THE EFFECTS OF MESCALINE ON MAZE LEARNING IN THE RAT

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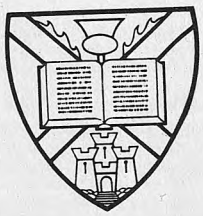

The effects of mescaline on maze learning in the rat.

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Foreword

The work reported in this dissertation was undertaken by the author as part of a large-scale long-term project which Dr. J.R. Smythies of the Department of Psychiatry, University of Edinburgh, is conducting on the psychopharmacology of hallucinogenic drugs, with particular reference to mescaline and its analogues.

The experimental study reported herein on the effects of mescaline on maze learning in the rat is entirely the work of the author.

Acknowledgments

I wish to express my appreciation of and gratitude for all the encouragement and help which I received from so many people during the course of this work. I should particularly like to thank Professor G.M. Carstairs, Dr. J.R. Smythies, Dr. K. Hope, the technical staff of the Department of Psychiatry, Miss S. Kirkup and my parents.

CONTENTS

SUMMARY

This study was undertaken as part of a large-scale long-term investigation of hallucinogenic compounds. The aim was to elucidate the effects of mescaline on original learning and recall of a maze habit by rats.

Literature relating to the chemistry, pharmacology and psychopharmacology of mescaline; the biochemical theories of schizophrenia; the neurophysiological theories of learning; and drug effects on learning and memory, is reviewed.

Three experiments designed to study the effects of 12.5 mg/kg and 25 mg/kg of mescaline after various time intervals on the acquisition, consolidation and recall of a maze-habit by rats are described and their results are enumerated. The findings are discussed, comparing control and experimental groups at each time interval and dose level, and are related to previous work on the psychopharmacology of mescaline and the effects of central stimulants and depressants on learning.

The following conclusions were reached:

i. 12.5 mg/kg of mescaline administered 0, 15 or 55 minutes before training trials probably inhibits learning during the acquisition phase; this may be due to reduced attention.

ii. 12.5 mg/kg of mescaline injected immediately after training trials does not affect acquisition.

iii. 12.5 mg/kg of mescaline injected 15 minutes before a trial has no effect on recall of a partially acquired habit. Injected 55 minutes before/

before recall it may increase errors and running time.

iv. 25 mg/kg of mescaline injected 15 minutes before training trials does not affect acquisition but markedly retards running speeds. This dose injected 55 minutes before training trials facilitates acquisition. Injected immediately before training it apparently has no effect.

v. 25 mg/kg of mescaline injected immediately after training trials does not affect acquisition.

vi. 25 mg/kg injected 15 minutes before a trial probably inhibits recall and retards running speed; injected 55 minutes before a trial it has no effect on recall or running speed.

Mescaline's dose-dependent, time dependent facilitating effect on acquisition of a maze-habit was tentatively attributed to a metabolic derivative having this property in common with some of the known CNS stimulants. The drug's retardation effect on motor performance may be dependent on autonomic arousal level.

REVIEW OF THE LITERATURE

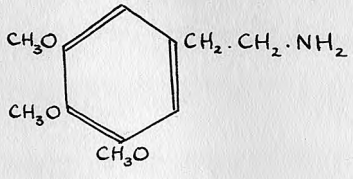
Review of the Literature

Since there appears to be no literature bearing directly upon the effects of mescaline on original learning, I shall review the relevant work basic to this study under the four general headings of: Mescaline; The Biochemistry of Schizophrenia; Learning; and, Drug Effects on Learning.

1. Mescaline.

a) Its chemical structure.

Mexican Indians have used the dried buttons of 'peyotl' in religious rites for centuries, but it was not until 1908 that the structure of the pure drug mescaline was elucidated and synthesized by Spath. It was found to be 3, 4, 5 - trimethoxy - β - phenylethylamine:



b) Its pharmacology.

In spite of intense experimental work in recent years, the pharmacology of the psychotropic compounds remains largely descriptive, since the biochemical or biophysical basis for their pharmacodynamic effects on the cells of the CNS is still obscure.

However, in 1961 Schopp, Kreuter and Guzak (58) published work on the neuromyal blocking action of mescaline. They reported that the intra-arterial injection of 4 - 5 mg/kg (or more) of mescaline causes partial or complete curare-like paralysis in the dog neuromuscular preparation/

preparation. Mescaline and curare tend to supplement one another with respect to their depressant actions on indirectly stimulated skeletal muscle. After complete blockade with mescaline, the muscle can readily be activated by direct electrical stimulation; following chronic denervation, the directly stimulated muscle fails to show an immediate depression of contractions when mescaline is administered. Adrenaline, KCl and prostigmine posess anticurare activity and these same agents also have an antimescaline effect. These authors point out that although the response of the muscle to direct stimulation following complete paralysis to nerve stimulation localizes the site of action somewhere in the neuromuscular complex, it does not necessarily follow that the blockade is occurring at the neuromuscular junction rather than at some point between the junction and the stimulation electrodes, though they seem to favour some such interpretation.

The question of whether mescaline is directly psychotomimetic or whether this action is a function of intermediates in its metabolism was expressed by Harley-Mason et al.(24). Two points are involved: (1) the psychotomimetic dose of mescaline is considerably higher than that of other such agents; and, (2) the peak behavioural effects of mescaline do not appear to coincide with the time of its maximum concentration inthe brain of animals, and in humans the maximal behavioural changes follow the period of maximal blood level and excretion of the drug by 1 to 2 hours. Friedhoff and Goldstein (20) used rats to investigate the in vivo formation of acid and alcohol from mescaline. From their results, Friedhoff and Goldstein concluded that mescaline, like dopamine, is metabolized to aldehyde and then oxidised to/

to acid or reduced to alcohol; the next question was whether it is one of these intermediates, rather than mescaline itself, which is hallucinogenic.

Slotta and Muller (59) showed in 1936 that the 3, 4, 5 - trimethoxyphenyl acetic acid derivative is biologically inactive, so Friedhoff and Goldstein turned to a closer examination of the pharmacological and behavioural effects of 3, 4, 5 - trimethoxyphenyl ethanol. The effects of 5 dose levels of mescaline were: chewing and licking, hind leg incoordination, hyperactivity followed by inactivity, hyperventilation, pupillary dilatation and cyanosis, becoming more severe at higher dose levels. An increase in unmetabolised mescaline brought about by pretreatment with iproniazid produced no behavioural differences in this pattern, indicating that neither mescaline alone nor a degradation product alone is responsible for the behavioural changes. Calcium carbimide (50 mg/kg) was given in combination with mescaline (10 mg/kg) to increase the concentration of the aldehyde derivative, and probably also of 3, 4, 5 - trimethoxyphenylethanol. This treatment greatly enhanced the mescaline effect in most ways, though some differences were apparent. It therefore seemed possible that some of the effects of mescaline resulted directly from the amine, while others were produced by a metabolite. The administration of synthetic 3, 4, 5 - trimethoxy - phenylethanol to rabbits (which are insensitive to mescaline) had a mild mescaline-like effect with a peak 30 minutes after injection which was greatly potentiated by calcium carbimide, especially if the latter was given 30 minutes after the alcohol. The authors suggested that it was not the alcohol itself but 3, 4, 5 - trimethoxyphenyl acetaldehyde, which can be formed/

formed from either the amine or the alcohol, that was responsible for the severe effects.

A different approach to the biochemical activity of mescaline suggests that it might be cyclized in vivo to an indolic compound. Fischer (18) proposed the convertion of mescaline in vivo to an LSD - like compound responsible for the psychotomimetic response; the hypothetical LSD - like molecule might be derived from partially demethylated mescaline and a tyramine-like compound, 5 — HT or norepinephrine. Waser and Itzbicki (73) showed that with respect to 5 — HT, norepinephrine and histamine, mescaline causes essentially the same shifts as LSD. But since the mode of action of LSD and its metabolic fate remains as much a mystery as does that of mescaline itself, these ideas, however interesting, do not shed very much light on the problem. There are also several reports of cross-tolerance between mescaline and LSD both in animals and in man, but until the mechanisms of tolerance have been elucidated the significance of these findings is obscure; they may or may not indicate an interaction of the psychotomimetic substances and common receptor sites.

Again, mescaline (or one or more of its derivatives) may exert its effects by interfering with some enzyme by competing with its natural substrate or it may interfere with the action of a co-enzyme or of some central transmitter substance. Speculations here might again concern the structurally similar dopamine, or acetyle choline and its receptor sites, or any of an almost infinite number of possible variations on this general theme.

c) Its psychopharmacology.

It is paradoxical that whereas the hallucinogenic properties of

mescaline administered to human subjects are so conspicuous and typical, yet the biochemical bases of these properties and their manifestations in terms of observable effects on animal subjects have remained obscure for so long.

In recent years Smythies has been concerned with studies of the structure-activity relationships of mescaline, that is to say with determining the structural features of the molecule that are necessary for its actions. In 1960 Smythies and Levy (61) timed rats climbing a rope under hunger drive before and after administration of some mescaline analogues. It was found that the loss of the methoxy group in the 5-position reduced the activity of the drug by half. The replacement of the methoxy group in the 4-position by a hydroxyl group abolished all activity (as measured by this test) and its replacement by a benzyloxy group increased activity. This test may have been subject to a motivational variable, since mescaline can cause sensations of nausea in humans; there is no experimental evidence on its effect on food intake in rats, but one might expect it to reduce hunger drive. And as has been mentioned, Schopp et al. have shown a direct curare-like effect of mescaline on muscle.

A more widely used technique in psychopharmacology has been the conditioned avoidance response (CAR); rats can be trained to a high level of efficiency under strictly controlled conditions, and the effects of even small doses of drugs on their performance can be accurately and objectively assessed. At the same time it should be kept in mind that drug effects tend to be less marked when measured against such a highly overlearned habit, and also that the effects of a drug on an animal working under stressful conditions which/

which might be expected to heighten arousal and stimulate the sympatho-adrenal system may well be influenced by these factors.

Cook and Weidley (12) used a pole-jump escape technique and gave oral doses of up to 100mg/kg. of mescaline to rats. They reported that the drug failed to block the CAR, but it is difficult to assess this result since oral drug administration is not a very reliable method. Chorover (11), using a shuttle box with sound as the conditioned stimulus (CS) and shock as the unconditioned stimulus (UCS), showed that intraperitoneal (i.p.) injections of 25 mg/kg. of mescaline sulphate extinguished the CAR, and that the response was disrupted for eleven days afterwards, provided the animal was tested immediately after the injection. If an interval of a day was left between the injection and testing, no effect was observed. Locomotor activity, as tested in the open field did not appear to be affected under either condition at this dosage, but animals given 50 mg/kg. and tested in an activity wheel became paralysed and ataxic.

Smythies and Sykes (62) trained rats on a CAR schedule in a shuttle box using sound as the CS and shock as the UCS, and tested them under 25 mg/kg. and 12.5 mg/kg. of mescaline hydrochloride. The results, in terms of reaction times, showed that 25 mg/kg. of mescaline exerted a biphasic effect, initially depressing the CAR, and then giving rise to a prolonged 'excitatory' phase (i.e. reduced R.T.) beginning about 50 minutes after the injection. The lower dose depressed the CAR less, especially in less sensitive animals, whereas the 'excitatory' phase was potentiated. Trimethoxyphenylalanine (the amino-acid derivative of mescaline) did not affect the CAR, even at doses of 100 mg/kg. Further structure-activity relationship studies were published by/

by these authors in 1966 (63), using rats trained on the same CAR buzzer CS - shock UCS schedule. 3, 4 - dimethoxyphenylethylamine (DMPE) was shown to depress the CAR with an apparent bimodal distribution of peak activities, in contrast to the biphasic inhibitory and excitatory effect of mescaline. N:N - dimethyl mescaline (DMM) did not have the inhibitory action of mescaline on the CAR, but had a marked 'excitant' action. Questions raised by these results are: a) is the biphasic effect found with mescaline typical of hallucinogens? and b) are the two phases of the drug's effect caused by its action on two different systems, or by different metabolites?

In a study of tolerance and cross-tolerance to mescaline, DMM and DMPE, Smythies, Sykes and Lord (64 and see inside back cover) found that seven successive daily doses of 25 mg/kg. of mescaline induced tolerance to its inhibitory effect, but that the 'excitatory' effect was increased. Tolerance developed to the predominantly inhibitory effect of DMPE and to the excitatory effect of DMM. There was marked cross-tolerance between DMPE and mescaline. An interesting finding was that despite the lack of tolerance produced by mescaline to its own excitatory action, it neverthless induced cross-tolerance for the excitatory effect of DMM; and DMM not only induced tolerance for itsown excitatory effect, but also exerted cross-tolerance for the excitatory effect of mescaline. It is difficult to envisage a mechanism which could be responsible for these interactions, but it seems fairly clear that the 'excitatory' and inhibitory phases which characterize the reaction to mescaline arise independently. Smythies et al. (64) presented some evidence that these effects were not due to peripheral factors or ataxia. These points must/

must be kept in mind throughout the present discussion, since the theoretical significance of the effects of any drug on learning and memory depends on whether the primary action of the drug is on the receptor or effector systems or on the CNS. It is probably fairly safe to assume that during some stage in the action of mescaline the CNS is directly affected.

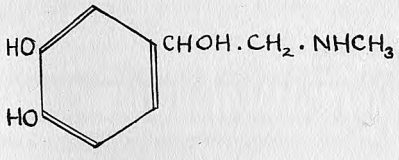
Johnston, Bradley and Smythies (31) have recently carried out a further study to estimate the relative contribution of various parts of the mescaline molecule to its psychotomimetic properties. Four behavioural parameters were measured during rats' performance of a discriminated continuous avoidance schedule: premature responses; late responses; efficient responses; and reaction time. Mescaline causes an increase in premature and late responses and reaction time, and a decrease in efficient responses. Bovet and Gatti (6) have tested a great variety of psychotropic drugs on a similar schedule, excluding the hallucinogens, and have found many distinct behavioural profiles. However, none of them bring about the behaviour changes induced by mescaline; this profile appears to be unique to hallucingenic drugs and has now been validated against LSD, DMT, TMA and psilocyn. Using this test, Johnston, Bradley and Smythies showed that the hallucinogenic activity of mescaline is completely dependent on the presence of the 3,4,5 - methoxy configuration. All other mono-, di- and tri-methoxy derivatives were inactive. Of the three possible tetra-methoxy compounds, only the 2,3,4,5 - tetra-methoxy -β- phenylethylamine was active, and it was considerably more potent than mescaline. The penta-methoxy compound (2,3,4,5,6 - methoxy) was even more active again. These findings suggest that hallucinogenic β- phenylethyl-

mines/

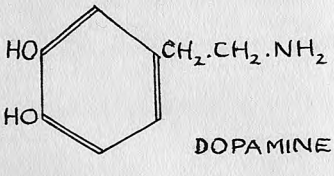
-mines must possess the 3,4,5 - methoxy configuration, and any additional methoxy group produces a considerable increase in potency.

2. The Biochemistry of Schizophrenia.

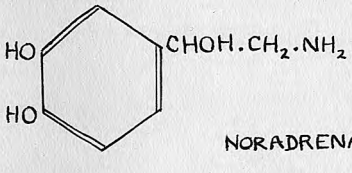
In 1952 Osmond and Smythies (47) pointed out the close structural similarity between mescaline and the sympathetic stimulating hormone adrenaline:



At the same time they drew attention to the marked similarities between the psychological effects of mescaline and the symptoms of an acute attack of schizophrenia, and suggested that a biochemical lesion in schizophrenia might be the disordered metabolism of adrenaline whereby methylation of the phenolic hydroxyl groups could produce a substance like mescaline ('M - substance'). A similar theory could presumably also involve either or both of the precursors of adrenaline, dopamine and noradenaline:



DOPAMINE



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With this kind of hypothesis in mind, several groups of workers have investigated possible 'psychotoxic' effects of injected schizophrenic serum or plasma in rats. Winter and Flataker (76) trained rats in rope-climbing then measured the effects of intraperitoneal injections of psychotic plasma/

plasma versus normal plasma on the speed of this response. For animals injected with psychotic plasma, they reported a highly significant decrement in performance and observed that these animals appeared generally sluggish and less active than the controls. However, equation of motor retardation with psychotoxic effect seems questionable, and even the conclusion of impaired motor performance (which was certainly justified by the data) may have been attributable to artifact in view of the failure of other investigators to confirm these findings. For example, Ghent and Freedman (23) replicated the experiment and found significant motor impairment following injection of either schizophrenic or normal plasma. Stern et al. (66) studied the effects of injections of schizophrenic plasma, normal plasma and saline on general activity in the open-field and activity-wheel. No differential effect of schizophrenic and normal plasma was found for either activity, but both schizophrenic and normal plasma produced a significant reduction of running in the activity wheel.

Bishop (2) questioned the use of the 'over-learned response' techniques in previous tests of the effects of schizophrenic plasma on animals, and designed an experiment to study the effects of schizophrenic versus normal plasma upon original learning (acquisition) of an avoidance response in the rat. The results confirmed his hypothesis that schizophrenic plasma injected in rats would produce significant impairment of original avoidance learning; that impairment of learning was not produced by injections of normal plasma; and that no such differential effects of schizophrenic and normal plasma are observed if the animals have received extensive pre-training

or/

or opportunity for over-learning of the response prior to plasma injection. Bishop imputes some of the decremental effect of the schizophrenic plasma injections on acquisition to an interaction with the stress inherent in the task of learning an adaptive avoidance response. He also emphasizes that rats performing tasks involving an element of stress fail to demonstrate the motor retardation which is revealed by non-stressful measures of spontaneous activity with either schizophrenic or normal plasma.

Bergen, et al. (1) reported that blood plasma and plasma protein fractions from both nonpsychotic Ss and from acute and chronic psychotic patients increased the rope-climbing time of rats trained under conditions of positive reinforcement, but significantly greater effects were produced by samples from the psychotics. Differential effects were not found when serum was used. In an addendum to this report, Smythies gave results from a similar experiment on trained mice injected with the protein-globulin precipitate which had had the greatest effect in the foregoing rat test. The decrement in climbing time showed a double peak, with maximum effect 5 m inutes and 20 minutes after the injection, and no change for animals tested 1 0 minutes after injection. An interesting comparison can be drawn between this finding and that of Smythies and Sykes (62) showing a similar double-peaked depression of reaction time in rats' performance of a CAR after treatment with the mescaline analogue DMPE.

DMPE itself has been the subject of a great deal of investigation, suspicion and discussion since 1962, when Friedhoff and Van Winkle (21) described an amine which they had isolated from the urine of 15/19 acute schizophrenic/

schizophrenic patients but could not detect in the urine of any of their 14 non-schizophrenic controls. All characteristics determined for this amine were consistent with those found for 3, 4 - dimethoxyphenylethylamine, which led these authors to suggest the interesting possibility that it had resulted from disturbed metabolism of dopamine in schizophrenia; however, as they added, this conclusion was not a justifiable interpretation of their evidence amd many uncontrolled factors remained to be eliminated. There was the possibility that the compound was a product of bacteria in the patients' digestive systems or in the collecting bottles, that its presence could be due to a common dietary factor, or could be related to activity levels. As Friedhoff and Van Winkle pointed out, the repetition of their tests by investigators in other hosptials would provide the best control situation for several of these factors.

There are now some ten reports in the literature, some confirming and some denying Friedhoff's claim. For example: Takesada et al. (69) in Japan in 1963, using an improved chromatography method detected 3-4 DMPE in the urine of 70/78 schizophrenics, but also in 21/46 normal subjects and 14/21 psychoneurotics, and presented some evidence negating the hypothesis that it might be a metabolite of dopamine. Friedhoff and Van Winkle (22) replied that whereas the higher incidence of DmPE found by Takesada et al. might be a result of more sensitive methods of detection, it was also possible that in normal Ss not selected specifically to exclude even mild schizoid tendencies (as were their normals), a genetic factor could give a bias to the results of qualitative rather than quantitative studies. They nevertheless/

nevertheless advocate considerable caution in the interpretation of the relationship of DMPE to schizophrenia.

Bourdillon, et al. (4) carried out a series of 'blind' surveys of 'pink spot' (DMPE?) in the urine of 808 individuals in England. Their results led them to conclude that pink spot is highly associated with schizophrenia and is not often present in other forms of mental disorder or in close relatives or controls. The family data obtained gave some evidence that DMPE arises as a result of the disease, but it is possible that it appears shortly before the disorder manifests itself so would not be apparent in non-schizophrenic siblings.

In 1966, Boulton and Felton (3) cast doubt on the identification of the 'pink spot' as DMPE in the chromatography studies of the previous investigations., They reported that of 31 urine samples collected from acute schizophrenic patients, only one exhibited 'pink spot' in the chromatographic zone corresponding exactly with that of authentic DMPE and having the correct sequence of colour changes. Two other samples showed a ninhydrin-positive substance in the appropriate position. Nothing was seen at this position in urine extracts from five 'normal' subjects. Further chromatography of the positive urine sample revealed a lack of fluorescence of the 'pink spot' and the addition of authentic DMPE to two positive but quantitatively different samples gave the same proportion of recoverable DMPE. Boulton and Felton concluded that the 'pink spot' shown in this sample was not DMPE, and emphasized the necessity for an unambiguous chemical identification of 'pink spot' before further attempts are made to assess the importance of its relationship/

relationship to schizophrenia.

Some other groups, notably Perry and his co-workers in Vancouver, have also been unable to confirm the excretion of DMPE in acute schizophrenics (52). In 1966 (51) they published results from chronic patients who had been given a potent monoamine oxidase inhibitor in an effort to increase the urinary excretion of amines, but there was still no DMPE detectable with any of several chromatographic techniques. Neither were they able to detect any significant differences between the pattern of amines excreted by schizophrenics and that by other non-schizophrenic mentally ill patients in the same hospital. They suggested the possibility that the compound may be a metabolite of certain drugs or plant foods excluded in these experiments, or that DMPE has been confused with other amines in previous chromatographic investigations. The latter explanation, considered in the light of Boulton and Felton's conclusions, obviously requires much more scrutiny. It is impossible to say at the present time in view of all the conflicting reports whether the 'pink spot' is associated in any significant way with the aetiology or metabolic disorders of schizophrenia, or whether it can be equated with 3,4 - dimethoxyphenylethylamine or any other amine. Conclusive evidence to implicate disorders of dopamine or adrenaline metabolism is still remote, but equally these possibilities cannot be discounted.

3. Learning.

There is no need here to stress either the central position which learning holds in psychology, as a basic process underlying all behaviour to

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a greater or lesser extent, or the theoretical controversies which have raged around the topic from the first. The theoretical definitions of the essential conditions which many writers have believed to be necessary for learning to occur do not affect general agreement on the facts of the case; namely, that learning refers to a more or less permanent change in behaviour which comes about as a result of practice. It is an article of faith that this 'learning' represents some change in the CNS, and that 'memory' is the preservation of that change. The questions of immediate concern are: i) where in the CNS does this change take place? and ii) what is its nature? Neurophysiological theories and the facts pertaining to them about the physical bases of this change are of obvious relevance to the study of drug effects on learning, and will be briefly reviewed.

The perseveration-consolidation theory was first proposed in 1900 by Muller and Pilzecker (46) and has been more recently developed by Hebb (26). According to this theory, the degree of fixation of the neurophysiological processes underlying learning depends upon the extent of perseveration of the neural activity initiated by a training trial. It is proposed by Hebb that a repeated stimulation of specific receptors will lead slowly to the formation of a'cell assembly' of association-area cells which can act briefly as a closed system after stimulation has ceased. The existence of such a consolidation period is strongly supported by numerous findings that, in rats, memory can be impaired by interference with CNS activity immediately after learning. This was demonstrated with post-trial administration of electroconvulsive shock (ECS) by Duncan (17), Thompson and Dean (70) and

Thomson/

Thomson et al. (71). Retrograde amnesia has also been demonstrated after anoxia by Thompson and Pryer (72), and after post-trial administration of depressant drugs by Leukel (35) and Pearlman et al. (44).

The consolidation period is seen as the time during which the structural changes of learning can occur, and the characteristics of the changes are postulated in anatomical terms. Hebb assumes that a growth process accompanying synaptic activity makes the synapse more readily traversed and proposes that the most likely mechanism of a lasting effect of reverberatory action would be that when one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs (or enlarges already existing ones) in contact with the soma of the second cell. Many cells would become interconnected in a complex net through which firing would reverberate, at the same time strengthening the connections. Forgetting can be explained by the over-laying occurring with the addition of new learning, or by the disappearance of knobs with disuse; Hebb favours the latter hypothesis, but both could conceivably operate in such a system. There is not much neurophysiological evidence to support these postulations implicating growth of synaptic knobs in learning, but Hebb draws on Kapper's conception of neurobiotaxis and Lorente de No's work on synaptic knobs showing that they are often simply a thickening in the unmyelinated part of an axon, rather than a terminal structure, and are related to the propinquity of a second cell.

But other interpretations of the nature of the change which takes place during the consolidation period following learning are equally speculative. Hydén (29) has proposed the biochemical possibility that memory storage may involve ribonucleic acid (RNA) and protein synthesis, which are known to vary with neuronal activity. The suggestion is that memory storage may/

may be based on specific alterations in RNA composition produced by the specific CNS activity occurring during learning. The last change in protein formation which would follow the alteration of RNA would, according to Hydén, provide a stable intraneuronal basis for memory. In support of this general hypothesis, Hydén and Egyházi (30) reported that the analysis of neuronal and glial RNA in rats' vestibular Deiter's nuclei showed an increase in the adenine:uracil ratio after training in a balancing task. Dingman and Sporn (16) reported that intracerebral injections of the antimetabolite 8 - azaguanine, which is readily incorporated into brain RNA, impaired the ability of rats to learn a maze without effecting their performance of a previously well-learned maze. The possibility that 8-azaguanine interferes with other aspects of brain metabolism necessary for memory but unrelated to RNA, or with attention factors critical in the early stages of learning, was not eliminated. Appel (unpublished work in 1964 reported by McGaugh and Petrinovich (39)) found no effect on learning and memory in mice of an injection of actinomycin-D sufficient to have stopped all RNA synthesis by the time of the animal's death. Flexner et al. (19) found loss of memory of avoidance discrimination learning in mice after intracerebral injections of puromycin, which inhibits brain protein synthesis, but the effects could have been due to effects of intracerebral injection quite unrelated to protein synthesis. While it would be surprising to find that RNA and protein synthesis had nothing to do with memory storage mechanisms, it has yet to be shown conclusively that they are concerned.

Other biochemical explanations of how synaptic resistance might be reduced in learning are concerned with chemical transmitter substances at synapses/

synapses. Straughan (68) has recently reviewed the subject of chemical transmission in the brain, and concludes that acetylcholine appears to satisfy many of the essential criteria for a central transmitter in the cerebral cortex, caudate nucleus and the Renshaw cell system in the spinal chord. Evidence to implicate 5-HT, noradrenaline, dopamine, glutamate and GABA is much less conclusive. In respect of this it is interesting that Krech and his co-workers (33,57) have searched for positive correlationships between problem-solving behaviour and brain cholinesterase activity in rats with some success. But Peirce (50) in similar experiments found a negative correlation; however, as Peirce emphasizes, the most important finding is that normally occurring differences in cortical cholinesterase activity are in some way related to behavioural differences.

A number of recent studies have shown that the anticholinergic drug atropine also impairs learning and performance. Whitehouse (75) demonstrated that atropine (2 mg/kg.) impaired successive discrimination learning in rats. Injections were given 1 hour before 10 daily training trials for seven days, then training was continued without the drug. The performance of the animals that had received atropine remained inferior to that of the controls for several days after drug administration had been discontinued, but the possibility that learning impairment was due to sensory or attentional influences cannot be excluded. Burešová et al. (9) found that at the height of the atropine effect (approximately 20 minutes after injection of 6 mg/kg.) one-trial learning of a CAR by rats was partially impaired, as was its extinction. Impairment in this experiment may have been due to interference/

interference with attention; no post-trial injections were given.

Recently, several studies have indicated that learning is facilitated by small doses of the reversible anticholinesterase compound, physostigmine. Bureš et al. (8) reported that the learning of a one-trial avoidance problem by rats was facilitated by small doses of physostigmine administered a few minutes before training trials. Learning was impaired by larger doses. The effect is not limited to avoidance learning, as was shown by Stratton and Petrinovich (67) who treated rats with small doses of physostigmine 30 seconds after each daily trial in a maze, and found that learning was facilitated as compared with controls. Again impairment occurred with larger doses. The evidence is that learning efficiency depends on levels of acetylcholine and acetylcholinesterase: learning is impaired by drugs (e.g. atropine) that block ACh and is facilitated by a drug (physostigmine) that inhibits AChE. This is not surprising in view of the evidence that ACh is involved in synaptic transmission and it lends weight to biochemical theories of learning processes.

At a very general level, evidence from various types of studies consistently indicates that learning and memory storage involves a sequence of processes (whose nature is not yet clear) which are active for some time after the termination of an experience. A common assumption is that short-term memory is based on transient neuronal processes such as reverberations in networks of cells stimulated by an experience, and that the formation of more 'permanent' traces is based on further changes initiated or produced by these transient neuronal processes, either anatomically within the neurones themselves/

themselves or biochemically by stimulating transmitter substances and enzymes to cause intra-cellular changes, e.g. in protein synthesis.

4. The Effects of Drugs on Learning and Memory.

This topic and its attendant methodological problems have recently been extensively reviewed by McGaugh and Petrinovich (39), so rather than repeat what they have said I shall select and emphasize the main trends of research relevant to this study. The only way of assessing learning is by the yard-stick of performance, and it is becoming a truism to draw the necessary distinction between performance and learning and the effects of any intervening variable on each. In the case of drugs, however, the many ways in which they can influence performance may not even be immediately apparent, and the problems of specifying their effects on learning as distinct from this require rigid controls. A variety of suitable procedures have been developed, and under appropriate conditions it has been shown that there are classes of drugs capable of impairing and also of facilitating both learning and memory processes.

Where the effects of drugs, particularly those which enhance learning, are difficult to interpret in terms of motivational and/or perceptual factors, the hypothesis is that they may facilitate acquisition, performance and retention by potentiating the neurophysiological processes underlying memory storage. Clear evidence of drug facilitation of memory storage, together with knowledge of the mechanism of drug action, could provide some leads concerning the nature of the processes involved in storing information/

information in the CNS. This section will deal with the start which has been made in this direction.

Many years ago, Lashley (34) reported that small doses of strychnine facilitated rats' acquisition of maze-learning. The strychnine animals ran more slowly than controls but made fewer errors. McGaugh and others have recently reported similar effects. McGaugh and Petrinovich (38) reported that rats treated daily with small doses of strychnine sulphate 10 minutes before five massed trials in a Lashley III alley maze made fewer errors than control Ss in attaining a criterion of 5/6 errorless trials. In a subsequent study, McGaugh (37) found both facilitative and disruptive effects of strychnine on maze learning by rats. With a small dose (0.33 mg/kg) the best strychnine-treated animals made significantly fewer errors than the best controls; with 1.0 mg/kg. the worst strychnine animals made significantly more errors than the worst controls. Evidence for strychnine's facilitating effect on learning has also been found with tasks other than maze learning. McGaugh and Thomson (40) found that 0.33 mg/kg, of strychnine facilitated rats' learning of a simultaneous visual discrimination task to a criterion of 9/10 correct responses. And Petrinovich (53) obtained further evidence of the generality of the effects of strychnine on learning; male rats were dosed with strychnine sulphate (1.0 mg/kg) 10 minutes before daily massed trials on a visual successive-discrimination problem. In spite of evidence that the strychnine-treated rats ate slightly less than the controls and were therefore possibly less highly motivated to learn for food reward, the drugged animals achieved the learning criterion in fewer trials than did the/

the controls.

Keleman and Bovet (32) found that small doses (0.3 to 1.0 mg/kg) of amphetamine facilitated rats' escape and avoidance learning. The latency of the response was only shortened by the higher dose, so it seems unlikely that the facilitative effect was due solely to an increase in activity. Rahmann (55) and Rensch and Rahmann (56) found that 0.5 mg/kg of methamphetamine facilitated discrimination learning in hamsters, and since in this case accuracy of choice was measured rather than latency of response, and learning was impaired by a dose (2.0 mg/kg) which produced a high activity level, the facilitation is not attributable to increased activity. Retention of the amphetamine-injected Ss tested over a 3-month period remained superior to that of controls. It seems then that learning is facilitated by small doses of amphetamine, and that the facilitation is probably not due solely to any temporary effect on performance; but the remaining possibilities of increased attention or a direct facilitation of memory storage processes have not yet been clarified.

Work on nicotine has emphasized its impairment of performance after long-term repeated administration, but it has recently been shown to have facilitating effects when given to experimental animals in small doses. Robustelli (57) found that 0.2 mg/kg of nicotine facilitated maze-learning with water motivation but not with food motivation, indicating a possible depressing effect on appetite. Bovet, et al. (5) reported facilitation of CAR acquisition, but the apparently learned response was lost when nicotine was withdrawn, which implies some dissociation.

Learning facilitation has been found with the synthetic compound

5/

5,7-diphenyl-1,3-diazadamantan-6-ol (1757 I.S), which is structurally unlike strychnine but has effects on CNS activity which are strikingly similar to those of strychnine. McGaugh, Westbrook and Burt (42) found facilitation by this compound of maze-learning in a strain of maze-dull rats, but none in maze-bright Ss. They suggested that under conditions of massed practice the strain differences in learning might be due to differences in rates of intertrial neural consolidation, and that 1757 I.S, facilitated learning in the maze-dull animals by increasing these rates. Keleman and Bovet (32) found that 1757 I.S. facilitated avoidance learning (as measured by the rate of improvement of responding from trial to trial) without affecting the latency of the initial successful jumping response.

The results of the above studies provide fairly strong evidence that learning, as measured by improvement in performance, can be facilitated by several CNS stimulants. But the methods employed could not preclude the possibility that learning improvement was due to enhanced arousal and/or attention, and their interpretation is therefore riddled with difficulties. A number of recent studies have shown that learning can be facilitated by dosing rats with CNS stimulants within a short period of time <u>after</u> training trials. These results are less easy to interpret in terms of motivation, perception or attention, since the animals are neither trained nor tested while under the immediate influence of the drug.

In an initial study using post-trial injections, McGaugh (36) found that rats given injections of strychnine (0.33 - 1.5 mg/kg) after each daily trial in a Lashley III maze made fewer errors than did rats given saline/

saline after each trial. In a subsequent, more extensive study, McGaugh et al. (41) gave daily injections of strychnine to rats either six minutes before each daily maze trial, or at one of the following intervals afterwards: 1 minute, 15 minutes, 30 minutes or 90 minutes. The animals dosed either before or within 15 minutes after each trial made fewer errors than those which were injected 30 or 90 minutes after each trial. As with findings on drug — and ECS — induced retrograde amnesia, the magnitude of this 'retrograde facilitation' was inversely related to the time interval between training and treatment. Hudspeth (28) reported that post-trial injections of strychnine sulphate (0.2 mg/kg) facilitated rats' learning of visual discrimination, discrimination reversal and oddity discrimination learning tasks, as compared with control animals given post-trial injections of saline. The strychnine animals learned the difficult 'oddity' problem, while the controls showed no evidence of learning after the same number of trials. Facilitation is thus not limited to tasks requiring fixed response patterns, as was also shown by Petrinovich et al. (54) who trained rats to alternate choice of goal boxes in a single-T maze on successive trials. Intertrial intervals were gradually increased, with injection of strychnine (or control saline) immediately following each trial. At intertrial intervals of up to $3\frac{1}{2}$ hours, the rats performed the delayed alternation equally well whether the previous trial had been followed by strychnine or saline. At intervals of between $3\frac{1}{2}$ and 8 hours, however, the rats made a significantly greater proportion of correct responses on trials which followed the strychnine injections. This cannot be interpreted as the effect of the drug on performance, since the greater the intertrial interval, the greater the period of time also between the/

the injection and the subsequent trial. Since there were no external differential cues at the choice point, the suggestion is that strychnine facilitated performance by enhancing the rat's memory of the previous trial.

Cooper and Krass (13) have challenged the interpretation by McGaugh and his colleagues that the improvement of performance with post-trial injections indicates that the memory trace undergoes better consolidation with strychnine. They carried out an experiment to test the assumption that the strychnine is rapidly destroyed by the body and does not remain in the animal to affect performance on subsequent trials. Their findings were that strychnine sulphate injected into two groups of rats 24 hours and 3 days respectively prior to initial maze-learning improved performance, with greater improvement after the shorter interval. They make no suggestions as to how this improvement could be brought about, and it cannot explain McGaugh's demonstration of 'retrograde facilitation' inversely related to time between training and treatment.

Evidence of learning facilitation using post-trial injections has also been found with 1757 I.S.. Westbrook and McGaugh (74) gave injections of this compound after unrewarded maze runs, and found upon introduction of reinforcement that 'latent' learning had been facilitated by the drug. McGaugh et al. (42) found facilitation of rewarded maze-learning by post-trial injections of 1757 I.S. Comparable effects have also been found with other CNS stimulants; for example, Breen and McGaugh (7) reported that small doses of picrotoxin injected after each trial facilitated the learning of a 14-unit maze by rats. Paré (48) found that visual discrimination learning by rats was facilitated by a post-trial injection of caffeine given 5 seconds after/

after massed training trials, but no facilitation was found when the injection came 2 minutes or 1 hour after training. Carlini and Kramer (10) injected rats with a Cannabis sativa extract (Marihuana) either 3 minutes before, or 30 seconds after maze-trials. Ss that had received the pre-trial injections performed better than the controls, whereas post-trial injections of the drug were found to increase the running times while the number of errors remained the same as in the controls. Carlini and Kramer favour increase in motivation as the most probable cause of improved performance with the pre-trial injections. Unfortunately, their 'control' group was insufficient to demonstrate that the improvement was in fact due to any effects of the drug, since all controls were given post-trial injections. An aversive stimulus 30 seconds after the rewarded maze-run may have had an unnoticed detrimental effect on the control animals, by comparison with which the pre-trial drugged Ss appeared better learners. The question of how pre-trial control injections would have compared with the pre-trial drug Ss remains unanswered, so doubt must be cast on the claim for a facilitating effect of marihuana.

Studies of drug impairment of learning and memory are beset with many of the problems already discussed in relation to facilitative effects. A large number of studies have shown that CNS depressants impair performance in acquisition tasks, and some attempts have been made to demonstrate that the impairment may be due to decreased efficiency of neurophysiolgical processes involved in learning or memory storage.

Barbiturates have been extensively studied, and there are many indications that they impede learning. In an early experiment, Mendenhall

(44)/

(44) showed that both learning and re-learning of a maze was retarded in rats treated with small doses of pentobarbital every other day to a total of 110 injections, even though the injections were discontinued 40 days before training began. Dews (15) reported that pentobarbital does not affect simple discriminations (e.g. red vs. blue light) in dosages which are sufficient to reduce the rate of pigeons' responses, but does impair more complex discriminations even in small dosages which do not affect the rate of responding. Headlee and Kellogg (25) showed that small doses of pentobarbital retarded the acquisition of a conditioned response in dogs. Rentention tests a week later (without the drug) indicated that some learning had occurred, but less than would have been predicted from an assumption that the pentobarbital merely interfered with the motor ability to perform the responses. Moroz (45) demonstrated that small doses of pentobarbital retarded problem-solving behaviour in rats without seriously affecting the performance of learned responses.

Assessments of the effects of the depressants on memory storage have been made using the technique of post-trial injections. Leukel (35) found that thiopental injected one minute after rats' daily trials in a water maze retarded their rate of learning. Pearlman, et al. (49) avoided repeated drug administration by using a 'one-trial learning' procedure. Rats were trained to press a lever, then were given a single electric shock through the lever. 24 hours later, control animals exhibited a markedly depressed rate of lever-pressing, while in Ss that had been anaesthetized with ether or pentobarbital a few minutes after the shock, the rate of lever pressing was less affected. As expected, the degree of this retrograde amnesia was inversely/

inversely related to the length of the interval between shock and drug administration. Paré (48) found that secobarbital impaired rats' retention of a visual discrimination 48 hours after training if injections were given within 2 minutes after massed trials.

Since the drugs that influence learning are known to affect the CNS, and learning is in some part a function of the CNS, it seems reasonable to assume (in the absence of contradictory evidence) that the drugs' effects on learning are related to their effects on CNS processes. The strongest evidence in support of this assumption is that from post-trial injection studies. Since most of the drugs which have been investigated are metabolized prior to the time at which retention is tested, it is indicated that their effects on subsequent behaviour are due to effects occurring shortly after training in the so-called 'consolidation' period. It is possible that some of the effects of post-trial injections can be attributed to influences other than those on the CNS, but the weight of the evidence would not appear to support this view. To make a very broad generalisation, it would appear at the present stage that CNS stimulants in some way facilitate learning processes and memory storage mechanisms, while CNS depressants somehow impair their functioning.

Introduction to the experimental study

In view of the present interest in hallucinogenic compounds concerning their mode and site of action, and the possibility of some connection between them and a postulated biochemical lesion in schizophrenia, it was decided to approach the matter from a slightly different angle. It was hoped that by elucidating the effects of mescaline on original learning it might be possible to answer some of the outstanding questions, e.g. the extent to which the drug affects the CNS; the sequence of drug effects following different dose levels; differential effects on learning and memory and so on. Consequently it was decided to investigate the effects of two dose-levels of mescaline at four time intervals with respect to the three distinct phases of learning, i.e. acquisition, consolidation and recall.

MATERIALS AND METHODS

Materials and Methods

1. Subjects.

The Subjects (Ss) of the experiments were 144 experimentally naive male hooded rats supplied by Fisons Pharmaceuticals Limited. They were each aged between 95 and 110 days and weighed approximately 200 grams at the beginning of training. They were caged singly and kept in an air-conditioned animal house with regulated temperature (70°F) and humidity and with a reversed light-cycle. All experiments took place in the same room in which the animals were housed. All Ss had free access to dry food (MRC 41B) at all times, and to water as specified in the experimental procedure.

2. Apparatus.

(a) Pretraining: i) The first pretraining apparatus consisted of an Open Field arena 3' in diameter with its segments marked out in white paint, which was surrounded by a wall of linoleum 18" high, (See Plate 1). A small dish of water was positioned in the centre of the arena. Illumination, which was the same throughout all experiments was provided by the diffused light of a 60w. electric light bulb in a metal Anglepoise shade which was inverted 7' above the central point of the arena and 2' below the white painted ceiling of the room from which the light was reflected down on to the arena.

ii) The second stage of pretraining took place in a straight matt black-painted runway 84 cm. long x 12 cm. wide, with walls 36 cm. high. At each end of the runway was a guillotine door set in runners; one of these served as the entrance to the runway, the other as the exit into a goal box 24 cm. square with walls 36 cm. high containing the water dish. Four 'doors' were placed/

placed at regular intervals along the length of the runway, blocking Ss' view of the goal box; each door consisted of a wooden block approximately 14 x 18 cm. and 1 cm. thick, with slots 12 cm. apart which fitted over the walls of the runway at any required position. On the bottom edge of each block was stapled a closely-fitting line of flexible plastic strips. These ribbon-screen doors were used because a pilot study showed them to be far less frightening to the Ss than were hardboard doors hinged at the top on to the wooden blocks. Illumination was the same as in (i) above.

(b) Maze-training: The main apparatus (See Plate 3) was a 4 choice-point multiple-T maze, built in three main sections with detachable start-box (S.B) and goal-box (G.B). The alleys were 12 cm. wide with walls 36 cm. high, and each arm of each T was 36 cm. long. The end boxes were each 24 cm. square with walls 36 cm. high, and the G.B contained the water dish. A guillotine door ran in slots at the exit from the S.B, at the entrance to the G.B, and at the end of each cul. The inside surfaces of the walls and floor of the whole maze were painted black, with a waterproof top-coat of colourless matt-finish polyurethane paint. At each choice-point both arms of the T were obscured from S's sight by ribbon-screen doors (as described in Pretraining (ii) above), which were set back 2 cm. from the corner on each side. The correct path through the maze was R.L.R.R. Illumination was the same as in (i) above.

3. Experimental Design.

Three experiments were designed to study respectively the effects of the two dose-levels of mescaline on: a) the acquisition of a maze habit; b/

b) the 'consolidation' period immediately following experience in the maze; and c) the recall of a partially acquired habit. All injections were given intraperitoneally, and mescaline was injected in solution in physiological saline.

a) Design of the acquisition experiment.

90 Ss were randomly assigned to two experimental groups and one control group of 30 animals each, to received injections of, respectively, mescaline hydrochloride 12.5 mg/kg of body weight, mescaline hydrochloride 25 mg/kg, and physiological saline solution. Within each of these three main groups, Ss were divided into three subgroups according to the time-interval by which injections preceded maze-training trials, which was either 0 mins., 15 mins. or 55 mins.

In order to avoid mescaline self-tolerance effects being built up in the experimental Ss, all trials took place at fortnightly intervals. The control group underwent seven such fortnightly trials. For the experimental groups, the drug was administered before the first six fortnightly trials, and saline solution alone was injected before the seventh trial. By this means it was hoped to separate out the influence of the drug on the amount of learning which had taken place from its direct effects on motor performance, vision, etc., and to show up any 'dissociation' effects.

b) Design of the consolidation experiment.

30 Ss were randomly assigned to three groups of 10 each receiving injections respectively of mescaline hydrochloride 12.5 mg/kg, mescaline hydrochloride 25 mg/kg and a comparable volume of physiological saline. In this experiment the injections were given to each animal immediately after receiving/

receiving reinforcement on completion of each run in the maze. Seven such trials took place at fortnightly intervals, as in the acquisition experiment.

c) Design of the recall experiment.

24 Ss were randomly assigned to six groups of four. All groups received seven successive days of training in the maze. For three groups injection of saline preceded each maze-run by 15 minutes; for the remaining three groups the injection was given 55 minutes before the run. Two days interval followed this training, then on the tenth day of the experimental session two control groups received saline again at the same 15 or 55 minute intervals, while recall trials for the four experimental groups followed 15 or 55 minutes (as in runs 1 - 7) after injection of 12.5 mg/kg or 25 mg/kg of mescaline.

4. Procedure.

a) Pretraining procedure.

Before being introduced into the maze for the first time, all of the 144 animals taking part in the three experiments underwent the same pretraining procedure, which was designed for three purposes: (i) to accustom animals used to drinking from a standard water bottle to lapping water from an open dish in the G.B. (ii) To reduce their initial fear of handling, the weighing procedure and a strange open environment; and (iii) to accustom them to the ribbon-screen 'doors' and general appearance of the passageways and end-boxes of the maze before maze-training began. In this way it was hoped to eliminate some of the fear-provoking stimuli inherent in a novel situation and thus lessen the conflict between fear and curiosity (freezing/

(freezing and exploratory behaviour) during each animal's first experience in the maze proper. Pretraining for each animal was as follows:

Day 1: Water bottle removed from S's home cage; time noted.

2: After 21 hours water deprivation, S removed from home cage, weighed, placed into Open Field arena and timed until it first drank from the water dish in the centre. A further 3 minutes were then allowed for drinking and exploration, the S was replaced in its home cage and allowed free access to water until its bottle was removed at the same time as on Day 1. Amount of defaecation was recorded and the arena was washed down with a deodorizing disinfectant.

3: After a further 21-hour period of water deprivation, S was weighed again then placed in the end of the straight runway where it was timed whilst passing through the four ribbon-screens to reach the G.B and water dish. One minute was allowed for drinking in the G.B, then S was returned to the home cage and allowed water as on Day 2.

4 & 5: Repeat Day 3 pretraining procedure.

Day 3 pretraining was also repeated fortnightly on the day preceding each maze-training trial for Ss taking part in the acquisition and consolidation experiments.

b) Maze-training procedure.

On Day 6, following the usual period of 21 hours water deprivation, pretrained animals received their first experience of the maze. At this stage slight procedural differences distinguish between the three experiments:

i) Procedure of the acquisition experiment.

Day/

Day 6: 21-hour water-deprived S removed from its home cage and weighed. An intraperitoneal injection of 2.5 ml/kg of a solution of mescaline hydrochloride in physiological saline at a concentration of 10 mg/ml (for the 25 mg/kg dose) or 5 mg/ml (12.5 mg/kg dose) was administered to Ss in the experimental groups, and of physiological saline (2.5 ml/kg) to control Ss. After the injection, animals in the sub-groups with a 15 or 55 minute interval between the injection and the start of the maze-run were returned to their home cages for the required period; Ss in the 0 minute interval sub-group were placed into the S.B immediately. Each maze-trial began with a 2-minute habituation period in the S.B, then E raised the guillotine door and simultaneously re-started the stopwatch to measure the Ss latency and the total running time. Each time S touched the screen at the entrance to a cul with its nose, one error for that choice-point was recorded by E. Retracing was recorded as a single error when S went back through the last correct screen, irrespective of the number of culs attempted, so as to avoid giving greater weighting to retracing errors occurring towards the G.B. When S reached the G.B, the guillotine door was lowered behind it and the total time taken to traverse the maze was recorded. S was allowed one minute's reinforcement time to drink from the water dish in the G.B, and was then removed from the apparatus, replaced in its home cage and given free access to water for 12 days. The maze was washed out with an amholytic (Tego M.H.G.) compound in preparation for the next S. In this experiment, days 1 and 3 of pretraining and day/

day 6 (maze-training) were repeated at fortnightly intervals to a total of six maze-training trials. After a further fortnight, days 1 and 3 of pretraining were followed by a maze run for which the procedure was the same as before except that all experimental animals received saline (instead of drug injections) as well as the control group.

ii) Procedure of the consolidation experiment.

Day 6: Control and experimental animals in these groups received exactly the same treatment as those in the acquisition experiment, except that all injections were given immediately after each maze trial, following the 1-minute reinforcement period in the G.B. Days 1 and 3 of pretraining and day 6 (maze-training) were repeated at fortnightly intervals to a total of seven maze-training trials; since the trials for this group did not take place under the influence of the drug, it was not necessary to give a final control run under saline.

iii) Procedure of the recall experiment.

Days 6 - 12: Animals in the two experimental and two control groups were weighed, received injections of saline 2.5 ml/kg and were returned to their home cages for 15 or 55 minutes before being placed in the S.B. The maze-training trials followed the same procedure as in the acquisition and consolidation experiments, but water was only available in the home cage for 3 hours after each trial, and trials took place under saline for seven successive days for each animal.

Days 13 & 14: No trials took place, but the 21-hour water deprivation schedule was/

was maintained.

Day 15: Animals in the two experimental groups received injections of 25 mg/kg or 12.5 mg/kg of mescaline at the appropriate 15 or 55 minute interval before the maze (recall) trial. Control groups received 2.5 ml/kg of saline as before.

RESULTS

Results

The results of the three experiments were recorded in terms of total maze-running time (including latency) and of errors, and are shown in Figures 1 - 12 (Appendix B). Individual results (error scores and running times) for all animals on all trials are given in Tables 1 - 12 (Appendix C). Only the error scores were statistically analysed, the time scores providing a useful, more qualitative, indication of drug effects.

1. Quantitative Results.

a. Results of the Acquisition Experiment.

These results are shown in Figs. 1 - 6 and Tables 1 - 6. The raw error score (Figs. 1, 2 and 3) for each of the 10 animals in the 9 groups on the first maze training trial was compared with the same animal's score on the sixth trial using Wilcoxon's Sign-rank Test of Differences (see Table 13, p. 41).

For the control (saline) groups, this test shows no significant difference between error scores on the first and sixth trial when the trials followed immediately or 15 minutes after the injections, but a significant difference ($p < 0.01$) between trials 1 and 6 when the trials were run 55 minutes after the injections.

For the experimental groups which received mescaline 12.5 mg/kg. at the same three time intervals there are no significant differences between error scores on the first and sixth maze-training trials.

For the experimental groups which received mescaline 25 mg/kg., there/

Experiment I. Acquisition. Results of within-group analysis of error scores by Wilcoxon's signed-ranks test of differences between trials 1 and 6 and between trials 6 and 7 for all groups (2-tailed).

Interval (Mins)	Group	Comparison	N	T	p
0	Saline	Trial 1 vs. Trial 6	9	7	n.s
	12.5 mg/kg mesc.		10	15	n.s
	25 mg/kg mesc.		9	13	n.s
15	Saline		9	18	n.s
	12.5 mg/kg mesc.		7	11.5	n.s
	25 mg/kg mesc.		10	8.5	n.s
55	Saline		8	0	.01
	12.5 mg/kg mesc.		10	14	n.s
	25 mg/kg mesc.		10	4	.02
0	Saline	Trial 6 vs. Trial 7	8	13.5	n.s
	12.5 mg/kg mesc.		7	12	n.s
	25 mg/kg mesc.		9	16.5	n.s
15	Saline		9	13	n.s
	12.5 mg/kg mesc.		5	6.5	n.s
	25 mg/kg mesc.		9	20	n.s
55	Saline		7	10	n.s
	12.5 mg/kg mesc.		9	18	n.s
	25 mg/kg mesc.		5	2.5	n.s

TABLE 13

Experiment I. Acquisition. Analysis of variance and interaction (with designed comparisons) for errors of all animals under all conditions and treatments on trial 6 (Data transformed to Log (x + 1)), showing no significant differences or interactions.

Source of variance	d.f.	s.s.	m.s.	F	p
Interval: 0' + 15' vs. 55' A	1	0.1079	0.1079	$\frac{0.1079}{0.0847} = 1.27$	n.s
Interval: 0' vs. 15' B	1	0.0225	0.0225	$\frac{0.0225}{0.0847} = 0.265$	n.s
Drug: Saline vs. 12.5 + 25 X	1	0.0135	0.0135	$\frac{0.0135}{0.0847} = 0.159$	n.s
Drug: 12.5 vs. 25 Y	1	0.1685	0.1685	$\frac{0.1685}{0.0847} = 1.99$	n.s
Interaction AX	1	0.0222	0.0222	$\frac{0.0222}{0.0847} = 0.26$	n.s
Interaction AY	1	0.0926	0.0926	$\frac{0.0926}{0.0847} = 1.09$	n.s
Interaction BX	1	0.1956	0.1956	$\frac{0.1956}{0.0847} = 2.30$	n.s
Interaction BY	1	0	0	$\frac{0}{0.0847} = 0$	n.s
Within group	81	6.8595	0.0847		
TOTAL	89	7.4825			

TABLE 14

there is no significant difference between error scores on trials 1 and 6 when the trial followed immediately or 15 minutes after the injection, but there is a difference ($p < 0.02$) for the group whose trials were run 55 minutes after the injection.

Wilcoxon's signed-ranks test was also used to compare error scores for each group on the sixth (final drug) trial with scores on the seventh (control saline) trial (Table 13, p. 41). There were no significant differences between the last two trials at any injection/trial interval for any of the control or experimental groups.

In order to compare results after training between the control and experimental groups by means of multi-variate analysis with designed comparisons, it was necessary to transform the data to fit a normal distribution with homogeneity of variance.

Accordingly, each error score (x) for each animal of the nine groups on trials 6 and 7 was corrected by a logarithmic transformation of $x + 1$ (to adjust for zero scores). Bartlett's Test was then applied to the transformed data and showed that the variance was

Experiment I. Acquisition. Analysis of variance and interaction (with designed comparisons) for errors of all animals under all conditions and treatments on trial 7, showing a significant difference between intervals 0' and 15' and a significant interaction between error scores of animals trained under drug doses 12.5 mg/kg and 25 mg/kg at 0' or 15' and at 55' intervals. (Data transformed to Log.(x + 1)).

Source of variance	d.f.	s.s.	m.s.	F	p
Interval: 0' + 15' vs. 55' A	1	0.0226	0.0226	$\frac{0.0226}{0.0586} = 0.386$	n.s
Interval: 0' vs. 15' B	1	0.2802	0.2802	$\frac{0.2802}{0.0586} = 4.782$	< 0.05
Drug: Saline vs. 12.5 + 25 X	1	0.1195	0.1195	$\frac{0.1195}{0.0586} = 2.039$	n.s
Drug: 12.5 vs. 25 Y	1	0.2199	0.2199	$\frac{0.2199}{0.0586} = 3.753$	n.s
Interaction AX	1	0.0725	0.0725	$\frac{0.0725}{0.0586} = 1.237$	n.s
Interaction AY	1	0.5558	0.5558	$\frac{0.5558}{0.0586} = 9.485$	< 0.005
Interaction BX	1	0.0081	0.0081	$\frac{0.0081}{0.0586} = 0.138$	n.s
Interaction BY	1	0.0001	0.0001	$\frac{0.0001}{0.0586} = 0.002$	n.s
Within group	81	4.7447	0.0586		
TOTAL	89	6.0234			

TABLE 15

Experiment II. Consolidation. Differences between error scores within groups on trials 2 and 7 and trials 3 and 7 compared by means of Wilcoxon's signed-rank test.

	Group	Comparison	N	T	p
Post-trial injection	Saline	Trial 2	9	14	n.s
	12.5 mg/kg mescaline	vs.	10	21.5	n.s
	25 mg/kg mescaline	Trial 7	10	15.5	n.s
Post-trial injection	Saline	Trial 3	9	7.5	n.s
	12.5 mg/kg mescaline	vs.	9	17.5	n.s
	25 mg/kg mescaline	Trial 7	10	17	n.s

TABLE 16

was now homogeneous (Trial 6: χ^2 = 5.9580. d.f. = 8; Trial 7: χ^2 = 4.8596, d.f. = 8; $p < 0.1$).

The results of the analysis of variance with designed comparisons on the transformed error scores of all animals on trial 6 are shown in Table 14 (p. 42). From this it will be seen that there were no significant differences between the various conditions or their interactions as compared here. Comparisons made were:

A. Intervals 0 minutes and 15 minutes with interval 55 minutes.

B. Interval 0 minutes with interval 15 minutes.

X. Saline injections with mescaline 12.5 mg/kg. and 25 mg/kg. injections.

Y. Mescaline 12.5 mg/kg. injections with mescaline 25 mg/kg. injections.

Interactions AX, AY, BX and BY were also studied.

The same comparisons were analysed for the error scores of all groups on trial 7 and the results are shown in Table 15 (p. 44). A significant difference ($p < 0.05$) was found here between errors scored by all injection groups when the trial followed immediately after the injection ($\bar{x}_7 = 3.03$) and errors scored when the trial followed 15 minutes after the injection ($\bar{x}_7 = 2.03$). There is also a significant interaction ($p < 0.005$) between the effects of the two drug dose-levels at the combined 0 minute and 15 minute intervals and their different effects at the 55 minute interval (interaction AY). No other significant comparisons were found in this analysis, but a t-test was carried out on the transformed data to test the significance of the difference between the error scores on Trial 7 of the control/

Experiment II. Consolidation. Mann-Whitney U-test of differences in error scores between groups on trials 1, 3, and 7.

Trial	Comparison	N	T	p
1	Saline vs. 12.5 mg/kg	10	92.5	n.s
	Saline vs. 25 mg/kg	10	99	n.s
	12.5 mg/kg vs. 25 mg/kg	10	101	n.s
3	Saline vs. 12.5 mg/kg	10	87.5	n.s
	Saline vs. 25 mg/kg	10	97.5	n.s
	12.5 mg/kg vs. 25 mg/kg	10	97.5	n.s
7	Saline vs. 12.5 mg/kg	10	97	n.s
	Saline vs. 25 mg/kg	10	98.5	n.s
	12.5 mg/kg vs. 25 mg/kg	10	104	n.s

TABLE 17

control group which had always received saline 55 minutes before the training trials, and the experimental group which had received 25 mg/kg of mescaline 55 minutes before the training trials, and the difference was found to be significant ($t = 3.68$, d.f = 18 $\therefore p<0.01$).

b. Results of the Consolidation Experiment

These results are shown in Figures 7 and 8 and in Tables 7 and 8. The error score for each of the 10 animals in the 3 groups on the second maze-training trial (i.e. after one injection) was compared with the same animal's score on the seventh trial by means of Wilcoxon's signed-ranks test of differences (see Table 16, p. 45). There were no significant differences. Trial 3 and Trial 7 were also compared in the same way, and no significant differences were found in this comparison either.

The Mann-Whitney U-test was used to test for differences in error scores between groups on trials 1,3 and 7, but none of the differences reached an acceptable level of significance (see Table 17, p. 47).

c. Results of the Recall Experiment

These results are shown in Figures 9 - 12 and Tables 9 - 12.

The effect of the daily training procedure was assessed as follows: Wilcoxon's signed-rank test was used to compare the error scores on trial 2 of all animals trained 15 minutes after injection with their errors on trial 7, and the difference was just below the level of significance ($N = 12$, $T = 14.5 > 14$, $\therefore$ n.s). The same comparison between trials 2 and 7 was made for all animals trained 55 minutes after injection, and this difference was significant ($N = 11$, $T = 3$, $p<0.01$).

Since/

Since there were so few animals in each group in this experiment, no further attempt was made to analyse the results statistically. However, from inspection of the raw data it is found that they fall into two distinct groups on the final (Recall) trial, as shown below in Table 18.

Experiment III. Recall. Mean error scores of four experimental and two control groups of animals on the final Recall Trial.

Interval (in mins.)	Group	Total Errors	N	Mean Errors
15	Saline	5	4	1.25
	12.5 mg/kg mesc.	5	4	1.25
	25 mg/kg mesc.	24	4	6
55	Saline	3	4	0.75
	12.5 mg/kg mesc.	20	4	5
	25 mg/kg mesc.	7	4	1.75

TABLE 18

There is a striking increase in mean error scores from approximately one, to six in the case of the animals running the recall trial 15 minutes after administration of 25 mg/kg of mescaline, and to five for the group running 55 minutes after 12.5 mg/kg of the drug.

2. Qualitative Results.

a. Acquisition experiment.

Figures 4 - 6 show the mean maze-running times of animals in this experiment. The graphs show fairly typical learning curves; running times are progressively reduced throughout training. On trials following immediately after/

after injection, the drug and control groups show little difference in running times, apart from a slight peak for both drug groups on trial 5. All three groups converge on the final saline trial. On trials following 15 minutes after injection, the 12.5 mg/kg. mescaline group and the saline control group show very similar running times throughout the training trials; the 25 mg/kg. drug group's running times are considerably slower on training trials, but converge with the other groups on the final saline trial. On trials run 55 minutes after injection, the control group and the 25 mg/kg. drug group show roughly similar running times throughout training, with the 25 mg/kg. mescaline group slightly quicker than the control group on each trial, whereas the 12.5 mg/kg. drug group are slower on all trials and on trials 4 - 7 the difference is considerable and convergence is not shown on trial 7.

A subjective impression of loss of muscle tone was recorded by E if its presence was apparent during the experiments. In the acquisition experiment, on trials following immediately after injection, loss of muscle tonus was not noted on any trial for any of the animals which had received 12.5 mg/kg. of mescaline, but in the group which had 25 mg/kg. of mescaline some loss of muscle tone was observed in one animal on trial 3, in one (different) animal on trial 4, and in two (different again) animals on trial 5. In the experimental groups whose injections preceded trials by 15 minutes, some loss of muscle tonus was noted on trials 2, 3 and 4 in one of the animals under 12.5 mg/kg. mescaline, and in a different animal in this group on trial 5. Of the 25 mg/kg. mescaline group, one animal showed severe loss of muscle tonus on all six training trials, a second on trials 3, 4, 5 and 6, a third on trials 2 and 5, and a fourth on trial 4. No loss of muscle tonus was shown by any/

any of the experimental animals in the groups receiving drug injections 55 minutes before training trials, but it was noted that three of the animals in the 12.5 mg/kg. group showed unusual nervousness (e.g. starting at slight noises and making a very "timid" approach to the screen doors) throughout training.

b. Consolidation experiment.

Fig. 8 shows mean maze-running times of the three groups which received post-trial injections throughout training in this experiment. The graphs show negative learning curves with a sharp rise from trials 1 to 2 in all groups, and little reduction in running times during training for any group. Running times for the 25 mg/kg. mescaline group are slower than those of the other two groups on each trial, and the difference is very marked on trials 4, 5 and 6.

E's impressions of the animals' behaviour during the experiment were recorded. It was noted that several of the animals were exceptionally nervous, attempting to jump out of the S.B during the two-minute habituation period, avoiding the correct door at choice-point D, and refusing to enter the G.B.

c. Recall experiment.

Figs. 11 and 12 show mean maze-running times of the six groups in the recall experiment. Compared with saline groups in the other experiments, the running times for the groups trained 15 minutes after daily saline are remarkably quick. No effect is shown on running time by 12.5 mg/kg of mescaline/

mescaline injected 15 minutes before the recall trial, but 25 mg/kg. of mescaline injected 15 minutes before recall increases mean running time from 88 seconds (trial 7) to 584 seconds (trial 8). Of the four animals involved, three were noted to have greatly impaired motor function and loss of muscle tonus on this trial, while the fourth appeared to be unaffected by the drug. None of the 12.5 mg/kg. group showed any motor impairment.

In the groups whose injections preceded training and recall by 55 minutes, mean running times during training are erratic from trial to trial, and in general much slower than those for the 15-minute interval groups. The group which received mescaline 12.5 mg/kg. on the recall trial showed an increase in running time from training trial 1 to training trial 7, and a further increase under the drug on the recall trial. The control group showed some reduction in running times through training which was maintained on the recall trial, as did the mescaline 25 mg/kg. group. No loss of muscle tonus or other abnormality was observed in any animal at the 55-minute interval after either drug dose.

DISCUSSION

Discussion

1. Interpretation of results.

a. Acquisition Experiment

In this experiment, training in the maze took place under the influence of two different dose-levels of the drug at three time intervals after administration of the drug (6 experimental groups), or under saline at three time intervals (3 control groups). Training was followed (all groups) by a control run under saline administered at the same pre-trial interval as the training injections.

Table 13 (p. 41), showing the results of an analysis of the errors scored within each experimental and control group, indicates the level of learning achieved by each group during training, and the level of performance maintained on the final control trial. A significantly lower error score on trial 6 as compared with trial 1, indicating that a statistically acceptable level of learning has been achieved during training, is shown by only one (55 minute interval) of the saline control groups, by none of the groups trained under 12.5 mg/kg mescaline, and by ~~one (0 and~~ (55 minute intervals) of the groups trained under 25 mg/kg. of mescaline; that is, under the conditions of this experiment, no learning is shown by groups of rats trained 0 minutes or 15 minutes after being injected with physiological saline, but learning is shown when the injections preceded training trials by 55 minutes. Training trials which were preceded by injections of 12.5 mg/kg. of mescaline at these three time intervals resulted in no statistically acceptable decrease in number of errors; that is, no learning was shown. Training under 25 mg/kg. of/

of mescaline produced demonstrable learning when injection preceded the trials by 55 minutes, but not when the interval was 0 minutes or 15 minutes.

The comparison between the final training trial and final control trial score for each group was carried out in order to test for any dissociation effect. As would be expected, there is no evidence of any difference in performance between these two trials for any of the control groups. No difference was found for any of the drug groups at any interval either, showing that performance under the drug was not directly or exclusively dependent on drug effects.

The between-group comparisons which were made by the multivariate analysis of error scores on trial 6 showed no significant differences or interactions between conditions. The indication is that the various injected substances and injection-trial intervals employed during training, and the different combinations of these conditions, had no differential effects on performance in the maze as measured by error scores at the end of training. Unfortunately, the assumption must be made that since animals were randomly assigned/

assigned to groups, the learning capacities of the groups were equivalent at the outset. This may or may not have been the case; but since there is no means of testing the assumption, any differences shown between groups at the beginning of training must be attributed to the experimental conditions, and not to differential learning effects. As learning was of primary interest, between-group error scores on early trials were not analysed.

It is interesting to observe from Figs, 4, 5 and 6 that maze-running times on trial 6 (and indeed throughout training) show a high degree of differentiation between groups. More particularly, the groups which received 25 mg/kg. of mescaline 15 minutes before training trials, or 12.5 mg/kg. of mescaline 55 minutes before training trials show a very marked increase in running times over control groups at these intervals which is not accompanied by increased error scores and therefore presumably indicates some motor disability. In the case of the group which had been injected with 25 mg/kg. of mescaline 15 minutes before the trial, this debilitating motor effect was expected, as previous work (e.g. (62)) has shown that after such an interval this dose frequently induces loss of muscle tone; this hypothesis is upheld by the fact that these animals achieved the maze-run in the same time as their control group on the last trial, when the drug had not been administered. The slowing down of the group whose training trials took place 55 minutes after injection of 12.5 mg/kg. of mescaline, on the other hand, was not expected from previous findings (if anything the opposite would seem to be indicated), does not appear to be correlated with observable loss of muscular control, and does not disappear upon withdrawal of the drug (trial 7).

The/

The analysis of variance between conditions on trial 7 shows that significantly more errors were scored by groups whose trial followed immediately after the injection, than by those groups which had an interval of 15 minutes between the injection and the maze-run. Since all groups received saline on this trial and conditions were identical apart from the injection-trial interval, the difference may be attributed to the immediate effects (e.g. discomfort or nervousness) of the injection. A comparable difference is apparent between all groups at these time intervals on trial 1 ($\bar{x}$ 0' = 5.4, $\bar{x}$ 15' = 4.1).

There is a significant interaction between the difference in errors scored on trial 7 (without the drug) by the experimental groups which had been trained under the two dose levels of mescaline at the combined 0 and 15 minute intervals and at 55 minutes. Performance on trial 7 reflects the learning which had taken place under the influence of the drug during the six training trials. The interaction signifies that through time the effects of the two dose levels changed in opposite directions. Performance on trial 7 indicated that a higher level of maze-running accuracy had been reached during training at 0 or 15 minutes after injection of mescaline 12.5 mg/kg. than at 0 or 15 minutes after mescaline 25 mg/kg., while training 55 minutes after 12.5 mg/kg was <u>less</u> effective and 55 minutes after 25 mg/kg was <u>more</u> effective than either.

A t-test showed that under identical conditions on trial 7, the group of animals trained 55 minutes after injection of 25 mg/kg of mescaline performed significantly better than the control group trained 55 minutes after injection of saline. There was no difference between these groups on the/

the first training trial, so the difference is attributable to a facilitating effect on learning of the high dose level of the drug after this time interval. The nature of this effect is considered below (p. 69).

b. Consolidation experiment.

There was no significant difference between error scores on trials 2 and 7 or trials 3 and 7 (table 16, p. 45) indicating that no learning was achieved by any of the groups in this experiment; all groups had a higher total of errors on their final run than on their initial run. There were no differences between the three groups on trials 1, 3 or 7 (Table 17, p.47). The lack of any learning is probably accountable in terms of a negative reinforcing effect of the post-trial injections; as can be seen from Fig. 8 (p. 94), the increase in number of errors was accompanied by increased running times, and this was particularly marked in the group receiving post-trial injections of 25 mg/kg of mescaline. These points are discussed in more detail below (p. 63, 70).

c. Recall experiment.

Learning during training was measured by comparing error scores on trials 2 and 7 for all animals. No significant difference was found for those Ss trained 15 minutes after injection, but there was a significant learning effect for the animals trained 55 minutes after injection. It would seem then that even an injection of saline given 15 minutes before training has some disrupting effect on learning and/or performance which it does not have after 55 minutes.

Performance on the Recall trial by the two control groups was a mean score of approximately one error, and this level was approximated also by the 15-minute/

minute 12.5 mg/kg. mescaline group and the 55-minute 25 mg/kg. mescaline group, in which the drug was thus not shown to affect recall. In the 15-minute 25 mg/kg. mescaline and the 55-minute 12.5mg/kg. mescaline groups, the mean error score on recall rose respectively to 6 and 5, indicating the possibility of a deleterious effect on recall of these dose-levels after these time intervals. In interpreting these data it must of course be kept constantly in mind that the numbers of Ss involved in the experiment were too small to permit any firm conclusions to be drawn. The results are suggestive, but may be an artefact of random individual variation both in learning capacity and in sensitivity to drug effects.

The maze-running time scores of the six groups in the recall experiment follow the pattern of their error scores very closely (Tables 9 and 10

10 c.f., Tables 11 and 12) except for the disproportionately great increase in running time on the recall trial of the group which received 25 mg/kg. of mescaline 15 minutes before the trial. The mean running time of this group is over 50% higher than that for any other group on this dosage of the drug in any of the experiments. Thus the degree of motor disability produced by 25 mg/kg. of mescaline after 15 minutes would seem to be situationally dependent. In Experiment I, where initial experience of the maze took place under the influence of 25 mg/kg. of the drug after 15 minutes the mean running time (n = 10) on trial 1 was 345 seconds, compared with a mean running time (n = 4) of 584 seconds for the recall trial which was run 15 minutes after injection of 25 mg/kg. of mescaline.

2. Discussion of findings.

The results of the saline control groups are of general interest and assistance in considering the experimental results and will be discussed first.

In the acquisition experiment, three control groups of 10 animals each received injections of saline 0, 15 or 55 minutes before seven fortnightly maze trials. In the recall experiment, two groups of 12 animals each received injections of saline 15 or 55 minutes before seven daily maze trials. In both experiments the only control group to reach a statistically acceptable level of learning (measured by reduction in number of errors) was that with an injection/trial interval of 55 minutes. This demonstrates two points of general relevance to the rest of the findings:

i. It is possible for a rat to achieve acquisition of a 4-choice maze habit in only seven trials, and such training is equally effective/

effective at daily and fortnightly intervals.

ii. Under otherwise identical conditions, learning is achieved when training is given 55 minutes after a saline injection while learning is not demonstrated under training which took place immediately or 15 minutes after a saline injection. A recent injection appears to be in some way disruptive of learning capacity as measured by performance. This is further borne out by the significant difference found between all groups at the 0 minute and 15 minute intervals in the analysis of variance of errors on trial 7 (Table 15, p. 44). The more recent the injection, the more disruptive it is.

The control group in the consolidation experiment illustrates a further point; errors and running times increase sharply from trial 1 to trial 3, then drop gradually to a level on trial 7 which is approximately the same as on trial 1. The post-trial injection, whilst acting as a negative reinforcement to acquisition of the maze habit during training trials, is also creating a situation of conflict with the positive reinforcement offered to the thirsty animal by the water in the G.B. In this situation, trial 1 represents a trial-and-error run at the end of which the thirsty animal found water and was then subjected to the discomfort of a saline injection. On trials 2 and 3 the conflict between approaching the positive reinforcement and avoiding the negative one causes an increase in both errors and running times and some attempts to escape from the situation which are typical of the "experimental neurosis" caused by such conflict situations. With the gradual onset of habituation to the injection procedure, the strength of the "avoidance drive" is lessened, whilst the need for the positive reinforcement/

reinforcement remains the same on each trial so that the comparative strength of the "approach drive" is increased. This process is seen at work during trials 4 - 7 where errors and running times are gradually reduced as the strength of the "avoidance drive" diminishes; by trial 7 the original trial-and-error level is reached.

The concept of avoidance itself presumes knowledge of the maze, and evidence from the control groups of the acquisition and recall experiments shows that without an immediately (0 - 15 minutes) preceding injection a significant level of learning could be expected by trial 7, therefore the existence of a pre-training level of errors on trial 7 in the control group of the consolidation experiment indicates that the avoidance factor has not been entirely eliminated by this stage. Unfortunately the experiment was terminated after trial 7, so no evidence was obtained to indicate whether further reduction in avoidance and consequent improvement in performance would have occurred had trials continued. Further interesting information might also have been obtained by continuing trials without giving any injections, and estimating learning by the 'savings' method (performance during this group's re-learning compared with other control groups' original learning) after extinction of the avoidance response. It is also possible that the injection was traumatic enough (at least on the early trials) to produce some retrograde amnesia for the maze.

To turn now to a consideration of the drug effects in the experiments in the light of the foregoing discussion: the 12.5 mg/kg. dosage of mescaline will be considered first. In the acquisition experiment, none of the groups trained immediately, 15 minutes or 55 minutes after this dosage/

dosage achieved a significant degree of learning. In the recall experiment, 12.5 mg/kg. of mescaline had no ~~significant~~ effect on recall at ~~either~~ the 15-minute interval, but it increased errors at the 55-minute interval. ~~or the 55 minute interval.~~ In the consolidation experiment, no learning was demonstrated during training by the animals receiving post-trial injections of 12.5 mg/kg. of mescaline, and the mean error score on the final trial was higher than on the first trial. It seems then that where some learning might have been expected on the basis of the control groups' results (i.e. where training took place 55 minutes after injection), such learning was in some way inhibited by the administration of a low dosage of mescaline. In other respects the 12.5 mg/kg. mescaline groups differ very little from their respective control groups. One remarkable finding, however, is the noticeably increased mean running-time for the 12.5 mg/kg. 55-minute interval group in the acquisition experiment as compared with their own control group and with 12.5 mg/kg. groups at the shorter time intervals. A similar increase in running time is seen on the recall trial 55 minutes after mescaline 12.5 mg/kg., but as already mentioned, the sample was too small and the individual variation too great for any reliable conclusions to be drawn from the results of the recall experiment.

The basis of the increased running times and inhibition of learning occurring 55 minutes after administration of 12.5 mg/kg. of mescaline cannot be attributed to direct effects of the drug on learning until several other possible factors have been eliminated. The first of these is the question of motivation; there is nothing in the experiments to test the hypothesis that the drug reduces (or alternatively increases) thirst, except the single control run on trial 7. In the event of the drug directly reducing motivation it/

it would be expected that a certain amount of latent learning would occur during training and would become evident on trial 7. This did not happen, so reduced motivation can reasonably be excluded. The second hypothesis, that the drug inhibited learning by interference with attention during training, cannot be discounted within the present frame of reference and must therefore be considered a possible determinant of performance 55 minutes after 12.5 mg/kg. of mescaline.

On the basis of the combined results of the three experiments it would seem that 12.5 mg/kg. of mescaline has little or no effect on performance or learning of a maze task after 0 minutes or 15 minutes. At 0 or 15 minutes after injection, 12.5 mg/kg. of mescaline had no observable motor effects in terms of either maze-running times or loss of muscle tonus. At these time intervals no learning was achieved and recall (15 minutes) was unaffected but performance was not significantly different from that of control groups so the drug injection was no more disruptive than the saline injection, nor was the direct effect of the drug shown to be in any way either inhibiting or facilitating to learning or performance. No differences were shown between trials 7 and 6 in Experiment I, so learning differences were not being masked by direct drug effects on performance. In the acquisition experimental groups whose trials took place immediately after the injections, it is, of course, possible that the relatively slow-acting drug did not take effect until the end of, or even after, each training trial. In this sense the control and experimental groups are not qualitatively strictly comparable, as the drug may be affecting the consolidation period to an unknown extent. The differential effects are difficult to assess, but the possibility that facilitation/

facilitation or inhibition during consolidation after each trial was being cancelled out on each subsequent performance respectively by greater or lesser immediate disruption by drug injection is contra-indicated by the similarity between experimental and control groups on trial 7.

In the consolidation experiment proper (Experiment II), the case which has already been argued in the discussion of the control groups' results is equally applicable to the 12.5 mg/kg. post-trial injections of mescaline. There are no significant differences between the saline and 12.5 mg/kg. mescaline group, and the only observable difference is that the peak at trial 3 is less evident in the 12.5 mg/kg. mescaline group and there is a more gradual increase in errors and running times throughout training. In view of the high individual variation shown by animals in this experiment, this is probably a meaningless observation though it might indicate slower learning of the maze and therefore less efficient avoidance in the early stages. The results of Experiment I have shown that the injection of 12.5 mg/kg. of mescaline is equivalent to injection of saline in disruptive effect, so any difference in the relative negative reinforcing or traumatic effects of the post-trial injections is discounted. This experimental design was probably unsuitable for testing the effects of mescaline on the consolidation period of learning, as the exact time necessary for the drug to take effect is not known but it is probably longer than the 1 - 2 minutes required for consolidation.

The experimental results from the groups which received the 25 mg/kg. dosage of mescaline are quite different again from both the control groups and the low dosage experimental groups. In the acquisition experiment,

a/

a significant learning level was reached during training trials which followed 55 minutes after injection of mescaline 25 mg/kg. Also, on trial 7 the 55-minute interval experimental group made significantly fewer errors than their control group. In the consolidation experiment, no learning was shown by the group receiving 25 mg/kg of mescaline by post-trial injection. In the recall experiment, there was an increase in errors during recall 15 minutes after injection of 25 mg/kg of mescaline, but no difference 55 minutes after injection.

From a comparison of the saline control groups and the 25 mg/kg drug groups in the acquisition experiment, it is observed that at the 0-minute interval no significant improvement was shown through training by drug group, i.e. as in the control group, no learning was achieved. The drug injectionwas therefore assumed to be equally as disruptive as the saline injection, and the drug itself was neither facilitating nor inhibiting to learning at this time interval. There was no slowing of maze-running when trials followed immediately after injection of 25 mg/kg. of mescaline, and loss of muscle tone was noted only rarely, so lack of learning is not attributed to a debilitating motor effect of the drug during training.

No/

No learning was demonstrated statistically for any of the groups trained 15 minutes after injection. In the case of the 25 mg/kg. drug group this absence of learning was accompanied on drug trials by the expected increase (c.f. 58,62) in maze-running times due to varying degrees of loss of muscle tonus; that this was a direct drug effect on motor aspects of performance is demonstrated on trial 7, where running times for this group are exactly equivalent to those of both the other groups at this time interval. That it is a pure motor effect is shown also; errors did not increase or decrease with running times. At 15 minutes after injection, 25 mg/kg. of mescaline has a debilitating motor effect, but little effect on motivational, attentional or neurological factors associated with maze-learning.

The group of animals receiving 25 mg/kg. of mescaline 55 minutes before maze training trials showed a significant level of learning through training and upheld improvement on control-trial 7, where they performed at a significantly better level than the comparable control group. This interval after 25 mg/kg. injection is the one shown by Smythies et al.(62, 63) to produce reduced reaction times in the conditioned avoidance situation. Maze-running times in the present experiment were also slightly reduced throughout training. At 55 minutes after injection, 25 mg/kg. has a stimulating effect, reflected in reduced reaction times, reduced maze-running times and improved maze-learning performance; the exact nature of this stimulating effect remains obscure. Increased motivation to reach the water in the G.B. of the maze would not account for reduced reaction-time in the shuttle-box. Increased "attention" or "awareness" would account for improved accuracy of performance in both situations, but would hardly cover reduced running/

running-times in the maze. The evidence points towards a stimulating effect on the central nervous system; after 55 minutes in the system, is this a direct effect of mescaline, or the effect of a metabolic derivative of the drug to which the CNS is more susceptible? Expansion of this general discussion is held over until consideration of the experimental results has been completed.

The results of the group receiving 25 mg/kg. of mescaline by post-trial injection in the consolidation experiment conform closely to the results of the other groups in this experiment, and the points which have already been raised during discussion of these are equally applicable. Errors increased from trials 1 to 3 of training, and then dropped gradually to remain slightly higher on trial 7 than on trial 1. The drug is not shown to have had any effect on learning under the approach-avoidance conflict situation of the experiment, but no direct interferences about the drug can be drawn from this observation as it is probable that the time-lag between completion of the trial and the onset of any drug effect was more than sufficient for consolidation to have taken place. In terms of retrograde amnesia, if this is seen as the cause of the absence of learning in this experiment, the deficit resulting from drug injection does not differ quantitatively, except perhaps in the increase in running times, from that produced by saline injection.

The animals in the recall experiment, who had had considerable training in the maze before running it under the influence of 25 mg/kg. of mescaline, showed a large increase in errors and running times 15 minutes after the drug compared with their final training trial, and a very slight

~~(non)~~ increase/

~~(no significant)~~ increase in errors and running times 55 minutes after the drug. Compared with the groups which received 25 mg/kg. of mescaline 15 and 55 minutes before acquisition trials, it can be seen that in the familiar recall situation the effect of this dose level on performance is much more devastating (particularly after 15 minutes) that is the same dosage after the same time interval when the animal is experiencing the maze for the first time. This would seem to point to some relationship between level of autonomic arousal and drug effect (c.f. 2); some such hypothesis might be stated thus: "Resistance to drug effects increases and decreases with autonomic arousal." But one would be led to predict from this hypothesis that during training in the acquisition experiment arousal would be gradually reduced from trial to trial by habituation and that the drug effects would therefore become more severe throughout training; Figs. 2 and 5 do not confirm the prediction. This does not necessarily negate the hypothesis - it may be, for example that each trial under the (minimised) effects of the drug in some way reinforced a fear response involving increased autonomic arousal, and that arousal therefore remained high throughout training. The hypothesis that some relationship exists between drug effects and arousal seems to require further investigation.

In summary, the results of the three experiments have shown that under these conditions acquisition of a maze ahbit can be achieved by rats in 7 trials even at fortnightly intervals; than an injection a short period before trials is disruptive to performance; and that a post-trial injection produces a conflict situation in which some animals display behaviour reminiscent of 'experimental neurosis'. Overlaid on this pattern are the drug/

drug effects in the experimental groups; 12.5 mg/kg did not produce any significant deviation from the controls' results at any time interval, and there was only one remarkable observation; after 55 minutes during acquisition and recall, this dose level appeared to increase maze-running times. 25 mg/kg of mescaline injected immediately before training trials had no effect on acquisition of the maze-habit; injected 15 minutes before trials it caused loss of muscle tone (without increased errors or demonstrable learning) during training, and impaired motor performance and recall; injected 55 minutes before trials it facilitated acquisition (reduced errors and time), but recall was unaffected. The consolidation experiment was unsatisfactory in terms of drug effects.

As has already been suggested, the facilitation of learning observed during acquisition of the maze habit 55 minutes after injection of 25 mg/kg of mescaline seems most likely to be due to a central stimulating effect of the drug. But no such stimulating result is apparent 15 minutes after the drug; here, all the evidence points to a debilitating motor effect. It is therefore postulated that 25 mg/kg of mescaline has two distinct effects of the organism:

i) a debilitating motor effect, becoming apparent 12 - 15 minutes after injection, suscebtible to autonomic arousal and wearing off after a maximum of about 30 minutes, comparable to the neuromyal blocking action described by Schopp et al (58); and

ii) a CNS stimulant effect apparent at full strength 50 - 60 minutes after injection when the masking muscular effect has subsided.

Although entirely hypothetical, this

would/

would seem to be the most parsimonious explanation of the observed drug effects. The processes involved in recall of a partially learned habit are apparently less susceptible to the stimulating effects of the drug than are the processes involved in ~~the~~ acquisition. Whether the two described functions are independent or not is a matter for further speculation; if independent, it seems likely in view of (58) that the peripheral effect is a direct product of mescaline, whilst a metabolic derivative of the drug, ~~beginning to be formed almost immediately after injection and~~ accumulating with greater in vivo stability than the drug itself, may be responsible for the central stimulation. The derivative may also be less susceptible than mescaline to factors involved in autonomic arousal, e.g. adrenaline, or such factors may speed up its formation.

It is unlikely that the two distinct drug effects are related to different levels of concentration of the drug in the blood stream, as at no stage during the time intervals studied did the results of injection of 12.5 mg/kg. of mescaline produce any evidence of central stimulation; no learning was achieved by these groups. Contrary to expectation, maze-running times were somewhat increased 55 minutes after injection of the low dosage. Evidence for a distinct differential effect of the two dose levels during acquisition comes from the analysis of interaction on trial 7; training 55 minutes after 25 mg/kg. of mescaline was significantly more effective than training a short interval after either dose or 55 minutes after 12.5 mg/kg. While 25 mg/kg. of mescaline shows a stimulating effect on acquisition ~~immediately, and~~ 55 minutes after administration, 12.5 mg/kg. of mescaline shows no such effect at any time interval, and indeed may have a slight inhibiting/

inhibiting effect on learning, though the evidence for this is by no means conclusive. If an inhibitory factor is present, its effects could be due to reduced attention combined with some degree of motor retardation (without loss of muscle tone). It is improbable that a low dose of a drug which in a higher dose has been shown to have central stimulating properties, should be centrally inhibiting.

Finally, the effects of mescaline on learning must be related to the general trends of allied work. Facilitation of maze learning in rats by CNS stimulants, e.g. strychnine, picrotoxin, 1757 I.S., has been profusely reported. Techniques and conditions have varied and opinions have diverged, but the consensus at the moment tends to associate facilitation with CNS stimulants and, to a lesser extent, inhibition of learning with central depressants. The results of the present study suggest the possibility that mescaline (25 mg/kg.) may be another candidate for the list of stimulants with a facilitating effect on learning, though some of the implications of the sequence of behavioural changes after this dosage, and of the effects of 12.5 mg/kg. need clarifying before any generalised claims are made about this drug.

It must also be kept constantly in mind that mescaline is, in at least one respect, quite distinct from the other identified CNS stimulants and as yet unique among the learning facilitators, its most obvious property being its hallucinogenic nature. Chemically, this is now known to depend upon the presence of at least three methoxy groups, which must occupy the 3-, 4- and 5- positions, on the phenethylamine molecule. Pharmacologically, however, the metabolic fate of the drug and its mode(s) of action are still obscure/

obscure. I have suggested that a metabolic derivative of mescaline facilitates one or more of the neurological processes at the level of the CNS which are involved in learning. Whether this involves stimulation at a cellular level and increase in spontaneous firing; or reduction of the cellular refractory period allowing more rapid reverberation; or facilitation of synaptic transmission by chemical means, or any other known or unknown mechanism of central transmission, remains to be seen. Even more obscure are the corollary questions of whether the central stimulating function of mescaline is neurologically analogous to that of other central stimulants, and whether mescaline's hallucinogenic and stimulant properties can be related to a single central function crucial to both perception and learning and vulnerable to biochemical lesion, for example in some types of schizophrenic illness showing perceptual distortion.

CONCLUSION

Conclusion

From the results of three experiments designed to investigate some of the effects of mescaline on maze-learning in the rat, the following conclusions are drawn:

i) A dose of 12.5 mg/kg of mecaline HCl administered i.p to a rat immediately, 15 minutes or 55 minutes before each of six fortnightly training trials in a 4-choice point maze probably inhibited some acquisition of the maze habit which might otherwise have been expected and may have had a retarding effect on recall and maze-running times after the 55-minute interval, Inhibition may have been due to reduced attention.

ii) A dose of 12,5 mg/kg of mescaline injected immediately after each of seven fortnightly training trials in the maze had no effect which would not have been expected. The drug was probably not active during consolidation.

iii) A dose of 12.5 mg/kg of mescaline injected 15 minutes before a recall trial in a maze previously practised once daily on 7 successive days had no effect on recall but the same dose may have had a retarding effect on recall and running times after the 55-minute interval.

iv) A dose of 25 mg/kg of mescaline injected 0 or 15 minutes before each of six fortnightly maze-training trials had no effect on acquisition of the habit but at the 15 minute interval it had a marked retardation effect on running times. A similar dose injected 55 minutes before training trials facilitated acquisition of the maze habit with little effect on running times. The biphasic effects of the high dose-level on acquisition are accounted for by postulating

a/

a primary debilitating drug effect on muscle, accompanied by a secondary (perhaps independent) central stimulating effect responsible for the facilitation of acquisition.

v) A dose of 25 mg/kg of mescaline injected immediately after training trials had no effect on maze-learning, but was probably not active until after sufficient time had elapsed for consolidation to have taken place.

vi) A dose of 25 mg/kg of mescaline injected 15 minutes before a recall trial had an adverse effect on recall and a marked retardation effect on running times. A similar dose injected 55 minutes before the trial had no effect on recall or running times.

Mescaline was found to have a dose-dependent time-dependent facilitating effect on acquisition of a maze habit and this was tentatively attributed to a metabolic derivative having this property in common with some of the known CNS stimulants. A retardation effect of the drug on motor performance may be dependent on autonomic arousal.

APPENDIX A:

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APPENDIX B:

FIGURES 1 - 12

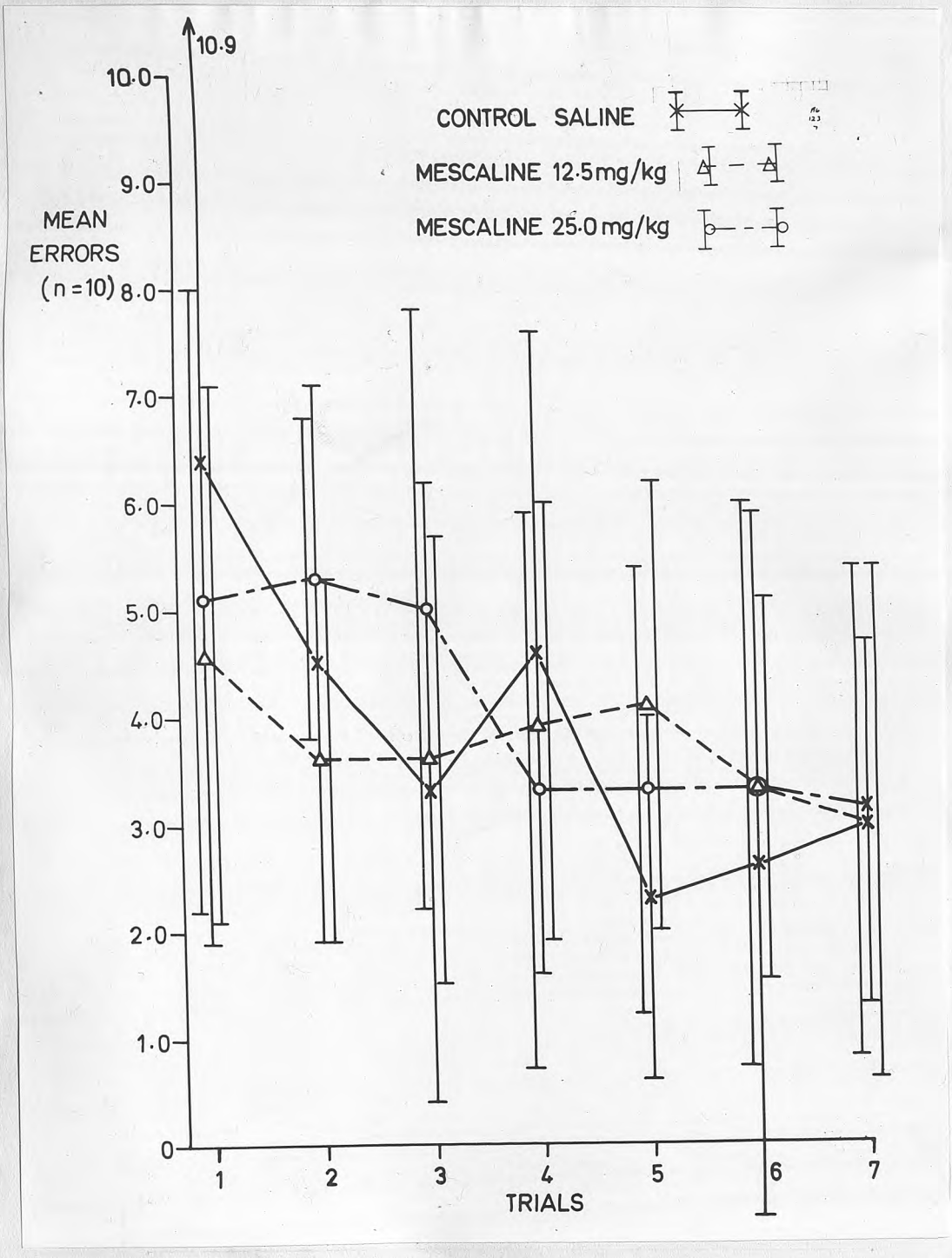

FIGURE 1: Experiment I, Acquisition. Mean number of errors (± S.D) made by 3 groups of 10 rats under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered immediately before each of 6 fortnightly trials in the maze. Animals of all groups received Saline immediately before trial 7.

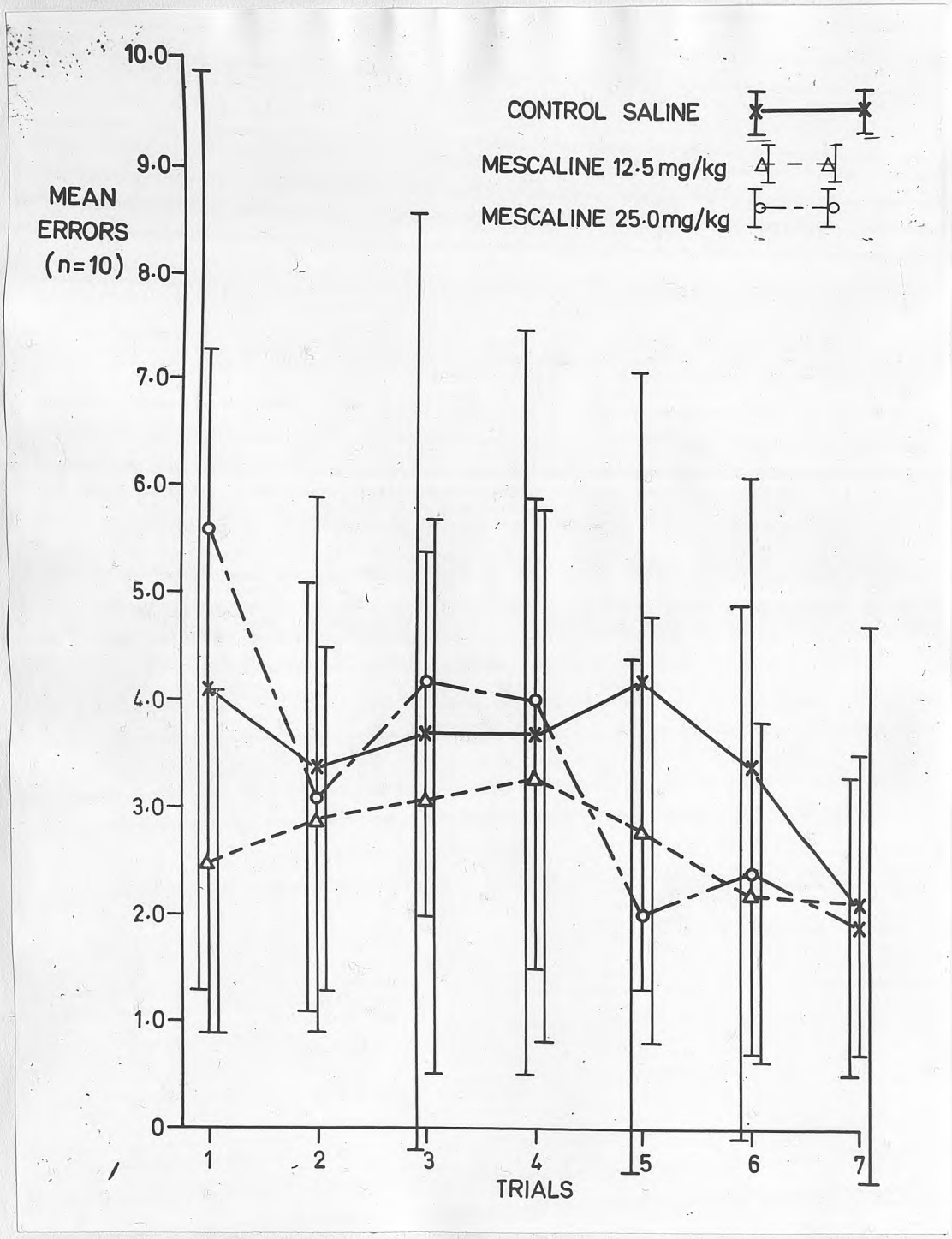

FIGURE 2: Experiment I. Acquisition. Mean number of errors (± S.D) made by 3 groups of 10 rats under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 15 minutes before each of 6 fortnightly training trials in the maze. Animals of all groups received Saline 15 minutes before trial 7.

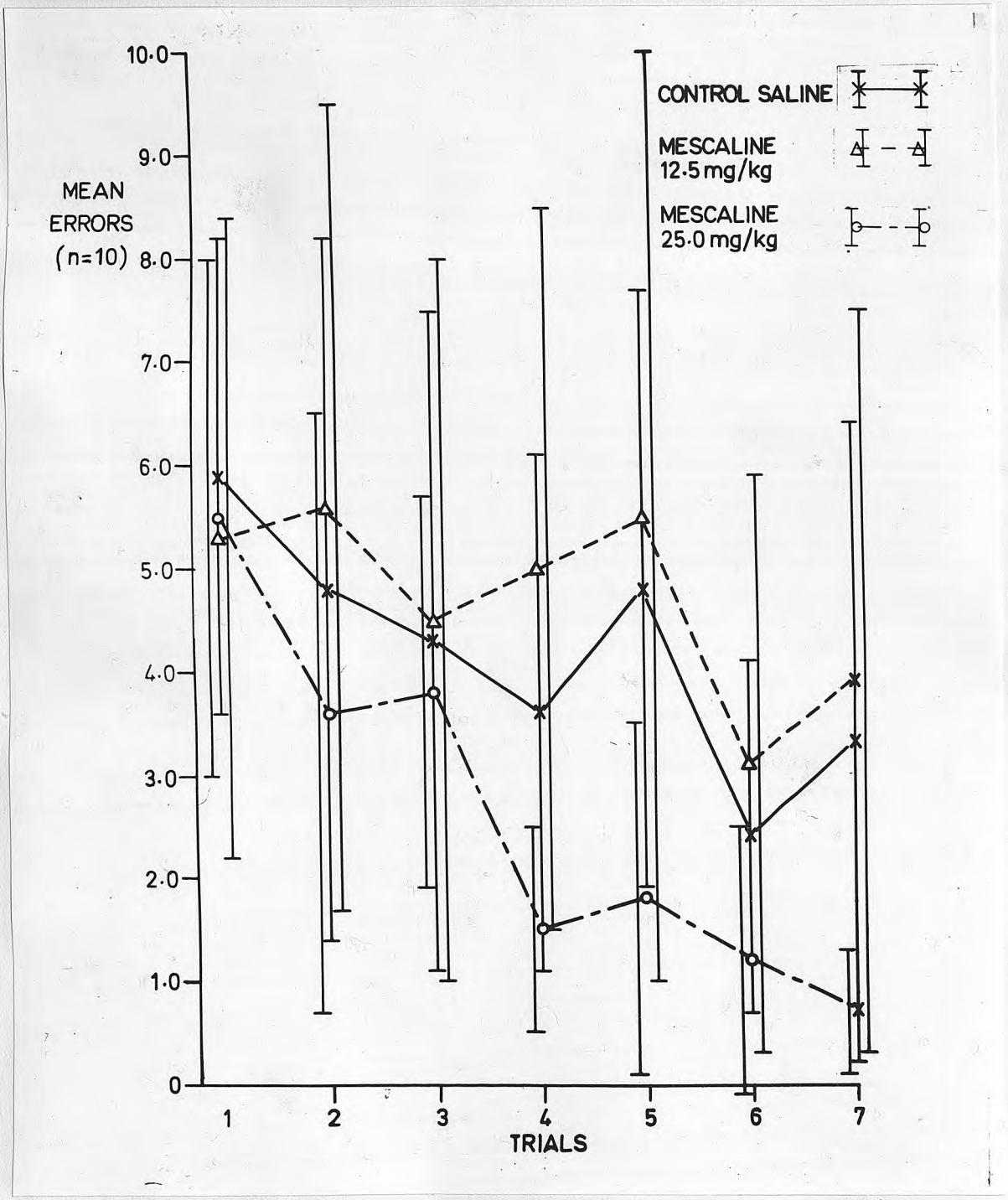

FIGURE 3: Experiment I. Acquisition. Mean number of errors (± S.D) made by 3 groups of 10 rats under Saline, Mescaline 12.5. mg/kg. or Mescaline 25 mg/kg. administered 55 minutes before each of 6 fortnightly training trials in the maze. Animals of all groups received Saline 55 minutes before trial 7.

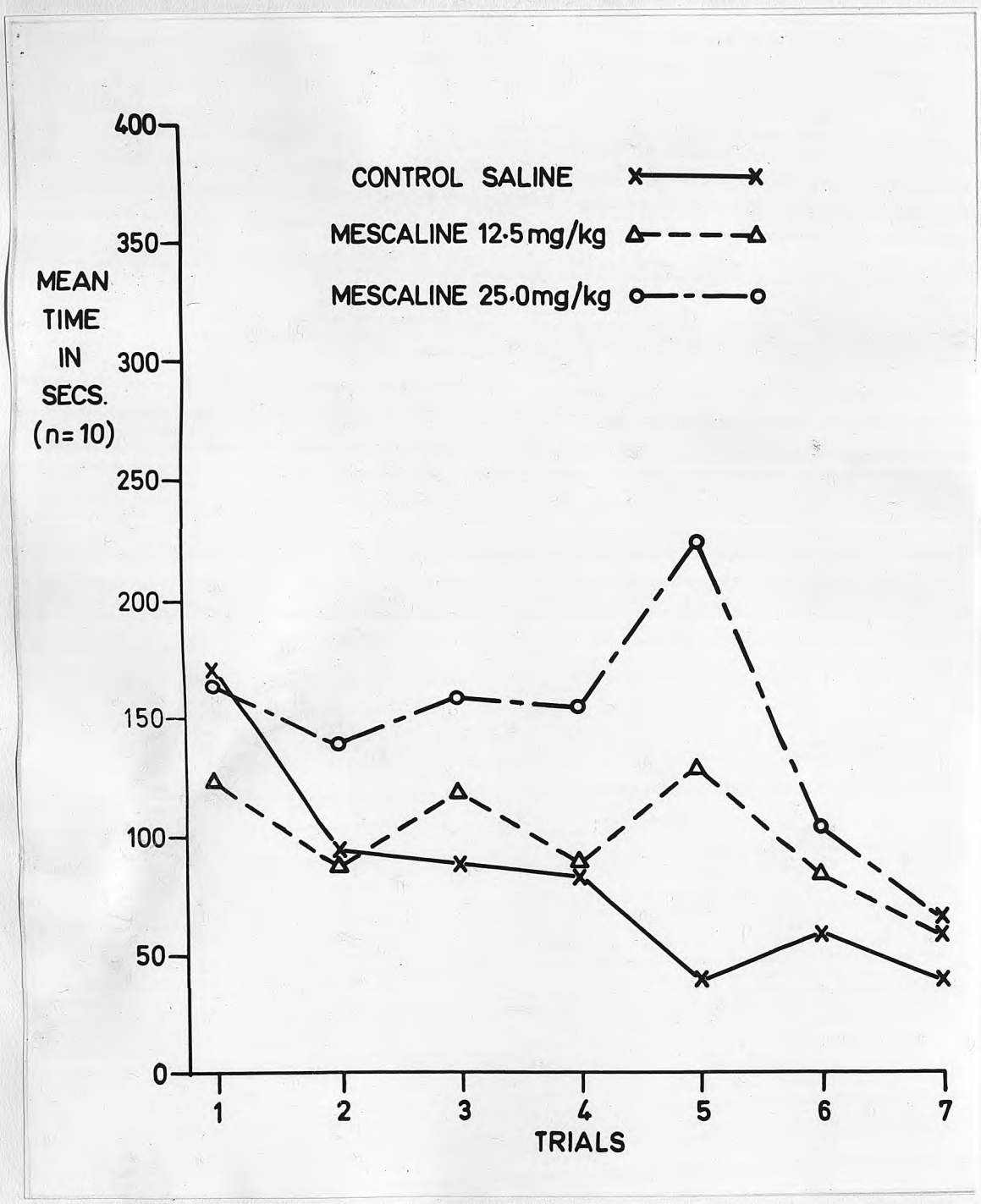

FIGURE 4: Experiment I. Acquisition. Mean time in seconds taken to run the maze by 3 groups of 10 rats under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered immediately before each of 6 fortnightly training trials. Animals of all groups received Saline immediately before trial 7.

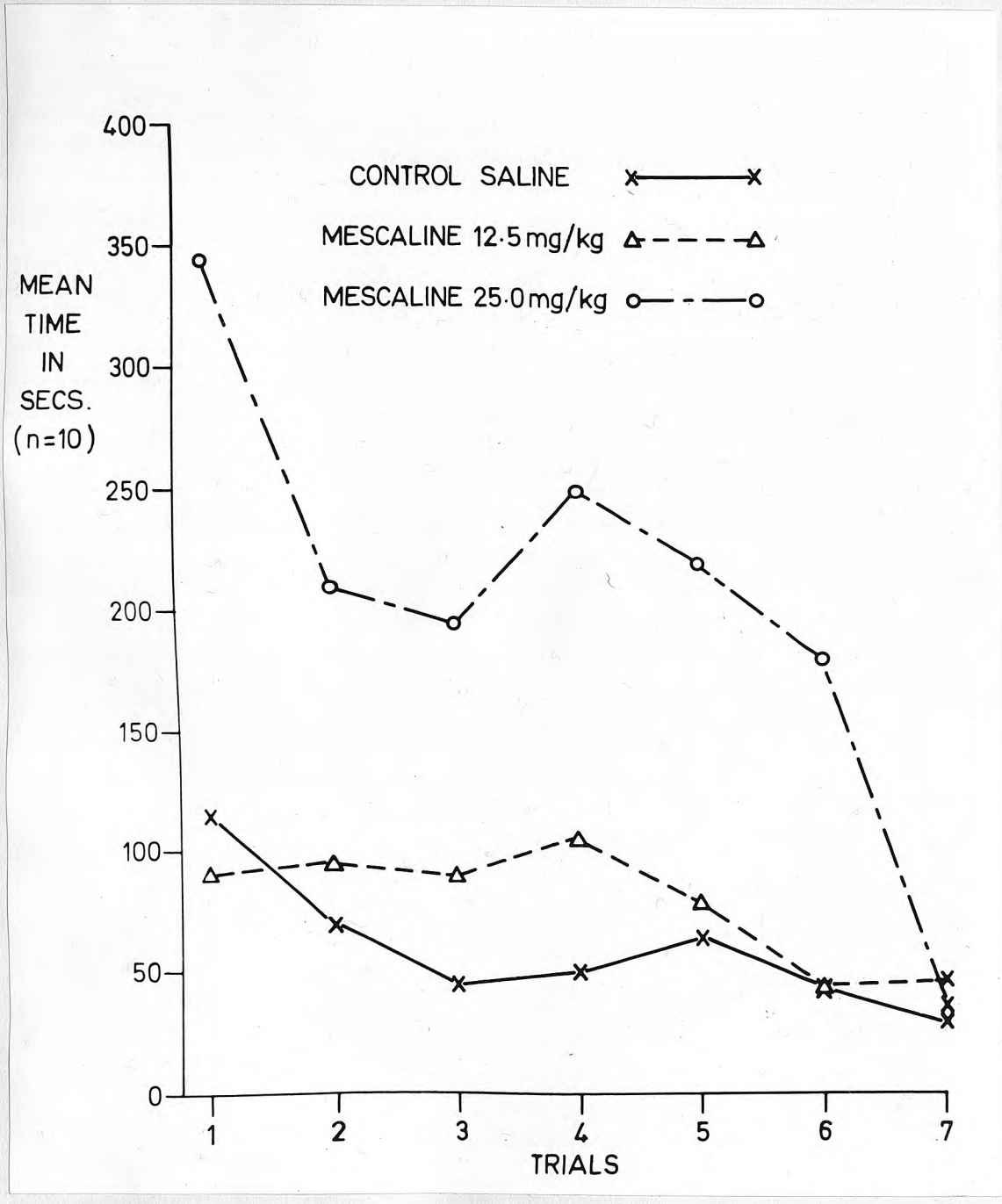

FIGURE 5: Experiment I Acquisition. Mean time in seconds taken to run the maze by 3 groups of 10 rats under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 15 minutes before each of 6 fortnightly training trials. Animals of all groups received Saline 15 minutes before trial 7.

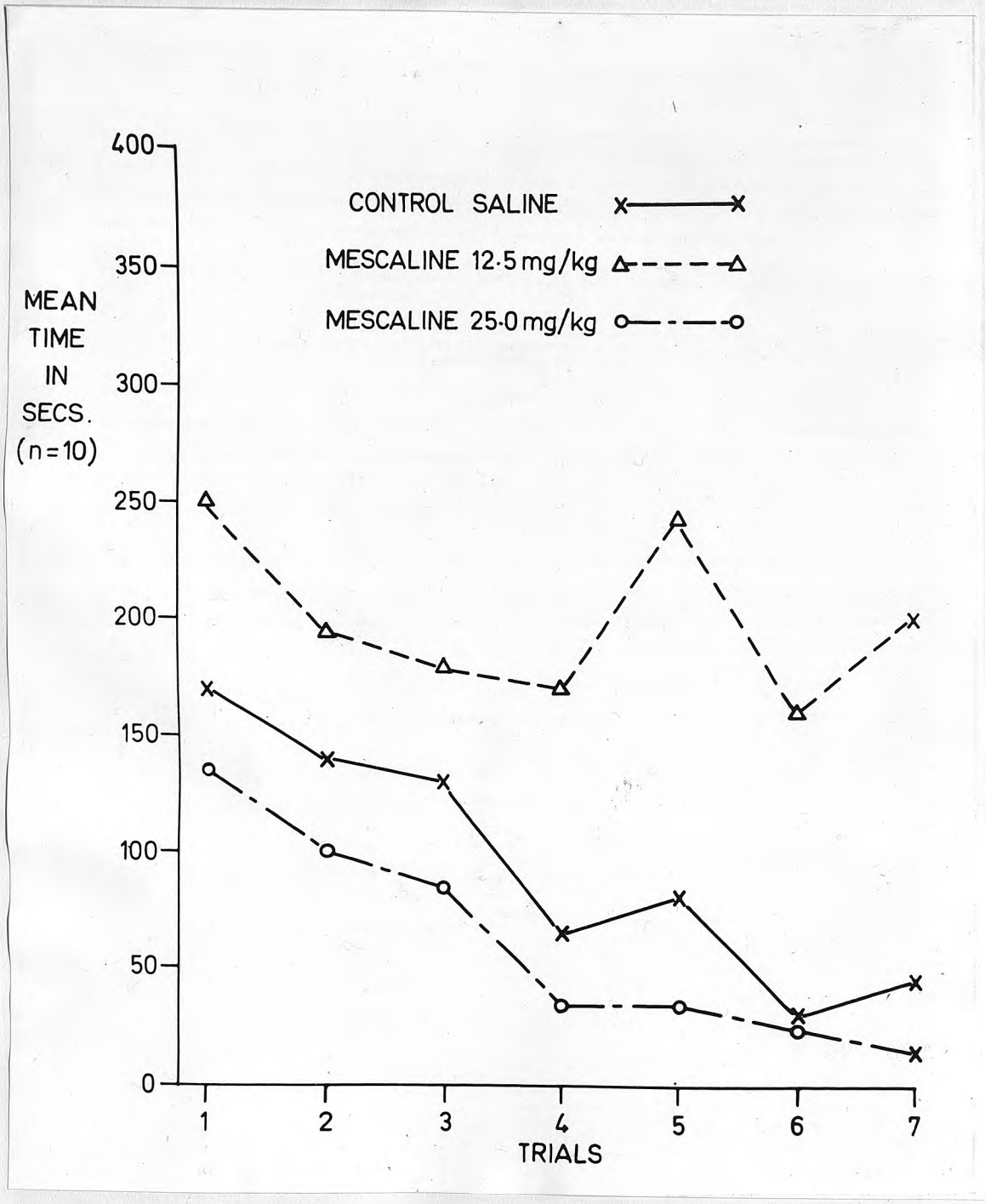

FIGURE 6: Experiment I Acquisition. Mean time in seconds taken to run the maze by 3 groups of 10 rats under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 55 minutes before each of 6 fortnightly training trials. Animals of all groups received Saline 55 minutes before trial 7.

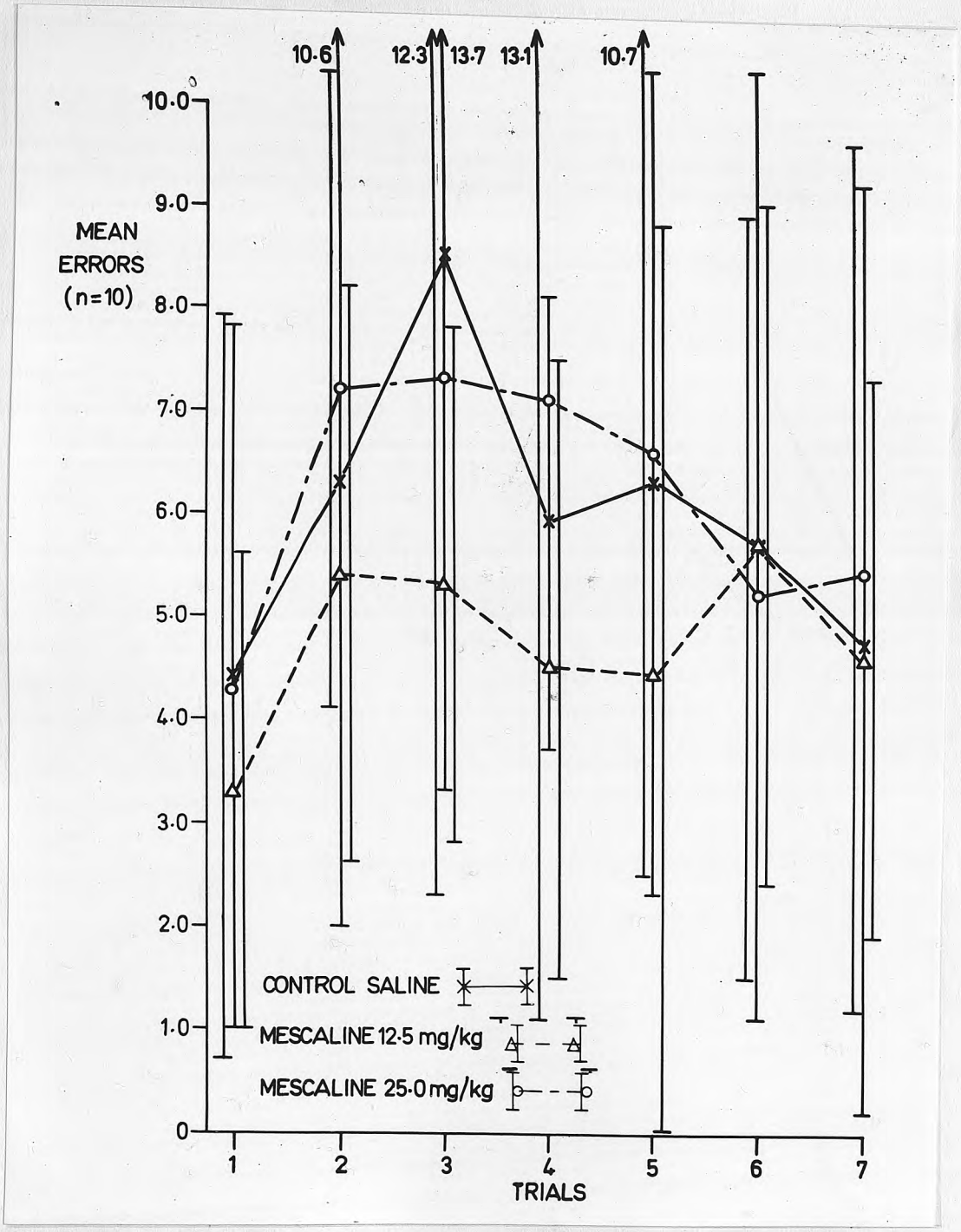

FIGURE 7: Experiment II Consolidation. Mean number of errors (± S.D) made by 3 groups of 10 rats on 7 fortnightly training trials; administration of Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. immediately followed reinforcement after each trial.

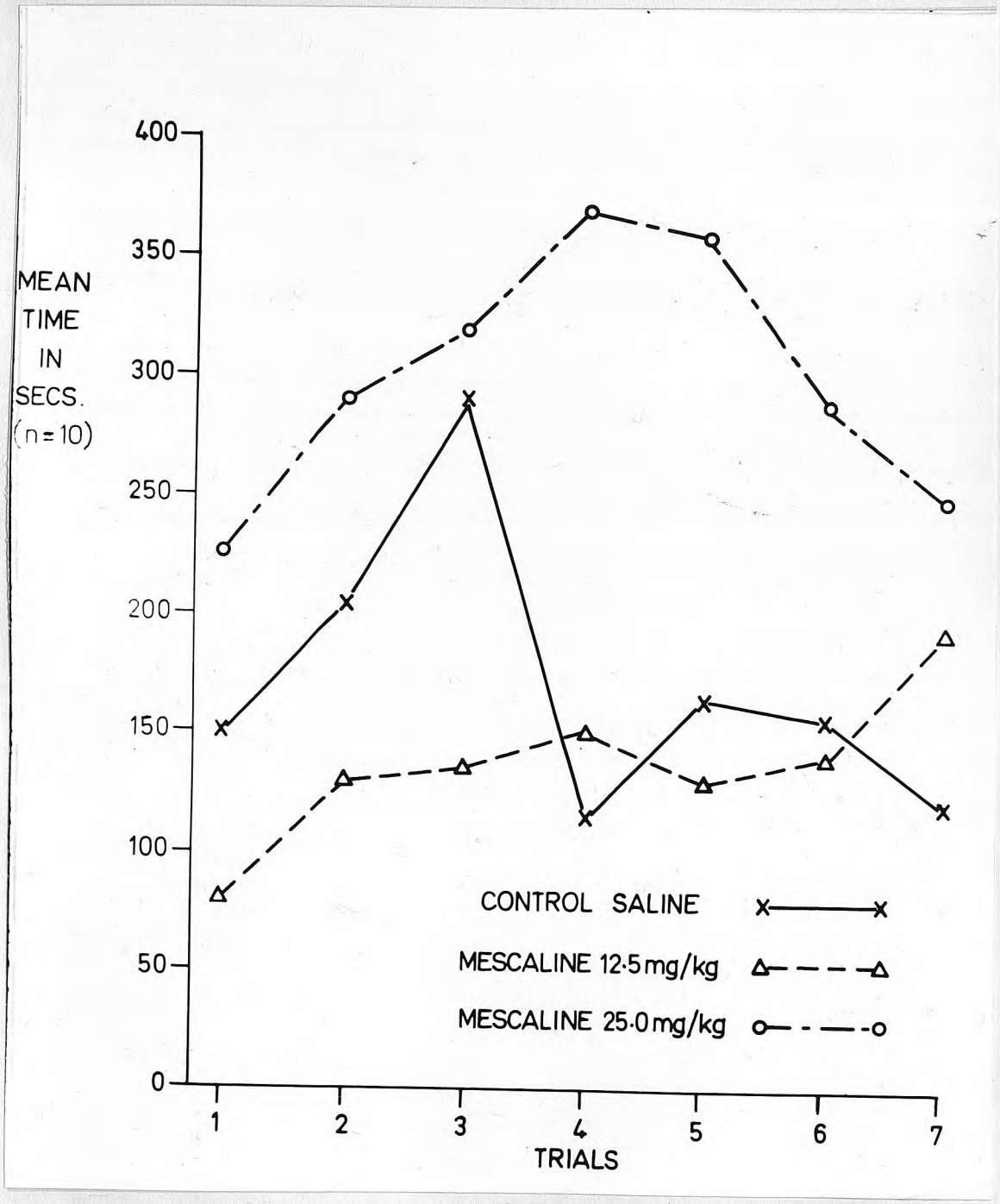

FIGURE 8: Experiment II Consolidation. Mean time in seconds taken to run the maze by 3 groups of 10 rats on 7 fortnightly training trials; administration of Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. immediately followed reinforcement after each trial.

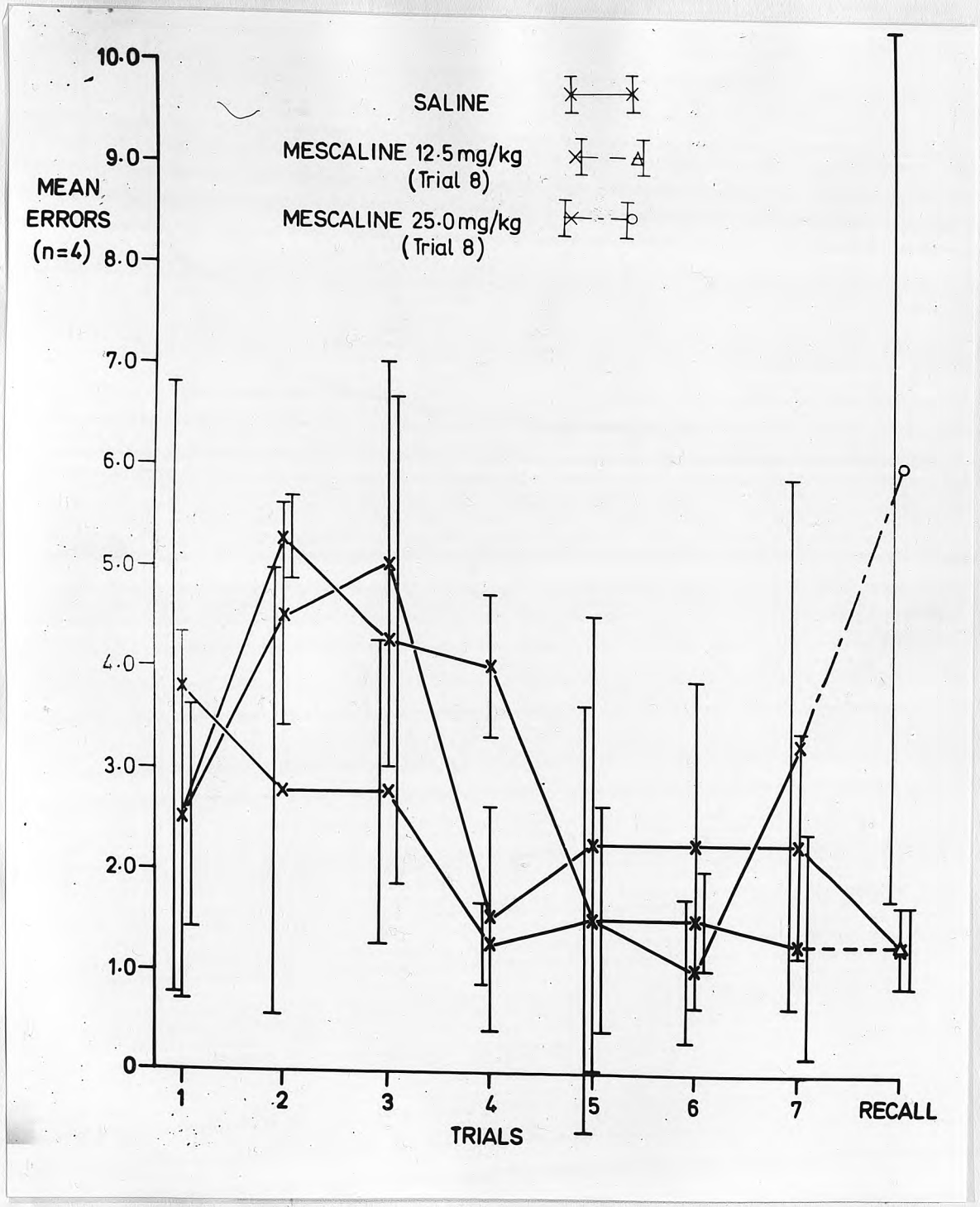

FIGURE 9: Experiment III, Recall. Mean number of errors ($\pm$S.D) made by 3 groups of 4 rats under Saline administered 15 minutes before 7 daily training trials in the maze, and under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 15 minutes before a Recall Trial three days later.

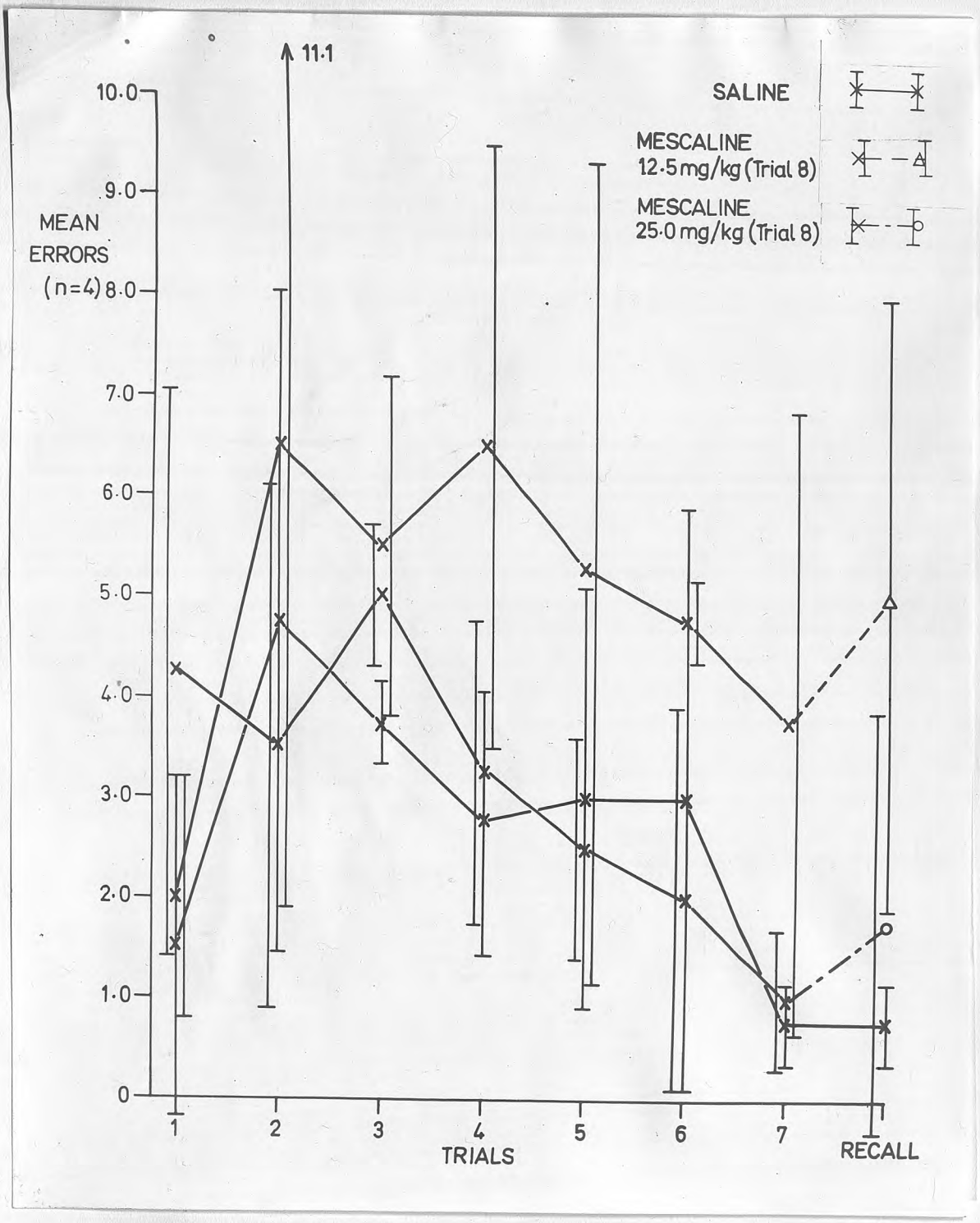

FIGURE 10: Experiment III, Recall. Mean number of errors (± S.D) made by 3 groups of 4 rats under Saline administered 55 minutes before 7 daily training trials in the maze, and under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 55 minutes before a Recall trial three days later.

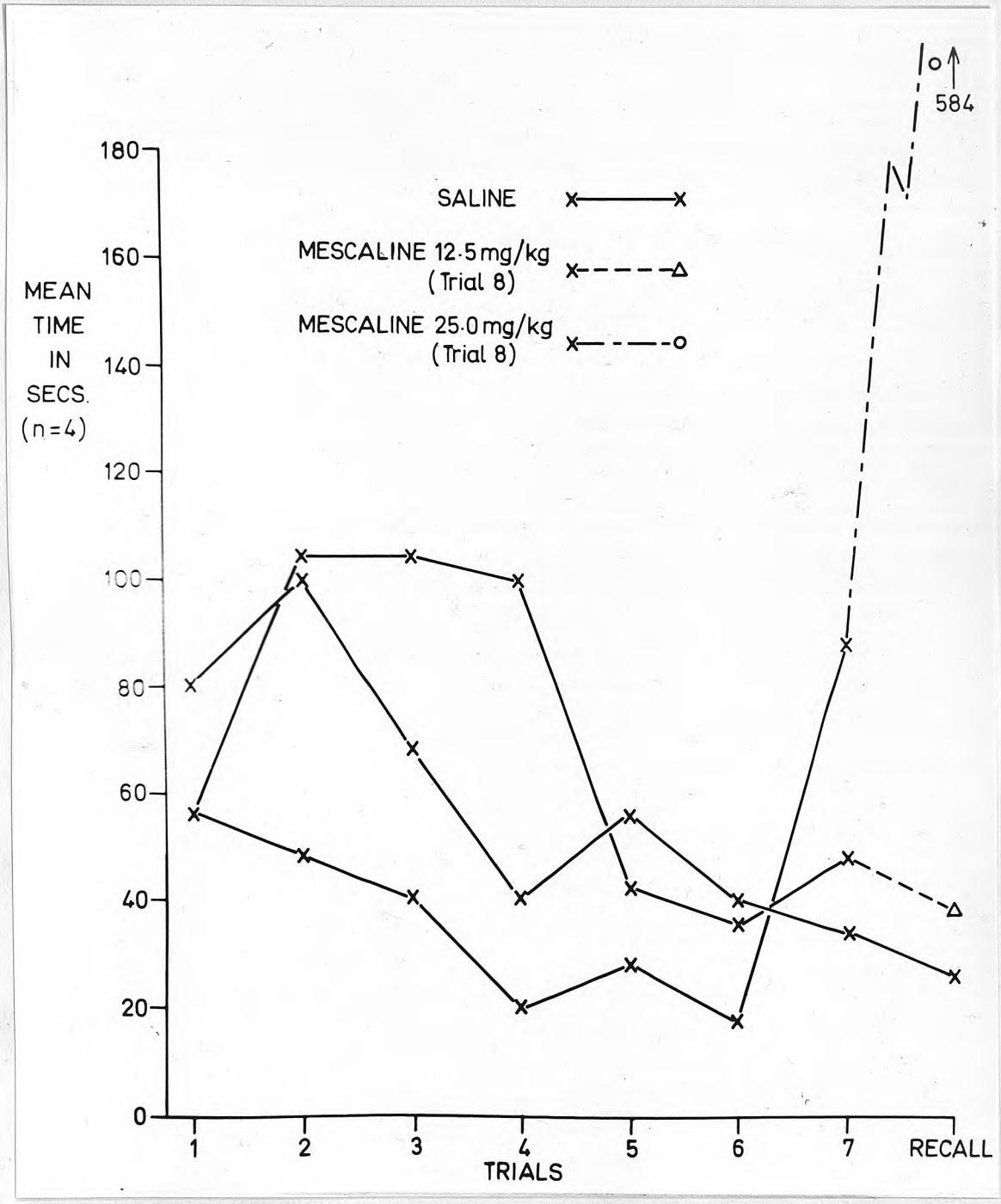

FIGURE 11: Experiment III, Recall. Mean time in seconds taken to run the maze by 3 groups of 4 rats under Saline administered 15 minutes before 7 daily training trials, and under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 15 minutes before a Recall trial three days later.

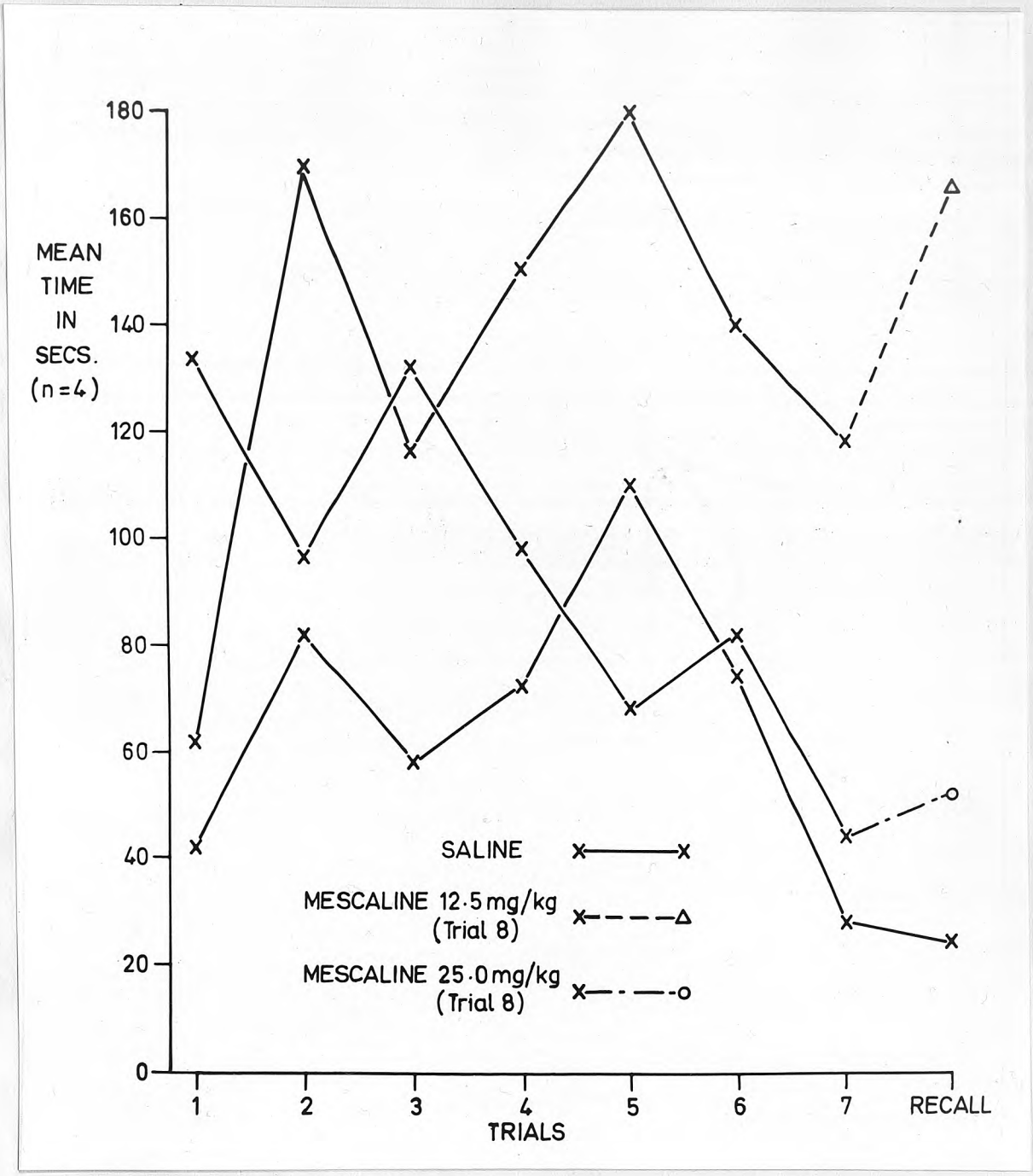

FIGURE 12: Experiment III, Recall. Mean time in seconds taken to run the maze by 3 groups of 4 rats under Saline administered 55 minutes before 7 daily training trials, and under Saline, Mescaline 12.5 mg/kg. or Mescaline 25 mg/kg. administered 55 minutes before a Recall trial three days later.

APPENDIX C:

TABLES 1 - 12

Experiment I. Acquisition. Individual error scores of 30 rats under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered immediately before each of 6 fortnightly training trials in the maze and under Saline (all animals) administered immediately before the 7th trial.

TABLE 1.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	18	13	2	2	11	2	3	1
	26	3	6	10	4	1	0	4
	62	16	4	0	4	4	1	5
	68	7	3	3	7	1	0	2
	90	8	4	4	2	1	12	6
	96	5	4	3	4	0	1	1
	111	5	3	7	4	4	2	1
	132	2	8	2	8	5	2	4
	140	2	10	2	1	4	3	4
	155	3	1	0	1	1	2	2
	Total	64	45	33	46	23	26	30

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 12.5 mg/kg	42	5	4	3	5	3	0	3
	48	0	0	5	4	8	6	2
	53	3	4	3	3	6	2	2
	59	7	3	5	4	1	4	9
	89	6	3	2	3	4	4	1
	104	9	3	7	4	3	5	2
	117	2	7	1	6	6	3	1
	149	4	4	6	8	3	3	4
	159	6	5	0	2	0	1	1
	160	4	3	4	0	7	5	5
	Total	46	36	36	39	41	33	30

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 25 mg/kg	21	2	4	5	2	1	2	4
	30	9	7	4	1	1	0	1
	44	6	4	3	2	4	7	9
	50	4	8	1	1	1	2	3
	95	2	6	3	3	3	6	2
	98	3	3	9	8	8	6	5
	100	9	6	9	8	3	3	1
	102	7	4	8	2	5	6	3
	115	8	6	6	1	3	1	1
	123	1	5	2	5	4	0	2
	Total	51	53	50	33	33	33	31

Experiment I. Acquisition. Individual error scores of 30 rats under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 15 minutes before each of 6 fortnightly training trials in the maze, and under Saline (all animals) administered 15 minutes before the 7th trial.

TABLE 2.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	20	1	2	4	3	9	10	1
	41	4	0	7	3	5	4	5
	52	1	2	3	7	6	5	4
	65	3	2	2	0	0	2	1
	116	11	5	2	4	4	1	3
	121	1	2	2	2	0	5	2
	129	1	2	6	5	4	0	2
	134	6	5	2	6	8	1	1
	147	6	5	5	1	4	3	1
	158	7	9	4	6	2	3	1
	Total	41	34	37	37	42	34	21

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 ($aline)
Mescaline 12.5 mg/kg	27	1	5	1	2	1	1	1
	47	4	0	7	3	1	1	0
	66	2	4	1	5	4	2	2
	67	3	3	0	2	7	1	9
	91	6	4	2	3	3	2	2
	101	2	1	3	0	5	1	1
	112	1	2	6	8	3	4	1
	125	1	2	7	7	3	6	0
	130	1	3	4	1	1	1	1
	153	4	5	0	2	0	3	4
	Total	25	29	31	33	28	22	21

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 25 mg/kg	25	2	6	2	5	1	0	1
	32	5	3	3	4	0	0	2
	39	3	2	17	13	8	7	2
	55	3	0	2	7	1	0	3
	93	1	7	2	2	5	2	4
	99	9	2	5	1	1	5	2
	107	12	3	1	2	1	6	0
	120	11	3	2	2	2	2	4
	142	0	4	4	1	1	1	0
	151	10	1	4	3	0	1	1
	Total	56	31	42	40	20	24	19

Experiment I. Acquisition. Individual error scores of 30 rats under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 55 minutes before each of 6 fortnightly training trials in the maze, and under Saline (all animals) administered 55 minutes before the 7th trial.

TABLE 3.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	17	3	9	2	5	1	2	4
	22	8	4	4	1	0	1	1
	28	6	0	6	5	5	1	1
	58	9	2	1	2	7	4	4
	94	5	3	5	0	8	1	12
	103	10	11	4	7	7	3	2
	119	4	8	3	6	6	4	3
	122	3	3	3	1	8	2	3
	124	6	2	13	7	5	6	1
	133	5	6	2	2	1	0	2
	Total	59	48	43	36	48	24	33

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 12.5 mg/kg	40	3	11	7	5	4	0	4
	43	3	6	1	4	1	0	2
	46	2	2	9	3	2	5	4
	54	4	12	11	10	16	5	13
	92	9	2	3	4	2	3	1
	97	10	3	2	10	11	2	6
	106	8	8	7	10	7	10	6
	114	3	2	2	1	5	2	1
	128	2	9	0	2	5	3	1
	144	9	1	3	1	2	1	1
	Total	53	56	45	50	55	31	39

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 25 mg/kg	19	6	2	8	0	6	1	0
	23	8	6	1	1	1	0	0
	60	5	3	3	1	0	0	1
	64	1	1	5	4	3	5	2
	105	4	10	1	2	3	1	0
	108	6	3	4	1	1	1	1
	110	4	1	3	2	2	1	0
	137	8	2	4	1	1	1	1
	145	3	1	4	1	1	1	1
	154	10	7	5	2	0	1	1
	Total	55	36	38	15	18	12	7

Experiment I. Acquisition. Time taken (to the nearest 10 seconds) to run the maze by each of 30 rats under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered immediately before each of 6 fortnightly training trials in the maze and under Saline (all animals) administered immediately before the 7th trial.

TABLE 4.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	18	320	90	40	210	30	50	20
	26	50	90	230	30	10	10	20
	62	390	120	20	60	90	20	40
	68	150	40	40	140	20	10	20
	90	390	60	150	40	20	350	140
	96	140	110	50	50	20	30	30
	111	100	60	310	60	40	30	20
	132	40	140	30	200	50	20	20
	140	70	190	30	20	50	50	50
	155	70	30	20	20	50	40	50
	Total	1720	930	920	830	380	610	410

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 12.5 mg/kg	42	110	150	270	120	50	20	60
	48	40	20	310	170	280	130	60
	53	90	50	50	90	380	40	70
	59	240	60	160	100	50	200	170
	89	120	50	60	60	150	90	30
	104	150	60	140	110	50	80	40
	117	40	190	20	60	60	30	20
	149	80	70	80	140	50	60	60
	159	190	180	30	50	50	30	20
	160	170	50	80	10	160	160	70
	Total	1230	880	1200	910	1280	840	600

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 25 mg/kg	21	40	40	60	20	20	30	30
	30	260	150	60	20	20	20	20
	44	310	220	110	120	800	330	330
	50	80	140	20	20	20	30	30
	95	70	150	40	20	50	150	20
	98	80	70	640	220	590	140	60
	100	310	110	110	970	440	100	20
	102	290	120	350	50	110	220	100
	115	190	270	170	50	150	30	30
	123	30	150	30	60	70	20	20
	Total	1660	1420	1590	1550	2270	1070	660

Experiment I. Acquisition. Time taken (to the nearest 10 seconds) to run the maze by each of 30 rats under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 15 minutes before each of 6 fortnightly training trials in the maze, and under Saline (all animals) administered 15 minutes before the 7th trial.

TABLE 5.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	20	20	30	40	30	220	130	20
	41	60	20	70	90	90	60	70
	52	100	50	30	100	40	60	60
	65	60	20	30	20	20	30	20
	116	540	130	30	60	40	10	20
	121	40	50	30	10	20	70	20
	129	20	20	80	50	20	10	20
	134	90	80	30	100	130	20	10
	147	110	90	70	20	40	30	20
	158	100	220	50	40	20	20	20
	Total	1140	710	460	520	640	440	880

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 12.5 mg/kg	27	60	70	30	20	20	20	10
	47	220	40	190	160	40	30	20
	66	80	160	50	90	240	40	30
	67	100	110	40	40	260	40	260
	91	140	290	110	220	50	100	20
	101	60	20	60	20	50	10	10
	112	30	40	140	210	60	30	10
	125	50	50	170	230	40	120	10
	130	50	60	80	20	10	10	10
	153	120	120	20	30	20	60	60
	Total	910	960	890	1040	790	460	440

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 25 mg/kg	25	60	140	70	300	30	20	20
	32	330	100	50	50	20	10	20
	39	80	120	1220	1250	970	1050	50
	55	160	40	70	440	120	40	60
	93	110	660	50	80	840	30	40
	99	410	50	110	40	70	90	20
	107	1250	430	130	230	70	470	30
	120	680	260	100	50	50	40	70
	142	50	250	100	30	30	20	10
	151	320	30	70	30	20	10	10
	Total	3450	2080	1970	2500	2220	1780	330

Experiment I. Acquisition. Time taken (to the nearest 10 seconds) to run the maze by each of 30 rats under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 55 minutes before each of 6 fortnightly training trials in the maze and under Saline (all animals) administered before the 7th trial.

TABLE 6.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	17	50	90	20	50	20	20	30
	22	210	90	50	20	20	20	20
	28	210	20	60	40	30	20	20
	58	230	40	50	60	100	50	50
	94	240	30	110	20	150	30	220
	103	360	780	360	150	110	40	20
	119	120	200	100	120	80	30	20
	122	60	30	20	20	190	20	30
	124	80	40	480	120	100	50	10
	133	140	100	30	30	20	10	20
	Total	1700	1420	1280	630	820	290	440

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 12.5 mg/kg	40	70	160	140	80	70	10	50
	43	100	160	40	40	20	10	20
	46	100	50	280	60	40	90	70
	54	100	390	300	300	620	480	850
	92	120	30	50	40	20	20	20
	97	560	620	320	680	1110	380	490
	106	600	310	530	430	430	510	420
	114	60	40	30	20	50	20	20
	128	50	110	10	30	50	40	30
	144	730	60	80	20	30	20	20
	Total	2490	1930	1780	1700	2440	1580	1990

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7 (Saline)
Mescaline 25 mg/kg	19	90	40	100	20	70	20	10
	23	130	130	30	20	20	10	10
	60	110	40	80	30	20	10	20
	64	50	30	90	40	40	50	30
	105	90	160	40	30	40	30	10
	108	160	70	60	30	30	20	10
	110	70	30	30	20	10	10	10
	137	180	90	110	20	20	20	20
	145	70	50	60	20	30	30	20
	154	390	350	250	140	50	40	20
	Total	1340	990	850	370	330	240	160

Experiment II. Consolidation. Individual error scores of 30 rats on 7 fortnightly training trials; Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg was administered immediately after reinforcement on each trial.

TABLE 7.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	24	4	3	10	10	14	11	7
	45	4	7	11	6	2	5	7
	63	14	16	19	5	8	16	12
	69	2	3	6	6	12	3	13
	113	3	8	8	5	7	1	2
	118	4	8	7	5	6	1	1
	126	5	11	15	9	6	5	1
	143	4	1	4	2	4	8	3
	150	2	4	0	7	1	6	0
	157	2	3	5	4	3	1	1
	Total	44	63	85	59	63	57	47

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Mescaline 12.5 mg/kg.	31	5	8	7	6	2	3	1
	49	9	3	8	8	10	10	6
	56	1	5	5	1	0	5	4
	57	3	8	7	8	15	13	11
	127	5	7	3	1	1	5	3
	131	2	9	1	2	4	1	7
	136	3	5	8	8	2	4	4
	138	2	2	8	5	2	4	3
	146	2	7	2	0	2	5	4
	156	1	0	4	6	6	7	3
	Total	33	54	53	45	44	57	46

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Mescaline 25 mg/kg.	29	2	3	6	1	1	3	5
	51	3	1	3	1	5	3	2
	61	0	7	5	6	1	3	1
	70	5	9	7	8	12	10	12
	109	9	11	11	9	7	10	12
	135	1	7	8	6	10	2	2
	139	3	11	5	5	5	2	6
	141	1	6	1	0	3	1	3
	148	8	8	7	16	9	7	1
	152	11	9	20	19	13	11	10
	Total	43	72	73	71	66	52	54

Experiment II. Consolidation. Time taken (to the nearest 10 seconds) to run the maze by each of 30 rats on 7 fortnightly training trials; Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg was administered immediately after reinforcement on each trial.

TABLE 8.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Saline	24	60	40	350	290	330	34	140
	45	250	140	280	130	40	80	70
	63	680	1010	1330	80	220	530	410
	69	70	50	100	150	650	40	350
	113	50	80	260	80	80	30	30
	118	90	250	150	80	110	20	20
	126	60	350	220	140	90	70	20
	143	100	20	80	30	60	250	110
	150	50	50	10	110	20	140	10
	157	90	60	140	50	30	40	30
	Total	1500	2050	2920	1140	1630	1540	1190

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Mescaline 12.5 mg/kg	31	80	200	130	90	30	40	20
	49	180	50	270	210	270	270	180
	56	50	110	90	40	20	50	90
	57	70	340	330	490	640	57	880
	127	190	130	40	20	30	60	40
	131	30	180	40	40	60	20	140
	136	50	70	170	260	50	50	70
	138	70	60	190	120	90	90	370
	146	50	120	30	20	40	90	120
	156	50	20	70	220	70	180	30
	Total	820	1280	1360	1510	1300	1420	1940

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Mescaline 25 mg/kg	29	30	40	80	20	30	80	120
	51	60	30	60	30	100	40	30
	61	20	220	130	120	60	70	40
	70	250	200	200	490	1010	1320	1320
	109	170	420	1010	930	850	610	380
	135	40	420	280	180	170	40	40
	139	70	380	130	120	130	50	250
	141	90	140	40	20	80	50	80
	148	340	750	150	570	240	170	60
	152	1190	270	1130	1240	950	440	180
	Total	2260	2870	3210	3720	3620	2870	2500

Experiment III. Recall. Individual error scores of 12 rats under Saline administered 15 minutes before 7 daily training trials in the maze and under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 15 minutes before a Recall trial three days later.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Recall	
Saline	35	3	3	7	2	1	2	1	1	Saline
	37	5	5	3	3	2	1	4	2	
	71	0	4	7	1	6	5	2	1	
	85	2	6	3	0	0	1	2	1	
	Total	10	18	20	6	9	9	9	5	
	33	4	5	3	5	3	2	1	1	Mescaline 12.5 mg/kg
	75	3	6	1	3	1	1	0	1	
	80	1	5	6	4	0	2	3	1	
	84	2	5	7	4	2	1	1	2	
	Total	10	21	17	16	6	6	5	5	
	36	1	3	2	1	5	2	8	11	Mescaline 25 mg/kg
	72	5	2	1	1	1	1	3	9	
	82	8	0	3	1	0	0	1	0	
	83	1	6	5	2	0	1	1	4	
	Total	15	11	11	5	6	4	13	24	

TABLE 9

Experiment III. Recall. Individual error scores of 12 rats under Saline administered 55 minutes before 7 daily training trials in the maze and under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 55 minutes before a Recall trial three days later.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Recall	
Saline	38	4	5	3	1	1	2	0	0	Saline
	74	2	2	4	4	4	8	1	1	
	78	0	10	4	2	1	1	1	1	
	88	0	2	4	4	6	1	1	1	
	Total	6	19	15	11	12	12	3	3	
	34	0	12	7	10	12	5	3	5	Mescaline 12.5 mg/kg
	76	3	10	7	8	5	5	9	10	
	81	3	2	5	2	2	5	2	2	
	86	2	2	3	6	2	4	1	3	
	Total	8	26	22	26	21	19	15	20	
	73	1	7	5	3	3	2	2	5	Mescaline 25 mg/kg
	77	7	4	4	1	1	0	0	0	
	79	7	3	5	4	4	5	1	0	
	87	2	0	6	5	2	1	1	2	
	Total	17	14	20	13	10	8	4	7	

TABLE 10

Experiment III. Recall. Time taken (in seconds) to run the maze by 12 rats under Saline administered 15 minutes before 7 daily training trials in the maze and under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 15 minutes before a Recall trial three days later.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Recall	
Saline	35	51	35	55	20	20	23	12	15	Saline
	37	163	130	53	58	47	21	65	24	
	71	35	82	73	37	129	94	20	43	
	85	70	153	94	41	29	25	42	23	
	Total	319	400	275	156	225	163	139	105	
	33	54	98	27	108	34	23	18	23	Mescaline 12.5 mg/kg
	75	61	134	32	59	19	16	15	13	
	80	53	90	245	161	85	60	139	40	
	84	56	93	112	71	29	43	23	78	
	Total	224	415	416	399	167	142	195	154	
	36	36	41	25	22	60	36	279	772	Mescaline 25 mg/kg
	72	121	35	20	22	29	15	48	1238	
	82	132	19	56	20	11	10	14	20	
	83	30	95	58	18	13	10	13	306	
	Total	319	190	159	82	113	71	354	2336	

TABLE 11

Experiment III. Recall. Time taken (in seconds) to run the maze by 12 rats under Saline administered 55 minutes before 7 daily training trials in the maze and under Saline, Mescaline 12.5 mg/kg or Mescaline 25 mg/kg administered 55 minutes before a Recall trial three days later.

	Animal	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Recall	
Saline	38	81	47	38	41	25	24	13	14	Saline
	74	39	47	60	81	139	163	28	22	
	78	24	203	78	29	45	28	28	26	
	88	26	28	60	138	233	77	39	30	
	Total	170	325	236	289	442	292	108	92	
	34	22	315	77	161	271	114	64	65	Mescaline 12.5 mg/kg
	76	122	317	266	244	319	215	314	395	
	81	52	23	63	23	24	52	24	49	
	86	50	26	61	170	105	176	69	155	
	Total	246	681	467	598	719	557	471	664	
	73	48	127	63	67	43	49	38	120	Mescaline 25 mg/kg
	77	280	167	182	98	88	85	27	15	
	79	153	70	124	119	110	161	69	40	
	87	53	23	158	109	33	30	45	32	
	Total	543	387	527	393	274	325	179	207	

TABLE 12

APPENDIX D:

PLATES 1 - 3

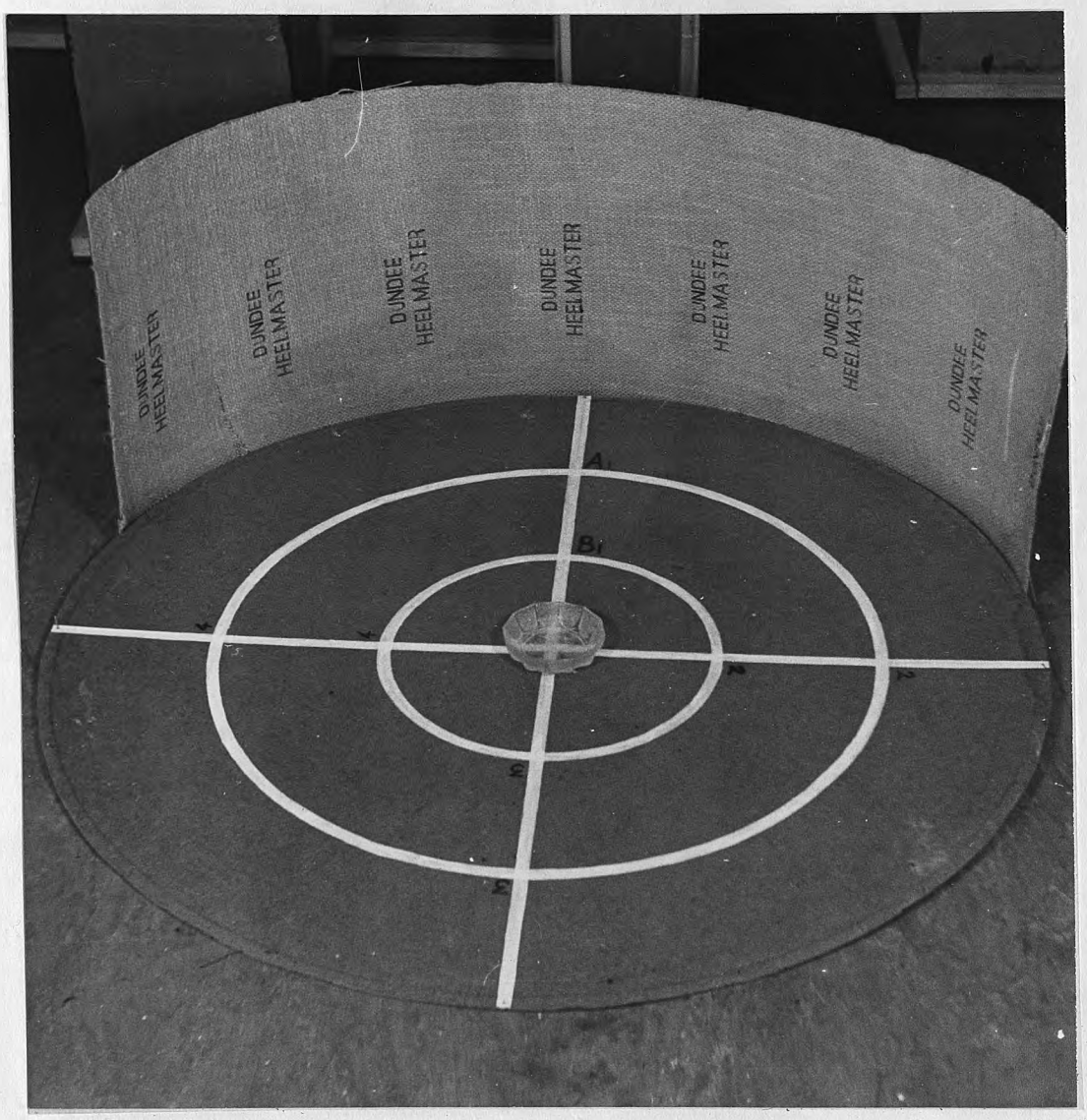

PLATE 1: The Open Field Apparatus, with part of its surrounding wall of linoleum and the water dish in place.

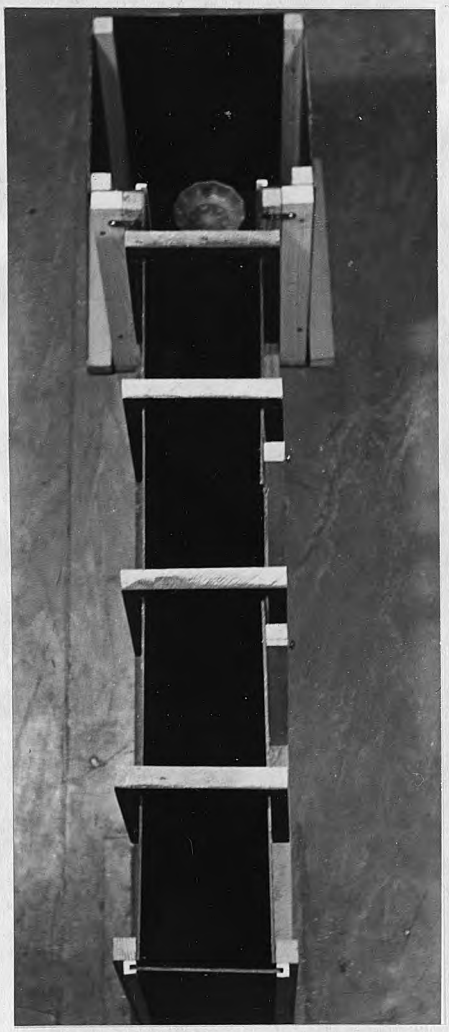

PLATE 2: The straight runway and goal box used in pretraining with four screen-doors in place.

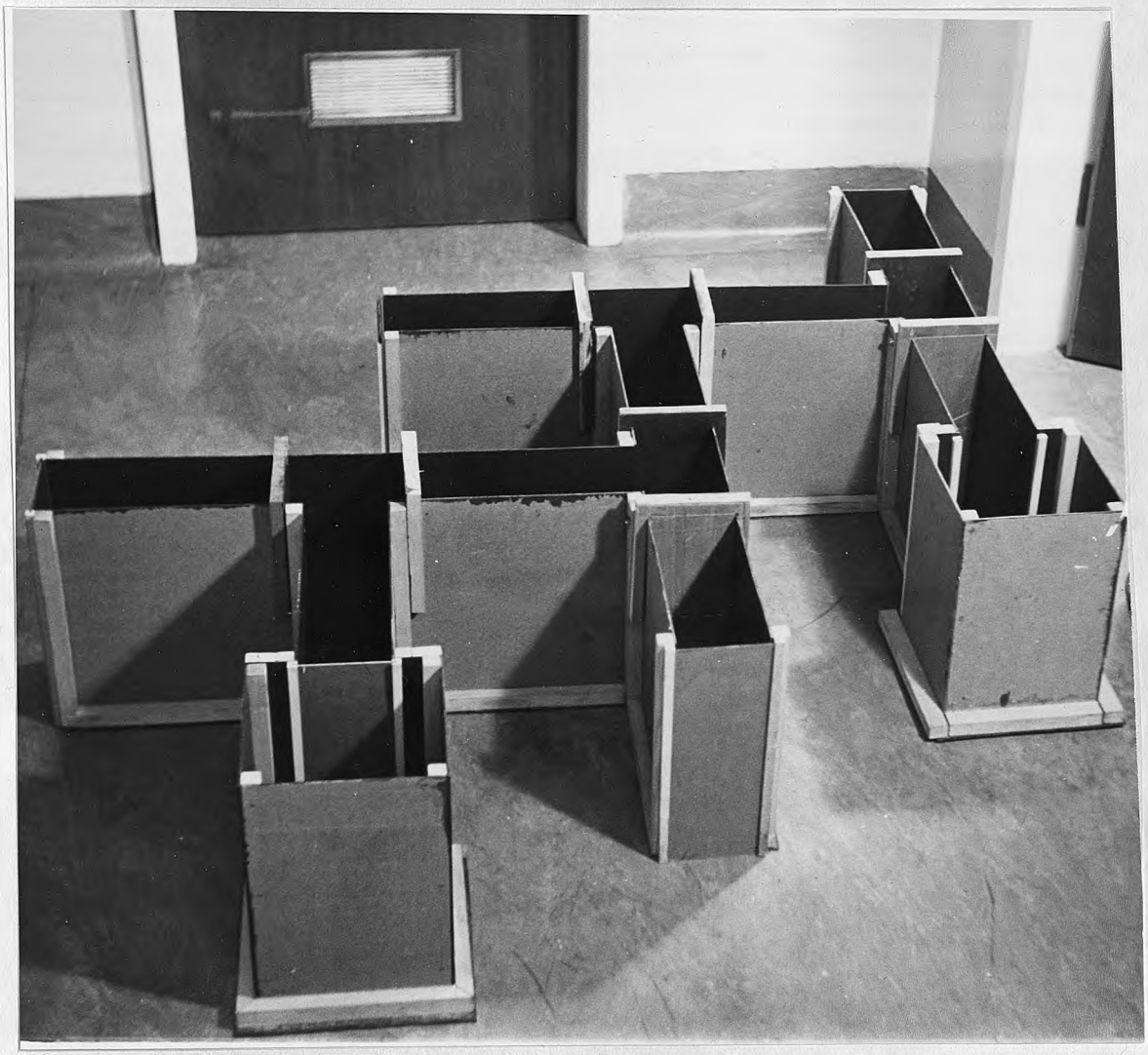

PLATE 3; General view of the maze with start-box, goal-box and all screen-doors in place.