36.9

SUBJECT R6 APPENDIX B

TREATMENT 0.5 mg/kg Chlorpromazine NO. 16

FREQUENCY OF BURST	25.0	PROBABILITY OF BURST	0.104
FREQUENCY OF PREMATURE	7.0	PROBABILITY OF PREMATURE	0.029
FREQUENCY OF EFFICIENT	115.0	PROBABILITY OF EFFICIENT	0.479
FREQUENCY OF LATE	93.0	PROBABILITY OF LATE	0.388

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	0	0	5	7	7	13	17	20	25	21
PROB.	0.000	0.000	0.021	0.029	0.029	0.054	0.071	0.083	0.104	0.087
IRT/OP	0.000	0.000	0.024	0.034	0.036	0.069	0.097	0.126	0.180	0.184

TOTAL RESPONSES 240.0 PERCENTAGE REACTION TIME 29.7

SUBJECT R6 APPENDIX B

TREATMENT 1.0 mg/kg Chlorpromazine NO. 17

FREQUENCY OF BURST	22.0	PROBABILITY OF BURST	0.094
FREQUENCY OF PREMATURE	8.0	PROBABILITY OF PREMATURE	0.034
FREQUENCY OF EFFICIENT	97.0	PROBABILITY OF EFFICIENT	0.415
FREQUENCY OF LATE	107.0	PROBABILITY OF LATE	0.457

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	1	2	4	7	9	10	20	21	20
PROB.	0.013	0.004	0.009	0.017	0.030	0.038	0.043	0.085	0.090	0.085
IRT/OP	0.015	0.005	0.010	0.020	0.036	0.048	0.056	0.119	0.142	0.157

TOTAL RESPONSES 234.0 PERCENTAGE REACTION TIME 29.8

SUBJECT R6 APPENDIX B

TREATMENT 2.0 mg/kg Chlorpromazine NO. 18

FREQUENCY OF BURST	20.0	PROBABILITY OF BURST	0.101
FREQUENCY OF PREMATURE	7.0	PROBABILITY OF PREMATURE	0.035
FREQUENCY OF EFFICIENT	77.0	PROBABILITY OF EFFICIENT	0.387
FREQUENCY OF LATE	95.0	PROBABILITY OF LATE	0.477

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	4	2	3	7	8	9	10	17	14
PROB.	0.015	0.020	0.010	0.015	0.035	0.040	0.045	0.050	0.085	0.070
IRT/OP	0.017	0.024	0.012	0.018	0.044	0.052	0.062	0.074	0.135	0.128

TOTAL RESPONSES 199.0 PERCENTAGE REACTION TIME 36.5

SUBJECT R1 APPENDIX B

TREATMENT 0.5 mg/kg Amphetamine NO. 19

FREQUENCY OF BURST	4.0	PROBABILITY OF BURST	0.014
FREQUENCY OF PREMATURE	36.0	PROBABILITY OF PREMATURE	0.128
FREQUENCY OF EFFICIENT	234.0	PROBABILITY OF EFFICIENT	0.830
FREQUENCY OF LATE	8.0	PROBABILITY OF LATE	0.028

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	14	72	51	37	20	17	8	9	4	2
PROB.	0.050	0.255	0.181	0.131	0.071	0.060	0.028	0.032	0.014	0.007
IRT/OP	0.058	0.316	0.327	0.352	0.294	0.354	0.258	0.391	0.286	0.200

TOTAL RESPONSES 282.0 PERCENTAGE REACTION TIME 11.7

SUBJECT R1 APPENDIX B

TREATMENT 1.0 mg/kg Amphetamine NO. 20

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.021
FREQUENCY OF PREMATURE	61.0	PROBABILITY OF PREMATURE	0.213
FREQUENCY OF EFFICIENT	213.0	PROBABILITY OF EFFICIENT	0.742
FREQUENCY OF LATE	7.0	PROBABILITY OF LATE	0.024

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	26	57	40	26	25	21	10	2	3
PROB.	0.010	0.091	0.199	0.139	0.091	0.087	0.073	0.035	0.007	0.010
IRT/OP	0.014	0.120	0.298	0.299	0.277	0.368	0.488	0.455	0.167	0.300

TOTAL RESPONSES 287.0 PERCENTAGE REACTION TIME 13.3

SUBJECT R1 APPENDIX B

TREATMENT 2.0 mg/kg Amphetamine NO. 21

FREQUENCY OF BURST	19.0	PROBABILITY OF BURST	0.057
FREQUENCY OF PREMATURE	130.0	PROBABILITY OF PREMATURE	0.393
FREQUENCY OF EFFICIENT	145.0	PROBABILITY OF EFFICIENT	0.438
FREQUENCY OF LATE	37.0	PROBABILITY OF LATE	0.112

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	17	39	33	14	16	6	1	5	12	2
PROBL	0.051	0.118	0.100	0.042	0.048	0.018	0.003	0.015	0.036	0.006
IRT/OP	0.093	0.236	0.262	0.151	0.203	0.095	0.018	0.089	0.235	0.051

TOTAL RESPONSES 331.0 PERCENTAGE REACTION TIME 14.3

SUBJECT R1 APPENDIX B

TREATMENT 4.0 mg/kg Amphetamine NO. 22

FREQUENCY OF BURST	12.0	PROBABILITY OF BURST	0.057
FREQUENCY OF PREMATURE	46.0	PROBABILITY OF PREMATURE	0.219
FREQUENCY OF EFFICIENT	110.0	PROBABILITY OF EFFICIENT	0.524
FREQUENCY OF LATE	42.0	PROBABILITY OF LATE	0.200

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	28	27	15	10	7	7	3	5	5
PROB.	0.014	0.133	0.129	0.071	0.048	0.033	0.033	0.014	0.024	0.024
IRT/OP	0.020	0.188	0.223	0.160	0.127	0.101	0.113	0.055	0.096	0.106

TOTAL RESPONSES 210.0 PERCENTAGE REACTION TIME 24.0

SUBJECT R4 APPENDIX B

TREATMENT 4.0 mg/kg Amphetamine NO. 23

FREQUENCY OF BURST	16.0	PROBABILITY OF BURST	0.070
FREQUENCY OF PREMATURE	36.0	PROBABILITY OF PREMATURE	0.157
FREQUENCY OF EFFICIENT	95.0	PROBABILITY OF EFFICIENT	0.415
FREQUENCY OF LATE	82.0	PROBABILITY OF LATE	0.358

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	15	19	26	12	6	3	3	5	2	4
PROB.	0.066	0.083	0.114	0.052	0.026	0.013	0.013	0.022	0.009	0.017
IRT/OP	0.085	0.117	0.182	0.103	0.057	0.030	0.031	0.054	0.023	0.047

TOTAL RESPONSES 229.0 PERCENTAGE REACTION TIME 27.9

SUBJECT R4 APPENDIX B

TREATMENT 4.0 mg/kg Amphetamine NO. 24

FREQUENCY OF BURST	11.0	PROBABILITY OF BURST	0.047
FREQUENCY OF PREMATURE	43.0	PROBABILITY OF PREMATURE	0.182
FREQUENCY OF EFFICIENT	113.0	PROBABILITY OF EFFICIENT	0.479
FREQUENCY OF LATE	69.0	PROBABILITY OF LATE	0.292

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	17	20	23	21	16	8	0	4	2	2
PROB.	0.072	0.085	0.097	0.089	0.068	0.034	0.000	0.017	0.008	0.008
IRT/OP	0.093	0.121	0.159	0.172	0.158	0.094	0.000	0.052	0.027	0.028

TOTAL RESPONSES 236.0 PERCENTAGE REACTION TIME 26.L

SUBJECT R1 APPENDIX B

TREATMENT 12.5 mg/kg Mescaline NO. 25

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.012
FREQUENCY OF PREMATURE	17.0	PROBABILITY OF PREMATURE	0.071
FREQUENCY OF EFFICIENT	197.0	PROBABILITY OF EFFICIENT	0.817
FREQUENCY OF LATE	24.0	PROBABILITY OF LATE	0.100

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	5	10	19	23	19	28	31	23	22	17
PROB.	0.021	0.041	0.079	0.095	0.079	0.116	0.129	0.095	0.091	0.071
IRT/OP	0.023	0.046	0.092	0.123	0.116	0.193	0.265	0.267	0.349	0.415

TOTAL RESPONSES 241.0 PERCENTAGE REACTION TIME 22.8

SUBJECT R1 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 26

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.039
FREQUENCY OF PREMATURE	39.0	PROBABILITY OF PREMATURE	0.171
FREQUENCY OF EFFICIENT	109.0	PROBABILITY OF EFFICIENT	0.478
FREQUENCY OF LATE	71.0	PROBABILITY OF LATE	0.311

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	8	12	20	6	13	14	17	7	9
PROB.	0.013	0.035	0.053	0.088	0.026	0.057	0.061	0.075	0.031	0.039
IRT/OP	0.017	0.045	0.071	0.127	0.044	0.099	0.119	0.163	0.080	0.113

TOTAL RESPONSES 228.0 PERCENTAGE REACTION TIME 31.3

SUBJECT R1 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 27

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.021
FREQUENCY OF PREMATURE	26.0	PROBABILITY OF PREMATURE	0.183
FREQUENCY OF EFFICIENT	62.0	PROBABILITY OF EFFICIENT	0.437
FREQUENCY OF LATE	51.0	PROBABILITY OF LATE	0.359

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	5	10	6	9	6	2	8	7	5
PROB.	0.028	0.035	0.070	0.042	0.063	0.042	0.014	0.056	0.049	0.035
IRT/OP	0.035	0.046	0.096	0.064	0.102	0.076	0.027	0.113	0.111	0.089

TOTAL RESPONSES 142.0 PERCENTAGE REACTION TIME 56.3

SUBJECT R2 APPENDIX B

TREATMENT 12.5 mg/kg Mescaline NO. 28

FREQUENCY OF BURST	2.0	PROBABILITY OF BURST	0.008
FREQUENCY OF PREMATURE	8.0	PROBABILITY OF PREMATURE	0.033
FREQUENCY OF EFFICIENT	217.0	PROBABILITY OF EFFICIENT	0.897
FREQUENCY OF LATE	15.0	PROBABILITY OF LATE	0.062

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	10	26	26	25	40	32	32	18	5
PROB.	0.012	0.041	0.107	0.107	0.103	0.165	0.132	0.132	0.074	0.021
IRT/OP	0.013	0.044	0.119	0.135	0.150	0.282	0.314	0.457	0.474	0.250

TOTAL RESPONSES 242.0 PERCENTAGE REACTION TIME 20.7

SUBJECT R2 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 29

FREQUENCY OF BURST	13.0	PROBABILITY OF BURST	0.050
FREQUENCY OF PREMATURE	59.0	PROBABILITY OF PREMATURE	0.228
FREQUENCY OF EFFICIENT	142.0	PROBABILITY OF EFFICIENT	0.548
FREQUENCY OF LATE	45.0	PROBABILITY OF LATE	0.174

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	5	16	18	16	18	17	17	21	8	6
PROB.	0.019	0.062	0.069	0.062	0.069	0.066	0.066	0.081	0.031	0.023
IRT/OP	0.027	0.088	0.108	0.108	0.136	0.149	0.175	0.262	0.136	0.118

TOTAL RESPONSES 259.0 PERCENTAGE REACTION TIME 24.2

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 30

FREQUENCY OF BURST	11.0	PROBABILITY OF BURST	0.060
FREQUENCY OF PREMATURE	48.0	PROBABILITY OF PREMATURE	0.261
FREQUENCY OF EFFICIENT	79.0	PROBABILITY OF EFFICIENT	0.429
FREQUENCY OF LATE	46.0	PROBABILITY OF LATE	0.250

DISTRIBUTION WITHIN AVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	0	5	9	8	14	18	9	3	8	5
PROB.	0.000	0.027	0.049	0.043	0.076	0.098	0.049	0.016	0.043	0.027
IRT/OP	0.000	0.040	0.075	0.072	0.136	0.202	0.127	0.048	0.136	0.098

TOTAL RESPONSES 184.0 PERCENTAGE REACTION TIME 48.7

SUBJECT R3 APPENDIX B

TREATMENT 12.5 mg/kg Mescaline NO. 31

FREQUENCY OF BURST	0.0	PROBABILITY OF BURST	0.000
FREQUENCY OF PREMATURE	5.0	PROBABILITY OF PREMATURE	0.021
FREQUENCY OF EFFICIENT	219.0	PROBABILITY OF EFFICIENT	0.916
FREQUENCY OF LATE	15.0	PROBABILITY OF LATE	0.063

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	6	7	33	52	47	29	22	15	7
PROB.	0.004	0.025	0.029	0.138	0.218	0.197	0.121	0.092	0.063	0.029
IRT/OP	0.004	0.026	0.031	0.150	0.278	0.345	0.330	0.373	0.405	0.318

TOTAL RESPONSES 239.0 PERCENTAGE REACTION TIME 20.9

SUBJECT R3 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 32

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.037
FREQUENCY OF PREMATURE	57.0	PROBABILITY OF PREMATURE	0.234
FREQUENCY OF EFFICIENT	129.0	PROBABILITY OF EFFICIENT	0.529
FREQUENCY OF LATE	49.0	PROBABILITY OF LATE	0.201

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	9	9	13	19	15	17	14	12	15	6
PROB.	0.037	0.037	0.053	0.078	0.061	0.070	0.057	0.049	0.061	0.025
IRT/OP	0.051	0.053	0.081	0.129	0.117	0.150	0.146	0.146	0.214	0.109

TOTAL RESPONSES 244.0 PERCENTAGE REACTION TIME 28.6

SUBJECT R3 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 33

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.061
FREQUENCY OF PREMATURE	25.0	PROBABILITY OF PREMATURE	0.169
FREQUENCY OF EFFICIENT	73.0	PROBABILITY OF EFFICIENT	0.493
FREQUENCY OF LATE	41.0	PROBABILITY OF LATE	0.277

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	9	8	13	10	12	7	7	5	1
PROB.	0.007	0.061	0.054	0.088	0.068	0.081	0.047	0.047	0.034	0.007
IRT/OP	0.009	0.060	0.077	0.135	0.120	0.164	0.115	0.130	0.106	0.024

TOTAL RESPONSES 148.0 PERCENTAGE REACTION TIME 57.5

SUBJECT R4 APPENDIX B

TREATMENT 0.5 mg/kg L.S.D. NO. 34

FREQUENCY OF BURST	15.0	PROBABILITY OF BURST	0.059
FREQUENCY OF PREMATURE	28.0	PROBABILITY OF PREMATURE	0.111
FREQUENCY OF EFFICIENT	192.0	PROBABILITY OF EFFICIENT	0.759
FREQUENCY OF LATE	18.0	PROBABILITY OF LATE	0.071

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	10	35	21	37	26	39	10	11	2
PROB.	0.004	0.040	0.138	0.083	0.146	0.103	0.154	0.040	0.043	0.008
IRT/OP	0.005	0.048	0.176	0.123	0.259	0.245	0.488	0.244	0.355	0.100

TOTAL RESPONSES 253.0 PERCENTAGE REACTION TIME 20.3

SUBJECT R4 APPENDIX B

TREATMENT 0.75 mg/kg L.S.D. NO. 35

FREQUENCY OF BURST	18.0	PROBABILITY OF BURST	0.073
FREQUENCY OF PREMATURE	77.0	PROBABILITY OF PREMATURE	0.312
FREQUENCY OF EFFICIENT	124.0	PROBABILITY OF EFFICIENT	0.502
FREQUENCY OF LATE	28.0	PROBABILITY OF LATE	0.113

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	12	16	21	9	14	23	13	9	3
PROB.	0.016	0.149	0.065	0.085	0.036	0.057	0.093	0.053	0.036	0.012
IRT/OP	0.026	0.081	0.118	0.175	0.091	0.156	0.303	0.254	0.225	0.097

TOTAL RESPONSES 247.0 PERCENTAGE REACTION TIME 28.2

SUBJECT R4 APPENDIX B

TREATMENT 1.0 mg/kg L.S.D. NO. 36

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.048
FREQUENCY OF PREMATURE	88.0	PROBABILITY OF PREMATURE	0.466
FREQUENCY OF EFFICIENT	57.0	PROBABILITY OF EFFICIENT	0.302
FREQUENCY OF LATE	35.0	PROBABILITY OF LATE	0.185

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	4	8	6	8	6	4	9	7	4
PROB.	0.005	0.021	0.042	0.032	0.042	0.032	0.021	0.048	0.037	0.021
IRT/OP	0.001	0.044	0.092	0.076	0.110	0.092	0.068	0.164	0.152	0.103

TOTAL RESPONSES 189.0 PERCENTAGE REACTION TIME 39.7

SUBJECT R5 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 37

FREQUENCY OF BURST	2.0	PROBABILITY OF BURST	0.013
FREQUENCY OF PREMATURE	38.0	PROBABILITY OF PREMATURE	0.248
FREQUENCY OF EFFICIENT	51.0	PROBABILITY OF EFFICIENT	0.333
FREQUENCY OF LATE	62.0	PROBABILITY OF LATE	0.405

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	3	5	8	7	8	4	6	3	4
PROB.	0.020	0.020	0.033	0.052	0.046	0.052	0.026	0.039	0.020	0.026
IRT/OP	0.027	0.027	0.047	0.078	0.074	0.092	0.051	0.080	0.043	0.061

TOTAL RESPONSES 153.0 PERCENTAGE REACTION TIME 55.4

SUBJECT R5 APPENDIX B

TREATMENT 1.0 mg/kg L.S.D. NO. 38

FREQUENCY OF BURST	4.0	PROBABILITY OF BURST	0.022
FREQUENCY OF PREMATURE	90.0	PROBABILITY OF PREMATURE	0.506
FREQUENCY OF EFFICIENT	38.0	PROBABILITY OF EFFICIENT	0.213
FREQUENCY OF LATE	46.0	PROBABILITY OF LATE	0.258

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	4	6	3	5	8	2	2	4	1
PROB.	0.017	0.022	0.034	0.017	0.028	0.045	0.011	0.011	0.022	0.006
IRT/OP	0.036	0.049	0.078	0.042	0.074	0.127	0.036	0.038	0.078	0.021

TOTAL RESPONSES 178.0 PERCENTAGE REACTION TIME 43.2

SUBJECT R5 APPENDIX B

TREATMENT 10.0 mg/kg N,N Dimethyltryptamine NO. 39

FREQUENCY OF BURST	0.0	PROBABILITY OF BURST	0.000
FREQUENCY OF PREMATURE	60.0	PROBABILITY OF PREMATURE	0.411
FREQUENCY OF EFFICIENT	48.0	PROBABILITY OF EFFICIENT	0.329
FREQUENCY OF LATE	38.0	PROBABILITY OF LATE	0.260

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	6	4	9	6	6	8	2	4	2
PROBL	0.007	0.041	0.027	0.062	0.041	0.041	0.045	0.014	0.027	0.014
IRT/OP	0.012	0.071	0.051	0.120	0.091	0.010	0.148	0.053	0.091	0.050

TOTAL RESPONSES 146.0 PERCENTAGE REACTION TIME 53.3

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 40

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.045
FREQUENCY OF PREMATURE	50.0	PROBABILITY OF PREMATURE	0.253
FREQUENCY OF EFFICIENT	86.0	PROBABILITY OF EFFICIENT	0.434
FREQUENCY OF LATE	53.0	PROBABILITY OF LATE	0.268

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	6	9	14	12	13	13	10	6	2
PROB.	0.005	0.030	0.045	0.071	0.060	0.066	0.066	0.051	0.030	0.010
IRT/OP	0.007	0.043	0.068	0.114	0.110	0.134	0.155	0.141	0.098	0.036

TOTAL RESPONSES 198.0 PERCENTAGE REACTION TIME 47.6

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg 2,3,4,5 Tetramethoxy-P. NO. 41

FREQUENCY OF BURST	11.0	PROBABILITY OF BURST	0.043
FREQUENCY OF PREMATURE	97.0	PROBABILITY OF PREMATURE	0.379
FREQUENCY OF EFFICIENT	81.0	PROBABILITY OF EFFICIENT	0.316
FREQUENCY OF LATE	67.0	PROBABILITY OF LATE	0.262

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	11	6	15	8	17	16	3	1	0
PROB.	0.016	0.043	0.023	0.059	0.031	0.066	0.063	0.012	0.004	0.000
IRT/OP	0.027	0.076	0.045	0.118	0.071	0.163	0.184	0.042	0.015	0.000

TOTAL RESPONSES 256.0 PERCENTAGE REACTION TIME 48.2

SUBJECT R2 APPENDIX B

TREATMENT 6.25 mg/kg 2,3,4,5,6 Pentamethoxy-P. NO. 42

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.032
FREQUENCY OF PREMATURE	104.0	PROBABILITY OF PREMATURE	0.471
FREQUENCY OF EFFICIENT	55.0	PROBABILITY OF EFFICIENT	0.249
FREQUENCY OF LATE	55.0	PROBABILITY OF LATE	0.249

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	6	8	3	3	10	2	11	9	2
PROB.	0.005	0.027	0.036	0.014	0.014	0.045	0.009	0.050	0.040	0.009
IRT/OP	0.009	0.005	0.078	0.032	0.033	0.112	0.025	0.143	0.136	0.035

TOTAL RESPONSES 221.0 PERCENTAGE REACTION TIME 50.1

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline (after drug sequence) NO. 43

FREQUENCY OF BURST	14.0	PROBABILITY OF BURST	0.059
FREQUENCY OF PREMATURE	61.0	PROBABILITY OF PREMATURE	0.257
FREQUENCY OF EFFICIENT	110.0	PROBABILITY OF EFFICIENT	0.464
FREQUENCY OF LATE	52.0	PROBABILITY OF LATE	0.219

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	9	17	11	21	13	7	19	4	3
PROB.	0.025	0.038	0.072	0.046	0.089	0.055	0.030	0.080	0.017	0.013
IRT/OP	0.037	0.058	0.116	0.085	0.176	0.133	0.082	0.244	0.067	0.055

TOTAL RESPONSES 237.0 PERCENTAGE REACTION TIME 47.1

SUBJECT R1 APPENDIX B

TREATMENT 25.0 mg/kg N-methyl Mescaline NO. 44

FREQUENCY OF BURST	5.0	PROBABILITY OF BURST	0.020
FREQUENCY OF PREMATURE	15.0	PROBABILITY OF PREMATURE	0.060
FREQUENCY OF EFFICIENT	203.0	PROBABILITY OF EFFICIENT	0.812
FREQUENCY OF LATE	27.0	PROBABILITY OF LATE	0.108

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	5	12	20	21	30	38	31	28	16
PROB.	0.008	0.020	0.048	0.080	0.084	0.120	0.152	0.124	0.112	0.064
IRT/OP	0.009	0.022	0.054	0.095	0.110	0.176	0.271	0.304	0.394	0.372

TOTAL RESPONSES 250.0 PERCENTAGE REACTION TIME 24.9

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg N-Methyl Mescaline NO. 45

FREQUENCY OF BURST	5.0	PROBABILITY OF BURST	0.021
FREQUENCY OF PREMATURE	13.0	PROBABILITY OF PREMATURE	0.054
FREQUENCY OF EFFICIENT	201.0	PROBABILITY OF EFFICIENT	0.831
FREQUENCY OF LATE	23.0	PROBABILITY OF LATE	0.095

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	6	19	19	27	36	32	28	18	12
PROB.	0.017	0.025	0.079	0.079	0.112	0.149	0.132	0.116	0.074	0.050
IRT/OP	0.018	0.027	0.089	0.097	0.153	0.242	0.283	0.346	0.340	0.343

TOTAL RESPONSES 242.0 PERCENTAGE REACTION TIME 23.6

SUBJECT R3 APPENDIX B

TREATMENT 25.0 mg/kg N-methyl Mescaline NO. 46

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.013
FREQUENCY OF PREMATURE	15.0	PROBABILITY OF PREMATURE	0.063
FREQUENCY OF EFFICIENT	199.0	PROBABILITY OF EFFICIENT	0.836
FREQUENCY OF IATE	21.0	PROBABILITY OF IATE	0.088

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	12	14	17	23	20	30	30	26	15	12
PROB.	0.050	0.059	0.071	0.097	0.084	0.126	0.126	0.109	0.063	0.050
IRT/OP	0.055	0.067	0.088	0.130	0.130	0.224	0.288	0.351	0.313	0.364

TOTAL RESPONSES 238.0 PERCENTAGE REACTION TIME 24.3

SUBJECT R1 APPENDIX B

TREATMENT 25.0 mg/kg Trimethoxyphenylethanol NO. 47

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.024
FREQUENCY OF PREMATURE	21.0	PROBABILITY OF PREMATURE	0.083
FREQUENCY OF EFFICIENT	204.0	PROBABILITY OF EFFICIENT	0.803
FREQUENCY OF LATE	23.0	PROBABILITY OF LATE	0.091

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	7	10	17	26	26	29	28	27	21	13
PROB.	0.028	0.039	0.067	0.102	0.102	0.114	0.110	0.106	0.083	0.051
IRT/OP	0.031	0.045	0.081	0.135	0.156	0.206	0.250	0.321	0.368	0.361

TOTAL RESPONSES 254.0 PERCENTAGE REACTION TIME 24.6

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Trimethoxyphenylethanol NO. 48

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.013
FREQUENCY OF PREMATURE	14.0	PROBABILITY OF PREMATURE	0.059
FREQUENCY OF EFFICIENT	201.0	PROBABILITY OF EFFICIENT	0.852
FREQUENCY OF LATE	18.0	PROBABILITY OF LATE	0.076

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	9	11	11	16	25	31	36	29	20	13
PROB.	0.038	0.047	0.047	0.068	0.106	0.131	0.152	0.123	0.085	0.055
IRT/OP	0.041	0.052	0.055	0.085	0.145	0.211	0.310	0.363	0.392	0.419

TOTAL RESPONSES 236.0 PERCENTAGE REACTION TIME 23.7

SUBJECT R3 APPENDIX B

TREATMENT 25.0 mg/kg Trimethoxyphenylethanol NO. 49

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.025
FREQUENCY OF PREMATURE	16.0	PROBABILITY OF PREMATURE	0.067
FREQUENCY OF EFFICIENT	198.0	PROBABILITY OF EFFICIENT	0.825
FREQUENCY OF LATE	20.0	PROBABILITY OF LATE	0.083

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	5	10	16	26	28	30	30	26	19	8
PROB.	0.021	0.042	0.067	0.108	0.117	0.125	0.125	0.108	0.079	0.033
IRT/OP	0.023	0.047	0.079	0.139	0.174	0.226	0.291	0.356	0.404	0.286

TOTAL RESPONSES 240.0 PERCENTAGE REACTION TIME 23.8

SUBJECT R1 APPENDIX B

TREATMENT 25.0 mg/kg Trimethoxyphenylacetic acid NO. 50

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.013
FREQUENCY OF PREMATURE	16.0	PROBABILITY OF PREMATURE	0.068
FREQUENCY OF EFFICIENT	196.0	PROBABILITY OF EFFICIENT	0.834
FREQUENCY OF LATE	20.0	PROBABILITY OF LATE	0.085

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	6	16	13	24	34	41	29	20	10
PROB.	0.013	0.026	0.068	0.055	0.102	0.145	0.174	0.123	0.085	0.043
IRT/OP	0.014	0.028	0.77	0.068	0.135	0.221	0.342	0.367	0.400	0.333

TOTAL RESPONSES 235.0 PERCENTAGE REACTION TIME 24.1

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Trimethoxyphenylacetic acid NO. 51

FREQUENCY OF BURST	2.0	PROBABILITY OF BURST	0.009
FREQUENCY OF PREMATURE	22.0	PROBABILITY OF PREMATURE	0.094
FREQUENCY OF EFFICIENT	199.0	PROBABILITY OF EFFICIENT	0.847
FREQUENCY OF LATE	12.0	PROBABILITY OF LATE	0.051

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	9	10	15	24	34	34	30	21	16
PROB.	0.026	0.038	0.043	0.064	0.102	0.145	0.145	0.128	0.089	0.068
IRT/OP	0.028	0.044	0.051	0.081	0.140	0.231	0.301	0.380	0.429	0.571

TOTAL RESPONSES 235.0 PERCENTAGE REACTION TIME 22.0

SUBJECT R3 APPENDIX B

TREATMENT 25.0 mg/kg Trimethoxyphenylacetic acid NO. 52

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.038
FREQUENCY OF PREMATURE	15.0	PROBABILITY OF PREMATURE	0.064
FREQUENCY OF EFFICIENT	195.0	PROBABILITY OF EFFICIENT	0.830
FREQUENCY OF LATE	16.0	PROBABILITY OF LATE	0.068

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	8	16	21	24	33	31	29	18	11
PROB.	0.017	0.034	0.068	0.089	0.102	0.140	0.132	0.123	0.077	0.047
IRT/OP	0.019	0.039	0.080	0.115	0.148	0.239	0.295	0.392	0.400	0.407

TOTAL RESPONSES 235.0 PERCENTAGE REACTION TIME 23.9

SUBJECT R5 APPENDIX B

TREATMENT 6.2 mg/kg 245 Trimethoxyamphetamine NO. 53

FREQUENCY OF BURST	18.0	PROBABILITY OF BURST	0.065
FREQUENCY OF PREMATURE	87.0	PROBABILITY OF PREMATURE	0.316
FREQUENCY OF EFFICIENT	111.0	PROBABILITY OF EFFICIENT	0.404
FREQUENCY OF LATE	59.0	PROBABILITY OF LATE	0.215

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	8	14	11	20	7	10	17	10	8
PROB.	0.022	0.029	0.051	0.040	0.073	0.025	0.036	0.062	0.036	0.029
IRT/OP	0.035	0.049	0.090	0.077	0.153	0.063	0.096	0.181	0.130	0.119

TOTAL RESPONSES 275.0 PERCENTAGE REACTION TIME 26.3

SUBJECT R2 APPENDIX B

TREATMENT 6.2 mg/kg 245 Trimethoxyamphetamine NO. 54

FREQUENCY OF BURST	29.0	PROBABILITY OF BURST	0.117
FREQUENCY OF PREMATURE	37.0	PROBABILITY OF PREMATURE	0.150
FREQUENCY OF EFFICIENT	146.0	PROBABILITY OF EFFICIENT	0.591
FREQUENCY OF LATE	35.0	PROBABILITY OF LATE	0.142

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	3	21	20	16	21	16	16	14	16
PROB.	0.012	0.012	0.085	0.081	0.065	0.085	0.065	0.065	0.057	0.065
IRT/OP	0.017	0.017	0.120	0.130	0.119	0.178	0.165	0.198	0.215	0.314

TOTAL RESPONSES 247.0 PERCENTAGE REACTION TIME 24.7

SUBJECT R4 APPENDIX B

TREATMENT 12.5 mg/kg 3,4,5 Trimethoxyamphetamine NO. 55

FREQUENCY OF BURST	19.0	PROBABILITY OF BURST	0.085
FREQUENCY OF PREMATURE	26.0	PROBABILITY OF PREMATURE	0.117
FREQUENCY OF EFFICIENT	125.0	PROBABILITY OF EFFICIENT	0.561
FREQUENCY OF LATE	53.0	PROBABILITY OF LATE	0.238

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	5	12	17	17	19	14	10	8	13	10
PROB.	0.022	0.054	0.076	0.076	0.085	0.063	0.045	0.036	0.058	0.045
IRT/OP	0.028	0.069	0.106	0.118	0.150	0.130	0.106	0.095	0.171	0.159

TOTAL RESPONSES 223.0 PERCENTAGE REACTION TIME 35.1

SUBJECT R5 APPENDIX B

TREATMENT 12.5 mg/kg 345 Trimethoxyamphetamine NO. 56

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.025
FREQUENCY OF PREMATURE	27.0	PROBABILITY OF PREMATURE	0.112
FREQUENCY OF EFFICIENT	165.0	PROBABILITY OF EFFICIENT	0.685
FREQUENCY OF LATE	43.0	PROBABILITY OF LATE	0.178

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	11	16	10	19	17	25	18	21	24
PROB.	0.017	0.046	0.066	0.041	0.070	0.071	0.104	0.075	0.087	0.100
IRT/OP	0.019	0.054	0.083	0.056	0.114	0.115	0.191	0.170	0.239	0.358

TOTAL RESPONSES 241.0 PERCENTAGE REACTION TIME 24.7

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg 246 Trimethoxyamphetamine NO. 57

FREQUENCY OF BURST	8.0	PROBABILITY OF BURST	0.031
FREQUENCY OF PREMATURE	58.0	PROBABILITY OF PREMATURE	0.227
FREQUENCY OF EFFICIENT	145.0	PROBABILITY OF EFFICIENT	0.566
FREQUENCY OF LATE	45.0	PROBABILITY OF LATE	0.176

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	10	13	24	14	23	15	20	13	10
PROB.	0.012	0.039	0.051	0.094	0.055	0.090	0.059	0.078	0.051	0.039
IRT/OP	0.016	0.053	0.073	0.146	0.100	0.183	0.146	0.227	0.191	0.182

TOTAL RESPONSES 256.0 PERCENTAGE REACTION TIME 25.3

SUBJECT R4 APPENDIX B

TREATMENT 25.0 mg/kg 246 Trimethoxyamphetamine NO. 58

FREQUENCY OF BURST	11.0	PROBABILITY OF BURST	0.046
FREQUENCY OF PREMATURE	39.0	PROBABILITY OF PREMATURE	0.162
FREQUENCY OF EFFICIENT	159.0	PROBABILITY OF EFFICIENT	0.662
FREQUENCY OF LATE	31.0	PROBABILITY OF LATE	0.129

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	5	18	19	23	15	27	19	10	17
PROB.	0.025	0.021	0.075	0.079	0.096	0.063	0.113	0.079	0.042	0.071
IRT/OP	0.032	0.027	0.101	0.118	0.162	0.126	0.250	0.247	0.172	0.354

TOTAL RESPONSES 240.0 PERCENTAGE REACTION TIME 27.3

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg 234 Trimethoxyamphetamine NO. 59

FREQUENCY OF BURST	11.0	PROBABILITY OF BURST	0.046
FREQUENCY OF PREMATURE	36.0	PROBABILITY OF PREMATURE	0.152
FREQUENCY OF EFFICIENT	161.0	PROBABILITY OF EFFICIENT	0.679
FREQUENCY OF LATE	29.0	PROBABILITY OF LATE	0.122

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	10	23	19	26	25	25	11	7	9
PROB.	0.025	0.042	0.097	0.080	0.110	0.105	0.105	0.046	0.030	0.038
IRT/OP	0.032	0.054	0.132	0.126	0.197	0.236	0.309	0.196	0.156	0.237

TOTAL RESPONSES 237.0 PERCENTAGE REACTION TIME 21.0

SUBJECT R5 APPENDIX B

TREATMENT 25.0 mg/kg 234 Trimethoxyamphetamine NO. 60

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.013
FREQUENCY OF PREMATURE	16.0	PROBABILITY OF PREMATURE	0.068
FREQUENCY OF EFFICIENT	185.0	PROBABILITY OF EFFICIENT	0.784
FREQUENCY OF LATE	32.0	PROBABILITY OF LATE	0.136

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	0	8	16	19	25	22	25	26	22	22
PROB.	0.000	0.034	0.068	0.081	0.106	0.093	0.106	0.110	0.093	0.093
IRT/OP	0.000	0.037	0.077	0.098	0.144	0.148	0.197	0.255	0.289	0.407

TOTAL RESPONSES 236.0 PERCENTAGE REACTION TIME 24.3

SUBJECT R5 APPENDIX B

TREATMENT 6.2 mg/kg 25 Dimethoxyamphetamine NO. 61

FREQUENCY OF BURST	41.0	PROBABILITY OF BURST	0.138
FREQUENCY OF PREMATURE	44.0	PROBABILITY OF PREMATURE	0.148
FREQUENCY OF EFFICIENT	159.0	PROBABILITY OF EFFICIENT	0.535
FREQUENCY OF LATE	53.0	PROBABILITY OF LATE	0.178

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	9	22	35	20	15	18	12	11	9	8
PROB.	0.030	0.074	0.118	0.067	0.051	0.061	0.040	0.037	0.030	0.027
IRT/OP	0.042	0.108	0.193	0.137	0.119	0.162	0.129	0.136	0.129	0.131

TOTAL RESPONSES 297.0 PERCENTAGE REACTION TIME 20.7

SUBJECT R4 APPENDIX B

TREATMENT 6.2 mg/kg 25 Dimethoxyamphetamine NO. 62

FREQUENCY OF BURST	20.0	PROBABILITY OF BURST	0.073
FREQUENCY OF PREMATURE	73.0	PROBABILITY OF PREMATURE	0.265
FREQUENCY OF EFFICIENT	131.0	PROBABILITY OF EFFICIENT	0.476
FREQUENCY OF LATE	51.0	PROBABILITY OF LATE	0.185

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	24	18	20	14	10	14	10	6	11
PROB.	0.015	0.087	0.065	0.073	0.051	0.036	0.051	0.036	0.022	0.040
IRT/OP	0.022	0.135	0.117	0.147	0.121	0.098	0.152	0.128	0.088	0.177

TOTAL RESPONSES 275.0 PERCENTAGE REACTION TIME 20.6

SUBJECT R2 APPENDIX B

TREATMENT 12.5 mg/kg 25 Dimethoxyamphetamine NO. 63

FREQUENCY OF BURST	14.0	PROBABILITY OF BURST	0.047
FREQUENCY OF PREMATURE	56.0	PROBABILITY OF PREMATURE	0.187
FREQUENCY OF EFFICIENT	226.0	PROBABILITY OF EFFICIENT	0.753
FREQUENCY OF LATE	4.0	PROBABILITY OF LATE	0.013

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	17	29	52	51	37	18	10	6	3	3
PROB.	0.057	0.097	0.173	0.170	0.123	0.060	0.033	0.020	0.010	0.010
IRT/OP	0.074	0.136	0.263	0.386	0.457	0.409	0.385	0.375	0.300	0.429

TOTAL RESPONSES 300.0 PERCENTAGE REACTION TIME 12.1

SUBJECT R2 APPENDIX B

TREATMENT 6.2 mg/kg 34 Dimethoxyamphetamine NO. 64

FREQUENCY OF BURST	2.0	PROBABILITY OF BURST	0.008
FREQUENCY OF PREMATURE	19.0	PROBABILITY OF PREMATURE	0.078
FREQUENCY OF EFFICIENT	201.0	PROBABILITY OF EFFICIENT	0.820
FREQUENCY OF LATE	23.0	PROBABILITY OF LATE	0.094

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	9	21	27	33	30	24	26	20	9
PROB.	0.008	0.037	0.086	0.110	0.135	0.122	0.098	0.106	0.083	0.037
IRT/OP	0.009	0.041	0.099	0.141	0.200	0.227	0.235	0.333	0.385	0.281

TOTAL RESPONSES 245.0 PERCENTAGE REACTION TIME 21.8

SUBJECT R4 APPENDIX B

TREATMENT 6.2 mg/kg 34 Dimethoxyamphetamine NO. 65

FREQUENCY OF BURST	20.0	PROBABILITY OF BURST	0.079
FREQUENCY OF PREMATURE	17.0	PROBABILITY OF PREMATURE	0.067
FREQUENCY OF EFFICIENT	175.0	PROBABILITY OF EFFICIENT	0.692
FREQUENCY OF LATE	41.0	PROBABILITY OF LATE	0.162

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	6	14	16	15	26	33	28	20	15
PROB.	0.008	0.024	0.055	0.063	0.059	0.103	0.130	0.111	0.079	0.059
IRT/OP	0.009	0.028	0.067	0.082	0.084	0.160	0.241	0.269	0.263	0.268

TOTAL RESPONSES 253.0 PERCENTAGE REACTION TIME 24.2

SUBJECT R5 APPENDIX B

TREATMENT 12.5 mg/kg 34 Dimethoxyamphetamine NO. 66

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.038
FREQUENCY OF PREMATURE	52.0	PROBABILITY OF PREMATURE	0.325
FREQUENCY OF EFFICIENT	35.0	PROBABILITY OF EFFICIENT	0.219
FREQUENCY OF LATE	67.0	PROBABILITY OF LATE	0.419

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	1	6	4	3	3	3	2	5	4
PROB.	0.025	0.006	0.038	0.025	0.019	0.019	0.019	0.012	0.031	0.025
IRT/OP	0.039	0.010	0.062	0.044	0.034	0.036	0.037	0.026	0.066	0.056

TOTAL RESPONSES 160.0 PERCENTAGE REACTION TIME 56.5

SUBJECT R4 APPENDIX B

TREATMENT 12.5 mg/kg 34 Dimethoxyamphetamine NO. 67

FREQUENCY OF BURST	14.0	PROBABILITY OF BURST	0.140
FREQUENCY OF PREMATURE	29.0	PROBABILITY OF PREMATURE	0.290
FREQUENCY OF EFFICIENT	18.0	PROBABILITY OF EFFICIENT	0.180
FREQUENCY OF LATE	39.0	PROBABILITY OF LATE	0.390

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	2	7	1	2	1	1	2	0	0
PROB.	0.020	0.020	0.070	0.610	0.020	0.010	0.010	0.020	0.000	0.000
IRT/OP	0.035	0.036	0.132	0.022	0.044	0.023	0.024	0.049	0.000	0.000

TOTAL RESPONSES 100.0 PERCENTAGE REACTION TIME 75.9

SUBJECT R2 APPENDIX B

TREATMENT 6.2 mg/kg 23 Dimethoxyamphetamine NO. 68

FREQUENCY OF BURST	8.0	PROBABILITY OF BURST	0.029
FREQUENCY OF PREMATURE	31.0	PROBABILITY OF PREMATURE	0.113
FREQUENCY OF EFFICIENT	221.0	PROBABILITY OF EFFICIENT	0.807
FREQUENCY OF LATE	14.0	PROBABILITY OF LATE	0.051

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	10	23	46	54	38	20	11	8	8	3
PROB.	0.036	0.084	0.168	0.197	0.139	0.073	0.040	0.029	0.029	0.011
IRT/OP	0.043	0.102	0.228	0.346	0.373	0.312	0.250	0.242	0.320	0.176

TOTAL RESPONSES 274.0 PERCENTAGE REACTION TIME 15.2

SUBJECT R4 APPENDIX B

TREATMENT 6.2 mg/kg 23 Dimethoxyamphetamine NO. 69

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.032
FREQUENCY OF PREMATURE	38.0	PROBABILITY OF PREMATURE	0.136
FREQUENCY OF EFFICIENT	219.0	PROBABILITY OF EFFICIENT	0.785
FREQUENCY OF LATE	13.0	PROBABILITY OF IATE	0.047

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	8	26	50	49	37	18	13	7	6	5
PROB.	0.029	0.093	0.179	0.176	0.133	0.065	0.047	0.025	0.022	0.018
IRT/OP	0.034	0.116	0.253	0.331	0.374	0.290	0.295	0.226	0.250	0.278

TOTAL RESPONSES 279.0 PERCENTAGE REACTION TIME 14.6

SUBJECT R5 APPENDIX B

TREATMENT 12.5 mg/kg 23 Dimethoxyamphetamine NO. 70

FREQUENCY OF BURST	23.0	PROBABILITY OF BURST	0.071
FREQUENCY OF PREMATURE	140.0	PROBABILITY OF PREMATURE	0.433
FREQUENCY OF EFFICIENT	124.0	PROBABILITY OF EFFICIENT	0.384
FREQUENCY OF LATE	36.0	PROBABILITY OF LATE	0.111

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	12	31	30	19	8	8	7	4	1
PROB.	0.012	0.037	0.096	0.093	0.059	0.025	0.025	0.022	0.012	0.001
IRT/OP	0.025	0.077	0.215	0.265	0.229	0.125	0.143	0.146	0.098	0.027

TOTAL RESPONSES 323.0 PERCENTAGE REACTION TIME 20.3

SUBJECT R4 APPENDIX B

TREATMENT 6.2 mg/kg 35 Dimethoxyamphetamine NO. 71

FREQUENCY OF BURST	24.0	PROBABILITY OF BURST	0.090
FREQUENCY OF PREMATURE	14.0	PROBABILITY OF PREMATURE	0.053
FREQUENCY OF EFFICIENT	187.0	PROBABILITY OF EFFICIENT	0.703
FREQUENCY OF LATE	41.0	PROBABILITY OF LATE	0.154

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	7	17	35	31	22	16	19	16	15	9
PROB.	0.026	0.064	0.132	0.117	0.083	0.060	0.071	0.060	0.056	0.034
IRT/OP	0.031	0.077	0.172	0.183	0.159	0.138	0.190	0.198	0.231	0.180

TOTAL RESPONSES 266.0 PERCENTAGE REACTION TIME 21.2

SUBJECT R5 APPENDIX B

TREATMENT 6.2 mg/kg 35 Dimethoxyamphetamine NO. 72

FREQUENCY OF BURST	15.0	PROBABILITY OF BURST	0.056
FREQUENCY OF PREMATURE	29.0	PROBABILITY OF PREMATURE	0.108
FREQUENCY OF EFFICIENT	204.0	PROBABILITY OF EFFICIENT	0.761
FREQUENCY OF LATE	20.0	PROBABILITY OF LATE	0.075

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	9	29	45	25	16	19	21	18	14	8
PROB.	0.034	0.108	0.168	0.093	0.060	0.071	0.078	0.067	0.052	0.030
IRT/OP	0.040	0.135	0.242	0.177	0.138	0.190	0.259	0.300	0.333	0.286

TOTAL RESPONSES 268.0 PERCENTAGE REACTION TIME 17.5

SUBJECT R2 APPENDIX B

TREATMENT 12.5 mg/kg 35 Dimethoxyamphetamine NO. 73

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.019
FREQUENCY OF PREMATURE	137.0	PROBABILITY OF PREMATURE	0.434
FREQUENCY OF EFFICIENT	157.0	PROBABILITY OF EFFICIENT	0.497
FREQUENCY OF LATE	16.0	PROBABILITY OF LATE	0.051

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	10	18	35	34	21	12	11	7	2	7
PROB.	0.032	0.057	0.111	0.108	0.066	0.038	0.035	0.022	0.006	0.022
IRT/OP	0.058	0.110	0.241	0.309	0.276	0.218	0.256	0.219	0.080	0.304

TOTAL RESPONSES 316.0 PERCENTAGE REACTION TIME 12.9

SUBJECT R2 APPENDIX B

TREATMENT 3.1 mg/kg 3 Methoxyamphetamine NO. 74

FREQUENCY OF BURST	34.0	PROBABILITY OF BURST	0.092
FREQUENCY OF PREMATURE	179.0	PROBABILITY OF PREMATURE	0.482
FREQUENCY OF EFFICIENT	152.0	PROBABILITY OF EFFICIENT	0.410
FREQUENCY OF LATE	6.0	PROBABILITY OF LATE	0.016

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	14	25	44	24	23	11	5	3	3	0
PROB.	0.038	0.067	0.119	0.065	0.062	0.030	0.013	0.008	0.008	0.000
IRT/OP	0.089	0.174	0.370	0.320	0.451	0.393	0.294	0.250	0.333	0.000

TOTAL RESPONSES 371.0 PERCENTAGE REACTION TIME 8.1

SUBJECT R4 APPENDIX B

TREATMENT 3.1 mg/kg 3 Methoxyamphetamine NO. 75

FREQUENCY OF BURST	61.0	PROBABILITY OF BURST	0.152
FREQUENCY OF PREMATURE	179.0	PROBABILITY OF PREMATURE	0.445
FREQUENCY OF EFFICIENT	146.0	PROBABILITY OF EFFICIENT	0.363
FREQUENCY OF LATE	16.0	PROBABILITY OF LATE	0.040

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	16	16	26	27	18	14	15	7	5	2
PROB.	0.040	0.040	0.065	0.067	0.045	0.035	0.037	0.017	0.012	0.005
IRT/OP	0.099	0.110	0.200	0.260	0.234	0.237	0.333	0.233	0.217	0.111

TOTAL RESPONSES 402.0 PERCENTAGE REACTION TIME 12.1

SUBJECT R4 APPENDIX B

TREATMENT 3.1 mg/kg 2 Methoxyamphetamine NO. 76

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.025
FREQUENCY OF PREMATURE	4.0	PROBABILITY OF PREMATURE	0.017
FREQUENCY OF EFFICIENT	206.0	PROBABILITY OF EFFICIENT	0.866
FREQUENCY OF LATE	22.0	PROBABILITY OF LATE	0.092

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	8	6	17	31	34	29	41	23	13
PROB.	0.017	0.034	0.025	0.071	0.130	0.143	0.122	0.172	0.097	0.055
IRT/OP	0.018	0.036	0.028	0.081	0.161	0.210	0.227	0.414	0.397	0.371

TOTAL RESPONSES 236.0 PERCENTAGE REACTION TIME 23.3

SUBJECT R5 APPENDIX B

TREATMENT 3.1 mg/kg 2 Methoxyamphetamine NO. 77

FREQUENCY OF BURST	4.0	PROBABILITY OF BURST	0.017
FREQUENCY OF PREMATURE	2.0	PROBABILITY OF PREMATURE	0.008
FREQUENCY OF EFFICIENT	218.0	PROBABILITY OF EFFICIENT	0.916
FREQUENCY OF LATE	14.0	PROBABILITY OF LATE	0.056

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	10	14	14	26	38	47	33	22	13
PROB.	0.004	0.042	0.059	0.059	0.109	0.160	0.197	0.139	0.092	0.055
IRT/OP	0.004	0.043	0.063	0.068	0.135	0.228	0.364	0.402	0.449	0.481

TOTAL RESPONSES 238.0 PERCENTAGE REACTION TIME 22.3

SUBJECT R2 APPENDIX B

TREATMENT 6.2 mg/kg 2 Methoxyamphetamine NO. 78

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.012
FREQUENCY OF PREMATURE	29.0	PROBABILITY OF PREMATURE	0.112
FREQUENCY OF EFFICIENT	214.0	PROBABILITY OF EFFICIENT	0.826
FREQUENCY OF LATE	13.0	PROBABILITY OF LATE	0.050

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	18	33	41	34	24	22	14	17	5
PROB.	0.023	0.069	0.127	0.158	0.131	0.093	0.085	0.054	0.066	0.019
IRT/OP	0.026	0.081	0.163	0.241	0.264	0.253	0.310	0.296	0.486	0.278

TOTAL RESPONSES 259.0 PERCENTAGE REACTION TIME 17.0

SUBJECT R4 APPENDIX B

TREATMENT 6.2 mg/kg 2 Methoxyamphetamine NO. 79

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.022
FREQUENCY OF PREMATURE	32.0	PROBABILITY OF PREMATURE	0.120
FREQUENCY OF EFFICIENT	219.0	PROBABILITY OF EFFICIENT	0.820
FREQUENCY OF LATE	10.0	PROBABILITY OF LATE	0.037

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	9	19	34	33	30	25	21	19	16	13
PROB.	0.034	0.071	0.127	0.124	0.112	0.094	0.079	0.071	0.060	0.049
IRT/OP	0.039	0.086	0.169	0.198	0.224	0.240	0.266	0.328	0.410	0.565

TOTAL RESPONSES 267.0 PERCENTAGE REACTION TIME 17.5

SUBJECT R4 APPENDIX B

TREATMENT 3.1 mg/kg 4 Methoxyamphetamine NO. 80

FREQUENCY OF BURST	5.0	PROBABILITY OF BURST	0.020
FREQUENCY OF PREMATURE	17.0	PROBABILITY OF PREMATURE	0.069
FREQUENCY OF EFFICIENT	208.0	PROBABILITY OF EFFICIENT	0.839
FREQUENCY OF LATE	18.0	PROBABILITY OF LATE	0.073

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	6	11	19	16	32	27	39	25	20	13
PROB.	0.024	0.044	0.077	0.065	0.129	0.109	0.157	0.101	0.081	0.052
IRT/OP	0.027	0.050	0.091	0.084	0.184	0.190	0.339	0.329	0.392	0.419

TOTAL RESPONSES 248.0 PERCENTAGE REACTION TIME 20.8

SUBJECT R5 APPENDIX B

TREATMENT 3.1 mg/kg 4 Methoxyamphetamine NO. 81

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.012
FREQUENCY OF PREMATURE	8.0	PROBABILITY OF PREMATURE	0.033
FREQUENCY OF EFFICIENT	216.0	PROBABILITY OF EFFICIENT	0.882
FREQUENCY OF LATE	18.0	PROBABILITY OF LATE	0.073

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	5	11	19	30	29	39	36	27	10	10
PROB.	0.020	0.045	0.078	0.122	0.118	0.159	0.147	0.110	0.041	0.041
IRT/OP	0.021	0.048	0.087	0.151	0.172	0.279	0.356	0.415	0.263	0.357

TOTAL RESPONSES 245.0 PERCENTAGE REACTION TIME 20.3

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg 3,4 Dimethoxyamphetamine after 50.0 mg/kg Iproniazid NO. 82

FREQUENCY OF BURST	34.0	PROBABILITY OF BURST	0.143
FREQUENCY OF PREMATURE	39.0	PROBABILITY OF PREMATURE	0.164
FREQUENCY OF EFFICIENT	99.0	PROBABILITY OF EFFICIENT	0.416
FREQUENCY OF LATE	66.0	PROBABILITY OF LATE	0.277

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	9	12	10	14	13	9	12	9	10
PROB.	0.004	0.038	0.050	0.042	0.059	0.055	0.038	0.050	0.038	0.042
IRT/OP	0.006	0.055	0.077	0.070	0.105	0.109	0.085	0.124	0.106	0.132

TOTAL RESPONSES 238.0 PERCENTAGE REACTION TIME 37.2

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg 2,3 Dimethoxyamphetamine after 50.0 mg/kg Iproniazid NO. 83

FREQUENCY OF BURST	12.0	PROBABILITY OF BURST	0.046
FREQUENCY OF PREMATURE	25.0	PROBABILITY OF PREMATURE	0.095
FREQUENCY OF EFFICIENT	201.0	PROBABILITY OF EFFICIENT	0.764
FREQUENCY OF LATE	25.0	PROBABILITY OF LATE	0.095

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	19	22	31	32	23	26	23	14	7
PROB.	0.015	0.072	0.084	0.118	0.122	0.087	0.099	0.087	0.053	0.027
IRT/OP	0.018	0.086	0.108	0.171	0.213	0.195	0.274	0.333	0.304	0.219

TOTAL RESPONSES 263.0 PERCENTAGE REACTION TIME 19.6

SUBJECT R3 APPENDIX B

TREATMENT 3.1 mg/kg 3 Methoxyamphetamine NO. 84

FREQUENCY OF BURST	1.0	PROBABILITY OF BURST	0.004
FREQUENCY OF PREMATURE	23.0	PROBABILITY OF PREMATURE	0.086
FREQUENCY OF EFFICIENT	242.0	PROBABILITY OF EFFICIENT	0.903
FREQUENCY OF LATE	2.0	PROBABILITY OF LATE	0.007

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	27	40	57	60	25	18	4	6	1
PROB.	0.015	0.101	0.149	0.213	0.224	0.093	0.067	0.015	0.022	0.004
IRT/OP	0.016	0.113	0.188	0.329	0.517	0.446	0.581	0.308	0.667	0.333

TOTAL RESPONSES 268.0 PERCENTAGE REACTION TIME 14.2

SUBJECT R3 APPENDIX B

TREATMENT 3.1 mg/kg 3 Methoxyamphetamine after 32.0 mg/kg ∝ Methyltyrosine NO. 85

FREQUENCY OF BURST	3.0	PROBABILITY OF BURST	0.012
FREQUENCY OF PREMATURE	6.0	PROBABILITY OF PREMATURE	0.025
FREQUENCY OF EFFICIENT	223.0	PROBABILITY OF EFFICIENT	0.918
FREQUENCY OF LATE	11.0	PROBABILITY OF LATE	0.045

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	7	7	18	26	39	40	33	28	16	9
PROB.	0.029	0.029	0.074	0.107	0.160	0.165	0.136	0.115	0.066	0.037
IRT/OP	0.030	0.031	0.082	0.129	0.222	0.292	0.340	0.438	0.444	0.450

TOTAL RESPONSES 243.0 PERCENTAGE REACTION TIME 20.3

SUBJECT R3 APPENDIX B

TREATMENT 3.1 mg/kg 3 Methoxyamphetamine NO. 86

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.023
FREQUENCY OF PREMATURE	17.0	PROBABILITY OF PREMATURE	0.064
FREQUENCY OF EFFICIENT	236.0	PROBABILITY OF EFFICIENT	0.894
FREQUENCY OF LATE	5.0	PROBABILITY OF LATE	0.019

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	9	26	36	50	36	36	24	11	5	3
PROB.	0.034	0.098	0.136	0.189	0.136	0.136	0.091	0.042	0.019	0.011
IRT/OP	0.037	0.112	0.175	0.294	0.300	0.429	0.500	0.458	0.385	0.375

TOTAL RESPONSES 264.0 PERCENTAGE REACTION TIME 15.5

SUBJECT R1 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 87

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.031
FREQUENCY OF PREMATURE	36.0	PROBABILITY OF PREMATURE	0.160
FREQUENCY OF EFFICIENT	114.0	PROBABILITY OF EFFICIENT	0.507
FREQUENCY OF LATE	68.0	PROBABILITY OF LATE	0.302

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	7	12	16	23	20	13	14	7	1
PROB.	0.004	0.031	0.053	0.071	0.102	0.089	0.058	0.062	0.031	0.004
IRT/OP	0.005	0.039	0.069	0.099	0.158	0.163	0.126	0.156	0.092	0.014

TOTAL RESPONSES 225.0 PERCENTAGE REACTION TIME 30.3

SUBJECT R1 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline after 25 mg/kg of 245 Trimethoxypheylethylamine. NO. 88

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.026
FREQUENCY OF PREMATURE	12.0	PROBABILITY OF PREMATURE	0.052
FREQUENCY OF EFFICIENT	175.0	PROBABILITY OF EFFICIENT	0.761
FREQUENCY OF LATE	37.0	PROBABILITY OF LATE	0.161

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	10	18	17	24	34	23	19	14	10	6
PROB.	0.043	0.078	0.074	0.104	0.148	0.100	0.083	0.061	0.043	0.026
IRT/OP	0.047	0.089	0.092	0.144	0.238	0.211	0.221	0.209	0.189	0.140

TOTAL RESPONSES 230.0 PERCENTAGE REACTION TIME 28.6

SUBJECT R2 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 89

FREQUENCY OF BURST	8.0	PROBABILITY OF BURST	0.029
FREQUENCY OF PREMATURE	56.0	PROBABILITY OF PREMATURE	0.201
FREQUENCY OF EFFICIENT	163.0	PROBABILITY OF EFFICIENT	0.586
FREQUENCY OF LATE	51.0	PROBABILITY OF LATE	0.183

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	7	13	16	21	17	30	18	15	16	10
PROB.	0.025	0.047	0.058	0.076	0.061	0.108	0.065	0.054	0.058	0.036
IRT/OP	0.033	0.063	0.082	0.118	0.108	0.214	0.164	0.163	0.208	0.164

TOTAL RESPONSES 278.0 PERCENTAGE REACTION TIME 25.6

SUBJECT R2 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline after 25 mg/kg of 245 Trimethoxyphenylethylamine. NO. 90

FREQUENCY OF BURST	6.0	PROBABILITY OF BURST	0.024
FREQUENCY OF PREMATURE	17.0	PROBABILITY OF PREMATURE	0.068
FREQUENCY OF EFFICIENT	200.0	PROBABILITY OF EFFICIENT	0.797
FREQUENCY OF LATE	28.0	PROBABILITY OF LATE	0.112

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	3	13	27	34	31	30	26	18	12	6
PROB.	0.012	0.052	0.108	0.135	0.124	0.120	0.104	0.072	0.048	0.024
IRT/OP	0.013	0.058	0.127	0.184	0.205	0.250	0.289	0.281	0.261	0.176

TOTAL RESPONSES 251.0 PERCENTAGE REACTION TIME 24.7

SUBJECT R1 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline after after 32.0 mg/kg ∝ Methyltyrosine NO. 91

FREQUENCY OF BURST	16.0	PROBABILITY OF BURST	0.079
FREQUENCY OF PREMATURE	21.0	PROBABILITY OF PREMATURE	0.104
FREQUENCY OF EFFICIENT	61.0	PROBABILITY OF EFFICIENT	0.302
FREQUENCY OF LATE	104.0	PROBABILITY OF LATE	0.515

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	4	7	9	3	4	8	8	5	9
PROB.	0.020	0.020	0.035	0.045	0.015	0.020	0.040	0.040	0.025	0.045
IRT/OP	0.024	0.025	0.045	0.060	0.021	0.029	0.060	0.063	0.042	0.080

TOTAL RESPONSES 202.0 PERCENTAGE REACTION TIME 40.9

SUBJECT R1 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline after 4.0 mg/kg Tetrabenazine NO. 92

FREQUENCY OF BURST	29.0	PROBABILITY OF BURST	0.119
FREQUENCY OF PREMATURE	22.0	PROBABILITY OF PREMATURE	0.019
FREQUENCY OF EFFICIENT	107.0	PROBABILITY OF EFFICIENT	0.440
FREQUENCY OF LATE	85.0	PROBABILITY OF LATE	0.350

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	5	12	14	7	11	13	11	14	10	10
PROBI.	0.021	0.049	0.058	0.029	0.045	0.053	0.045	0.058	0.041	0.041
IRT/OP	0.026	0.064	0.080	0.043	0.071	0.091	0.085	0.118	0.095	0.105

TOTAL RESPONSES 243.0 PERCENTAGE REACTION TIME 31.2

SUBJECT R1 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 93

FREQUENCY OF BURST	5.0	PROBABILITY OF BURST	0.020
FREQUENCY OF PREMATURE	43.0	PROBABILITY OF PREMATURE	0.173
FREQUENCY OF EFFICIENT	121.0	PROBABILITY OF EFFICIENT	0.486
FREQUENCY OF LATE	80.0	PROBABILITY OF LATE	0.321

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	2	9	16	14	21	20	19	8	11
PROB.	0.004	0.008	0.036	0.064	0.056	0.084	0.080	0.076	0.032	0.044
IRT/OP	0.005	0.010	0.045	0.085	0.0 81	0.132	0.145	0.161	0.081	0.121

TOTAL RESPONSES 249.0 PERCENTAGE REACTION TIME 29.7

SUBJECT R3 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline after 32.0 mg/kg ∝ Methyltyrosine NO. 94

FREQUENCY OF BURST	21.0	PROBABILITY OF BURST	0.093
FREQUENCY OF PREMATURE	54.0	PROBABILITY OF PREMATURE	0.238
FREQUENCY OF EFFICIENT	78.0	PROBABILITY OF EFFICIENT	0.344
FREQUENCY OF LATE	74.0	PROBABILITY OF LATE	0.326

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	3	8	6	16	11	11	8	6	7
PROB.	0.009	0.013	0.035	0.026	0.070	0.048	0.048	0.035	0.026	0.031
IRT/OP	0.013	0.020	0.054	0.043	0.120	0.094	0.104	0.084	0.069	0.086

TOTAL RESPONSES 227.0 PERCENTAGE REACTION TIME 41.2

SUBJECT R3 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline after 4.0 mg/kg Tetrabenazine NO. 95

FREQUENCY OF BURST	31.0	PROBABILITY OF BURST	0.126
FREQUENCY OF PREMATURE	57.0	PROBABILITY OF PREMATURE	0.232
FREQUENCY OF EFFICIENT	84.0	PROBABILITY OF EFFICIENT	0.341
FREQUENCY OF LATE	74.0	PROBABILITY OF LATE	0.301

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	3	9	4	14	14	16	8	7	7
PROB.	0.008	0.012	0.037	0.016	0.057	0.057	0.065	0.033	0.028	0.028
IRT/OP	0.013	0.019	0.059	0.028	0.100	0.111	0.143	0.083	0.080	0.086

TOTAL RESPONSES 246.0 PERCENTAGE REACTION TIME 38.5

SUBJECT R3 APPENDIX B

TREATMENT 17.5 mg/kg Mescaline NO. 96

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.028
FREQUENCY OF PREMATURE	61.0	PROBABILITY OF PREMATURE	0.243
FREQUENCY OF EFFICIENT	136.0	PROBABILITY OF EFFICIENT	0.542
FREQUENCY OF LATE	47.0	PROBABILITY OF LATE	0.187

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	4	10	13	15	21	16	20	21	9	7
PROB.	0.016	0.040	0.052	0.060	0.084	0.064	0.080	0.084	0.036	0.028
IRT/OP	0.022	0.056	0.077	0.096	0.149	0.133	0.192	0.250	0.143	0.130

TOTAL RESPONSES 251.0 PERCENTAGE REACTION TIME 30.0

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 97

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.047
FREQUENCY OF PREMATURE	51.0	PROBABILITY OF PREMATURE	0.266
FREQUENCY OF EFFICIENT	83.0	PROBABILITY OF EFFICIENT	0.432
FREQUENCY OF LATE	49.0	PROBABILITY OF LATE	0.255

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	4	12	12	16	17	12	7	2	0
PROB.	0.005	0.021	0.063	0.063	0.083	0.089	0.063	0.036	0.010	0.000
IRT/OP	0.008	0.031	0.094	0.104	0.155	0.195	0.171	0.121	0.039	0.000

TOTAL RESPONSES 192.0 PERCENTAGE REACTION TIME 48.6

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline after 40.0 mg/kg Imipramine NO. 98

FREQUENCY OF BURST	2.0	PROBABILITY OF BURST	0.008
FREQUENCY OF PREMATURE	6.0	PROBABILITY OF PREMATURE	0.025
FREQUENCY OF EFFICIENT	214.0	PROBABILITY OF EFFICIENT	0.895
FREQUENCY OF LATE	17.0	PROBABILITY OF LATE	0.071

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	0	10	13	27	35	36	37	32	17	7
PROB.	0.000	0.042	0.054	0.113	0.146	0.151	0.155	0.134	0.071	0.029
IRT/OP	0.000	0.043	0.059	0.130	0.193	0.247	0.336	0.438	0.415	0.292

TOTAL RESPONSES 239.0 PERCENTAGE REACTION TIME 21.8

SUBJECT R2 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 99

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.033
FREQUENCY OF PREMATURE	61.0	PROBABILITY OF PREMATURE	0.288
FREQUENCY OF EFFICIENT	96.0	PROBABILITY OF EFFICIENT	0.453
FREQUENCY OF LATE	48.0	PROBABILITY OF LATE	0.226

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	5	8	19	14	24	17	6	1	0
PROB.	0.009	0.024	0.038	0.090	0.066	0.113	0.080	0.028	0.005	0.000
IRT/OP	0.014	0.035	0.058	0.147	0.127	0.250	0.236	0.109	0.020	0.000

TOTAL RESPONSES 212.0 PERCENTAGE REACTION TIME 51.1

SUBJECT R6 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 100

FREQUENCY OF BURST	7.0	PROBABILITY OF BURST	0.045
FREQUENCY OF PREMATURE	38.0	PROBABILITY OF PREMATURE	0.245
FREQUENCY OF EFFICIENT	73.0	PROBABILITY OF EFFICIENT	0.471
FREQUENCY OF LATE	37.0	PROBABILITY OF LATE	0.239

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	1	5	13	10	18	11	10	4	0	1
PROB.	0.006	0.032	0.084	0.065	0.116	0.071	0.065	0.026	0.000	0.006
IRT/OP	0.009	0.046	0.125	0.110	0.222	0.175	0.192	0.095	0.000	0.026

TOTAL RESPONSES 155.0 PERCENTAGE REACTION TIME 46.3

SUBJECT R6 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline after 40.0 mg/kg Imipramine NO. 101

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.036
FREQUENCY OF PREMATURE	17.0	PROBABILITY OF PREMATURE	0.068
FREQUENCY OF EFFICIENT	198.0	PROBABILITY OF EFFICIENT	0.789
FREQUENCY OF LATE	27.0	PROBABILITY OF LATE	0.108

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	7	8	10	19	27	34	36	24	21	12
PROB.	0.028	0.032	0.040	0.076	0.108	0.135	0.143	0.096	0.084	0.048
IRT/OP	0.031	0.037	0.048	0.095	0.149	0.221	0.300	0.286	0.350	0.308

TOTAL RESPONSES 251.0 PERCENTAGE REACTION TIME 24.9

SUBJECT R6 APPENDIX B

TREATMENT 25.0 mg/kg Mescaline NO. 102

FREQUENCY OF BURST	9.0	PROBABILITY OF BURST	0.053
FREQUENCY OF PREMATURE	40.0	PROBABILITY OF PREMATURE	0.234
FREQUENCY OF EFFICIENT	79.0	PROBABILITY OF EFFICIENT	0.462
FREQUENCY OF LATE	43.0	PROBABILITY OF LATE	0.251

DISTRIBUTION WITHIN PREAVERSIVE STIMULUS IN CATEGORIES OF SECOND

	1	2	3	4	5	6	7	8	9	10
FREQ.	2	6	7	12	12	12	14	8	4	2
PROB.	0.012	0.035	0.041	0.070	0.070	0.070	0.082	0.047	0.023	0.012
IRT/OP	0.016	0.050	0.061	0.112	0.126	0.145	0.197	0.140	0.082	0.044

TOTAL RESPONSES 171.0 PERCENTAGE REACTION TIME 47.8

APPENDIX C

SECOND ORDER DATA

SUBJECT R5 APPENDIX C

TREATMENT 0.5 mg/kg Chlorpromazine NO. 1

	SECOND RESPONSE IS A .. BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	3.000	2.000	7.000	7.000
First Response is a PREMATURE	0.000	0.000	4.000	7.000
First Response is a EFFICIENT	1.000	2.000	107.000	34.000
First Response is a ..... LATE	15.000	7.000	26.000	17.000
PROBABILITIES				
First Response is a ..... BURST	0.012	0.008	0.029	0.029
First Response is a PREMATURE	0.000	0.000	0.017	0.029
First Response is a EFFICIENT	0.004	0.008	0.446	0.142
First Response is a ..... LATE	0.063	0.029	0.108	0.071
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.158	0.105	0.368	0.368
First Response is a PREMATURE	0.000	0.000	0.364	0.636
First Response is a EFFICIENT	0.007	0.014	0.743	0.236
First Response is a ..... LATE	0.227	0.106	0.394	0.258

SUBJECT R5 APPENDIX C

TREATMENT 1.0 mg/kg Chlorpromazine NO. 2

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	2.000	1.000	7.000	19.000
First Response is a PREMATURE	0.000	1.000	3.000	8.000
First Response is a EFFICIENT	0.000	4.000	48.000	34.000
First Response is a ..... LATE	27.000	6.000	28.000	32.000
PROBABILITIES				
First Response is a .... BURST	0.009	0.005	0.032	0.086
First Response is a PREMATURE	0.000	0.005	0.014	0.036
First Response is a EFFICIENT	0.000	0.018	0.217	0.154
First Response is a ..... LATE	0.122	0.027	0.127	0.145
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.069	0.034	0.241	0.655
First Response is a PREMATURE	0.000	0.083	0.250	0.667
First Response is a EFFICIENT	0.000	0.047	0.558	0.395
First Response is a ..... LATE	0.287	0.064	0.298	0.340

SUBJECT R5 APPENDIX C

TREATMENT 2.0 mg/kg Chlorpromazine NO. 3

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	1.000	1.000	5.000	12.000
First Response is a PREMATURE	0.000	2.000	4.000	5.000
First Response is a EFFICIENT	0.000	4.000	24.000	32.000
First Response is a ..... LATE	18.000	4.000	26.000	74.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.023	0.056
First Response is a PREMATURE	0.000	0.009	0.019	0.023
First Response is a EFFICIENT	0.000	0.009	0.113	0.150
First Response is a ..... LATE	0.085	0.019	0.122	0.347
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.053	0.053	0.263	0.632
First Response is a PREMATURE	0.000	0.182	0.364	0.455
First Response is a EFFICIENT	0.000	0.067	0.400	0.533
First Response is a ..... LATE	0.146	0.033	0.211	0.602

SUBJECT R6 APPENDIX C

TREATMENT 0.5 mg/kg Chlorpromazine NO. 4

	SECOND RESPONSE IS A .. BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	2.000	0.000	20.000	3.000
First Response is a PREMATURE	0.000	0.000	2.000	5.000
First Response is a EFFICIENT	0.000	4.000	42.000	68.000
First Response is a ..... LATE	23.000	3.000	51.000	16.000
PROBABILITIES				
First Response is a .... BURST	0.008	0.000	0.083	0.012
First Response is a PREMATURE	0.000	0.000	0.008	0.021
First Response is a EFFICIENT	0.000	0.017	0.175	0.283
First Response is a ..... LATE	0.096	0.012	0.212	0.067
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.080	0.000	0.800	0.120
First Response is a PREMATURE	0.000	0.000	0.286	0.714
First Response is a EFFICIENT	0.000	0.035	0.365	0.591
First Response is a ..... LATE	0.247	0.032	0.548	0.172

SUBJECT R6 APPENDIX C

TREATMENT 1.0 mg/kg Chlorpromazine NO. 5

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	2.000	4.000	13.000	3.000
First Response is a PREMATURE	0.000	0.000	3.000	5.000
First Response is a EFFICIENT	0.000	2.000	29.000	66.000
First Response is a ..... LATE	20.000	2.000	52.000	32.000
PROBABILITIES				
First Response is a .... BURST	0.009	0.017	0.056	0.013
First Response is a PREMATURE	0.000	0.000	0.013	0.021
First Response is a EFFICIENT	0.000	0.009	0.124	0.282
First Response is a ..... LATE	0.085	0.009	0.222	0.137
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.091	0.182	0.591	0.136
First Response is a PREMATURE	0.000	0.000	0.375	0.625
First Response is a EFFICIENT	0.000	0.021	0.299	0.680
First Response is a ..... LATE	0.187	0.019	0.486	0.299

SUBJECT R1 APPENDIX C

TREATMENT 0.5 mg/kg Amphetamine NO. 7

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	0.000	4.000	0.000
First Response is a PREMATURE	0.000	11.000	24.000	1.000
First Response is a EFFICIENT	3.000	23.000	201.000	6.000
First Response is a ..... LATE	1.000	2.000	5.000	0.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.014	0.000
First Response is a PREMATURE	0.000	0.039	0.085	0.004
First Response is a EFFICIENT	0.011	0.082	0.713	0.021
First Response is a ..... LATE	0.004	0.007	0.018	0.000
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.000	1.000	0.000
First Response is a PREMATURE	0.000	0.306	0.667	0.028
First Response is a EFFICIENT	0.013	0.098	0.859	0.026
First Response is a ..... LATE	0.125	0.250	0.625	0.000

SUBJECT R1 APPENDIX C

TREATMENT 1.0 mg/kg Amphetamine NO. 8

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	0.000	5.000	1.000
First Response is a PREMATURE	1.000	22.000	38.000	0.000
First Response is a EFFICIENT	4.000	36.000	168.000	4.000
First Response is a ..... LATE	1.000	3.000	2.000	1.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.017	0.003
First Response is a PREMATURE	0.003	0.077	0.132	0.000
First Response is a EFFICIENT	0.014	0.125	0.585	0.014
First Response is a ..... LATE	0.003	0.010	0.007	0.003
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.833	0.167
First Response is a PREMATURE	0.016	0.361	0.623	0.000
First Response is a EFFICIENT	0.019	0.169	0.789	0.019
First Response is a ..... LATE	0.143	0.429	0.286	0.143

SUBJECT R1 APPENDIX C

TREATMENT 2.0 mg/kg Ampetamine NO. 9

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	2.000	9.000	6.000	2.000
First Response is a PREMATURE	14.000	65.000	42.000	9.000
First Response is a EFFICIENT	1.000	41.000	84.000	18.000
First Response is a ..... LATE	2.000	15.000	13.000	7.000
PROBABILITIES				
First Response is a .... BURST	0.006	0.027	0.018	0.006
First Response is a PREMATURE	0.042	0.196	0.127	0.027
First Response is a EFFICIENT	0.003	0.124	0.254	0.054
First Response is a ..... LATE	0.006	0.045	0.039	0.021
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.105	0.474	0.316	0.105
First Response is a PREMATURE	0.108	0.500	0.323	0.069
First Response is a EFFICIENT	0.007	0.283	0.579	0.124
First Response is a ..... LATE	0.054	0.405	0.351	0.189

SUBJECT R1 APPENDIX C

TREATMENT 12.5 mg/kg Mescaline NO. 10

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	0.000	2.000	1.000
First Response is a PREMATURE	1.000	4.000	11.000	1.000
First Response is a EFFICIENT	0.000	10.000	168.000	18.000
First Response is a ..... LATE	2.000	3.000	15.000	4.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.008	0.004
First Response is a PREMATURE	0.004	0.017	0.046	0.004
First Response is a EFFICIENT	0.000	0.041	0.697	0.075
First Response is a ..... LATE	0.008	0.012	0.062	0.017
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.667	0.333
First Response is a PREMATURE	0.059	0.235	0.647	0.055
First Response is a EFFICIENT	0.000	0.051	0.853	0.091
First Response is a ..... LATE	0.083	0.125	0.625	0.167

SUBJECT R1 APPENDIX C

TREATMENT 17.5 mg/kg Mescaline NO. 11

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	3.000	4.000	2.000
First Response is a PREMATURE	1.000	10.000	19.000	9.000
First Response is a EFFICIENT	1.000	15.000	58.000	34.000
First Response is a ..... LATE	7.000	11.000	27.000	26.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.013	0.018	0.009
First Response is a PREMATURE	0.004	0.044	0.083	0.039
First Response is a EFFICIENT	0.004	0.066	0.254	0.149
First Response is a ..... LATE	0.031	0.048	0.118	0.114
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.333	0.444	0.222
First Response is a PREMATURE	0.026	0.256	0.487	0.231
First Response is a EFFICIENT	0.009	0.138	0.532	0.312
First Response is a ..... LATE	0.099	0.155	0.380	0.366

SUBJECT R1 APPENDIX C

TREATMENT 25.0 mg/kg Mescaline NO. 12

SECOND RESPONSE IS A	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	1.000	1.000	1.000
First Response is a PREMATURE	1.000	5.000	12.000	8.000
First Response is a EFFICIENT	2.000	11.000	30.000	18.000
First Response is a ..... LATE	0.000	9.000	18.000	24.000
PROBABILITIES				
First Response is a ... BURST	0.000	0.007	0.007	0.007
First Response is a PREMATURE	0.007	0.035	0.085	0.056
First Response is a EFFICIENT	0.014	0.077	0.211	0.127
First Response is a ..... LATE	0.000	0.063	0.127	0.169
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.333	0.333	0.333
First Response is a PREMATURE	0.038	0.192	0.462	0.308
First Response is a EFFICIENT	0.032	0.177	0.484	0.290
First Response is a ..... LATE	0.000	0.176	0.353	0.471

SUBJECT R2 APPENDIX C

TREATMENT 12.5 mg/kg Mescaline NO. 13

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	0.000	2.000	0.000
First Response is a PREMATURE	0.000	0.000	7.000	0.000
First Response is a EFFICIENT	0.000	8.000	195.000	14.000
First Response is a ..... LATE	2.000	0.000	12.000	1.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.008	0.000
First Response is a PREMATURE	0.000	0.000	0.029	0.000
First Response is a EFFICIENT	0.000	0.033	0.806	0.058
First Response is a ..... LATE	0.008	0.000	0.050	0.004
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.000	1.000	0.000
First Response is a PREMATURE	0.000	0.000	0.875	0.000
First Response is a EFFICIENT	0.000	0.037	0.899	0.065
First Response is a ..... LATE	0.133	0.000	0.800	0.067

SUBJECT R2 APPENDIX C

TREATMENT 17.5 mg/kg Mescaline NO. 14

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	3.000	1.000	6.000	3.000
First Response is a PREMATURE	0.000	12.000	38.000	9.000
First Response is a EFFICIENT	0.000	36.000	84.000	22.000
First Response is a ..... LATE	10.000	9.000	14.000	11.000
PROBABILITIES				
First Response is a .... BURST	0.012	0.004	0.023	0.012
First Response is a PREMATURE	0.000	0.046	0.147	0.035
First Response is a EFFICIENT	0.000	0.139	0.324	0.085
First Response is a ..... LATE	0.039	0.035	0.054	0.042
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.231	0.077	0.462	0.231
First Response is a PREMATURE	0.000	0.203	0.644	0.153
First Response is a EFFICIENT	0.000	0.254	0.592	0.155
First Response is a ..... LATE	0.222	0.200	0.311	0.244

SUBJECT R2 APPENDIX C

TREATMENT 25.0 mg/kg Mescaline NO. 15

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	1.000	1.000	6.000	3.000
First Response is a PREMATURE	3.000	17.000	16.000	11.000
First Response is a EFFICIENT	1.000	16.000	46.000	16.000
First Response is a ..... LATE	6.000	13.000	11.000	16.000
PROBABILITIES				
First Response is a .... BURST	0.005	0.005	0.033	0.016
First Response is a PREMATURE	0.016	0.092	0.087	0.060
First Response is a EFFICIENT	0.005	0.087	0.250	0.087
First Response is a ..... LATE	0.033	0.071	0.060	0.087
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.091	0.091	0.545	0.273
First Response is a PREMATURE	0.063	0.354	0.333	0.229
First Response is a EFFICIENT	0.013	0.203	0.582	0.203
First Response is a ..... LATE	0.130	0.283	0.239	0.348

SUBJECT R3 APPENDIX C

TREATMENT 12.5 mg/kg Mescaline NO. 16

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	0.000	0.000	0.000	0.000
First Response is a PREMATURE	0.000	0.000	5.000	0.000
First Response is a EFFICIENT	0.000	5.000	198.000	15.000
First Response is a ..... LATE	0.000	0.000	15.000	0.000
PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.000	0.000
First Response is a PREMATURE	0.000	0.000	0.021	0.000
First Response is a EFFICIENT	0.000	0.021	0.828	0.063
First Response is a ..... LATE	0.000	0.000	0.063	0.000
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.000	0.000	0.000	0.000
First Response is a PREMATURE	0.000	0.000	1.000	0.000
First Response is a EFFICIENT	0.000	0.023	0.904	0.068
First Response is a ..... LATE	0.000	0.000	1.000	0.000

SUBJECT R3 APPENDIX C

TREATMENT 17.5 mg/kg Mescaline NO. 17

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	3.000	2.000	3.000	1.000
First Response is a PREMATURE	0.000	12.000	39.000	6.000
First Response is a EFFICIENT	0.000	33.000	76.000	19.000
First Response is a ..... LATE	6.000	10.000	10.000	23.000
PROBABILITIES				
First Response is a .... BURST	0.012	0.008	0.012	0.004
First Response is a PREMATURE	0.000	0.049	0.160	0.025
First Response is a EFFICIENT	0.000	0.135	0.311	0.078
First Response is a ..... LATE	0.025	0.041	0.041	0.094
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.333	0.222	0.333	0.111
First Response is a PREMATURE	0.000	0.211	0.684	0.105
First Response is a EFFICIENT	0.000	0.256	0.589	0.147
First Response ia a ..... LATE	0.122	0.204	0.204	0.469

SUBJECT R3 APPENDIX C

TREATMENT 25.0 mg/kg Mescaline NO. 18

SECOND RESPONSE IS A ..	BURST	PREMATURE	EFFICIENT	LATE
FREQUENCIES				
First Response is a .... BURST	1.000	1.000	3.000	4.000
First Response is a PREMATURE	0.000	3.000	15.000	7.000
First Response is a EFFICIENT	0.00	12.000	45.000	15.000
First Response is a ..... LATE	8.000	9.000	9.000	15.000
PROBABILITIES				
First Response is a .... BURST	0.007	0.007	0.020	0.027
First Response is a PREMATURE	0.000	0.020	0.101	0.047
First Response is a EFFICIENT	0.000	0.081	0.304	0.101
First Response is a ..... LATE	0.054	0.061	0.061	0.101
CONDITIONAL PROBABILITIES				
First Response is a .... BURST	0.111	0.111	0.333	0.444
First Response is a PREMATURE	0.000	0.120	0.600	0.280
First Response is a EFFICIENT	0.000	0.164	0.616	0.205
First Response is a ..... LATE	0.195	0.220	0.220	0.366

APPENDIX D

CONDITIONED INFLATION AND DISCRIMINATION DATA

SUBJECT R7 APPENDIX D

TREATMENT Saline NO. 1

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	8	1	1	1	0	9	0
2	1	9	1	0	0	10	0
3	9	0	0	0	0	9	0
4	0	7	0	0	0	7	0
5	8	0	0	0	0	8	0
6	0	7	0	0	0	7	0
7	8	0	0	0	0	8	0
8	0	8	0	0	0	8	0
9	7	0	0	0	0	7	0
10	0	9	0	0	0	9	0
11	7	0	0	0	0	7	0
12	0	8	0	0	0	8	0
13	7	0	0	0	0	7	0
14	0	8	0	0	0	8	0
15	8	0	0	0	0	8	0
16	0	7	0	0	0	7	0
17	7	0	0	0	1	7	0
18	0	8	0	0	0	8	0
19	8	0	0	0	0	8	0
20	0	8	0	0	0	8	0
Total	78	80	2	1	1	158	0

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R. - Total responses

E_F - Escape failures

Periods 7 - 15 are shown in Fig. 22

SUBJECT R7 APPENDIX D

TREATMENT 1.0 mg/kg Amphetamine NO. 2

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	0	9	0	0	0	9	0
2	8	0	0	0	0	8	0
3	0	9	0	0	0	9	0
4	12	1	1	0	1	13	0
5	0	14	0	0	0	14	0
6	12	0	0	0	0	12	0
7	0	9	0	0	0	9	0
8	13	0	0	0	0	13	0
9	0	16	0	0	0	16	0
10	15	2	2	0	0	17	0
11	0	21	0	0	0	21	0
12	13	0	0	0	0	13	0
13	0	15	0	0	0	15	0
14	14	1	1	0	0	15	0
15	0	10	0	0	0	10	0
16	15	0	0	0	0	15	0
17	0	13	0	0	0	13	0
18	13	0	0	0	0	13	0
19	0	13	0	0	0	13	0
20	9	0	0	0	0	9	0
Total	124	133	4	0	1	257	0

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R. - Total responses

E_F - Escape failures

Periods 7 - 15 are shown in Fig. 23

SUBJECT R7 APPENDIX D

TREATMENT 17.5 mg/kg Mescaline NO. 3

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	7	0	0	0	1	7	0
2	0	9	0	0	1	9	0
3	8	1	1	0	1	9	0
4	0	9	0	0	2	9	0
5	8	0	0	0	1	8	0
6	0	8	0	0	3	8	1
7	9	0	0	0	1	9	0
8	1	11	1	0	1	12	0
9	8	0	0	0	4	8	0
10	0	12	0	0	6	12	2
11	10	3	3	1	4	13	1
12	1	7	1	0	6	8	0
13	7	0	0	0	3	7	1
14	0	9	0	0	4	9	1
15	12	0	0	0	5	12	1
16	0	11	0	0	4	11	0
17	12	0	0	0	0	12	0
18	0	10	0	0	2	10	0
19	11	0	0	0	4	11	0
20	0	11	0	0	3	11	0
Total	94	101	6	1	56	195	7

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R.- Total responses

E_F - Escape failures

SUBJECT R7 APPENDIX D

TREATMENT 2.0 mg/kg C.P.Z. NO. 4

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	0	7	0	0	1	7	0
2	6	1	1	1	1	7	0
3	1	5	1	1	4	6	1
4	6	0	0	0	3	6	0
5	1	6	1	1	5	7	1
6	5	1	1	1	4	6	1
7	0	6	0	0	5	6	1
8	5	1	1	1	6	6	2
9	1	6	1	0	6	7	1
10	5	0	0	0	5	5	0
11	0	6	0	0	4	6	0
12	4	1	1	1	6	5	1
13	0	5	0	0	4	5	1
14	5	1	1	1	6	6	1
15	1	5	1	0	6	6	1
16	6	0	0	0	4	6	1
17	1	5	1	1	6	6	2
18	6	1	1	1	4	7	1
19	1	5	1	1	4	6	2
20	6	0	0	0	4	6	1
Total	60	62	12	10	86	122	18

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R. - Total responses

E_F - Escape failures

Periods 7 - 15 are shown in Fig. 24

SUBJECT R7 APPENDIX D

TREATMENT 25.0 mg/kg Mescaline NO. 5

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	9	0	0	0	1	9	0
2	1	9	1	0	1	10	0
3	9	1	1	1	0	10	0
4	2	11	2	1	1	13	0
5	6	1	1	0	2	7	1
6	3	4	3	0	8	7	3
7	7	0	0	0	3	7	1
8	5	4	5	1	9	9	2
9	8	10	10	0	6	18	1
10	7	4	7	1	7	11	2
11	6	5	5	0	9	11	2
12	2	9	2	0	1	11	0
13	7	6	6	1	0	13	0
14	0	10	0	0	0	10	0
15	6	3	3	1	0	9	0
16	6	5	6	0	0	11	0
17	2	6	6	0	0	8	0
18	4	3	4	1	1	7	1
19	3	4	4	0	1	7	0
20	2	7	2	1	0	9	0
Total	95	102	68	8	50	197	13

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R. - Total responses

E_F - Escape failures

Periods 7 - 15 are shown in Fig. 25

SUBJECT R7 APPENDIX D

TREATMENT 1.0 mg/kg C.P.Z. NO. 6

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	0	8	0	0	0	8	0
2	7	0	0	0	0	7	0
3	0	6	0	0	0	6	0
4	7	0	0	0	1	7	0
5	1	4	1	1	0	5	0
6	6	0	0	0	1	6	0
7	0	4	0	0	3	4	0
8	4	0	0	0	4	4	0
9	0	5	0	0	2	5	0
10	8	0	0	0	6	8	1
11	1	6	1	1	2	7	0
12	3	0	0	0	4	3	0
13	0	4	0	0	1	4	0
14	5	0	0	0	3	5	0
15	0	8	0	0	1	8	0
16	6	1	1	1	2	7	0
17	1	7	1	1	2	8	0
18	4	0	0	0	3	4	0
19	0	4	0	0	4	4	0
20	8	0	0	0	1	8	0
Total	61	57	4	4	40	118	1

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R.- Total responses

E_F - Escape failures

SUBJECT R7 APPENDIX D

TREATMENT 4.0 mg/kg Amphetamine NO. 7

3 min. Periods	R_1	R_2	D_E	C_E	S_2^{-R}	T.R.	E_F
1	8	0	0	0	0	8	0
2	0	9	0	0	0	9	0
3	11	1	1	0	1	12	0
4	0	14	0	0	0	14	0
5	15	0	0	0	3	15	0
6	2	13	2	1	6	15	3
7	9	4	4	0	3	13	1
8	1	13	2	1	3	14	1
9	10	1	1	1	3	11	0
10	1	9	1	0	2	10	0
11	12	3	3	1	10	15	4
12	4	10	4	1	6	14	3
13	13	3	3	0	5	16	2
14	3	15	3	0	7	18	2
15	14	3	3	1	1	17	0
16	2	12	2	1	2	14	1
17	10	1	1	1	1	11	0
18	2	9	2	1	3	11	1
19	10	1	1	0	6	11	2
20	1	9	1	0	1	10	0
Total	128	130	34	9	65	258	20

R_1 - Responses on first lever

R_2 - Responses on second lever

D_E - Discrimination errors

C_E - Change-over errors

S_2^{-R} - Shock

T.R. - Total responses

E_F - Escape failures

SUBJECT R10

APPENDIX D

CONDITIONED INFLATION EXPERIMENT

NO. 8

C.S. PRESENTATIONS		1	2	3	4	5	6
	3 min. pre C.S.	14	17	15	15	16	15
SALINE (AV. DATA)	3 min. C.S.	19	34	33	31	31	34
	Inflation Ratio	1.4(±5)	2.0(±3)	2.2(±3)	2.1(±3)	1.9(±3)	2.3(±3)
	3 min. pre C.S.	13	10	10	9	8	8
C.P.Z. (1mg/kg)	3 min. C.S.	19	14	16	12	8	8
	Inflation Ratio	1.5	1.4	1.6	1.3	1.0	1.0
	3 min. pre C.S.	15	12	12	6	9	9
C.P.Z. (2mg/kg)	3 min. C.S.	22	16	18	6	11	20*
	Inflation Ratio	1.5	1.3	1.5	1.0	1.2	2.2
	3 min. pre C.S.	17	21	24	22	20	20
AMPHET. (1mg/kg)	3 min. C.S.	34	60	54	59	39	43
	Inflation Ratio	2.0	2.9	2.3	2.7	2.0	2.1
	3 min. pre C.S.	19	13	13	10	13	24
AMPHET. (4mg/kg)	3 min. C.S.	36	14	14	15	19	38
	Inflation Ratio	1.9	1.1	1.1	1.5	1.5	1.6
	3 min. pre C.S.	15	13	14	16	18	16
MESC. (12.5mg/kg)	3 min. C.S.	30	34	34	40	36	30
	Inflation Ratio	2.0	2.6	2.4	2.5	2.0	1.9
	3 min. pre C.S.	13	6	13	12	15	19
MESC. (17.5mg/kg)	3 min. C.S.	20	9	25	26	30	33
	Inflation Ratio	1.5	1.5	1.9	2.2	2.0	1.7
	3 min. pre C.S.	12	8	0	0	3	10
MESC. (25.0mg/kg)	3 min. C.S.	14	10	0	0	4	10
	Inflation Ratio	1.2	1.3			1.3	1.0

* Unusually high due to six burst responses following a shock.

SUBJECT R9

APPENDIX D

CONDITIONED INFLATION EXPERIMENT

NO. 9

C.S. PRESENTATIONS		1	2	3	4	5	6
SALINE (AV. DATA)	3 min. pre C.S.	14	13	12	13	15	15
	3 min. C.S.	16	27	27	25	30	32
	Inflation Ratio	1.1(±6)	2.1(±3)	2.3(±3)	1.9(±3)	2.0(±3)	2.1(±3)
C.P.Z. (1mg/kg)	3 min. pre C.S.	17	16	12	13	13	12
	3 min. C.S.	28	32	14	17	19	12
	Inflation Ratio	1.6	2.0	1.1	1.3	1.5	1.0
C.P.Z. (2mg/kg)	3 min. pre C.S.	17	11	13	11	9	11
	3 min. C.S.	28	14	20	10	13	10
	Inflation Ratio	1.6	1.3	1.5	0.9	1.4	0.9
AMPHET. (1mg/kg)	3 min. pre C.S.	20	20	25	26	18	18
	3 min. C.S.	41	49	63	51	39	33
	Inflation Ratio	2.1	2.5	2.5	2.0	2.2	1.8
AMPHET. (4mg/kg)	3 min. pre C.S.	21	10	9	10	11	18
	3 min. C.S.	41	16	6	10	12	30
	Inflation Ratio	2.0	1.6	0.7	1.0	1.1	1.7
MESC. (12.5mg/kg)	3 min. pre C.S.	17	16	16	17	17	17
	3 min. C.S.	33	34	41	26	39	29
	Inflation Ratio	1.9	2.1	2.6	1.5	2.3	1.7
MESC. (17.5mg/kg)	3 min. pre C.S.	18	14	15	16	13	16
	3 min. C.S.	35	27	31	28	24	32
	Inflation Ratio	1.9	1.9	2.1	1.8	1.8	2.0
MESC. (25.0mg/kg)	3 min. pre C.S.	6	3	3	0	11	15
	3 min. C.S.	1	0	5	1	13	23
	Inflation Ratio	0.2	0.0	1.7		1.2	1.5

APPENDIX E

PARTITION COEFFICIENTS

Method for determining partition coefficients

Reagents:- (1) Chloroform (Analar grade B.D.H.)

(2) 0.1 Molar phosphate buffer pH 7.5 (NaH_2PO_4)

Method:- (1) Each compound was dissolved in 10 ccs of the phosphate buffer and the spectrum recorded against a buffer blank. The peak height (in the 250-300 millimicron range) was noted (A).

(2) 10.0 ccs of chloroform were then added to each sample (including the blank) and the tubes shaken for 10 minutes.

(3) The samples were centrifuged at 3,500 r.p.m. for 5 minutes.

(4) The spectra were re-recorded against the 'exhausted' buffer blank. The peak height (in the 250-300 millimicron range) was again noted (B).

(5) The partition coefficients were calculated from the equation:-

$$\text{Partition Coefficient} = \frac{A - B}{B}$$

PARTITION COEFFICIENTS RELATIVE

TO MESCALINE

Phenylethylamines

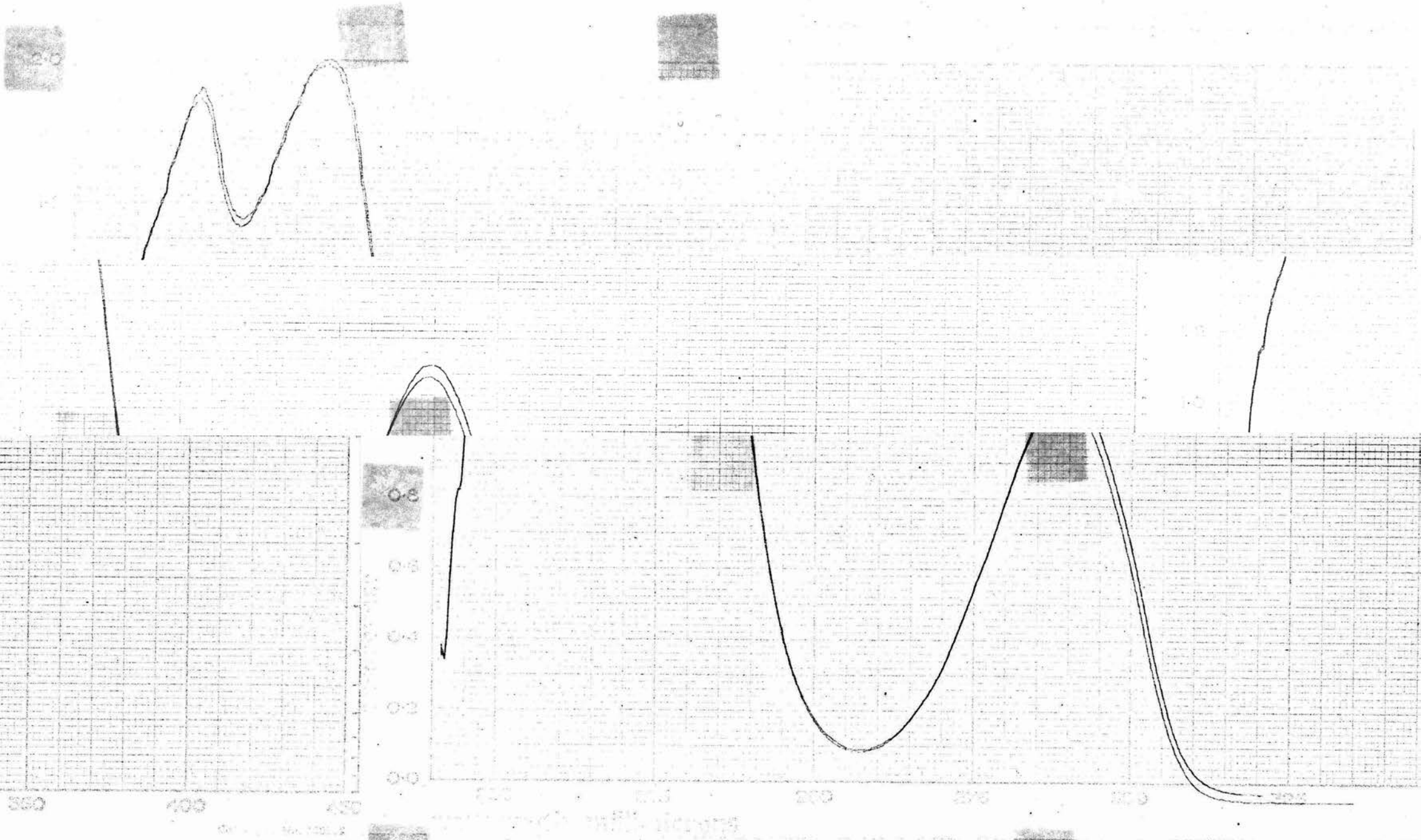
METHOXY GROUP POSITION	REIATIVE PARTITION COEFFICIENT
345	1.0
246	1.3
235	1.6
245	0.8
236	1.0
2346	1.6
2345	2.5
23456	4.1

Amphetamines

AMPHET.	0.9
2	1.6
3	2.1
4	3.3
34	2.1
25	2.7
35	4.5
23	2.4
245	2.5
345	1.5
234	1.0
246	2.1

APPENDIX F

U.V. SPECTRA



ol X 245 TMA and 245 TMPE 2.5×10^{-4} m