THE EFFECTS OF UNILATERAL LOCUS COERULEUS LESIONS ON HYPOTHALAMIC INTRACRANIAL SELF-STIMULATION AND SLEEP IN THE RAT

by

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Abstract

The Effects of Unilateral Locus Coeruleus Lesions on Hypothalamic Intracranial Self-Stimulation and Sleep in the Rat

by

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The role of the nucleus locus coeruleus (LC) of the pons in intracranial self-stimulation (ICSS) and sleep was investigated in this study. Rats were implanted with ICSS electrodes aimed at the LC, hypothalamus, and substantia nigra. One group of subjects were also implanted with EEG and EMG electrodes. This group underwent a sleep-drug paradigm which tested the effects of d- and l-amphetamine (1 and 2 mg/kg) on hypothalamic ICSS before and after the LC lesion, and the effects of this lesion on the sleep cycle. Baseline sleep recordings and drug and saline rate-intensity functions were obtained. Unilateral LC lesions were then placed under the LC electrode ipsilateral to the ICSS sites with the use of a radio frequency lesion maker. Subjects' sleep cycle was then recorded for 72 hours, followed by a 20-day ICSS drug paradigm identical to the pre-lesion sequence. In a second group of subjects, stabilized hypothalamic ICSS

rate-intensity functions were obtained. In addition, substantia nigra ICSS baseline was obtained in two subjects of this group. Following the LC lesion, rate-intensity functions were gathered for at least 14 days.

The following results were obtained: (1) LC lesions which destroyed at least 90% of the LC or its ascending bundles differentially affected hypothalamic ICSS. ICSS from sites in the hypothalamus that are innervated by the dopaminergic nigrostriatal bundle and/or the noradrenergic dorsal bundle, was markedly reduced or abolished by the LC lesion (Fields of Forel, crus cerebri, and internal capsule) with no recovery up to three months after the lesion. (2) ICSS from hypothalamic sites that are primarily innervated by the noradrenergic ventral bundle was not reduced by the LC lesions (MFB-LH and periformical region). In two subjects, ICSS was facilitated as a result of the lesion. (3) LC lesions permanently reduced or abolished substantia nigra ICSS without recovery up to two months after the lesion. (4) Pre-lesion d-amphetamine was more effective in enhancing ICSS from those sites that were detrimentally affected by the LC lesion (9 : 1 over saline baseline) than hypothalamic sites that were not reduced by the LC lesions (2 : 1). L-amphetamine did not produce these differential effects. (5) Post-lesion d-amphetamine, but not l-amphetamine, returned reduced

hypothalamic ICSS response rates and decreased ICSS threshold to pre-lesion levels. (6) Extensive unilateral lesions of the dorsal tegmentum of the pons which included the LC reduced REM sleep without affecting slow wave sleep, while lesions that did not destroy the LC completely were not effective in the long-term. (7) No behavioral deficits of weight losses were caused by these unilateral LC lesions. (8) Extent of hindbrain lesion was not related to magnitude of effect on ICSS. (9) In one rat tested for stimulus-bound eating, the threshold of the behavior was drastically increased by the LC lesion, while ICSS in the same area remained virtually unaffected.

These results show that distant and discrete unilateral lesions can reduce and abolish ICSS behavior. It is thus proven that the central reward system is not redundant and capable of recovery. Furthermore, the differential LC lesion effects on hypothalamic ICSS demonstrate that the hypothalamus is not a unitary ICSS center, but rather a site that receives inputs from different ICSS systems.

Given that unilateral lesions of the noradrenergic LC either abolish or drastically reduce ICSS from sites rich in dopamine (substantia nigra, crus cerebri, internal capsule, and Fields of Forel), it is postulated that ICSS

from both the noradrenergic dorsal bundle and the dopaminergic nigrostriatal system depend on the integrity of the LC. The results of this experiment lend support to a REM sleep-ICSS hypothesis which postulates an anatomical and functional relationship between REM sleep and central reward.

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I dedicate this thesis to my parents. Their encouragements and sacrifices during difficult times ensured the completion of my education. For this, I thank them wholeheartedly.

"Ils jouissent les autres
plaisirs comme ils font
celui du sommeil, sans les
connaître. A celle fin que
le dormir même ne m'echappât
ainsi stupidement, j'ai
autrefois trouvé bon qu'on
me le troublât pour que je
l'entrevisse."

(They enjoy the other pleas-
ures like they enjoy the
pleasure of sleep, without
understanding them. In order
that sleep itself would not
slip away from me so stupidly,
I have found it beneficial at
times to have it disturbed,
so that I could catch a glimpse
of it.)

Montaigne, Essays, III

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GLOSSARY

ALH	anterolateral hypothalamus
AMPT	alpha-methyl-para-tyrosine
BL	baseline
CA	catecholamine
CC	crus cerebri
DA	dopamine
DB	dorsal NE bundle
DB-NS group	dorsal bundle-nigrostriatal group (ICSS from CC or D-H)
DEDTC	diethyldithiocarbamate
D-H	ICSS site dorsal to hypothalamus (Fields of Forel and zona incerta)
DTN	dorsal tegmental nucleus
F-H	perifornical area
5-HT	serotonin
ICSS	intracranial self-stimulation
LC	locus coeruleus
L-BL	long-term ICSS baseline up to 20 days post-lesion
LH	lateral hypothalamus
Mesc $\overline{V}$	mesencephalic nucleus of $\overline{V}$
MFB	medial forebrain bundle
MLF	medial longitudinal fasciculus
NA	noradrenergic
NE	norepinephrine

NHTS	neurohumoral transmitter substance
NS	nigrostriatal
PCPA	p-chlorophenylalanine
REM	rapid eye movement sleep
RF	radio frequency
RI	rate intensity
R-BL	recovery check ICSS baseline - at least one month post-lesion
SB	stimulus-bound
SC	sub-coeruleus
SCP-BC	superior cerebellar peduncle (Branchium conjectivum)
SN	substantia nigra
S-BL	short-term ICSS baseline - first four days post-lesion
VB	ventral NE bundle
VT	ventral tegmentum
ZI	zona incerta

Introduction

A. The REM Sleep ICSS Hypothesis

In 1969, Ellman and Steiner hypothesized that the intracranial self-stimulation (ICSS) system is part of the rapid eye movement (REM) sleep network. This "REM-ICSS hypothesis" postulates, among other things, that ICSS and REM sleep are related and interchangeable, and that pontine sites involved in the phenomenon of REM sleep are part of the ICSS system. This hypothesis, which is part of a theory on the function of REM sleep (Steiner & Ellman, 1972), has generated a number of predictions that have been tested in the last five years and which will be described in this section. First, however, the various aspects of REM sleep will be reviewed.

After Aserinsky and Kleitman's (1953) discovery that rapid eye movements regularly occurred during "low voltage fast" sleep, as measured by electroencephalographic (EEG) recording, and this REM stage highly correlated with dreaming, a new era of research was launched on the psychophysiological aspects of REM sleep. This stage of sleep occurs periodically during the night in the mammalian organism (REM sleep does not seem to be present in substantial amounts in most non-mammals). The REM stage has also been referred to as "paradoxical" sleep (Jouvet et al., 1964) because of its similarities to the waking state. Aside from the phasic occurrences of rapid eye movements,

the cortex (Loomis, Harvey, & Hobart, 1937) and other central nervous system (CNS) areas (Brooks & Bizzi, 1963) are intensely activated. Yet, muscle activity is by and large inhibited (Berger, 1961; Jouvet, 1967; Swisher, 1962), and the organism's threshold for arousal is at its highest (Foulkes, 1967). One of the most striking features of REM sleep has been termed the "REM rebound effect". Dement (1960) found that when human subjects are not allowed to have REM sleep for a period of time, a large percentage of the lost REM sleep will be made up on the next uninterrupted night. This phenomenon has been shown in other mammals as well (Jouvet, Virnon, Dolcime, & Jouvet, 1964; Khazan & Sawyer, 1963).

From the results of a series of pharmacological, biochemical, and anatomical studies, Jouvet (1967, 1969) has proposed that the serotonergic nuclei of the raphé are responsible for non-REM sleep, while the noradrenergic nuclei of the pontine locus coeruleus (LC) are involved in the triggering and maintaining of REM sleep. (The neurophysiological aspects of REM sleep will be described in fuller detail in the next section.) Although a large amount of research has been conducted in the area of REM sleep, and a number of interesting theories on the function of REM sleep have been postulated, a description of the findings and different views is beyond the scope of

this overview. However, we would like to describe three lines of thought on the function of REM sleep which have been influential in the formation of Ellman and Steiner's theory. Dement (1965) has proposed that REM sleep is an homeostatic mechanism which during the REM period discharges any "drive" build-up that has occurred during the waking state. An overflow of "drive" charge will bring about a REM period. The two other theories are more neurophysiologically inclined. They postulate that extreme activation of the CNS serves as endogenous stimulation to the organism. Roffwarg, Muzzio and Dement (1966) have maintained that the high levels of REM sleep seen in infants serves to facilitate CNS maturation. Ephron and Carrington (1966) believe that REM sleep provides cortical tonus in response to the functional deafferentation caused by non-REM sleep.

Ellman and Steiner's theory accepts, at least partially, the notion that the function of REM sleep is to provide stimulation and innervation to the sleeping mammalian CNS, as postulated by Ephron and Carrington (1966) and Roffwarg, Muzio and Dement (1966). However, since the mechanism under which REM sleep functions is part of the REM-ICSS system, REM sleep has vital influence on the waking state. The REM-ICSS system is primarily a motivational one, and therefore the organism depends on it for survival.

In general terms, it can be described as follows: During the waking state, the mammalian organism engages in its species-specific repertoire of appetitive and consummatory behaviors (food seeking, aggressive behaviors, sexual attempts, etc.) triggered by a build-up in "drive" due to internal stimulation. During sleep, this build-up continues and its release is marked by the REM period. Thus, the same mechanism which, during the waking state triggers the consummatory behaviors, is also activated during REM sleep. This may be why the motor outflow is inhibited during REM sleep. If the inhibitory nuclei that cause the atonia during REM sleep are destroyed, as Jouvet has shown in the cat (1967), the organism will still have REM sleep and, during the REM period, "act out" a whole range of consummatory behaviors.

A two-part network subserves the REM-ICSS system and its mediation of the organism's motivational (or "drive") state. The "central reward" aspect of the system is an interconnected network that extends from the pons through all "drive" centers in the brain, and provides non-specific excitation to all positively reinforcing "drive" centers. In this system, ICSS originates from the LC and activates the whole network without eliciting any specific behavior other than ICSS. The second aspect of the REM-ICSS system involves the brain areas responsible for specific consum-

matory behaviors ("drives"). These different loci are interconnected by way of the ICSS network. Whenever a REM period occurs, and with it the activation of the REM-ICSS system, the ICSS network is fired and the threshold of any or all "drive" behaviors is lowered. This two-part network is operative during wakefulness as well as during REM sleep. Thus, the state of the ICSS system in general, and the state of any "drive" level in particular, will be determined by the status of the REM-ICSS system and its locus of origin, the LC.

In order to render this theory testable, its authors have described the REM-ICSS system in anatomical and operational terms. First, since under such a system (a) ICSS and REM are subserved by the same neural network, (b) the activation of ICSS is dependent on the REM sleep mechanisms, and (c) dissipation of the "drive" build-up depends on the REM period and ICSS system activity, a relationship and interchangeability between ICSS and REM sleep was predicted. Steiner and Ellman (1972) found that ICSS thresholds are lowered and ICSS rates increase if the subjects, in this case rats, have been previously REM-deprived. In another experiment, they found that allowing previously REM-deprived subjects to self-stimulate, significantly reduces the expected REM rebound. These results are in full support of the REM-ICSS hypothesis. REM deprivation pre-

vents release and dissipation of the build-up in the two-part REM-ICSS system, since it is not fired during the REM period. This will lead to a lowering of the threshold in the ICSS system, as was demonstrated in the first experiment. Since REM rebound is a reflection of a REM-ICSS system build-up brought about by REM deprivation, stimulation of the system will result in a release of the build-up and thus less pressure on REM sleep to make up its deprivation. This was demonstrated in the second experiment. The two findings were subsequently replicated by Cohen, Edelman, Bowen, & Dement (1972).

Second, since the REM-ICSS system provides the organism with the stimulation necessary for the maintenance of a motivational state, the neuronanatomical loci responsible for the phenomenon of REM sleep are central to the two-part network and should therefore support ICSS behavior. We (Ellman, Ackermann, Farber, Mattiace, & Steiner, 1974; Farber, Steiner, & Ellman, 1971) and others (Crow, Spear, & Arbuthnott, 1972; Ritter & Stein, 1973) confirmed this prediction with the finding that the LC of the pons, a noradrenergic (NA) nucleus, is an ICSS site.

Third, since REM sleep acts as a mechanism that periodically releases the build-up in the REM-ICSS system, if such a release can be activated by direct stimulation of the system, REM sleep itself would not be necessary until

a new build-up occurred. Spielman, Mattiace, Steiner, and Ellman (1973) found that lateral hypothalamic (LH) ICSS significantly reduces the amount of REM sleep during the first four hours following stimulation, thus confirming the above prediction.

Fourth, since the ICSS system is part of the REM sleep neural network, and is fired during REM sleep, it was postulated that the ICSS system at least partly originates in the LC (an ICSS site involved in the triggering and maintaining of REM sleep) and that the fibers stemming from the LC interconnect this nucleus with limbic ICSS sites. Ellman, Ackermann, Bodnar, Jackler, and Steiner (1975) report a behavioral relationship between the LH and the LC, by way of an ICSS interaction. They demonstrated that below ICSS-threshold intensities presented simultaneously at the LH and the LC will support high ICSS response rates.

In order to understand the function of the REM-ICSS system in the organism's motivational (or "drive") state, an operational definition of these terms is required. The term "drive" behaviors can be substituted by the term "stimulus-bound" (SB) behaviors. These behaviors can be elicited through electrical stimulation of brain sites which also support ICSS. The elicited behavior would be specific (eating, drinking, sex, carrying, etc.), part of

the behavioral repertoire of the subject, and appropriately goal-oriented toward an accessible object. By and large, these SB behvior sites are located in the hypothalamus (Valenstein, Cox, & Kakolewski, 1970). According to the REM-ICSS theory, firing of the REM-ICSS system in the waking state will either activate or lower the activation threshold of the SB behavior nuclei in the hypothalamus. Duirng REM sleep, these nuclei are also activated but motor outflow inhibition will prevent exhibition of the behavior. Duirng the waking state, an increased "drive" level will yield a specific behavior or lower its threshold. During sleep, such an increase would dissipate during the REM period. Thus, ICSS and SB behavior thresholds will be regulated, among other factors, by the REM-ICSS system. The factors which will increase "drive" levels in the organism will be both internal (neurohumoral, neurophysiological, learned) and external (available stimulus). Steiner and Ellman's (1972) experiments have demonstrated the dependence of the ICSS threshold on the state of REM. A further prediction of the theory would be that SB behavior thresholds would be lowered by REM deprivation due to the fact that the REM period was not allowed to decrease the "drive" level in the specific aspect of the REM-ICSS system. Since this system stems from, and is dependent on nuclei in the pons and their activation, the theory pos-

tulates direct connections between the LC and the hypothalamus. The possibility of such a connection has been suggested in Ellman's et al.'s (1975) simultaneous ICSS study. We now predict that lesioning of the LC area will disrupt the REM-ICSS system and either abolish ICSS or drastically increase the threshold of ICSS and SB behavior. Theoretically, bilateral lesions of the LC would detrimentally affect the REM-ICSS system, and thus the motivational state of the organism. Aside from being involved in the phenomenon of REM sleep and being an ICSS site, the likelihood of the LC being the origin of the REM-ICSS system is enhanced because its pattern of collateral innervation influences the whole brain in a unique way (which will be described in more detail in the next section).

In summary, the present study is based on the following postulates: (a) The REM-ICSS system provides stimulation to the non-specific ICSS network and the specific SB behavior nuclei; (b) the LC, an ICSS site playing a central role in the REM sleep phenomenon, is the nucleus from which the REM-ICSS system originates. Therefore, unilateral lesions of the LC will lead to the abolishment or drastic reduction in LH ICSS. They will also reduce the amount of REM sleep. Methodological considerations will be discussed in a later section dealing specifically

with lesions.

B. The Locus Coeruleus and its Role in REM Sleep

Since the hypothesis of this experiment assigns a pivotal role in central reward, motivation, and REM sleep to the pontine nucleus LC, it seems necessary at this point to describe its known anatomical and functional properties. The LC is a densely packed nucleus of large cell bodies, about 1400 in number (Descarries & Saucier, 1972). It lies at the floor of the fourth ventricle and is bordered by the dorsal tegmental nucleus on its medial side and by the nucleus of the mesencephalic $\overline{V}$ on its lateral side (Zeman & Innes, 1963). By use of the histochemical fluorescence technique of Falck, Hillarp, Thieme and Torp (1962), it has been shown that the cell bodies of the LC of the rat are of the catecholaminergic (CA) type (Dahlstrom & Fuxe, 1964), a large amount of which is norepinephrine (NE) (Corrodi, Fuxe, Hamberger, & Ljungdahl, 1970; Fuxe, Goldstein, Hokfelt, & Hyub, 1970; Hillar, Fuxe, & Dahlstrom, 1966). The area just ventral to the anterior aspects of the LC has been referred to as the "subcoeruleus (SC) (Maeda & Shimizu, 1972; Olson & Fuxe, 1971) and is an integral part of the coerulear system in terms of its anatomical and functional characteristics. The cell bodies of the SC, which contain NE, form a row of

multipolar cells that pass from the antero-ventral LC towards the more ventrally located NA cell bodies in the pons (described by Dahlstrom and Fuxe as areas A5 and A7). (As will be described further on in more detail, the cell bodies in the antero-ventral LC and SC are the origin of a pontine-limbic system pathway.)

The LC has been described as unique in its pattern of innervation in both the rat's (Olson & Fuxe, 1971; Ross & Reis, 1974; Ungerstedt, 1971) and cat's (Chu & Bloom, 1974) CNS. One single nerve cell of the dorsolateral LC is capable of innervating all cortices of the brain. By means of its diffuse collateral innervation, the LC influences the brain in a unique way.

Jouvet (1969) has shown that bilateral destruction of the LC in the cat abolishes REM sleep. Specifically, he and others (Henley & Morrison, 1969) have found that bilateral lesions of the caudal part of the LC do not suppress the physiological characteristics of REM sleep, but produce the so-called "hallucinatory behavior". The cat will orient itself, attack, and mount inappropriate objects or no objects at all.

Bilateral lesions of the entire LC suppress REM sleep totally. Lesions of the most anterior aspects of the LC and its ascending bundle will temporarily increase both REM and non-REM sleep. Jouvet (1972) concludes that

the anterior LC is concerned with prosencephalic innervation, while the phasic and tonic components of REM sleep depend on the caudal two-thirds of the "coeruleus complex". Thus, Jouvet has shown that: (1) the LC is central in the phenomenon of REM sleep, and (2) at least in the cat, the LC can be divided into two functionally distinct systems. This second point is important because, as will be seen in the next section, distinction within the LC will be necessary in order to specify CNS interconnections.

C. The Projections of the LC and other CA Systems

According to the REM-ICSS hypothesis, the LC plays a pivotal role in the innervation of the specific and nonspecific aspects of the REM-ICSS system. It is therefore postulated that direct connections exist between the LC and hypothalamic ICSS sites. Aside from the behavioral evidence for such an interconnection (Ellman et al., 1975), the anatomical data is controversial. Dahlstrom and Fuxe (1964) have postulated that the monoaminergic nuclei, which seem exclusively located in the lower brainstem and the mesencephalon, are an important part of the "afferent link to the limbic system" (p. 47). Although a number of studies have shown that the LC and other hindbrain nuclei are accountable for a large percentage of NE supplies to the brain (Anden, Dahlstrom, Fuxe, & Larrson, 1965; Anden, Dahlstrom, Fuxe, Larsson, Olson, & Ungerstedt,

1966; Anden, Butcher, Corrodi, Fuxe, & Ungerstedt, 1970), Ungerstedt (1971) has reported tha LC innervation, although very diffuse, is minimal in areas of the hypothalamus associated with ICSS (LH and medial forebrain bundle [MFB]). Ungerstedt has identified two ascending NE bundles which stem from NE nuclei in the pons and medulla. The dorsal bundle (DB) originates from cell bodies in the LC and ascends parallel and slightly latero-ventral to the central gray of the mesencephalon. The DB innervates the geniculate bodies and enters the thalamic nuclei. It then joins the other CA pathways in its brief passage in the MFB. After passing through the septum, it ultimately innervates the whole cerebral cortex. The cell bodies in the lateral aspects of the LC give rise to cerebellar NE terminals. Thus, the LC gives rise to NE terminals throughout the brain, in a widespread and diffuse manner (Figure 1).

The ventral bundle (VB) originates from NE cell bodies in the medulla and pons (areas A1, A2, A5, and A7). This pathway takes a ventro-medial direction along the mesencephalon and diencephalon, and innervates the ventral tegmentum, the entire hypothalamus, including the perifornical region (Figure 1).

Although Ungerstedt's results indicate that the hypothalamus is mainly innervated by the VB with minor contributions of the LC, two recent studies have reported results

to the contrary. These new findings are primarily due to the fact that the investigators were able to separate the LC into morphologically and functionally different aspects. They have thus been able to identify a third bundle in addition to the VB and DB, which originates from the SC. As described above, the NE cell group encompasses the anteroventral aspect of the LC and includes cell bodies that connect the LC with more ventrally located NE nuclei. Maeda and Shimizu (1972) claim that the SC cell bodies innervate the periventricular hypothalamus by way of an "intermediate bundle". This bundle travels between the DB and VB. Olson and Fuxe (1971) report virtually the same finding with the difference that the SC, according to them, sends its fibers together with the VB, rather than a third, distinct one. According to both studies, the DB stems from the dorso-lateral LC (the "principal" LC) and its function is the innervation of all cortices. The SC sends its fibersin a more ventral direction and forms a ponto-hypothalamic connection. The VB stems from cell bodies in the medulla and innervates the ventral tegmentum and the hypothalamus. Both studies also report that the cell bodies in the SC are larger than those in the principal LC.

Ross and Reis (1974) looked at the levels of dopamine-beta-hydroxylase in different brain areas after LC lesions. They found that the LC innervates virtually the

entire neuroaxis. In particular, they found a 40% to 60% decrease of the enzyme's activity in the medial and lateral hypothalamus. The optimal level of decrease was reached within 12 days after the lesion.

With the use of a new and more sensitive fluorescence technique which employs a glyoxylic acid tissue treatment, Lindvall and Björklund (1974) have found that the CA systems of the brain are more numerous and more complex than previously believed. In brief, they describe four major CA conduction pathways that project rostrally from the medullary pontine and mesencephalic CA cell groups. Although most cells from the LC project along one bundle, the dorsal tegmental bundle which is identical to the dorsal bundle of Ungerstedt (1971), the LC also gives rise to fibers that project along the dorsal periventricular system and the central tegmental tract.

Although tentative, the following conclusions can be drawn from the above mentioned results: The LC is not a homogeneous nucleus, but rather an area with anatomically and functionally distinct cell groups. The principal LC (dorso-lateral and caudal aspects of the LC area) is primarily involved in the NE innervation of all cortices and thalamus. The SC (antero-ventral aspect of the LC area) is involved in the innervation of hypothalamic areas. Therefore, any LC lesion that affects hypothalamic ICSS

must involve the SC. Furthermore, according to Ross and Reis' results, the optimum level of effect may not be seen until 12 days post-lesion.

D. Brain Lesions on ICSS: An Overview

By and large, most lesion studies on ICSS have dealt with the MFB-LH area and its role in "central reward". Although ICSS can be elicited from a number of limbic and tegmental areas, many investigators have considered the MFB-LH area as essential for positive reinforcement. This assumption was supported by a number of findings. First, it had been shown that the MFB was more sensitive to ICSS (lower threshold, higher rates) than any other ICSS site (Olds & Olds, 1964). In addition, if allowed to, rats would self-stimulate for many days taking only short breaks, as if they could not be sated. Second, Nauta (1960) had demonstrated that the MFB is deeply involved in the limbic system and its circuits, and is an important pathway to mesencephalic structures. Also, Guillery (1957) and Nauta (1958) had shown that the MFB interconnects the septal area, the lateral preoptic and hypothalamic areas, and the tegmentum, all of which are ICSS sites, by way of its ascending and descending fibers. Thus, many investigators, noticing the high correlation between ICSS sites and the distribution of the MFB (Gallistel, 1973; Lorens, 1966; Olds & Olds, 1969; Valenstein & Campbell, 1966) postulated

that the MFB is the anatomical "substratum" that mediates ICSS.

The results of the experiments to be reviewed in this section are very variable and, in many cases, this variability seems as high within one experiment as between all of them. Therefore, certain methodological factors should be discussed before these experiments are reviewed. (a) A number of these studies investigated the effects of bilateral MFB-LH lesions on septal or tegmental ICSS. Teitelbaum and Stellar (1954) and Teitelbaum and Epstein (1962) have shown that such lesions often produce hypophagia and adipsia, and that recovery thereof, if at all possible, is a lengthy process. Some studies report body weight loss in their subjects, and others report the need for intragastric feeding. Thus, it appears crucial that subjects be given ample time for recovery after the lesions in order to avoid a non-specific effect which may be due to some bodily debilitation caused by the lesion. Certain standardized measures must be taken to see if there are any lesion side effects. One sensitive measure would be weighing of the animals. A subject that continuously loses weight might very well show an ICSS decrement because of debilitation rather than because of the lesion's effect on ICSS.

(b) The experiments that report ICSS decrements due

to brain lesions by and large report that the larger the lesion and the closer to the ICSS electrode, the larger the effect. Although in most cases there is no evidence that the lesion has traveled under the ICSS electrode, specificity of effect is not enhanced by a size-distance-effect correlation. Any statements of the involvement of a specific area in the phenomenon of ICSS becomes stronger the smaller the area destroyed, and accompanied by the reassurance that the lesion has not traveled to the ICSS site.

(c) The biochemical and anatomical effects of lesions do not reach their optimal level until five to 12 days post-lesion (Mizuno & Nakamura, 1970; Ross & Reis, 1974; Ungerstedt, 1971). On the other hand, regeneration of fiber tracts is at times possible due to sprouting (Katzman, Björklund, Owman, Stenedi, & West, 1971). Such a regeneration could occur within the first two weeks after the lesion. It is therefore crucial that ICSS measures be taken relatively soon after the lesion (within days), and that these measurements be taken over a reasonable period of time (at least two weeks) with periodic checks for ICSS recovery up to at least 40 days after the lesion (Ross & Reis, 1974).

(d) If a given lesion affects ICSS at a distant site, this effect may be due to either one or both of the follow-

ing possibilities: (1) the lesion has caused a decrease in the neurohumoral transmitter substance at the ICSS site; or (2) the lesion has caused degeneration of some or all fibers under the ICSS electrode. If either possibility has occurred, the change in ICSS performance will probably be reflected in the threshold measure, while it may not be reflected in the bar-press rates. The system has been rendered less sensitive to stimulation and now more intensity is needed to elicit the behavior. A threshold measure would reveal such a change. Bar-press rates may or may not change, depending on the relative intensity used in the study. A number of investigators have shown that bar-press rates are neither the best measurement for ICSS performance (Hodos & Valenstein, 1962; Steiner, 1966), nor for its "valance" (Valenstein, 1964). A typical rate-intensity function in most ICSS sites takes an inverted U shape. Thus, two different intensities may yield the same rates, yet one is a pre-peak intensity while the other is a post-peak intensity. All the studies looking at the effects of lesions on ICSS measured the rates of <u>one</u> intensity as their dependent variable. A change in this one measure will not necessarily indicate the new state of the organism. For instance, a rat may have its ICSS threshold at 20 uA, and its peak intensity at 60 uA where it presses 200 times per minute. An intensity above 60 uA will yield

lower response rates than peak intensity. If the pre-lesion intensity chosen is 40 uA, where the rat responds with 100 presses per minute, a lowering of response rates after the lesion may not reflect a decrement in the subject's ICSS behavior. It may be that 40 uA now represents an intensity above peak, and that the animal would be more responsive at a lower intensity. This would reflect an increase in the subject's sensitivity to stimulation, similar to the effect observed after administration of an enhancing drug (see next section). Also, if the pre-lesion bar-press level is high, any side effect caused by the lesion (such as accentuation of motor involvement during ICSS) may very well debilitate to the extent that it cannot respond at such high rates as it may desire. A threshold measure, on the other hand, where the effort required by the subject would be minimal and sensitivity to stimulation best evaluated, would reflect more accurately ICSS sensitivity changes. We therefore propose that a rate-intensity (RI) function that measures threshold, peak, post-peak, and at least two intermediate intensities, would best depict changes in ICSS due to lesions.

(e) This lengthy and strict criteria in methodology for lesion studies is absolutely necessary in order to fully evaluate lesion effects. Since such conservative criteria were not employed in the studies to be described,

it is not surprising that the results were very variable and difficult to later explain and replicate.

These lesion studies had primarily one or both of the following objectives: (1) to see if lesioning of the MFB-LH area, the hypothesized "substratum" of ICSS, will abolish ICSS at other sites; and (2) to see the effects of different brain lesions on MFB-LH ICSS.

Two studies tested the effects of MFB-LH and mesencephalic lesions on septal ICSS. Both experiments (Boyd & Celso, 1970; Valenstein & Campbell, 1966) showed that lesions in and around the MFB-LH areas do not affect septal ICSS. A small reduction in septal ICSS rates was observed for about ten days if the lesions were relatively small. Larger bilateral lesions required post-operative care, which in some instances lasted over one month. Once the animals recovered from the operation, septal ICSS returned to pre-lesion levels. It should be noted that, in both studies, the pre-lesion baseline rates for the one intensity chosen were quite high, and that threshold measures were not taken. Boyd and Celso (1970) report on one subject that stopped pressing in the septum after a large bilateral lesion that extended over the mamillothalamic tract and reached caudally into the habenulointerpeduncular tract This subject did not lose weight and never bar-pressed again for ICSS. In most of Boyd and Celso's cases, the

rates became much more variable than they were before the lesion. Both studies conclude that the system underlying ICSS behavior contains redundancy and a high capacity for reorganization. Boyd and Celso conclude from this study and a previous one conducted in the same laboratory (Boyd & Gardner, 1967) that a small area just anterior to the intrapeduncular nucleus is central to ICSS behavior. Whereas in the previous study LH ICSS was reduced by ipsilateral lesions of the area anterior to the intrapeduncular nucleus, septal ICSS disruption required bilateral destruction of the area. Their explanation for this difference is that either the septal ICSS system is more diffuse, or that this area is not as important for septal ICSS as it is for LH ICSS.

The authors' conclusion that an area extending from the anterior mamillothalamic tract to the habenulointerpedencular nucleus, and an area anterior to the interpeduncular nucleus, are involved in septal and LH ICSS is very tempting, yet speculative at best. First, the effective lesions in both studies are very extensive and overlap with a number of surrounding areas. Second, of the three animals with identical lesions (as described by the authors) involving the mamillothalamic tract, only one suffered an abolition of septal ICSS. Another rat died, and the third one recovered fully within a week post-

lesion. Third, although mamillothalamic tract lesions in the Boyd and Gardner (1967) study did indeed reduce LH ICSS, the most effective lesions involved areas in the ventral midbrain. These types of lesions did not affect septal ICSS. Although Boyd and Celso's (1970) effort to postulate an area (other than the MFB) to be central to ICSS behavior is indeed exciting, their own data does not support this attempt.

The notion that the ICSS system is very diffuse and redundant finds tentative support in a study by Asdourian, Stutz, and Rocklin (1966). Of 21 rats with bilateral hippocampal and thalamic lesions, two subjects showed a decrement in the one rate measured, nine subjects showed a significant increase, and ten showed no effect. Their argument that inhibitory and facilitory pathways have been interfered with is extremely weakened by the fact that post-lesion baselines were taken for only three to five days.

Since the previous studies cited above have shown that ICSS is not dependent on the integrity of the MFB, a number of studies have looked at the effects of different MFB component lesions and differential brain lesions on MFB-LH ICSS itself.

Lorens (1966) investigated the effects of lesions in the basal diencephalon and tegmental components of the MFB on LH ICSS. In summary, Lorens finds significant reduc-

tions in LH-MFB ICSS stimulation time (total amount of time the bar was depressed and subject was getting stimulation) when the lesions involve the antero-lateral hypothalamus (35% reduction) alone, the antero-lateral hypothalamus (ALH) in combination with the ventral midbrain tegmentum (33% reduction), the central grey (53% reduction) the pontine reticular formation (39% reduction), and the ALH and the dorsomedial tegmentum (53% reduction). All lesions, except the ALH lesion, were bilaterally placed. Interestingly enough, bilateral lesions of the midbrain reticular formation in combination with the ALH had no effect on ICSS, while lesioning of the midbrain reticular formation by itself enhanced ICSS significantly (21% increase), suggesting that the combination lesions cancelled each other out. Thus, the only site which would affect LH ICSS by itself when lesioned would be the ALH, which is spacially very near the LH. Lorens concludes that LH ICSS is not solely dependent on the rostral or caudal projections of the MFB, or both.

Since the major projections of the MFB were damaged, the author concurs with the previously stated suggestion by Valenstein and Campbell (1966) and others that the MFB does not seem to be the mediator of the ICSS reward system, and that the pathways mediating the behavior are very diffusely organized. One criticism that could be leveled at

this study is that the subjects were tested for six days, 12 to 14 days after the lesion. Since recovery over time has been reported in another study (Valenstein & Campbell, 1966), the post-lesion data seems insufficient. Also, Lorens does not report any systematic procedure that tested for any side effects of these large lesions.

Since, according to Olds and Olds (1969), the data on the effects of lesions on ICSS was inconclusive and conflicting due to the variance in the results of various experiments and the different recovery periods allowed, they decided to re-investigate the role of the MFB as a possible substratum of ICSS. They aimed their study at the question of whether ICSS can be abolished, and whether destruction of the anterior or posterior aspects of the MFB is more effective in reducing ICSS. Three experiments were conducted where small, medium, and large lesions were placed at the telencephalic or mesencephalic boundaries of the MFB and their effects were tested on LH ICSS. Post-lesion bar-press rates were taken eight weeks after the lesion for a period of two weeks. The highest rate achieved during the five-day pre-lesion baseline was compared to the highest rate achieved during the post-lesion runs. The lesions were, in most cases, bilateral but not symmetrical, in order to avoid killing the animals. Small anterior lesions had no effect or very insignificant effect on posterior MFB

ICSS, while smaller posterior MFB lesions markedly impaired anterior MFB ICSS (57% to 96% decrements). Large lesions at either the anterior or posterior MFB caused large decrements in LH ICSS in six of seven rats. Medium size lesions in the posterior MFB caused larger decrements in LH ICSS than anterior MFB lesions did.

The authors point out that given the large size of the lesions, it is difficult to delineate one or more specific anatomical regions as crucially related to the ICSS impairment. However, they suggest that their data points to an ascending system in ICSS, since the posterior lesions were always more effective. They also point out that the magnitude of the impairment depends on "the size of the tissue destroyed and the proximity of this destruction to the self-stimulation point" (p. 1263). The larger the lesion and the closer to the ICSS site, the stronger the effect.

In addition to Olds and Olds' (1969) own evaluation of the detrimental effects of their lesions in terms of their large size, proximity to the ICSS electrode, and non-specificity of the areas destroyed, a number of other procedural criticisms can be raised. First, they tested for the effects of the lesions eight weeks after the operations, thus missing the rate of recovery, if any, of the less affected animals, and more important, the time course of the

ICSS post-lesion decrements. This would have allowed comparison with previous studies and, in addition, given some insight into the possible degeneration rate of the destroyed pathways. Second, their post-lesion data for comparison was only the highest rate achieved during a two-week run. Since another lesion study has reported that post-lesion ICSS rates in the septum are much more variable than during pre-lesion runs (Boyd & Celso, 1970), Olds and Olds' (1969) pre- versus post-lesion ICSS comparisons leave out statistical information, and are thus incomplete.

Keesey and Powley (1973) continued the examination of LH-MFB contribution to central reward and to the regulation of body weight. Bilateral lesions were placed at the LH and their effects on posterior hypothalamic and ventral tegmental ICSS were measured. Immediately after the lesion, the rats either failed to self-stimulate or did so at very low rates. However, within five days, the rates of responding started a steady increase which lasted for two weeks. After the second week post-lesion, ICSS rates stabilized and remained so for the rest of the eight-week testing period. This terminal level corresponded to about 55% of pre-lesion rates. Body weight was also reduced after the lesion and it reached a constant level (83% of normal) in the third week after the lesion. The authors concluded that LH damage is inversely related to

both post-lesion ICSS levels and weight maintenance, and that body weight maintenance is directly related to the chronic reduction of ICSS rates.

Although their results seem to support our view that the non-specific reward system is interconnected with the loci responsible for specific drive behaviors (in this case, food intake), their effects on body weight loss could be directly due to bilateral LH lesions (Epstein & Teitelbaum, 1962), and the debilitating effect thereof could have directly affected ICSS rates in terms of performance and not motivation. In other words, the LH lesions may not have reduced ventral tegmental ICSS per se, but rather they affected body weight which in turn affected ICSS. The actual effect on ICSS may have been lost due to the fact that only one intensity was used and a more reliable measure of sensitivity, the threshold, was not taken.

A different experimental approach to study the role of the MFB was employed by Madrigan and Albert (1971) and Nakajima (1972). Since the lesion studies described above produced controversial and inconclusive results, these investigators produce temporary lesions injecting procaine into the MFB-LH area. Procaine becomes a useful local anesthetic since it reduces the transfer of sodium ions across the neuronal membrane and thus prevents the genera-

tion of nerve impulses.

Madrigan and Albert (1971) unilaterally injected procaine into the MFB region while the rats were self-stimulating from either the septum or preoptic area. This procedure was proposed by the investigators because of its immediate effect and short duration. Procaine produced strong suppressions of ICSS rates on the ipsilateral side, while contralateral injections resulted in significantly less severe decrements. These effects were produced with injections all along the MFB. Injections into the MFB-LH area associated with feeding behavior produced a suppression in bar-pressing for food. Injections into areas not associated with feeding did not suppress bar-pressing for food. The authors concluded that the MFB in its entirety is important for septal and preoptic ICSS. They claim the previous lesion studies did not affect the MFB in its entirety and therefore recovery occurred.

We believe that these results are better explained by our model of specific ICSS pathways stemming from localized CA nuclei. Ross and Reis (1974), Ungerstedt (1971), and Loizou (1969) showed that large portions of the septum and preoptic areas are innervated by the LC by way of the dorsal bundle. Since this DB travels through a relatively small portion of the MFB, lesions placed in the MFB in order to affect septal and preoptic ICSS, will necessarily

have to be very precise and specific. Valenstein and Campbell (1969) and Boyd and Celso (1970) did not place specific MFB lesions and therefore may have affected the DB only some of the time, and thus affected septal ICSS on an almost random basis. Madrigan and Albert (1971), on the other hand, affect the whole MFB and thus the area through which the DB passes on its way to the septum, and consequently reduced septal ICSS.

Nakajima (1972) postulated that both the LH and the ventral tegmentum (VT) are part of the same ICSS system. He reasons that since the VT is an ICSS site into which MFB fibers send its projections to form the limbic midbrain area (Nauta, 1958), the VT could be considered as the caudal extension of the MFB. Some of the results of lesion studies described above, which tested VT lesions on LH ICSS and vice versa, support Nakajima's hypothesis (Boyd & Gardner, 1967; Keesey & Powley, 1973; Olds & Olds, 1969), while others do not (Boyd & Gardner, 1967; Lorens, 1966). In addition to procaine injections, Nakajima also placed glutamate injections into either the LH or VT and looked at their effects on the other site's ICSS. Glutamate has the opposite effect of procaine, namely, it produces neural excitation. In summary, it was found that unilateral procaine injections into the VT or LH reduced, but did not abolish, ICSS from the LH or VT respectively.

Glutamate enhanced VT ICSS when injected into the LH, but when injected into the VT, it enhanced LH ICSS in some animals, but it also suppressed LH ICSS in other sujbects. Contralateral injections affected the ipsilateral and contralateral sides similarly. The author concludes that ICSS in any part of the system activates the entire system through the descending as well as the ascending pathways, and through bilateral as well as unilateral connections.

As in the previously described experiments, this one only used one intensity and measured presses as an index of the injection effects. It would seem logical that since the author employes glutamate and procaine as an action potential manipulation, a threshold measure of ICSS would be more appropriate. Also, it is hard to explain why glutamate had differential effects on LH ICSS when injected into the VT. One possible explanation may be that glutamate injections into the LH will always enhance VT ICSS because either the essential ICSS terminals are in the LH, or the LH is truly a mixed dopaminergic and NE ICSS system (as proposed by Calvier & Routtenberg, 1974). Glutamate injections into the VT may vary according to what neurohumoral site in the VT is affected. If it affects the dopaminergic A9 cell group, it may affect LH ICSS differently than if it affects the NE fibers of passage towards the MFB-LH area. It must be pointed out that any conclu-

sions as to specific ICSS pathways are only tentative, since Nakajima was not able to determine the extent of spread of the injection.

In summary, all the lesion studies described above have contradictory results and do not elucidate the influence and role played by a specific neuroanatomical site in the phenomenon of ICSS. This is due to a number of factors: (1) Lesions are, most of the time, too extensive to determine one or more loci that affect the behavior; (2) Recovery periods are insufficient and do not trace the long-term effects of the lesions; (3) Possible side effects caused by the lesion are not evaluated and can, at times, be the direct cause for the ICSS effects seen; (4) All studies use one intensity where a full-range rate-intensity function is desirable due to expected sensitivity changes in ICSS; (5) Since almost all studies are concerned with the question if the MFB is the substratum for ICSS, primary attention is geared towards a complete abolition of the ICSS phenomenon, and partial effects are not properly evaluated. This last point is very important in terms of our own REM-ICSS hypothesis. Rather than postulate that ICSS is a diffuse, unspecified system capable of reorganization, our model proposes a non-specific system which touches upon all ICSS sites and that stems from nuclei in the hindbrain. Therefore, we believe that ICSS

from specific sites will be abolished if the nuclei of origin are destroyed. But we also believe that some sites will be only partially affected because: (a) at times, a lesion may not completely destroy the nuclei of origin; or (b) the ICSS site is mixed and receives innervation from a number of nuclei which, although interconnected, are in and by themselves sufficient to support ICSS. It, therefore, becomes very important to fully evaluate even partial effects of lesions on ICSS in order to determine the amount of input the ICSS site receives from the lesioned locus. By adopting this view, we may be able to explain the amount of variance in the results of the studies summarized above. The ICSS system is not necessarily a diffuse one, but each ICSS site may receive one or several pathways originating in hindbrain nuclei. The results in these experiments may reflect a by-chance effect in a system where the specific pathways innervating specific ICSS sites are disrupted through a procedure where these pathways are unknown and the locus of origin of an ICSS site is also unknown. In other words, ICSS site A has a main pathway of innervation, X, and an additional pathway, Y, which also innervates it but to a lesser extent. In addition, other ICSS sites can be innervated by either Y or X or other pathways. An experiment which will not postulate these possibilities and specify the

ICSS loci and pathways involved will rarely place a lesion that entirely abolishes ICSS.

Recently, German and Bowden (1974) have tried to explain the above-mentioned lesion studies in terms of a CA ICSS system. They have suggested that the effective lesions which disrupted LH and septal ICSS interrupted NE innervation by the bundles stemming from the pons and the medulla. They base their claim on comparisons between the effective lesions and Ungerstedt's (1971) diagrams of the CA systems. Althought this hypothesis is very tempting, a number of effective "CA bundle lesions" were in combination with hypothalamic lesions close to the ICSS electrode. Furthermore, some of the lesioned areas that appear to overlap with Ungerstedt's bundles did not produce the effect, while other areas that do not overlap with any bundles did not affect ICSS. In addition, such comparisons are weakened by the fact that they are based on hand-drawn diagrams rather than the actual histology.

E. Neurohumoral Transmitter Substances and ICSS

Many investigators have been searching for the neurohumoral transmitter substance (NHTS) responsible for the mediation of "central reward", or ICSS. Research in this area of ICSS has intensified due to Dahlstrom and Fuxe's (1964) and subsequent delineations of the monoaminergic

pathways in the brain. In addition to the MFB-LH area, which is largely "mixed" in terms of NHTS's, ICSS behavior can also be elicited from the LC (Crow et al., 1972; Ellman et al., 1974; Ritter & Stein, 1973) which has primarily NE cell bodies (Ungerstedt, 1971), from the substantia nigra (SN) (Crow, 1972; Routtenberg & Malsbury, 1969) which is largely a dopaminergic structure (Anden et al., 1966; Dahlstrom & Fuxe, 1964; Ungerstedt, 1971), and from the area surrounding the dorsal raphé (Margules, 1969), which is serotonergic (Dahlstrom & Fuxe, 1964). The question of interest is whether ICSS behavior at these sites is being subserved by either: (a) the specific monoaminergic cell bodies and fibers which lie in the immediate vicinity of the electrode; (b) a NHTS whose cell bodies send fibers of passage under the electrode; or (c) a combination of NHTS's which are mutually potentiating. In order to ascertain NHTS specificity in ICSS behavior, studies have made use of pharmacological agents which will cause either an enhancement of NHTS transmission at the synapse, its blockage, its depletion, or the destruction of the NHTS-producing cell bodies and their terminals.

Aside from its presence in a number of ICSS sites, serotonin (5-HT) is also released when ICSS sites are stimulated (Aghajanian, Rosecrans, & Sheard, 1967). This is not very surprising, since one such site (the MFB-LH area)

regulates the maintenance of 5-HT and NE in the rat brain transsynaptically (Heller & Moore, 1965). Although a number of studies have suggested that 5-HT plays a role, albeit minor, in the mediation of MFB-LH ICSS (Gibson, McGeer, & McGeer, 1970; Poschel & Ninteman, 1968; Stark, Boyd, & Fuller, 1964), others have reported that 5-HT depletion does not affect ICSS (Black & Cooper, 1970; Cooper, Black, & Paolino, 1971; Margules, 1969).

The studies that suggest 5-HT involvement in ICSS studied the effects of 5-HT depletors and enhancers on ICSS thresholds rather than on one intensity where relatively high rates are yielded. It has been pointed out that intensities around threshold generally appear to be most sensitive to drugs (Steiner, 1966). For instance, amphetamine raises response rates at threshold intensities, leaves middle intensities relatively unaffected, and decreases rates at high intensities (Steiner & Stokely, 1973). Thus, an intensity above threshold may be left unaffected, or be affected in the opposite direction in relation to the action of the drug.

Black and Cooper (1970) and Cooper et al. (1971) looked at the effects of DL-p-chlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor that depletes 5-HT, and found no decrements in LH and septal ICSS at an intensity that yielded high response rates. Stark et al. (1964)

found that one drug that causes an elevation of brain 5-HT (DL-pheniprazine hydrochloride) and one drug that acts as a 5-HT antagonist (D-2-bromolysergic acid diethylamide) lowered ICSS thresholds in dogs. Gibson et al. (1970) found that agents which deplete 5-HT (DL-5-bromotryptophan, PCPA, DL-6-fluorotryptophan) mildly raise ICSS threshold in rats.

Those studies which looked at threshold intensities rather than the less drug-sensitive high intensities showed that different 5-HT levels differentially affect ICSS. It appears, therefore, that this NHTS is involved in the mediation of ICSS. These same studies, however, also showed that the role of CA's in ICSS is significantly more influential than that of 5-HT. (The role of CA's in ICSS will be described in detail further along in this section.)

Margules (1969) investigated the NHTS properties of the ICSS site in the vicinity of the serotonergic dorsal raphé. He found that ICSS rates were increased under administration of d-amphetamine, a NE releaser. These rates decreased if chlorpromazine, a NE blocker, was administered. ICSS rates were, however, unaffected by the 5-HT depletor, PCPA. Margules concluded that ICSS in the dorsal tegmentum is subserved by noradrenergic fibers of passage, rather than 5-HT cell bodies in the vicinity of the electrode.

The fact that CA's play a major role in the mediation of MFB-LH and septal ICSS has been demonstrated in a number of studies. Depletion of CA's after systemic administration of alpha-methyl-para-tyrosine (AMPT), a tyrosine hydroxylase inhibitor, decreases ICSS rates and increases ICSS threshold in the MFB-LH area (Black & Cooper, 1970; Cooper et al., 1971; Gibson et al., 1970; Poschel & Ninteman, 1966), the LC (Ritter & Stein, 1973), and the septum (Cooper et al., 1971). The suppressive effects of AMPT were reversed by a small dose of methamphetamine, a CA mimic (Poschel & Ninteman, 1966). It is not clear from these studies which one of the CA's, dopamine or NE, is involved in ICSS, since AMPT affects both CA's equally (Spector, Sjoerdsman, & Undenfriend, 1965). Breese, Howard and Leahy (1971) demonstrated that dopamine and NE concentration reductions through the administration of 6-hydroxydopamine reduced MFB ICSS by 50%.

Stein and coworkers have postulated that the CA involved in the mediation of ICSS is NE rather than dopamine. First, it was shown that NE was released into the synapse after ICSS at the MFB (Stein & Wise, 1969). Second, Wise and Stein (1969) looked at the effects of selective NE depletion. Administrations of either disulfiram or diethyldithiocarbonate (DEDTC) sharply reduced MFB ICSS. Both drugs inhibit dopamine-beta-hydroxylase and thus de-

plete NE. They were able to reinstate ICSS with intraventricular injections of l-NE, the biologically active isomer. Intraventricular administration of dopamine or 5-HT did not restore ICSS. Third, Stein and Wise (1975) reported that: (a) d-amphetamine is nine times as potent in the enhancement of internal capsule ICSS than l-amphetamine; (b) suppression of ICSS by apomorphine could be reversed by d-amphetamine but not by l-amphetamine; and (c) intra-ventricular injections of l-NE but not dopamine, significantly increased MFB ICSS. Since Taylor and Snyder (1970) had shown that d-amphetamine is eight to ten times as potent as l-amphetamine in NE terminals, but equipotent in dopaminergic terminals, Stein and Wise interpreted their findings to support their notion that NE is central in the phenomenon of ICSS. Ritter and Stein (1973) found that chlorpromazine and AMPT suppressed LC ICSS, while pimozide, a dopaminergic receptor blocker, had no effect. Ellman et al. (1975) have shown that LC ICSS is enhanced by d-amphetamine to a significantly greater extent than by l-amphetamine. Thus, a number of experiments have shown that ICSS in many sites is subserved by NE.

However, the notions that NE is the most important NHTS in ICSS, and that ICSS is basically a NA system, have recently been challenged. Poschel (1969) found that monoamine oxidase blockade did not enhance ICSS in the

SN as it did in the MFB. Although Poschel did not propose a different NHTS for ICSS at that level of the mesencephalon, Phillips and Fibiger (1973) did, after obtaining differential effects of d- and l-amphetamine from the SN and the MFB. They found that d-amphetamine was seven to ten times more effective in enhancing MFB ICSS than the l-isomer. However, the two isomers enhanced SN ICSS equally. Their hypothesis that two systems, one NE, the other dopaminergic, mediate ICSS finds support in a recent experiment reported by Ellman, Ackermann, Bodnar, Jackler, and Steiner (1976). They found that the LC and the DB ICSS is more sensitive to d- than l-amphetamine, whereas ICSS sites at the midventral periaqueductal area are equally sensitive to both isomers.

Belluzzi, Ritter, Wise, and Stein (1975) attempted to show that SN ICSS is primarily a function of the ascending NE bundles passing in the vicinity of the mesencephalic dopaminergic cell groups tested by Phillips and Fibiger. Belluzzi et al. showed that knife transsections and 6-hydroxydopamine lesions of both the DB and VB together virtually abolished SN ICSS for three days. After 12 days, SN ICSS had returned to 40% to 60% of the pre-cut level. They found that both the knife-cut and the 6-hydroxydopamine lesion separately had greatly reduced NE brain levels, with little reduction of striatal dopaminergic levels. They

also found that NE inhibition through DEDTC injections decreased SN ICSS, but this decrease was reversed through intraventricular injections of l-NE. This reversal was not obtained with dopamine injections. They conclude that SN ICSS is not independent of NE.

Recently, Cooper, Cott, and Breese (1974) have claimed that they were able to differentially affect dopaminergic and NE levels through different treatments of 6-hydroxydopamine. They report that the enhancing effects of d-amphetamine and the reducing effects of AMPT in MFB ICSS were dependent on the brain levels of dopamine and not NE. According to these investigators, the findings support their hypothesis that the dopaminergic system is deeply involved in the maintenance of ICSS.

In summary, although 5-HT has been shown to be involved in the mediation of ICSS, the data suggest that the main responsibility for the maintenance of this behavior lies with the CA's. Despite the fact that d- and l-amphetamine will differentially affect ICSS depending on the locus of stimulation, the puzzle still remains as to: (a) the existence of two separate ICSS systems, one NE, the other dopaminergic, as proposed by Phillips and Fibiger; or (b) the predominance of one system (NE) with the potentiation of a second, less significant one (dopaminergic), as proposed by Stein and coworkers. Whichever the case may

be, the results detailed above do assign a role, albeit controversial, to the dopaminergic system in the mediation of ICSS. Clavier and Routtenberg (1974) have reported that lesions placed at the MFB will produce degenerations in all three systems of passge, the DB, the VB, and the nigro-neostriatal system stemming from the SN. If the dopaminergic system is involved in MFB-LH ICSS, as has been suggested, the question remains as to why ICSS in this area is so much more affected by d-amphetamine than l-amphetamine. The possibility exists that the NE influence in this area overwhelms the dopaminergic input, but the dopaminergic input is significant nonetheless. Therefore, it can be hypothesized that once the NE input is reduced, the dopaminergic input will become more apparent and the d-amphetamine over l-amphetamine ratio will be reduced. We wanted to test this possibility, and therefore ran one group of subjects on d- and l-amphetamine before and after LC lesion, in order to assess any changes in d- or l-amphetamine effects due to lesions in the NE nuclei of the LC. If SN ICSS is part of a separate dopaminergic system, LC lesions will not affect this ICSS site.

F. The Hypotheses and Some Procedural Considerations

Given that the LC is important in the phenomenon of REM sleep and has been postulated to be the nucleus of origin of the REM-ICSS system, the following hypotheses

have been made:

(1) LC lesions will decrease rates and increase thresholds in LH ICSS;

(2) These lesions should not affect SN ICSS if this site is part of a separate dopaminergic ICSS system;

(3) D-amphetamine, but not l-amphetamine, will temporarily restore LH ICSS to pre-lesion levels;

(4) If the lesions reduce NE levels at the ICSS site and dopamine also participates in the potentiation of the behavior, the ratio of d-amphetamine over l-amphetamine effects on ICSS will be reduced after the lesion;

(5) If the LC lesions affect LH ICSS, they will also bring about a reduction in REM sleep.

In order to test these hypotheses, a number of procedural criteria must be established. First, since bilateral lesions in many parts of the brain cause general detrimental effects on the organism (see section D on lesions), LC lesions will be placed unilaterally and their effects will be tested at least on the ipsilateral site. Second, given that special considerations must be taken with degeneration time course, possible sprouting, temporary post-lesion side effects, and ICSS "reorganization" (terms described in section D), the effects of the lesions are monitored for a minimum amount of time that will allow

for the occurrence of any of these factors (14 to 16 days). This is followed by periodic checks on ICSS up to a minimum of one month after the lesion. Fourth, subjects' weights will be continuously monitored in order to ascertain any non-specific effects on ICSS other than the lesion itself. Fifth, a full rate-intensity function is obtained that encompasses threshold, intermediate, peak, and after-peak intensities in order to better assess the effects of the drugs and the lesions. This type of strict procedure reduces to a minimum the amount of variance experienced in the above-described lesion studies.

Lesion technique. Since a number of investigators have demonstrated that the morphology of brain lesions depend largely on both types of electrode used and current applied (DiCara et al., 1974; Gold, 1975; Rabin, 1968; Reynolds, 1963), the use of this technique demands careful application. Gold (1975) reports that direct current (DC) reduces iron deposits. Furthermore, "slow lesions" (e.g. 100 μA for 200 seconds) destroy more tissue than "fast lesion" (e.g. 2 mA for 10 seconds), although the same number of coulombs are delivered. He proposes the possibility that iron deposits expand the lesion over time.

Reynolds' (1963) finding that radio-frequency (RF) lesions placed in the ventromedial hypothalamus by way of stainless steel electrodes do not produce the hyperphagic

symptoms that result from DC lesions further demonstrates the differential effects that result from various lesion parameters. Reynolds proposes that hyperphagia effects are due to irritation produced by metallic deposits. This has been supported by the findings by Rabin (1968).

DiCara et al. (1974) found that while RF was equally effective for destroying nuclei and fibers, DC current destroys nuclei but spares peripheral fiber tracts. Thus, unless the electrode is impinging directly on the fiber tracts, DC lesions will curve around fibers in the vicinity and produce uneven destruction.

Since our aim was to destroy LC nuclei and their ascending projections, RF parameters were chosen. In addition, the RF current was passed via stainless steel electrodes. This approach has been shown to prevent metallic deposits (Aronow, 1960; Reynolds, 1963).

In terms of the amount of mA delivered in this site, in order to produce the lesions (see Procedure), the following consideration must be taken: RF currents in the magnitude of 10.0 to 40.0 mA delivered for the duration of 5 to 50 seconds, produce brain lesions from 0.5 to 2.0 mm. in diameter. These parameters produce the same size lesions as DC currents varying from 0.8 to 2.0 mA for six to 20 seconds (DiCara et al., 1974).

Stimulation technique. Our aim was to stimulate specific areas within the hypothalamus and to test for the differential effects of the LC lesions at these sites. Valenstein and Beer (1962) have shown that bipolar stimulation is more discrete than conventional monopolar techniques. We have thus chosen bipolar stimulation parameters in order to allow precise specification of the anatomical sites under the electrode.

Method

Subjects

Forty-four male albino rats (Holtzman) weighing 350-515 gms. at the time of the operation were used.

Surgery

Subjects were anesthetized with a mixture of sodium pentobarbitol and chloral hydrate combination (Equithesin, Jensen) injected intraperitoneally (i.p.) (dose approximately 3 ml/kg). They were then implanted with the use of a Kopf stereotaxic instrument with bipolar, stainless steel electrodes (Plastic Products) which were completely insulated except at the tip (0.24 mm. width between the tips). In all subjects, electrodes were aimed at the LC unilaterally or bilaterally. In addition to the LC electrode, 30 subjects had electrodes aimed at the LH (LC-LH group), eight subjects had electrodes aimed at the LH and SN (LC-SN-LH group), and in six subjects, the zona incerta was aimed for (LC-ZI group) (Table 1). In order to maximize the success rate of ICSS implants, 14 of the 30 LC-LH subjects were implanted at both sites bilaterally. In such cases, due to the close proximity of the ICSS sites to midline, electrodes were entered at a mediolateral angle. The lambda and bregma suture lines served as points of reference for the derivation of coordinates (Figure 2). The incisor bar was set at -5 mm. in order to avoid puncturing

of the transverse sinus with the LC electrode.

The LC coordinates were: 0.3 mm. posterior to lambda line, 1.0 mm. lateral to the mid-saggital suture, and 7.0 mm. from the surface of the skull for straight entry; and 0.3 mm. posterior to lambda line, 3.0 mm. at a 16° angle lateral to the mid-saggital suture, and 7.3 mm. from the surface of the skull for angled entry. Lambda line was a hypothetical transverse line aligned with the lambda suture at 2.0 mm. lateral from lambda point (Figure 2).

The coordinates for the LH implants were: 0.2 mm. anterior to the midpoint between lambda point and bregma, 1.5 mm. lateral to the mid-saggital suture, and 8.7 mm. from the surface of the skull for straight entry; 0.3 mm. anterior to the midpoint between lambda point and bregma, 2.9 mm. at a 10° angle lateral to the mid-saggital suture, and 9.1 mm. from the surface of the skull.

ZI electrodes were aimed at the midpoint between lambda point and bregma, 1.7 mm. lateral to the mid-saggital suture, and 8.5 mm. from the surface of the skull.

SN coordinates were 2.2 mm. posterior to the midpoint between lambda point and bregma, 2.0 mm. lateral to the mid-saggital suture, and 8.2 mm. from the surface of the skull. In most cases, unilateral implants were on the left side of the brain.

Cortical screws and muscle electrodes were attached in 22 of the operated subjects (four LC-ZI, two LC-SN-LH, six LC-LH unilateral, and ten LC-LH bilateral subjects) (Table 1) in order to obtain EEG and EMG recordings. EEG leads were connected to two stainless steel screws of 6.0 mm. length. One screw was placed at 2.0 mm. anterior to the midpoint between lambda point and bregma, 1.0 mm. lateral to the mid-saggital suture, and at 1.0 mm. anterior to bregma; the other screw was placed at 1.0 mm. lateral to the mid-saggital suture. Both screws were placed ipsilaterally. A bipolar stainless steel electrode was unwound, stripped of about 1.0 cm. of the Teflon Formvar insulation, and each pole was tightly wound around one screw, separately, making sure that contact was made between the pole and the skull. A second bipolar stainless steel electrode was stripped bare of insulation for approximately 3.0 cm. and wrapped around the belly of the nuchal muscle for EMG recording. In all subjects, the plastic electrode caps were fixed to the skull with dental acrylic and stainless steel screws. Following the operation, the skin was sutured and a 5 to 10 day recovery period was allowed.

This new EMG recording technique was developed in our laboratory, since others (personal communication) have reported difficulties in recording tonus changes in the rat's

neck muscles.

Procedure

All subjects were maintained on an ad lib schedule for food and water, and were housed individually. After recovery from the operation, subjects were trained to press a bar for electrical stimulation delivered to each electrode site. ICSS tests were run in a 20 cm. wide, 40 cm. long, 22 cm. high Plexiglas operant chamber, placed in an open, sound-deadened Lafayette enclosure. A Lehigh Valley retractable lever, 2.0 cm. long and 3 cm. wide, located 4.0 cm. above the floor, protruded into the chamber. A force of 20 gms. on the lever was sufficient to activate a microswitch and constituted the measurable response. Solid state and electromechanical programming equipment delivered a .25-sec. train duration of 60-cycle, sinusoidal wave stimulation after each response. The stimulator and monitoring oscilloscope were all isolated from ground. Stimulation was adjustable from 0-10 volts root mean square (RMS). Wave form and stimulus intensity were continuously monitored by observing the voltage drop across a 1,000-ohm resistor in series with the subject on a Hewlett Packard #110-B cathode ray oscilloscope. Subjects were allowed to self-stimulate at each intensity for 7-min. periods. Changes in current intensity occurred during a 1-min. timeout between each 7-min. period when the lever was re-

tracted from the chamber.

Subjects were shaped by the method of successive approximation at several intensities from 15-250 microamps (μA) during a 1-1/2 hour session over several consecutive days. Training always began with the LH site and was then followed by the LC or SN locus. LC ICSS was maximized by shaping the subject for at least four days at that site, and in some cases, alternating stimulation between the LC and the LH. Subjects with electrodes that supported ICSS at bilateral LH placements were run each day at both LH sites. The LH site ipsilateral of the LC electrode that yielded the highest response rate was run first. We employed this procedure because we assumed that high response rates at the pontine site reflected direct impingement of the electrode on the LC (Ellman et al., 1974).

Following ICSS training, LH rate-intensity functions were obtained daily at the same time each day. Only subjects that reliably self-stimulated were used in the experiment. Subjects were tested at a minimum of six different intensities, chosen to encompass the range of intensities over which the subjects would reliably self-stimulate. At the end of each session, a 7-min. extinction period was run. Rate-intensity functions contained one intensity which yielded a mean response rate of less than an arbitrarily defined threshold of ten responses per minute

over the last five minutes of the 7-min. period, one intensity at or above threshold, and four or more intensities above threshold, including the intensities which yielded peak rates. This procedure was repeated until rate-intensity functions stabilized. Rate-intensity functions collected over the next four days were considered as either pre-lesion or pre-drug baseline, depending on which group the subject was assigned to. Subjects were separated into two groups; one group underwent a sleep-drug paradigm, while the other group underwent LC lesions immediately after the four-day baseline run.

A. The sleep-drug paradigm. The subjects that were tested for the effects of d- and l-amphetamine before and after LC lesions were also recorded to assess the effects of LC lesions on the sleep cycle (see Figure 3). Subjects were kept continuously in red-light illumination and not stimulated for a minimum of four days. Seventy-two (72) hours of continuous EEG and EMG recordings were obtained on each rat. Recordings were made on a Grass polygraph, model #78. Following this procedure, the four-day pre-drug baseline was run, followed by a 24-day drug paradigm which tested for the effects of saline, d- and l-amphetamine (1 and 2 mg/kg i.p.) on LH rate-intensity functions. Subjects were run for four consecutive days at the same time each day and at the same values and sequence of intensities.

Each drug was administered two times over two successive 3-day sequences. Drug was administered on the second day of each sequence; days one and three served as pre- and post-drug saline controls. The low dose (1 mg/kg) of either d- or l-amphetamine was administered first, followed by the 2 mg/kg dose. The sequence of d- or l-amphetamine was counterbalanced across animals.

On drug days, subjects were injected intraperitoneally with either d- or l-amphetamine at a dosage of 1 or 2 mg/kg of body weight, administered in concentrations of 1 or 2 mg/ml in 0.9% normal saline solution, 25 minutes before the session. On pre- and post-drug days, only saline (1 or 2 ml. 0.9% normal saline/kg. body weight) was injected 25 minutes before the session.

Following the drug test, subjects were run again on rate-intensity functions until stable. They were then placed in red-light illumination for a period of three days. During this adaptation period, subjects were not given access to ICSS. They were then anesthetized and lesions were placed at the LC site with a radio frequency Grass Lesion Maker, model #LM4A. The lesions are produced by passing a 2-8 mA anodal current through the electrode tip to an indifferent cathode (metal plate or anal tube) for a duration of 30 secs. Following the lesions, 72 hours of continuous EEG and EMG polygraph recordings were obtained in each sub-

ject. Ten to 14 days after the LC lesion, self-stimulation baseline and drug paradigm identical to the pre-lesion paradigm was run. Subjects that showed a reduction of LH ICSS post-LC lesion were checked for recovery periodically up to three months after the lesions.

Those subjects that did not show an LH ICSS decrement were sacrificed after termination of the post-lesion drug paradigm, since the time course for possible fiber degeneration or neurohumoral transmitter depletion is a maximum of 12 days (Ross & Reis, 1974; Ungerstedt, 1971). All subjects that had self-stimulated from the LC site before the lesion were tested at that site after the lesion, to make sure that at least the fibers or cell bodies directly under the electrode had been destroyed. Had the subject still self-stimulated from that electrode, that site would have been lesioned again.

Since it had been reported that bilateral LC lesions affect memory consolidation (Anlezark et al., 1973), the post-lesion paradigm for those subjects that showed a LH ICSS decrement included priming and shaping at all intensities during the first two minutes of the 7-min. trial if the subject failed to emit a response within that time. They were also tested at higher intensities, in addition to the pre-lesion intensities, to establish if high response rates could still be elicited. After the post-lesion drug paradigm,

subjects were not run for approximately one month, and were then re-run on a four-day post-lesion "recovery check".

After completion of the ICSS paradigm, all subjects were again adapted to red-light illumination for three days, and 24 hours of EEG and EMG recordings were obtained. Following this, the animals were injected with an overdose of Equithesin and perfused via an intracardiac needle with 0.9% normal saline solution followed by 10% formalin solution. The brains were then removed from the crania and kept in 10% formalin for at least three days. Frozen coronal sections, 40um thick, were stained with luxol fast blue and cresyl violet, according to the method of Klüver-Barrera (1953).

Sleep recordings were scored "blind" in units of 30-sec. epochs. Scorable epochs were classified as either "awake", "REM", "slow wave sleep", "awake-REM" (A-R),"sleep-REM" (S-R), or "mixed". This last category was used for epochs in which neither of the three other stages occupied the majority of the epoch. All three categories, "A-R", "S-R", and "mixed" were used when the epoch contained a fragment but not a majority of REM sleep. In such cases, REM was tabulated in units of one-fifth of the epoch ("periods REM") and was included in the final tally of sleep stages. Thus, all REM sleep of 3 seconds' or more

duration was accounted for.

B. Non-drug paradigm. In this paradigm, subjects were lesioned immediately after the four days pre-lesion baseline run described above. This procedure included the LC-LH and LC-SN groups. All subjects that self-stimulated from the LC electrode that was lesioned were tested for ICSS at that site following the lesion. If ICSS could still be elicited, the site was lesioned again within two days and re-tested for ICSS.

One day following the LC lesion, the subjects were started on a 14-day baseline run. If the subjects showed LH or SN ICSS decrements, they were "shelved" for approximately one month, and then run again for a four-day recovery baseline. In three subjects, this procedure was repeated one month later. The subjects that did not show an ICSS decrement after the LC lesion were either sacrificed after the 14-day run, or were lesioned again at the same site at a higher voltage. If the second lesion was ineffective, the subject was sacrificed and processed in the manner described above.

C. Electrode placement and lesion size assessments. The stained brain sections were examined under the microscope and electrode locus and size of lesions were evaluated "blind" by two independent judges. ICSS placements were classified in terms of the neuroanatomical site under

the tip of the electrode and in terms of Ungerstedt's (1971) description of the monoaminergic nuclei and pathways. The size of the lesions placed under the LC electrode were evaluated in terms of the percentage destruction of the neuroanatomical sites affected by the lesion and Ungerstedt's (1971) description of these areas.

Results

Seventeen subjects completed the experiment. Table 2 summarizes the extent of the LC lesions in each subject in terms of the areas affected and percentage damaged. A secondary lesion at the LC contralateral to the electrolytic lesion was found in subject 95E (Figure4B). It was estimated that the LC in this subject had been bilaterally obliterated and therefore this subject's data was analyzed separately. In two subjects (62E and 10F), it was estimated that 20% to 35% of LC cell bodies could still innervate anterior areas of the brain by way of intact DB fibers. In addition, a secondary lesion was found in subject 62E which destroyed 20% of the VB in its ascent through the posterior midbrain. These two subjects were therefore excluded from the experimental groups and formed a separate control group. Figure 4A illustrates the extent and overlap of the LC lesions in these two subjects in a caudo-rostral series of brain sections.

LC lesions in the remaining 14 subjects either destroyed 100% of the LC cell bodies at the levels of the anterior pons and the pons-midbrain transition area, intercepted and destroyed the DB in its ascent from the LC, or damaged enough LC cell bodies and aspects of the DB so that no more than 10% of LC cell bodies from either level could innervate rostral brain areas. Figure 5 illustrates the ex-

tent and overlap of the LC lesions in these 14 subjects and shows Ungerstedt's (1971) maps of hindbrain CA nuclei pathways.

Photomicrographs of histological sections (Figure 6, 7, 8, 9, 10, 11, and 12) show the extents of the pontine lesions in 7 subjects. The spread of these lesions into the areas adjacent to the LC are described in Table 2. Although the destruction of neighboring structures is minimal in subjects 69F and 1G (Figures 9 and 12), it is more extensive in subjects 57E and 76E (Figures 6 and 7).

Table 3 lists the brain sites impinged upon by the hypothalamic electrodes ipsilateral to the LC lesion in all 17 subjects. Each neuroanatomical site is also described in terms of the monoaminergic nuclei and axons of passage under the electrode tip, according to Ungerstedt's (1971) descriptions and diagrams. Reference to Konig and Klippel's (1963) diagrams is given for each electrode site. Figure 13 illustrates the areas directly under each electrode in an anterior-to-posterior series of brain sections, and compares them to Ungerstedt's illustrations.

The hypothalamic electrode tips of the 14 subjects with 90% to 100% of the entire LC lesioned were located in gour general areaas. Table 4 summarizes the histological placements of the hypothalamic electrodes in terms of these four areas, and the number of subjects in each group.

Four electrodes were localized in the zona incerta-H2

Fields of Forel area, dorsal to the hypothalamus (D-H group). Of these, two were at the level of the anterior aspects of the subthalamic nucleus, in areas largely innervated by the DB and DA nigostriatal (NS) bundles (subjects 60E and 69F). Figure 14B shows a photomicrograph of subject 60E's hypothalamic electrode impingement. The third subject's electrode was located dorsolateral to the dorsomedial nucleus of the hypothalamus (pars dorsalis) at the level of the mamillothalamic tract (subject 7F). This area receives axons from the DB and coincides with the DA cell group A13 which is part of the tubero-infundibular DA system. The third subject's electrode (subject 86E) was at a more anterior level, ventrolaterally to the mamillothalamic tract and dorsal to the LH nucleus. This area is also innervated by the DB in its passage into the MFB (Ungerstedt, 1971) and to some extent by the nigrostriatal bundle (L (Lindvall & Bjorklund, 1974).

In three subjects, the hypothalamic electrodes impinged on the tip of the crus cerebri (CC-H group). Of these, two were located at the level of the posterior hypothalamic nucleus (subjects 76E and 70F), and one was at a more anterior placement, internal capsule (subject 68E) at the level of the anterior portions of the dorsomedial hypothalamic nucleus. The area directly under these three electrodes is largely and primarily innervated by the DA nigrostriatal system ascending from the SN (Anden et al., 1965; Lindvall &

Björklund, 1974; Ungerstedt, 1971). Photomicrographs of these three subjects' electrode tips are shown in Figures 14A (S 68E), 15B (S 76E), and 15D (S 70F).

The location of the electrode tips in five subjects was along the MFB at various levels of the hypothalamus (MFB group). In two subjects, the electrodes were located on the lateral part of the MFB, brushing the crus cerebri. One electrode placement (subject 92F) was posterior to the lateral hypothalamic nucleus (Figure 15C). The other (subject 57E) was in the posterior MFB-LH area (Figure 15A). Two other electrode placements (subjects 96E and 1G) were in the MFB-LH at the level of the dorsomedial hypothalamic nucleus. Figure 14C shows the electrode tip of subject 1G. The fifth electrode was located in the dorsal aspect of the MFB-LH at the anterior level of the dorsomedial nucleus (subject 78E). The extent of the MFB on which these five electrodes impinge is heavily innervated, throughout, by the VB, with contributions of the DB and the DA systems at the MFB's dorsolateral level (Lindvall & Björklund, 1974; Ungerstedt, 1971).

The hypothalamic electrodes of two subjects were located in the perifornical region ventral to the fornix and medial to the MFB-LH (F-H group). Subject 75E's electrode was at the level of the subthalamic nucleus, subject 15F's electrode was at the level of the anterior aspects of the

dorsomedial hypothalamic nucleus. Figure 14D shows the histological section of subject 15F's hypothalamic placement. The extent of the lesions in these four separate hypothalamic groups is illustrated in Figure 16.

Of the two subjects with less than 80% of the entire LC lesioned, one (62E) had its hypothalamic elecgrode impinging on the MFB-LH at the level of the anterior hypothalamic nucleus, the second subject (10F) had its electrodes on the dorsomedial nucleus of the hypothalamus. Subject 95E's hypothalamic electrode ipsilateral to the electrolytic LC lesion was located under the fornix, at the level of the anterior hypothalamic nucleus.

Two of the 14 subjects with over 90% of the LC destroyed also had electrodes aimed at the SN (SN group). Both electrodes impinged on the SN, one on the zona compacta (subject 1G), and one on the SN pars lateralis (subject 69F). This area is described as rich in DA cell bodies (group A9). Figure 17 illustrates the electrode placements and the catecholamines present at that level. A photomicrograph of subject's 1G SN electrode is shown in Figure 18. Table 5 shows the five intensities chosen to encompass the rate-intensity functions of hypothalamic and SN ICSS in the 14 subjects.

Of the four hypothalamic area groups described above, two showed a significant and permanent decrease in ICSS rates accompanied by a large increase in ICSS threshold. Both the CC-H and D-H groups showed this effect during the

four-day post-lesion baseline trials. Figures 19 and 20 show the proportional changes of both the CC-H and D-G groups, respectively, at each of the five intensities. (chosen to encompass the subjects' rate-intensity functions). The curves represent standardized scores where pre-lesion response rates at each intensity is unity, and post-lesion response rates are expressed as a ratio of the pre-lesion rates. These two groups showed no recovery of ICSS to pre-lesion levels, either during the long-term post-lesion baseline days or the recovery check tests (Figures 19 and 20). Figures 21-27 show the rate-intensity function curves for pre-lesion, long-term post-lesion, and recovery check baseline meausres of the seven subjects from the CC-H and D-H groups. Figures 22 and 24 also show that the additional intensities on post-lesion trials do not yeild response rates comparable to pre-lesion baseline days.

Two subjects in the CC-H group showed an immediate and permanent abolition in ICSS (Figures 21 and 22). The third subject (70F) showed no post-lesion ICSS effect, and was re-lesioned 16 days later. There was no immediate effect on ICSS after the second lesion (see Figure 28); however, a gradual increase of threshold and decrease of response rates occurred over the next 12 days, after which the subject stabilized.

Table 6 shows that all four subjects in the D-H group show a marked reduction in ICSS response rates,

accompanied by an increase in ICSS threshold after the LC lesion. Figures 24, 25, 26, and 27 illustrate for each individual subject the RI functions of pre- and post-lesion baseline runs. The post-lesion affect was immediate and permanent. However, in none of these subjects was ICSS completely abolished. Of the five intensities chosen to represent the full range of the subjects' RI function, the first two intensities were the most affected by the lesion. The percentage ICSS response reductions at these two intensities, as compared to pre-lesion measures, in all subjects ranged from 49% to 96% immediately after the lesion (S-BL), 56% to 88% during the long-term BL (L-BL), and 40% to 100% during the recovery check BL (R-BL). Reductions at the three high intensities ranged from 14% to 88% during short-term BL runs, 10% to 74% during long-term BL days, and 27% to 100% on recovery check BL runs. Figures 24 and 26 show the full RI function was affected by the LC lesion in two subjects (60E and 7F). This reduction of ICSS response rates and increase in threshold occurred immediately after the lesion, and remained unchanged up to three months after the lesion. Subject 86E (Figure 25) showed a post-lesion decrement at the first two intensities above threshold, and at peak intensity during both S-BL and L-BL trials. However, the two intermediate intensities were not affected. The

fourth subject in this group (69F) was affected by the lesion at all intensities on all three post-lesion baseline measures, except at the lowest intensity above threshold during R-BL. Although the average response rates at the first intensity during the R-BL was lower than during the pre-lesion trial, response rates for these two measures overlap in terms of the standard error of the mean (Figure 27).

Figures 29 and 30 illustrate the RI functions of pre- and post-lesion trials of subjects 75E and 15F (F-H group). Average response rates for five intensities representing the full RI function for pre-lesion and post-lesion measures, and the post- over pre-ratio of response rates are shown in Table 6. The first LC lesion in subject 15F proved not effective in reducing response rates at any of the intensities. Thus, subject 15F was lesioned a second time at a higher voltage. During both the immediate and long-term BL runs, the first two intensities above thresholds were not affected by the lesion; the third intensity showed an increase in response rates following the lesion, while the two peak intensities were reduced after the lesion. Since this subject showed no marked reduction overall in ICSS after LC lesions, it was sacrificed after L-BL run.

The second subject in this group, 75E, did not show

an affect after the first lesion, and was lesioned again at the higher voltage. As seen in Figure 29, this subject showed a marked reduction at all intensities immediately after the lesion and during the long-term post-lesion baseline run. However, when tested for recovery one month after the lesion, the RI function as compared to pre-lesion levels, yielded an increase in response rates at the first above-threshold intensity, no affect at the two intermediate intensities, and a reduction of response rates at the two last intensities.

Figures 31 to 35 illustrate the RI functions of pre-lesion and post-lesion trials for the subjects in the MFB-H group. Means of five intensities for pre- and post-lesion trials and the post : pre-lesion response rate ratio are summarized in Table 6. Except for subject 57E, at the first intensity above threshold, all five subjects showed recovery from LC lesions when tested on the R-BL trial. However, the rates and patterns of recovery differed among subjects. Subjects 57E and 92F (Figures 31 and 34) showed a strong reduction of ICSS response rates immediately after the lesion (S-BL). This reduction was still apparent during L-BL trial. However, during recovery baseline measures, both subjects had returned to pre-lesion response rate levels at all intensities except at the first intensity of subject 57E and the last intensity of subject 92F. The hypothalamic electrodes in these two subjects have been described above as impinging on the lateral as-

pects of the MFB bordering with the crus cerebri. The area under 96F's LC electrode was lesioned three times with intervals of 14 to 18 days between lesions. None of the lesions proved effective in either abolishing ICSS, decreasing or increasing ICSS thresholds, or reducing ICSS response rates at all intensities (Figure 33). Immediately after the third lesion, only the last two intensities (the highest two intensities) were affected by the lesion by a reduction of 15% of response rates. On the long baseline run, this reduction was lowered to 5% to 9%. This animal was sacrificed after the long baseline trial. Subject 78F showed a reduction of ICSS at all intensities on the S-BL trial (Figure 36). However, this subject's response rates returned to pre-lesion levels during the L-BL run. During this sequence, the third intensity was reduced by 39%, as compared to pre-lesion measures. The last two intensities showed an increase in response rates. The recovery baseline showed response rates approximating pre-lesion levels. Subject 1G (Figure 35) showed no decrease of response rates immediately after the lesion. However, response rates increased gradually over L-BL and R-BL. Ultimately, post-lesion rates reached a 126% to 297% increase over pre-lesion rates.

In summary, as illustrated in Figures 21 to 36 and Table 6, LC lesions affect ICSS differentially, depending on the specific anatomical site impinged on by the ICSS

electrode. These figures show that the CC-H group and the D-H group have a marked and permanent reduction of ICSS response rates, while the MFB-H and F-H groups show an initial reduction immediately after the lesion, with recovery over time and actual facilitation in two subjects.

The 14 subjects described above were grouped into two separate groups, according to the ventral bundle involvement under the hypothalamic ICSS electrode. In other words, subjects of groups F-H and MFB-H were grouped together (VB-H group) and compared to the two hypothalamic groups with nigrostriatal and DB involvement (NS-DB group). The two sets of grouped data were tested for homogeneity of variance. It was found that in both sets, as illustrated in Table 6, the pre-post lesion variance across intensities was not homogeneous. Therefore, no analysis of variance could be employed, as it would violate the assumptions of the F test. However, there is homogeneity in the pre-post lesion variance across subjects. Therefore, a t-test analysis was performed to test if the lesion significantly affected response rates at each intensity. Table 7 summarizes the data in terms of the two groups, their pre- and post-lesion rates, and proportional changes after the the lesion. By the use of a t-test for related measures,

it was found that the VB-H group was significantly affected by the lesion at the first intensity during the S-BL trial ($p<.05$); however, no other intensity was significantly reduced during that run. No other significant reductions were found at any intensity during the L-BL and R-BL tests ($p>.10$). The NS-DB group, on the other hand, showed a significant difference between pre- and post-measures at all intensities, throughout the experiment. Response rates at all intensities during S-BL, L-BL, and R-BL were significantly reduced ($p<.05$).

In order to evaluate the relative effect of the lesion at each intensity, standardized scores were derived from the post-lesion baseline measures. In other words, intensities were compared in terms of the percentage ICSS rate reductions produced by the lesions. These standardized scores were also used to compare the VB-H group to the NS-DB group to see if these two groups differed from each other at all intensities on post-lesion BL measures. NS-DB ICSS rates were significantly more reduced than ICSS rates of the VB group (Mann-Whitney U Test, $p<.001$).

Since it is already known that the lesions will significantly affect all intensities of the NS-DB group and not the MFB group, according to the previously described

statistics, a nonparametric statistic was employed to determine if intensity is a significant variable in terms of lesion effects. Assuming that each pre-lesion BL levels at each intensity is unity, one can assess the effect of the lesion at each individual intensity by calculating the post-lesion BL : pre-lesion BL ratio and ranking each intensity for each individual subject in terms of the effect of the lesion. Table 8 shows the ranked data for each subject in all post-lesion conditions and at each intensity. The Friedman two-way analysis of variance by ranks (X_r^2)(Siegel, 1956) determines whether the rank totals differ significantly. This test compares favorably with the most powerful parametric test, the F test. Since the importance of the intensity in determining the lesion effect applies only where ICSS has not been totally abolished, the two CC-H subjects (76E and 68E) that showed complete abolition of ICSS after the lesion, were not included in this analysis. While the effects of the lesion in the VB group were not dependent on the intensities testes ($p > .30$), the NS-DB groups' percentage decrease in ICSS performance depends on the intensity tested ($p < .001$).

Table 9 summarizes the results obtained from the SN subjects during pre-lesion BL and the post-lesion S-LB, L-LB, and R-LB trials. Figure 37 illustrates the results of subject 1G. In this case, the subject did not show a

lesion effect immediately after the lesion. However, its response rates decreased for all intensities during the L-BL run, and stabilized without any further decrease when tested again during the R-LB test. Subject 69F, on the other hand, showed a strong post-lesion effect with an increase in ICSS threshold immediately after the lesion, and maintained this effect with a slight recovery, up to the R-BL (Figure 38). Proportional measures for these two subjects as a group are represented in Figure 39 for all three post-lesion baseline trials. Both subjects as a group showed significant decrements at all intensities during the long baseline and recovery baseline as measured by a t-test of related means ($p < .05$).

Figures 40, 41, and 42 summarize the above mentioned findings for all three groups: the VB group, the NS-DB group, and the SN group, for all three post-lesion baseline measures in terms of the proportional effects of the lesion.

D- and L-Amphetamine Effects

In order to assess the d- and l-amphetamine effects on ICSS, pre- and post-lesion, subjects were pooled and analyzed according to the histological results. Two groups were formed: a VB-H group, and a NS-DB group. Of the 18 subjects run in the paradigm, eight subjects were tested for the effects of d- and l-amphetamine effects before the LC lesion. One of the subjects, 10F, was excluded

from the analysis for two reasons: (1) the LC lesion was too small; (2) its hypothalamic electrode impinged on the dorsomedial hypothalmus, an area not clearly defined in terms of its neurohumoral innervation. The MFB group included subject 62E in addition to subjects 87E and 57E. Although this subject was excluded from a post-lesion analysis, given that the LC was less than 90% destroyed, the pre-lesion data is included so that a larger sample of the MFB under pre-lesion screening procedures can be obtained. The NS-DB group included subjects 68E, 60E, 7F, and 86E. Subject 86E was not tested on the post-lesion drug paradigm since the subject had to be sacrificed for a reason unrelated to the experiment. However, it is believed that the inclusion of this subject to the NS-DB group adds information about pre-lesion d- and l-amphetamine effects and their differentiation. Table 10 summarizes the data of both groups in terms of the multiplicative effect of the data for pre-lesion amphetamine tests. The first two intensities represent at-threshold and above-threshold intensities, the three last intensities represent an intermediate response rate intensity and two peak rate intensities, respectively. Figures 43 and 44 illustrate the effects of one mg/kg of amphetamine, d- and l-, on hypothalamic ICSS. Although both groups were affected by d-amphetamine but not by l-amphetamine, the NS-DB group

was significantly more affected by d-amphetamine than was the VB group (Mann-Whitney U test, $p > .05$). No differences were observed in the l-amphetamine effects between both groups. The affects are most striking at the two intensities corresponding to threshold intensities. The 2 mg/kg amphetamine trials are illustrated in Figures 45 and 46. In this case, again, at threshold and intermediate intensities, the NS-DB group shows a more marked d-amphetamine effect than does the VB group. The number of samples for the 2 mg/kg groups are reduced by the fact that signs of hyperactivity caused by the high dosages automatically voided the test.

Figure 47 illustrates the effects of d- and l-amphetamine on NS-DB self-stimulation after LC lesions. Figures 48 to 51 illustrate the effects of d- and l-amphetamine, 1 and 2 mg/kg, for subject 76E after LC lesions (Table 11). Figure 52 illustrates the proportional d- and l-amphetamine effects after LC lesions in relation to pre-lesion baseline which is held as unity. As described before, post-lesion baseline is markedly lower than pre-lesion unity baseline. One mg/kg of l-amphetamine does not produce any marked return to pre-lesion levels. However, 1 mg/kg of d-amphetamine returns response rates to pre-lesion levels. Two mg/kg of l-amphetamine returns ICSS threshold to pre-lesion levels, while 2 mg/kg of d-amphetamine is more effective at higher intensities.

LC Lesions on the Sleep Cycle

The sleep data was analyzed by comparing time awake and percentage REM for the same time of day periods on pre-lesion as post-lesion BL, for all subjects tested. Table 12 summarizes the findings in terms of REM percentage and time awake during pre-lesion, post-lesion, and recovery BL's. Both pre- and post-lesion measures include 30 hours of EEG and EMG recording; recovery check covers 12 hours of recording. All measures include the nightly part of the circadian rhythm. Subjects were divided into two categories: those with complete LC lesions (subjects 60E, 68E, 57E, and 7F)(Group I), and subjects with partial lesions (Ss 62E & 10F)(Group II)(Figure4A).Given that small sample involved, the only significant difference revealed by a t-test of related differences occurred in Group I, comparing pre-lesion and post-lesion REM percentage ($p < .05$). No differences were found in both REM percentage and time awake in Group II and time awake in Group I; nor were there any differences in time awake between Groups II and I. Post-lesion recovery checks were not obtained from subjects 7F and 10F since their EEG and EMG recordings were unscorable. Of the three subjects from which recovery readings were obtained, subjects 60E and 68E did not show a REM percent return to pre-lesion BL, subject 62E showed a slight increase in REM percent, and subject 57E's REM level returned to a pre-lesion level.

Discussion

In summary, the following results were found in this experiment: (1) LC lesions which destroy at least 90% of the LC or its ascending bundles markedly reduce ICSS response rates and drastically increase ICSS thresholds, and in some animals abolish ICSS entirely, in subjects whose electrodes are located in the hypothalamic region innervated by the DB, the nigrostriatal bundle, or both; (2) ICSS in subjects whose hypothalamic electrodes impinge on areas that are largely and primarily innervated by the VB are not reduced by these lesions; (3) LC lesions reduce SN ICSS response rates; (4) d-amphetamine affects NS-DB ICSS differently than it does VB-H ICSS; While threshold intensities are enhanced by d-amphetamine in a 9 : 1 ratio over saline measures in the NS-DB area, this ratio is 2 : 1 at most in the VB-H area. Neither hypothalamic area is enhanced by l-amphetamine; (5) d-amphetamine, but not l-amphetamine, returns reduced NS-DB ICSS response rates and decreased ICSS threshold to pre-lesion levels; (6) unilaterally placed LC lesions will reduce REM sleep, while lesions that do not destroy one side of the LC completely will not be as effective.

The LC lesions greatly reduce hypothalamic self-stimulation and, in some cases, abolished the behavior

entirely. The serendipity of these findings appear two-fold: (1) this abolition or reduction is selective within the hypothalamic area; (2) the lesions of this NA nucleus has a detrimental effect on hypothalamic sites rich in dopamine. This surprising finding is additional to the demonstration that hypothalamic self-stimulation can be abolished with a relatively small, discrete unilateral and distant lesion. Thus, this experiment shows that self-stimulation can be abolished and that ICSS behavior is not necessarily a diffuse system which is redundant and capable of recovery.

Before different and complex hypotheses that can explain the obtained results are postulated, a number of important procedural and control aspects must be pointed out. First, these unilateral lesions did not result in weight losses in the rats, nor were there any behavioral deficits observed. Thus, the obtained results were not artifactual non-specific side effects caused by neurological injury. Second, the size of the lesion does not correlate with the size of the effect. Comparisons of photomicrographs of the LC lesions and corresponding effects illustrate this point. While the hindbrain lesions in subjects 70F (Figure 10), 69F (Figure 9), and 1G (Figure 12) were small and limited themselves to the LC, these lesions differentially affected hypothalamic

ICSS. Subjects 69F and 70F's response rates were greatly reduced, while ICSS in subject 1G was facilitated. On the other hand, subjects with extensive hindbrain lesions (Subject 57E, Figure 6; Subject 76E, Figure 7) were also differentially affected by the lesions (Figures 31 and 22). In addition, subject 1G showed ICSS facilitation at the MFB-LH (Figure 35), but ICSS abolition in the SN (Figure 37). Thus, given the limited extent of these lesions to begin with as long as the LC is destroyed, the magnitude of the effect depends on the ICSS site impinged on rather than lesion size.

Third, a possible argument that spread of current puts limits to the case of differentiation within the hypothalamus can be ruled out on two counts: (1) Stimulation was delivered through bipolar electrodes. This method allows anatomical specificty as opposed to monopolar stimulation (Valenstein & Beer, 1962). (2) If some spread of current to an adjacent area did not occur, the fact still remains that the LC lesion abolished ICSS behavior, even if it were from an adjacent ICSS site. Even so, there can be no question that ICSS from that adjacent site depends on the integrity of the LC.

The spread of current argument is, furthermore, weakened by the results of subjects 60E and 76E. Both subjects showed either ICSS reduction or abolition fol-

lowing the LC lesion (Figures 24 and 22). In both cases, post-lesion intensities were increased up to 80 μA over pre-lesion intensities. Yet, no increase of ICSS response rates could be elicited. In addition, pre-lesion ICSS thresholds for both subjects were similar to thresholds of subjects that were not affected by the lesion (Table 5).

Fourth, the method employed in this experiment to test subjects for long periods of time after the lesion, revealed valuable information in terms of recovery or decrements over time and patterns thereof, in conjunction with the specificity of the ICSS site involved. This was the case of most subjects tested in this experiment. While ICSS from some placements was immediately affected (subjects 60E, 68E, and 76E), other sites showed gradual decrements (70F) or gradual recovery (87E, 92F, 1G).

From the factors enumerated above, the results of this experiment show that lesion studies on ICSS require a strict methodology, without which confounded and random results can be obtained.

The results of these experiments, some of which were predicted while others were surprising, require a model capable of explaining and integrating the results of previous lesion and pharmacological ICSS studies.

First, this experiment confirms the hypothesis that ICSS behavior can be abolished and is not a redundant phenomenon capable of recovery. However, the finding that ICSS from areas rich in dopamine requires the integrity of the NA nuclei of the LC, seems paradoxical in light of Stein and Wise's (1969) and Cooper et al.'s (1974) findings and the proposed distinction between different DA and NA ICSS systems (Phillips & Fibiger, 1973). Second, the effects of the lesions on ICSS are far more consistent in the differential effects than previous lesion studies (Boyd & Gardner, 1967; Lorens, 1966; Olds & Olds, 1969; Valenstein & Campbell, 1966). Third, the differential effects of d- and l-amphetamine on ICSS vary according to hypothalamic sites involved. The variation correlates with the magnitude of the LC lesion effect. This finding in conjunction with the restoration of ICSS after its decrease due to the LC lesion, requires the postulation of a complex polysynaptic and mixed ICSS system.

The fact that the effects of these lesions on ICSS are more consistent and reliable than those obtained in previous lesion studies is explained by a number of reasons:

(1) The hypotheses of this experiment predicted that specific ICSS sites are part of one or several ICSS

systems innervated by known noradrenergic nuclei. Thus, the lesions in this experiment were placed in an area that innervates a known monoaminergic system, namely the LC-DB system. The prediction that ICSS from anatomical sites which receive fibers from this system would be detrimentally affected by the LC lesion was confirmed. Previous lesion studies did not postulate specific ICSS networks, but rather searched for one ICSS center. These studies were based on the hypothesis that such a "reward center" would mediate all ICSS behavior. In these studies, account was not taken of the fact that the neurohumoral transmitter substances involved at anatomical sites related to ICSS may be different, although this was implied by the work of Dahlstrom and Fuxe in 1964. Rather, these studies took neuroanatomical and behavioral factors into consideration. For one, the MFB was thought to interconnect all ICSS sites, and also ICSS from the MFB-LH area seemed most sensitive. In addition, ICSS models that did take the monoamines into account also postulated one ICSS sytem (Arbuthnott et al., 1970; Dresse, 1966).

Although an explanation for the few positive findings in previous lesion studies is at best speculative, a tentative hypothesis can be based, within limits, on

the results of this study and the CA maps outlined by the Sweidsh investigators (Lindvall & Björklund, 1974; Ungerstedt, 1971).

It is possible that in Lorens' (1966), Boyd and Gardner's (1967) and Olds and Olds' (1969) studies, the lesions which reduced hypothalamic ICSS destroyed parts of the CA bundles which innervate the ICSS sites. However, as the results of the present study indicate, lesion effects on ICSS not only depend on which bundles are destroyed, but also on the specific site within the hypothalamus which receives mixed inputs from different CA pathways and in actuality be a locus of two ICSS systems. Therefore, those hypothalamic ICSS sites described in the previous lesion studies as a single ICSS site are, in fact, recipients of two or more CA innervation bundles. Our results clearly indicate that the hypothalamus is not a unitary ICSS center, but rather a pool of different ICSS systems which can be differentiated by way of specific hindbrain lesions that involve specified CA nuclei.

(2) The possible time course of lesion effects was not taken into consideration. Some studies looked only at a short time period which satisfied the 5 to 9 day time course for fiber degeneration to occur, but not the 12-day time course for NHTS depletion(Ross & Reis, 1974).

The different time courses of ICSS abolition or recovery found in this present study and illustrated above, supports this last point.

(3) This experiment has demonstrated that even those sites which do not show a permanent ICSS decrement from the LC lesion are affected for about 4 to 6 days after the lesion (S-BL), with the first intensity above threshold being significantly decreased. Those studies that did not follow-up for a long enough period may not have allowed for full recovery in sites which do not have the ICSS behavior mediated by the lesioned site.

(4) Assessing the effects of a lesion on only one intensity measure which varied from study to study in terms of its value on the rate-intensity function could have either accentuated or missed the effects. In this experiment, it was found that in the MFB group, only the first intensity was significantly affected during S-BL (immediately after the lesion). On the other hand, the NS-DB and the SN groups did not show the same magnitude of effect at all intensities. Peak intensities, although significantly affected, were proportionally less reduced than intensities that yielded lower rates (Table 8).

(5) The usual side effects resulting from bilateral lesions (hypophagia, adipsia, turning, etc.) were not observed in this study (Table 14).

In summary, the need for the procedural considerations outlined in the introduction section were confirmed by the results. The procedure enabled the discrimination between temporary and long-term lesion effects, and also the evaluation of the effects on a complete rate-intensity function. Thus, reliable results were obtained with small, distant, and unilaterally placed lesions.

To what extent were the hypotheses confirmed? First, the lesions not only greatly reduced hypothalamic ICSS, but in some cases they also abolished this behavior entirely. However, some areas of the hypothalamus were not affected by these lesions. Specifically, ICSS from the MFB-LH and perifornical areas which receive large contributions from the NA ventral bundle, were not reduced by the LC lesion on a long-term basis. There was recovery over time. Areas that are primarily innervated by the dopaminergic nigrostriatal pathway (crus cerebri-internal capsule) stemming from the SN and areas that are innervated by both dopaminergic fibers and NA dorsal fibers (Fields of Forel) were markedly affected by the LC lesion. In addition, ICSS from one area that has been associated with a DA system, the SN, was also greatly affected by the lesion. This had not been predicted by the hypotheses. These results by no means weaken the proposed REM-ICSS model. On the con-

trary, they seem to support some of the principal notions and add new dimensions to it, which will be discussed later in this section.

Since the LC lesions differentially affected hypothalamic self-stimulation, depending on the neuroanatomical structure impinged on by the electrode and the neurohumoral innervation of the site, these findings require a new non-unitary outlook into the hypothalamic area in terms of central reward.

Second, the prediction that d-amphetamine but not l-amphetamine would temporarily restore the abolished or reduced ICSS behavior was confirmed by the results of this experiment. The fact that d-amphetamine but not l-amphetamine (1 mg/kg) restores hypothalamic ICSS to pre-lesion levels appears to point towards a dependence of this area's reward properties on NA innervation. This finding is even more striking since these hypothalamic sites (crus cerebri and Fields of Forel) receive large contributions from DA fibers. Since a number of subjects which showed ICSS abolition were tested at intensities reaching up to 75 uA above pre-lesion peak intensity currents without restoring ICSS behavior (Figures 22 and 24), it seems unlikely that the post-d-amphetamine effect is on spared neighboring NA fibers. In addition, l-amphetamine did not show a more enhancing

effect after the lesion than it did pre-lesion. This indicates that the DA system involved in this region has not taken over ICSS behavior and thus is not a sufficient condition for central reward. The return of ICSS behavior to pre-lesion baseline with d-amphetamine may be evidence that this isomer is acting as a NA post-synaptic agonist to the LC dorsal bundle whose link and potentiation to the DA ICSS system has been discontinued by the LC lesion. These results support the notion of ICSS potentiation by, and the necessity of, a REM-ICSS system stemming from the NA nuclei of the LC. In addition, the pre- and post-lesion amphetamine effects indeed reflect an interesting mixed catecholaminergic system. The full model and explanation thereof will be described later in this section.

Third, this experiment has demonstrated that ICSS from the dopaminergic SN, where ICSS is equally potentiated by both d- and l-amphetamine and which gives rise to the nigrostriatal system, is strongly affected by the LC lesion. A tentative conclusion from these results (to be detailed later in this section) is that this self-stimulation system depends on the integrity of the noradrenergic LC and its potentiation. This argument is strengthened by the fact that this dopaminergic system innervates the crus cerebri-internal capsule area and partly the Fields of Forel (Lindvall &

Björklund, 1974; Ungerstedt, 1971), areas from which ICSS was either abolished on decreased. Given that no known direct anatomical connections exist between the LC and the SN, and that SN ICSS is virtually abolished after LC lesions, it cannot be claimed that SN ICSS is a result of stimulation of ventral noradrenergic fibers of passage under the SN electrode (Belluzzi et al., 1974).

Fourth, the results of the sleep data suggest, although not conclusively, that the LC in the rat is involved in the phenomenon of REM sleep. The fact that REM sleep was not completely abolished, and that it showed some return over time (subject 57E) is probably due to the fact that the lesions were unilateral.

The restoration of hypothalamic ICSS behavior by d-amphetamine, the selective abolition of LC lesions of ICSS from hypothalamic sites rich in dopamine, in addition to the SN abolition, points to the possibility that the locus of interaction between ICSS from the dopaminergic SN-nigrostriatal system and ICSS from the NA LC-DB system is anterior to the SN. These results suggest that the LC lesions have disrupted the supply of the neurohumoral transmitter substances necessary to support or potentiate ICSS at the affected sites.

This is the first study that reveals an ICSS system that is abolished by a distant and specific lesion. It

also reveals the existence of at least one additional LC-independent ICSS system, the ventral bundle-hypothalamic system, that in addition to not being affected by the destruction of the LC, responds to one pharmacological agent, d-amphetamine, differently than does the NS-DB system (Figures 43 to 46).

Whereas it was predicted that LH-MFB ICSS would be permanently and markedly reduced by the lesion, and ICSS associated with the DA system would not be affected, the reverse was found in the experiment. While it is not surprising that ICSS obtained from the hypothalamic area that is innervated by the DB is reduced by the destruction of this pathway's cell bodies, it seems peculiar at first thought that the DA system, which has no known connections with the LC system, should be so markedly affected by the LC lesion. Furthermore, it would have been expected that the LH-MFB area, which interacts with the LC in terms of ICSS (Ellman et al., 1975) and which reportedly receives between 40% to 60% of its NE innervation from this nucleus (Ross & Reis, 1974), would be detrimentally affected by the LC lesion. The results of this study, however, indicate that the DA system and the LC system interact in their mediation of ICSS. The question arises, then, how does this interaction manifest itself, and where is the neuroanatomical locus of the in-

teraction?

In an attempt to understand how the two NE systems (DB and VB) are independent of each other in terms of ICSS behavior and how the DA and DB systems interact in this behavior, it seems worthwhile to analyze first the VB area system and its possible mediation of an independent ICSS network. The results clearly indicate that the LC system is not necessary for the maintenance of MFB ICSS and F-H. The redundancy and recovery ability of this area manifests itself within days after the lesion. However, post-lesion ICSS patterns in MFB-LH and F-H subjects was not uniform. Their RI functions were slightly, though not significantly, altered by the lesions. Immediately after the lesion, the threshold intensity first shows a reduction of response rates. Also, rates at peak level intensities remained reduced throughout the experiment in some subjects (78E and 92F), while they are enhanced in others (57E and 1G). Furthermore, the ICSS threshold in one subject (57E) remained raised throughout the experiment.

One tentative explanation is that high response rates at higher intensities produces recruitment of DB fibers and enhance ICSS. It might be that after the LC lesion, these fibers do not respond to stimulation any more, and response rates at those intensities are re-

duced. This hypothesis is tentatively supported in particular by the results in two subjects, 78E and 92F (Figures 32 and 34).

The return of ICSS rates to pre-lesion levels in these two subjects was particularly slow. The hypothalamic electrodes of these two subjects impinged on the lateral aspects of the MFB bordering on the crus cerebri and possibly innervating some of the dopaminergic system fibers. Evidence for this explanation is found in the photomicrograph of subject 92F's ICSS electrode placement at its most caudal extent (Figure 54). While the tip of the electrode was predominantly in the MFB (Figure 15C), a small part of one electrode pole impinged on the crus cerebri.

Although 57E's threshold was raised after the lesion, it seems significant that,after recovering from the lesion during S-BL or L-BL trials, the VB-H group as a whole had higher response rates at the first two intensities. A possible interpretation of this finding is that this ICSS system is compensating for the loss of the "reward" properties of the NS-DB ICSS network. This hypothesis requires the postulation of a facilitatory interaction between both ICSS systems.

The lesion effects on two subjects (57E and 1G) ICSS give support to the "facilitation" hypothesis. Although

the LC lesion abolished SN ICSS in 1G, it increased response rates and lowered the threshold of that same subject's MFB-LH ICSS site (Figures 35 and 37). In addition, the LC lesion greatly increased the SB eating threshold elicited from subject 57E's lateral hypothalamic electrode (Table 13). However, ICSS response rates in this subject were elevated. A recent study (Marshall et al., 1974) suggests that the hypothalamic syndrome (aphagia and adipsia) is a phenomenon related to the nigrostriatal system stemming from the SN. By implication, it would seem that the involvement of the hypothalamus in eating is related to the DA fibers of the NS system. Thus, in both 1G and 57E, the LC lesion detrimentally affected behaviors wich by implication are part of a DA network.(SN ICSS because of d- and l-amphetamine equipotentiation, Phillips & Fibiger, 1973; hypothalamic eating because of the occurrence of the hypothalamic syndrome with NS lesions, Marshall et al., 1974). At the same time, MFB-LH ICSS from both the subjects was facilitated. From this, at least two hypotheses can be formulated:

(1) That the ICSS network (VB-ICSS) which is not dependent on the potentiation and integrity of the LC compensates for the deficit of the disrupted reward system, i.e., LC nigrostriatal system. The facilitation re-

sulting in these two cases may be a direct observation of CNS recovery of function, which in this case is compensation of one reward system for a deficit created in another. Definite evidence for the phenomenon of ICSS facilitation in different ICSS sites following hindbrain lesions has been demonstrated by Mattiace (personal communication).

(2) The second explanation for the facilitatory effect at some MFB ICSS sites is that the LC input is inhibitory. Such an explanation, however, is speculative at best and requires further investigation.

The possibility that a separate NE ventral bundle system operates independently from DB and DA inputs in the mediation of central reward is raised in studies by Arbuthnott et al. (1970, 1971) and Dresse (1966). Although their conclusions are not always in agreement, they have shown that stimulation of areas which receive primarily ventral bundle fibers cause NE depletion of ventral limbic areas. Mattiace (personal communication) postulated that if this is indeed the case, ICSS from areas of the hypothalamus which are heavily innervated by the ventral bundle (LH-MFB and perifornical region) should be detrimentally affected by lesions of NA nuclei in the pons and medulla which contribute to the ventral bundle. This hypothesis finds tentative support in Mattiace's current study.

Although MFB-LH and F-H ICSS is not drastically reduced by the lesions, and even facilitated in some cases, the effects are not uniform. The reductions of NS-DB ICSS, although drastic, are not uniform either. From the results of lesions on FB-H described up to this point, and those on NS-DB ICSS yet to be described, one tenable conclusion seems the most evident: The characteristics of CA innervation throughout the hypothalamus differs from site to site. This fact has recently been clarified by Lindvall and Bjorklund's (1974) elucidating study of CA pathways. The results of our study are in full agreement with their findings. It is clear from our results that the magnitude of the LC lesion effects on ICSS is dependent on the amount of different CA inputs to the ICSS site.

An added characteristic of interest in this VB-H group is the fact that 1 mg/kg of d-amphetamine does not markedly enhance ICSS, in contrast to the DB-NS group, and as it has generally been reported to do at other CA ICSS sites. It is quite possible that this ICSS system, being mainly noradrenergic and generally activated at low thresholds, already functions at an optimal level. Thus, enhancement of the responsible neurohumoral substance will not greatly facilitate the system. In addition, a dose of 1 mg/kg of d-amphetamine may be too

large and over-activate the system to the extent that no clear behavioral effects can be observed. If this is indeed the case, a smaller dose will produce a more marked enhancement of self-stimulation. This hypothesis seems to be supported by the fact that the effect of 2 mg/kg of d-amphetamine on MFB-LH ICSS thresholds is markedly smaller than the 1 mg/kg dose. At any rate, the results clearly show that the two ICSS systems, the VB system and the DB-SN system, respond differently to the same doses of this pharmacological agent.

The possibility should not be discounted that ICSS at the MFB-LH may also be subserved by an additional neurohumoral substance other than the known CA's. A number of studies (Dahlstrom & Fuxe, 1964; Ungerstedt, 1971) have revealed that this MFB area also receives 5-HT and acetylcholinergic innervation. It would, therefore, not be surprising if these neurohumoral substances had a role in the mediation of CISS at that site.

Besides having demonstrated that at least two ICSS systems can function independently of each other, the results of this experiment make it possible to explain the conflicting results of previous experiments. For, whenever an experiment claims to have demonstrated that ICSS in general is subserved by one or another system or neurohumoral substance, one will now have to consider the

possibility that what is necessary and sufficient for one system may not be for another. A second important consideration is our finding that close structures within the hypothalamus are not necessarily part of the same ICSS network.

A number of experiments have addressed themselves to the investigation of the involvement of the different monoamines in the mediation of reward. Some have claimed that lateral hypothalamic ICSS is mediated by NE (Stein & Wise, 1969). Others have shown that DA (Cooper et al., 1974) or 5-HT (Stark et al., 1964; Gibson et al., 1970) may be necessary for the maintenance of the ICSS system. Given the results of this experiment, it is quite possible that the above-mentioned results are not in conflict, but rather each result reflects the predominant operation of a system among two or more.

Evidence for the existence of different NE ICSS systems stems from Clavier and Routtenberg's (1973) investigation of the role of the monoaminergic pathways in ICSS by way of lesioning hypothalamic ICSS sites. The conclusions from their extensive and careful study is that the main monoaminergic inputs for ICSS rise from the LC via the NA DB and the DA systems originating from areas A9 and A10. Although they minimize VB involvement in ICSS behavior, they did find the MFB lesions cause de-

generations along the VB as well.

In summary, the studies by Stein and Wise (1969), Dresse (1966) and both Arbuthnott et al. (1970, 1971) on one hand, and Clavier and Routtenberg (1974) on the other support our contention that DB and VB ICSS systems are independent and differentiable.

At this point, the enigma to be solved is the relationship between DA ICSS and DB ICSS. As mentioned before, no known neuroanatomical connections between those systems have been described. In terms of the results obtained in this experiment, it is not surprising that self-stimulation from the hypothalamic area associated with the DB is reduced by LC lesions. In addition, however, self-stimulation is practically abolished from the hypothalamic area through which the DA systems, stemming from the SN, pass. Also, ICSS in both subjects with SN electrodes was drastically affected by the lesion. Accordingly, Phillips and Fibiger's (1973) claim that the NA and DA systems are separate is not borne out by the results of this experiment. On the other hand, Belluzzi et al.'s (1974) claim that SN self-stimulation is NA rather than DA does not seem tenable in light of the finding that both d- and l-amphetamine equally enhance ICSS at this site. The results of this experiment seem to indicate an intricate relationship between the

LC-DB and DA-NS systems. This relationship and interaction between both systems does not take place at the SN, but rather at the hypothalamus or more anterior site.

Some evidence supporting this hypothesis is obtained from Huang and Routtenberg's (1970) study. They found that lesions of hypothalamic self-stimulation sites produced degeneration of fibers traceable to the SN pars compacta. In addition, SN pars compacta lesions resulted in retrograde chromatolysis in hypothalamic neurons. Stimulation of the LH resulted in a decrease of activity in neurons located in the SN pars compacta. They conclude that "an intimate, though poorly understood relation between the lateral hypothalamus and substantia nigra pars compacta" (p. 430) is indicated by their convergent data. Of great interest to our hypothesis is their finding that lesioning of the H2 Fields of Forel did not produce chromatolysis in the lateral hypothalamus. However, they were able to demonstrate chromatolysis in the SN pars compacta following lesions at the H2 Fields of Forel ICSS site. They expressed their uncertainty "whether self-stimulation from H2 Fields of Forel depends on the integrity of fibers running from MFB to H2" (p. 431).

The results of the present study propose an ICSS model which will explain the interaction and relation-

ship between DB and NS ICSS. In addition, it will try to intergrate conflicting results from previous studies. The ICSS interaction between the different systems can be explained in terms of a DB potentiation role in SN and NS ICSS. A lesion of the LC would reduce the NA innervation at the point of interaction between the DB and NS systems. Once this occurs, ICSS from the DA system is abolished. The fact that DB ICSS was not abolished, whereas SN and NS ICSS were either completely abolished or markedly reduced, can be interpreted in terms of the levels of NE needed in order to maintain DA ICSS, and also in terms of synaptic mediation of the interaction between both systems. Thus, if the LC lesion reduces the available NE in the DB system by 50%, this amount would still be sufficient to at least partially sustain the behavior. However, this may not be the case in terms of the NA potentiation of the DA system, for if the amount of stimulation of the DA system which would normally be sufficient to produce ICSS produces synaptic transmission into the DB system, which in turn mediates the reinforcing properties of ICSS, this same amount of stimulation on the DA system may not be sufficient to excite the DB, now functioning at 50% of its capacity. If this were in fact the case, the LC system would be implicated in a unique role as a potentiator of ICSS. However, if this were the role of the LC system, it seems

at least at first glance, difficult to explain the results of the pre-lesion d- and l-amphetamine paradigm. It would have been expected that l-amphetamine be as effective as d-amphetamine in enhancing ICSS, since we are also dealing with a DA system. However, the postulation of a NA potentiation system explains these results. If the mediator of ICSS in this system is the DB, which also potentiates the DA pathways, then it is the enhancement of NE release which will facilitate ICSS, rather than l-amphetamine, which would not act on the potentiator. In addition, d-amphetamine also enhances dopamine and the results reflect an additive effect of d-amphetamine on both CA's. The post-lesion d- and l-amphetamine results also tend to support the postulated role of the LC as a potentiating system in the mechanisms of ICSS. The fact that a temporary return of response rates to pre-lesion levels is achieved through the administration of d-amphetamine, indicates the necessity of this transmitter substance in the mediation of ICSS in both the DA and NA systems.

If the lesion results of representative subjects are plotted as power functions by transforming the intensity and rate values into logarithmic scales, the results give further information about the mechanisms of the reward systems. First, it will be assumed that no changes

in the post-lesion function as compared to the pre-lesion function indicates that the system has not been affected. Second, the possible changes in a post-lesion function will reflect the new states in the system the following way: a change in the intercept alone, but not the slope, is reflective of a quantitative but not qualitative change. In terms of ICSS, this would mean that, experientially, the rewarding properties and the relationship between the stimulus and the sensation of reward have not been affected. However, the stimulus intensity necessary for the behavior has changed. This could reflect a decrease or increase in the neurohumoral transmitter involved. An example of such a case would be the effects of d-amphetamine on the rate-intensity function, where the whole function is shifted to the left Steiner & Stokely, 1973). In a power curve representation, it would differ from the saline RI function in terms of a higher intercept value, but no slope change.

A change in the slope, however, would reflect that the qualitative, or experiential, aspect of the stimulus-sensation relationship has changed. In other words, the reward properties of the stimulation have been altered. Figure 53 illustrates the log-log function of pre-lesion and post-L-BL and R-BL in four subjects representing each ICSS group (CC-H, D-H, MFB-LH, and SN). Sequence A

(subject 96E) shows that the pre- and post-lesion functions do not differ in either slope or intercept measures. The results are different, however, in the other three groups. The two D-H group subjects show an effect in both the intercept and the slope values (Figure 53). In other words, the LC lesion has not only drastically reduced the reinforcing properties of this system, but the characteristics of the stimulation have been changed. In terms of the stimulus-sensation relationship, the subject is now responding to an experientially different system. Although the SN subject's (1G) functions differ in terms of both the slope and the intercept (or threshold), the latter has not been as drastically increased as in the DB-NS group. Thus, the quantitative value of the stimulation at low intensities has not been drastically changed, but the stimulation-sensation relationship has been greatly altered.

This psychophysical analysis of the data confirms the previously stated hypothesis that the MFB-LH ICSS is not affected by the LC lesions and may be part of a different ICSS system. However, the differential effects of the lesion on threshold intensities (intercept) in the DB-NS group, on one hand, and SN group on the other, may add information as to the relationship between these two systems. The fact that the quality of the ICSS in both

systems has been altered by the LC lesion reflects the reliance of their reward properties on the integrity of the LC-DB. The surprisingly smaller effect on SN-ICSS threshold could be explained by postulating an axoaxomic connection between these two systems at a level anterior to the SN.

In order to understand the interaction between the DA SN system and the NA LC system, a number of factors already described in the Introduction should be restated. First, Phillips and Fibiger (1973) have shown that d- and l-amphetamine have an equivalent enhancement on SN ICSS. Second, Cooper et al. (1974) claim that the enhancing properties of d-amphetamine on hypothalamic ICSS are not observed if the DA system is disrupted. If this is indeed the case, the amphetamine effects on post-LC lesion ICSS reported in this experiment indicate that these lesions have not disrupted the DA system. The interaction between the SN and the LC system could, therefore, be explained the following way: Stimulation of the SN produces excitation of the LC system by way of a synaptic dopamine transmission. Therefore, both the d- and l-isomers which affect DA and NE equally, will enhance ICSS elicited from the SN. In terms of the above-mentioned LC lesion effects on SN ICSS, this innervation of the LC system by the SN fibers would still occur if the LC ICSS

system had not been completely abolished. Thus, the effects of the LC lesion on SN ICSS would not be as drastic at threshold intensities, which reflect the elicitation of an action potential of the LC-DB fibers, as on the overall RI function which depends on the NE levels at the DB terminals. It is predicted from this model that a SN lesion will not affect DB or LC ICSS, since the DB-LC reward system is not dependent on the integrity of the SN. Figure 55 is a schematic representation of the proposed SN-DB model of interaction.

How does this DB-NS ICSS system correspond to the postulated REM-ICSS system? We had postulated that the REM-ICSS system mediates the non-specific ICSS and the specific "drive" behavior systems. The first part of the hypothesis is partially supported by these results. It appears that the LC, in addition to mediating the DB ICSS system, acts as a potentiator of the DA=ICSS system. At this point in time, it seems that MFB-ICSS is largely independent of the REM network. However, a number of factors must be taken into account. It is very possible that complete abolition of all ICSS activity will require a bilateral destruction of the REM sleep center. In addition, although the sleep data tends to show that the LC in the rat is involved in the mechanisms of REM sleep, other areas in the pons may also be involved. Hobson and

McCarley (1973) have claimed that in the cat, nuclei which lie ventral to the LC regulate REM sleep.

The role of the REM-ICSS system in the mediation of "drive", or SB behaviors, is touched on in some pilot data gathered in this experiment. Subject 57E, in addition to supporting ICSS from its MFB electrode, was also a SB eater. It was found that, although lesioning of the LC produced only a temporary reduction in ICSS, the threshold for SB eating was drastically raised after the lesion, and remained raised for the duration of the experiment, long after ICSS had returned to pre-lesion levels (Table 13). This data gives tentative support to the notion that the ICSS system subserved by the LC includes the specific system that mediates SB behaviors, and that these behaviors are not part of the VB system.

In addition to the postulated role of the REM-ICSS system in NE and DA ICSS and "drive" behaviors partially supported by this study, the results of this experiment add an additional component to the REM-ICSS system in terms of the role of reinforcement and motivation in learned behaviors. A number of studies have shown that long-term retention is dependent on REM sleep (Fishbein, 1967, 1970; Leconte et al., 1973). In addition, Anzelark et al. (1973) have shown that bilateral LC lesions produce learning deficits. Zis et al. (1974)

demonstrated that SN lesions interfere with the acquisition of learned instrumental responses. The SN and its crus cerebri tracts have been described as a "way-station" in cortical extrapyramidal discharge (Elliott, 1969). Thus, the SN, playing a major role in the modulation of motor outflow, is also involved in learning. It is postulated that the functioning of this specific system relies on the integrity of the REM-ICSS system and its mediation of reinforcement, in other words, the firing of the non-specific ICSS system. Thus, not only are "drive" behaviors mediated by the REM-ICSS system, but this system, because of its reinforcement mediation properties, is necessary for the occurrence of learning. This hypothesis can be carried further into the role of the LC in the ontogensis of the organisms and its acquisition of adaptive behaviors. Such behaviors would be internally reinforced by the firing of the REM-ICSS system. (It is meedless to say that the organism's experience of positive reinforcement through the firing of the REM-ICSS system will occur without the artificially supplied electrical stimulation.) Therefore, the organism will acquire its behavioral repertoire in the form of motor output through the modulation of positive reinforcement by the REM-ICSS system. This hypothesis, therefore, also explains the results relating learning to REM sleep,

the LC, and the SN.

In contrast to Olds and Olds (1969) finding that the lesions that most affect ICSS are close to the electrode site and large in size, we have found that small, distant, and specific unilateral lesions are capable of abolishing a complete ICSS system. These findings indicate that the LC, which is involved in the mechanisms of REM sleep, mediates an ICSS system by way of its own particular pathways and by potentiating a dependent DA system. Thus, the results of this experiment at least partially support the notion of a REM-ICSS system, and add a new and exciting dimension to the interaction between this system and the substnatia nigra DA system. This dimension is in the nature of a REM-ICSS network involved in the reinforcement properties of motivated and learned behaviors.

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TABLE 1

Subject Groups - ICSS Sites Aimed For

Group	N	Implants	N with recording electrodes
LC-LH	14	Bilateral	10
	16	Unilateral	6
LC-SN-LH	8	Unilateral	2
LC-ZI	6	Unilateral	4
	44		22

TABLE 2

Percentage Destruction of LC and Adjacent Areas by Electrolytic Lesion

S #	Level	LC	DB	VB	MLF	Mesc V	SCP-BC	DTN
60#	Anterior pons	100%	100%	0	100%	100%	20%	100%
	Transitional area	100%	100%	0	100%	100%	30%	100%
	Posterior midbrain	(100%)	100%	15%	100%	100%	40%	100%
68E	Anterior pons	100%	100%	0	0	100%	90%	20%
	Transitional area	100%	100%	35%	100%	100%	100%	100%
	Posterior midbrain	(100%)	100%	25%	100%	0	0	100%
76E	Anterior pons	100%	100%	0	0	100%	20%	70%
	Transitional area	100%	100%	0	0	50%	20%	50%
	Posterior midbrain	(40%)	100%	10%	0	0	0	0
86E	Anterior pons	100%	90%	0	0	100%	100%	0
	Transitional area	100%	100%	5%	0	95%	30%	40%
	Posterior midbrain	(65%)	80%	0	0	50%	15%	0

continued

TABLE 2 (continued)

S #	Level	LC	DB	VB	MLF	Mesc V	SCP-BC	DTN
7F	Anterior pons	15%	20%	0	0	50%	0	0
	Transitional area	40%	70%	0	0	100%	30%	0
	Posterior midbrain	(100%)	100%	0	0	100%	10%	0
70F	Anterior pons	10%	0	0	0	80%	0	0
	Transitional area	100%	100%	0	0	100%	50%	95%
	Posterior midbrain	(20%)	50%	0	0	0	0	0
69F	Anterior pons	40%	0	0	0	0	0	0
	Transitional area	100%	100%	0	0	100%	20%	20%
	Posterior midbrain	(95%)	0	0	0	0	0	0
92F	Anterior pons	95%	95%	0	0	100%	70%	0
	Transitional area	100%	100%	0	0	100%	95%	5%
	Posterior midbrain	(0)	100%	15%	0	0	0	0
57E	Anterior pons	100%	100%	0	0	80%	0	70%
	Transitional area	100%	100%	0	100%	100%	80%	100%

continued

TABLE 2 (continued)

S #	Level	LC	DB	VB	MLF	Mesc V	SCP-BC	DTN
	Posterior midbrain	(100%)	100%	0	100%	100%	100%	100%
75E	Anterior pons	65%	0	0	0	0	0	0
	Transitional area	80%	40%	0	0	40%	0	40%
	Posterior midbrain	(0)	15%	0	0	0	0	0
78E	Anterior pons	15%	0	0	0	0	0	0
	Transitional area	100%	70%	0	0	40%	15%	0
	Posterior midbrain	(100%)	80%	5%	100%	90%	20%	0
96E	Anterior pons	95%	60%	0	0	5%	5%	0
	Transitional area	100%	70%	0	0	60%	5%	5%
	Posterior midbrain	(90%)	70%	0	0	60%	5%	0
15F	Anterior pons	0	0	0	0	0	0	0
	Transitional area	100%	90%	0	0	90%	15%	90%
	Posterior midbrain	(90%	30%	0	40%	0	0	0

continued

TABLE 2 (continued)

S #	Level	LC	DB	VB	MLF	Mesc V	SCP-BC	DTN
1G	Anterior pons	70%	0	0	0	100%	0	0
	Transitional area	100%	30%	0	0	100%	20%	40%
	Posterior midbrain	(50%)	20%	0	0	0	0	0
62E	Anterior pons	0	0	0	0	0	0	0
	Transitional area	50%	20%	0	0	50%	15%	0
	Posterior midbrain	(100%)	60%	20%*	0	70%	20%	0
10F	Anterior pons	80%	0	0	0	0	0	30%
	Transitional area	30%	0	0	0	0	0	70%
	Posterior midbrain	(0)	0	0	0	0	0	0
95E	Anterior pons	0	0	0	0	0	0	0
	Transitional area	100%	95%	0	0	90%	70%	20%
	Posterior midbrain	(100%)	100%	30%	80%	100%	90%	100%
95E*	Anterior pons	90%*	0%*	0	0	10%*	5%*	10%*
	Transitional area	90%	10%*	0	0	90%*	5%*	20%*

continued

TABLE 2 (continued)

S #	Level	LC	DB	VB	MLF	Mesc V	SCP-BC	DTN
	Posterior midbrain	(100%)*	60%	0	50%*	80%*	10%*	20%*

* Secondary lesion

TABLE 3

Hypothalamic ICSS Sites Ipsilateral to LC Lesion

Subject No.	Anatomical site	Monoaminergic nuclei or fibers	Konig & Klippel Atlas
60E	H2 Forel	Dorsal NE bundle, NS-DA	p. 39
68E	Internal capsule	Nigrostriatal-DA system	33
76E	Crus cerebri	Nigrostriatal-DA system	39
86E	H2 Forel	Dorsal NE bundle, NS-DA	35
7F	H2 Forel	Dorsal NE bundle-A13	36
70F	Crus cerebri	Nigrostriatal-DA system	38
69F	H2 Forel	Dorsal NE bundle, NS-DA	37
92F	MFB	Ventral NE bundle	40
57E	MFB-LH	Ventral NE bundle	37
75E	Perifornical	Ventral NE bundle	38
78E	MFB-LH	Ventral NE bundle	32
96E	MFB-LH	Ventral NE bundle	36

continued

TABLE 3 (continued)

Subject No.	Anatomical site	Monoaminergic nuclei or fibers	Konig & Klippel Atlas
15F	Perifornical	Ventral NE bundle	p. 34
1G	MFB-LH	Ventral NE bundle	36
62E	MFB-LH	Ventral NE bundle	31
10F	Dorsomedial nucleus	Mixed NE terminals	36
95E	Perifornical	Ventral NE bundle	33

TABLE 4

Hypothalamic ICSS Groups

Group	Area	CA systems involved		Subject No.
D -H group	Fields of Forel (H2) - zona incerta	NS-DA, NE-DB	4	60E,86E,7F,69F
CC-H group	Crus cerebri - internal capsule	NS-DA	3	68E, 76E, 70F
MFB group	Medial forebrain bundle	NE-VB	5	57E,78E,92E,90E,1G
F -H group	Perifornical area	NE-VB	2	75E, 15F
			14	

TABLE 5

Current Values (uA) of Five Intensities
Chosen to Encompass Rate-Intensity Function
in Hypothalamic and Substantia Nigra ICSS

S #	ICSS site	Intensities (uA)				
		1	2	3	4	5
60E	D-H	24.8	28.3	35.4	42.4	56.6
68E	C-C	63.6	70.7	77.8	84.8	91.9
76E	C-C	28.3	35.4	38.9	42.4	46.0
86E	D-H	31.8	35.4	56.6	70.7	99.0
7F	D-H	31.8	35.4	42.4	56.5	-
69F	D-H	84.8	88.4	99.0	106.1	127.3
70F	C-C	42.4	56.6	70.7	127.3	141.4
57E	MFB-LH	17.7	21.2	24.8	28.3	31.8
78E	MFB-LH	42.4	49.5	56.6	84.8	99.0
96E	MFB-LH	21.2	24.8	28.3	42.4	49.5
92F	MFB	21.2	24.8	28.3	42.4	56.6
1G	MFB-LH	28.3	35.4	42.4	56.6	70.7
75E	F-H	35.4	38.9	56.6	70.7	48.8
15F	F-H	31.8	35.4	70.7	91.9	106.1
69F	SN	113.0	121.1	141.4	155.5	169.5
1G	SN	141.4	155.5	169.5	183.8	212.1

TABLE 6

Pre- and Post-Lesion ICSS Rates, and Post-Lesion/Pre-Lesion Response Percentages at Five Intensities of Rate-Intensity Functions

Subject No.	Condition	S-BL (post-lesion)				
		I1	I2	I3	I4	I5
CC-H group						
68E	Pre-lesion	11.80	13.00	16.10	16.60	16.80
	Post-lesion	1.70	1.30	2.30	1.50	1.10
	Post/pre	0.14	0.10	0.14	0.09	0.06
76E	Pre-lesion	15.90	72.60	58.80	55.20	41.40
	Post-lesion	0.50	0.0	0.10	0.0	0.0
	Post/pre	0.00	0.00	0.00	0.00	0.00
70F	Pre-lesion	25.70	82.60	118.20	143.60	136.40
	Post-lesion	8.30	30.20	83.40	136.00	140.40

continued

TABLE 6 - continued

Subject No.	Condition	S-BL (post-lesion				
		I1	I2	I3	I4	I5
	Post-lesion	3.6	12.3	33.5	60.8	93.5
	Post/pre	0.27	0.51	0.53	0.53	0.72
	pre	122.6	368.6	532.2	676.5	470.3
	post	26.9	82.8	246.1	397.7	319.5
	$\bar{X}$ post/pre	0.19	0.21	0.39	0.44	0.46

continued

TABLE 6 - continued

Subject No.	Condition	S-BL (post-lesion)				
		I1	I2	I3	I4	I5
	Post/pre	0.30	0.36	0.70	0.95	1.03
		DB-H group				
60E	Pre-lesion	12.60	17.60	37.60	48.30	40.30
	Post-lesion	2.00	0.70	4.60	10.30	10.90
	Post/pre	0.16	0.04	0.12	0.21	0.27
86E	Pre-lesion	16.90	33.90	67.00	79.60	106.50
	Post-lesion	2.40	4.00	57.80	57.30	73.60
	Post/pre	0.14	0.18	0.86	0.72	0.69
7F	Pre-lesion	25.90	125.00	171.00	217.50	-
	Post-lesion	8.40	34.30	65.50	121.80	-
	Post/pre	0.32	0.26	0.38	0.61	-
69F	Pre-lesion	13.80	23.90	63.50	115.70	129.00

continued

TABLE 6 (continued)

Subject No.	Condition	L-BL (post-lesion)				
		I1	I2	I3	I4	I5
CC-H group						
68E	Pre-lesion	11.8	13.0	16.1	16.6	16.8
	Post-lesion	3.3	1.9	2.8	2.1	3.0
	Post/pre	0.28	0.15	0.17	0.13	0.18
76E	Pre-lesion	15.9	72.6	58.8	55.2	41.4
	Post-lesion	0.3	0.7	0.3	1.5	1.9
	Post/pre	0.03	0.01	0.02	0.00	0.03
70F	Pre-lesion	25.7	82.6	118.2	143.6	136.4
	Post-lesion	1.8	9.1	30.9	90.1	98.1
	Post/pre	0.07	0.11	0.26	0.63	0.72

continued

TABLE 6 (continued)

Subject No.	Condition	L-BL (post-lesion)				
		I1	I2	I3	I4	I5
DB-H group						
60E	Pre-lesion	12.6	17.6	37.6	48.3	40.3
	Post-lesion	3.3	6.9	9.8	20.0	22.6
	Post/pre	0.26	0.39	0.26	0.41	0.56
86E	Pre-lesion	16.9	33.9	67.0	79.6	106.5
	Post-lesion	2.1	6.1	60.4	74.2	78.2
	Post/pre	0.12	0.18	0.90	0.92	0.73
7F	Pre-lesion	25.9	125.0	171.0	217.5	-
	Post-lesion	6.4	23.7	54.1	158.4	-
	Post/pre	0.25	0.19	0.32	0.73	-
69F	Pre-lesion	13.8	23.9	63.5	115.7	129.0
	Post-lesion	2.2	6.6	24.8	58.8	109.0

continued

TABLE 6 (continued)

Subject No.	Condition	L-BL (post-lesion)				
		I1	I2	I3	I4	I5
	Post/pre	0.16	0.28	0.39	0.51	0.85
	pre	122.6	368.6	532.2	676.5	470.3
	post	19.3	55.0	183.1	405.1	312.8
	$\bar{X}$ Post/pre	0.17	0.19	0.33	0.47	0.51

continued

TABLE 6 (continued)

Subject No.	Condition	R-BL(post-lesion)				
		I1	I2	I3	I4	I5
CC-H group						
68E	Pre-lesion	11.8	13.0	16.1	16.6	16.8
	Post-lesion	0.4	0.2	0.5	0.2	0.9
	Post/pre	0.03	0.02	0.03	0.01	0.05
76E	Pre-lesion	15.9	76.6	58.8	55.2	41.4
	Post-lesion	0.4	1.5	1.9	6.2	2.2
	Post/pre	0.00	0.00	0.00	0.10	0.05
70F	Pre-lesion	25.7	82.6	118.2	143.6	136.4
	Post-lesion	0.8	0.1	0.7	93.4	84.7
	Post/pre	0.03	0.00	0.00	0.65	0.62

continued

TABLE 6 (continued)

Subject No.	Condition	R-BL (post-lesion)				
		I1	I2	I3	I4	I5
DB-H group						
60E	Pre-lesion	12.6	17.6	37.6	48.3	40.3
	Post-lesion	1.2	0.1	6.1	11.4	15.7
	Post/pre	0.10	0.00	0.16	0.24	0.39
7F	Pre-lesion	25.9	125.0	171.0	217.5	-
	Post-lesion	0.3	16.9	48.9	148.5	-
	Post/pre	0.01	0.14	0.29	0.68	-
69F	Pre-lesion	13.8	23.9	63.5	115.7	129.0
	Post-lesion	8.3	6.5	21.9	45.4	93.8
	Post/pre	0.60	0.27	0.35	0.39	0.75
	pre	105.7	334.7	465.2	596.9	363.8
	post	11.4	25.3	80.0	305.1	197.2

continued

TABLE 6 (continued)

Subject No.	Condition	R-BL (post-lesion)				
		I1	I2	I3	I4	I5
	$\bar{X}$ Post/pre	0.13	0.14	0.14	0.34	0.37

continued

TABLE 6 (continued)

Subject No.	Condition	S-BL				
		I1	I2	I3	I4	I5
	MFB-H group					
57E	Pre-lesion	42.0	85.6	146.2	188.4	197.0
	Post-lesion	4.8	19.7	48.6	77.0	104.7
	Post/pre	0.11	0.25	0.57	0.41	0.53
78E	Pre-lesion	12.4	16.7	46.7	96.3	105.4
	Post-lesion	9.1	9.9	22.9	82.4	84.9
	Post/pre	0.73	0.59	0.49	0.86	0.81
96E	Pre-lesion	21.3	56.0	112.2	198.1	188.7
	Post-lesion	24.7	64.8	105.6	169.2	167.1
	Post/pre	1.16	1.16	0.94	0.85	0.89

continued

TABLE 6 (continued)

Subject No.	Condition	S-BL				
		I1	I2	I3	I4	I5
92F	Pre-lesion	26.8	63.2	100.3	215.7	214.8
	Post-lesion	7.5	24.3	46.5	186.6	0.81
1G	Pre-lesion	21.0	72.9	167.1	203.9	190.6
	Post-lesion	20.7	95.9	178.5	217.8	213.8
	Post/pre	0.99	1.31	1.07	1.07	1.12
	F-H group					
75E	Pre-lesion	22.7	64.3	162.2	203.4	189.7
	Post-lesion	2.8	17.0	119.6	154.0	145.7
	Post/pre	0.12	0.26	0.74	0.76	0.77
15F	Pre-lesion	16.3	25.6	81.0	89.3	98.5
	Post-lesion	12.1	25.0	88.8	81.7	77.6
	Post/pre	0.74	0.98	1.10	0.91	0.79

continued

TABLE 6 (continued)

Subject No.	Condition	S-BL				
		I1	I2	I3	I4	I5
	Pre	162.5	384.2	815.7	1195.1	1184.7
	Post	81.7	256.6	610.5	968.7	967.3
	$\bar{X}$ Post/pre	0.59	0.73	0.77	0.82	0.82

continued

TABLE 6 - continued

Subject No.	Condition	L-BL				
		I1	I2	I3	I4	I5
	MFB-H group					
57E	Pre-lesion	42.0	85.6	146.2	188.4	197.0
	Post-lesion	6.2	45.2	111.3	143.7	165.9
	Post/pre	0.15	0.53	0.78	0.76	0.84
78E	Pre-lesion	12.4	16.7	46.7	96.3	105.4
	Post-lesion	12.8	14.2	21.3	118.4	124.7
	Post/pre	1.03	0.85	0.69	1.22	1.18
96E	Pre-lesion	21.3	56.0	112.2	198.1	188.7
	Post-lesion	22.4	66.8	98.6	180.7	179.0
	Post/pre	1.05	1.19	0.88	0.91	0.95

continued

TABLE 6 - continued

Subject No.	Condition	L-BL				
		I1	I2	I3	I4	I5
92F	Pre-lesion	26.8	63.2	100.3	215.7	214.8
	Post-lesion	13.2	32.3	56.2	195.0	177.3
	Post/pre	0.49	0.51	0.56	0.90	0.83
1G	Pre-lesion	21.0	72.9	167.1	203.9	190.6
	Post-lesion	43.2	120.8	203.9	224.4	221.0
	Post/pre	2.50	1.67	1.35	1.12	1.21
F-H group						
75E	Pre-lesion	22.7	64.3	162.2	203.4	189.7
	Post-lesion	14.4	21.6	133.9	174.0	171.7
	Post/pre	0.64	0.34	0.83	0.85	0.90
15F	Pre-lesion	16.3	25.6	81.0	89.3	98.5
	Post-lesion	13.2	269.8	92.6	88.2	84.1

continued

TABLE 6 - continued

Subject No.	Condition	L-BL				
		I1	I2	I3	I4	I5
	Post/pre	0.81	1.05	1.14	0.99	0.85
	pre	162.5	384.2	815.7	1195.1	1184.7
	post	125.4	327.9	728.8	1124.2	1123.5
	$\bar{X}$ Post/pre	0.95	0.88	0.89	0.96	0.97

TABLE 6 - continued

Subject No.	Condition	R-BL				
		I1	I2	I3	I4	I5
		MFB-H group				
57E	Pre-lesion	42.0	85.6	146.2	188.4	197.0
	Post-lesion	6.1	96.2	151.3	196.6	195.0
	Post/pre	0.15	1.12	1.03	1.04	0.99
78E	Pre-lesion	12.4	16.7	46.7	96.3	105.4
	Post-lesion	8.3	20.9	37.8	91.6	116.1
	Post/pre	0.67	1.26	0.81	0.95	1.0.
92F	Pre-lesion	26.8	63.2	100.3	215.7	214.8
	Post-lesion	37.4	73.1	111.6	198.2	169.7
	Post/pre	1.40	1.16	1.11	0.92	0.79

continued

TABLE 6 - continued

Subject No.	Condition	R-BL				
		I1	I2	I3	I4	I5
1G	Pre-lesion	21.0	72.9	167.1	203.9	190.6
	Post-lesion	62.4	167.8	254.4	257.4	244.2
	Post/pre	2.97	2.30	1.52	1.26	1.28
F-H group						
75E	Pre-lesion	22.7	64.3	162.2	203.4	189.7
	Post-lesion	37.0	72.4	136.1	158.3	137.0
	Post/pre	1.62	1.12	0.84	0.78	0.72
	pre	124.9	302.6	703.5	997.0	996.0
	post	151.2	430.4	691.2	902.1	862.0
	$\bar{X}$ Post/pre	1.36	1.39	1.06	0.99	0.96

TABLE 7

Summary of Pre- and Post-Lesion ICSS Rates and Percentages of Hypothalamic Subjects

Subject	Condition	I1	I2	I3	I4	I5
S-BL (post-lesion)						
NS-DB group (n = 7)	pre	122.6	368.6	532.2	676.5	470.3
	post	26.9	82.8	246.1	397.7	319.5
	$\bar{X}$ Post/pre	0.19	0.21	0.39	0.44	0.46
L-BL (post-lesion)						
NS-DB group (n = 7)	pre	122.6	368.6	532.2	676.5	470.3
	post	19.3	55.0	183.1	405.1	312.8
	$\bar{X}$ Post/pre	0.17	0.19	0.33	0.47	0.51
R-BL (post-lesion)						
NS-DB group n = 6)	pre	105.7	334.7	465.2	596.9	363.8
	post	11.4	25.3	80.0	305.1	197.2
	$\bar{X}$ Post/pre	0.13	0.14	0.14	0.34	0.37
S-BL (post-lesion)						
VB-H group (n = 7)	pre	162.5	384.2	815.7	1195.1	1184.7
	post	81.7	256.6	610.5	968.7	967.3
	$\bar{X}$ Post/pre	0.59	0.73	0.77	0.82	0.82

continued

TABLE 7 - continued

Subject	Condition	I1	I2	I3	I4	I5
		L-BL (post-lesion)				
VB-H group (n = 7)	pre	162.5	384.2	815.7	1195.1	1184.7
	post	125.4	327.9	728.8	1124.2	1123.5
	$\bar{X}$ Post/pre	0.95	0.88	0.89	0.96	0.97
		R-BL (post-lesion)				
VB-H group (n = 5)	pre	124.9	302.6	703.5	997.0	996.0
	post	151.2	430.4	691.2	902.1	862.0
	$\bar{X}$ Post/pre	1.36	1.39	1.06	0.99	0.96

TABLE 8
Ranked Lesion Effects

S no.	S-BL					L-BL					R-BL				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
70F	1	2	3	4	5	1	2	3	4	5	3	1	1	5	4
60E	3	1	2	4	5	1.5	3	1.5	4	5	2	1	3	4	5
86E	1	2	5	4	3	1	2	4	5	3	1	2	3	4	5
7F	2	1	3	4	5	2	1	3	4	5	-	-	-	-	-
69F	1	2	3.5	3.5	5	1	2	3	4	5	1	2	3	4	5
	8	8	16.5	19.5	23	6.5	10	14.5	21	23	7	6	11	17	19

TABLE 9

SN-IC Post-Lesion Rates and Post/Pre Ratios

Subject No.	Condition	S-BL				
		I1	I2	I3	I4	I5
SN group						
69G	Pre-lesion	24.1	34.1	47.2	53.7	61.0
	Post-lesion	2.8	0.8	12.9	25.0	27.3
	Post/pre	0.12	0.02	0.27	0.46	0.45
1G	Pre-lesion	31.4	65.9	84.7	97.6	101.4
	Post-lesion	52.7	63.8	76.0	69.0	91.0
	Post/pre	1.68	0.97	0.90	0.71	0.90
	pre	55.5	100.8	131.9	151.3	162.4
	post	55.5	64.6	88.9	94.0	118.3
	$\bar{X}$ Post/pre	0.90	0.49	0.59	0.59	0.67

continued

TABLE 9 - continued

Subject No.	Condition	L-BL				
		I1	I2	I3	I4	I5
69G	Pre-lesion	24.1	34.9	47.2	53.7	61.0
	Post-lesion	7.4	9.3	16.4	27.2	26.8
	Post/pre	0.30	0.26	0.34	0.51	0.44
1G	Pre-lesion	31.4	65.9	84.7	97.6	101.4
	Post-lesion	28.3	33.7	43.2	45.7	61.8
	Post/pre	0.90	0.51	0.51	0.47	0.61
	pre	55.5	100.8	131.9	151.3	162.4
	post	35.7	43.0	59.6	72.9	88.6
	$\overline{X}$ Post/pre	0.60	0.39	0.43	0.49	0.53

continued

TABLE 9 - continued

Subject No.	Condition	R-BL				
		I1	I2	I3	I4	I5
69G	Pre-lesion	24.1	34.9	47.2	53.7	61.0
	Post-lesion	5.2	7.2	12.5	15.5	16.9
	Post/pre	0.21	0.21	0.26	0.29	0.28
1G	Pre-lesion	31.4	65.9	84.7	97.6	101.4
	Post-lesion	14.0	18.3	21.2	22.9	18.1
	Post/pre	0.45	0.28	0.25	0.23	0.18
	pre	55.5	100.8	131.9	156.3	162.4
	post	19.2	25.5	33.7	38.4	35.0
	$\overline{X}$ Post/pre	0.33	0.25	0.25	0.26	0.23

TABLE 10

Multiplicative Pre-lesion D- and L-amphetamine Effects over Saline (1 and 2 mg/kg) on Two Hypothalamic Groups at Five Intensities

	D-amphetamine						L-amphetamine					
	1 mg/kg						1 mg/kg					
DB-NS group	n=4	9.80	3.50	1.80	1.40	1.20	n=4	1.30	1.50	1.10	1.00	0.90
VB-H group	n=3	0.64	1.44	1.62	1.16	1.08	n=3	0.50	0.80	0.80	1.10	1.00
		1	2	3	4	5		1	2	3	4	5
	2 mg/kg						2 mg/kg					
DB-NS group	n=4	3.40	2.15	1.54	1.29	1.13	n=3	2.46	2.16	1.45	1.13	0.90
VB-H group	n=2	1.27	1.67	1.80	1.19	1.21	n=2	1.89	0.57	0.89	1.16	1.20
		1	2	3	4	5		1	2	3	4	5

TABLE 11

Pre- and Post-LC Lesion ICSS and Post-LC Lesion D- and L-amphetamine Effects on ICSS - Subject #76E - Crus Cerebri

Intensity (uA)	Baseline n = 8	Baseline n = 4	Saline n = 8	D-amphetamine 1 mg/kg n = 2	D-amphetamine 2 mg/kg n = 2	L-amphetamine 1 mg/kg n = 2	L-amphetamine 2 mg/kg n = 2
21.2	0.1	0.0	-	-	-	-	-
24.7	2.7	0.3	-	-	-	-	-
28.3	15.9	0.0	0.4	0.6	1.8	0.4	0.2
31.8	53.1	0.0	-	-	-	-	-
35.4	72.6	0.2	1.0	0.4	71.0	0.3	0.1
38.9	58.8	0.0	0.5	11.1	87.7	3.9	7.7
42.4	55.2	0.0	2.1	14.3	80.2	14.6	37.7
46.0	41.4	0.0	2.8	36.1	84.5	9.9	26.3
49.5	41.2	0.3	1.6	28.3	84.3	11.4	21.5
53.0	-	0.0	2.7	33.9	77.3	4.9	29.4
56.5	18.7	0.0	0.5	24.0	76.6	9.5	31.6

continued

TABLE 11 - continued

Intensity (uA)	Baseline n = 8	Baseline n = 4	Saline n = 8	D-amphetamine 1 mg/kg n = 2	D-amphetamine 2 mg/kg n = 2	L-amphetamine 1 mg/kg n = 2	L-amphetamine 2 mg/kg n = 2
63.6	-	-	1.1	9.0	46.6	12.6	10.6
70.7	-	0.3	1.8	9.5	37.5	11.5	9.0
0	0.1	0.0	0.2	0.3	0.2	0.0	0.1

TABLE 12

Comparison of Sleep Stages Pre- and Post-LC Lesion

	S no.	Extent lesion		Pre-lesion BL (30 hrs.recording)	Post-lesion BL (30 hrs.recording)	Recovery check (12 hrs.recording, 3 mos.post-lesion)
		LC	DB	REM %	REM %	REM %
Group I	60E	100%	100%	16.1	7.9	4.5
	68E	100%	100%	17.6	11.9	11.2
	57E	100%	100%	14.1	8.4	18.3
	7F	30%	100%	11.6	3.4	-
	$\bar{X}$	-	-	14.9	7.9	-
Group II	62E	25%	60%	18.8	12.4	13.7
	10F	55%	0%	14.6	13.6	-
	$\bar{X}$	-	-	17.6	13.0	-

TABLE 13

Stimulus-Bound Eating Threshold in μA (R50) for Subject #57E

in the Left Lateral Hypothalamus

	Baseline			Saline			D-ampheta-mine 1 mg/kg			D-amphe-tamine 2 mg/kg			L-ampheta-mine 1 mg/kg			L-ampheta-mine 2 mg/kg		
	n	R 50	SD	n	R 50	SD	n	R 50	SD	n	R50	SD	n	R 50	SD	n	R 50	SD
Pre-LLC*	7	10.46	0.57	8	11.17	1.34	2	17.32	1.98	1	did not eat	-	2	13.08	1.98	2	16.61	1.98
Post-LLC lesion	13	15.70	1.67	6	18.38	2.56	2	did not eat	-	1	did not eat	-	2	16.97	1.98	2	did not eat	

* Left locus coeruleus

Table 14

Weights of Four Subjects Before and After the Hindbrain Lesion

S #	Pre-lesion weights	Weights 1 week after lesion	Weights 2 weeks after lesion
60E	490 mg.	445 mg.	489 mg.
62E	497 mg.	490 mg.	505 mg.
68E	507 mg.	495 mg.	497 mg.
7F	533 mg.	512 mg.	527 mg.

FIGURE LEGENDS

Figure 1. Schematic Representation of CA Pathways from Ungerstedt (1971) - NE and DA Systems Stemming from Hindbrain and Mesencephalon

Figure 2. Rat's Cranial Landmarks and Estimated Lambda Line used for ICSS Electrode Implants

Figure 3. Sequence of Sleep-Drug Paradigm

Figure 4. Schematic Representation of Hindbrain Lesions Shown in a Series of Coronal Brain Sections

A. Extent and Overlap (solid area) of Lesion in Subjects 62E and 10F

B. Electrolytic Lesion (Right Side) and Secondary Lesion (Left Side) found in Subject 95E

Figure 5. Serial Hindbrain Sections Illustrating the Full Extent of the Lesions in 14 Subjects (Solid and Shaded Areas) and Area of Overlap of all Lesions (Solid Area) as compared to Ungerstedt's Illustration of the Hindbrain CA Systems

Figure 6. Photomicrographs of Subject 57E's Hindbrain Lesion Shown in a Sequence from Anterior Pons to Posterior Midbrain (For a full description of areas affected by the lesion in this and subsequent illustrations, see Table 2)

logorithmic units.

Figure 54. This photomicrograph of Subject 92F's Hypothalamic Electrode Placement, at its most posterior extent, shows limited impingement on crus cerebri.

Figure 55. Illustration of a Saggital Section of the Rat's Brain Showing the Proposed ICSS Model of Dorsal Bundle LC and NS-DA ICSS Interaction

FIGURE 1

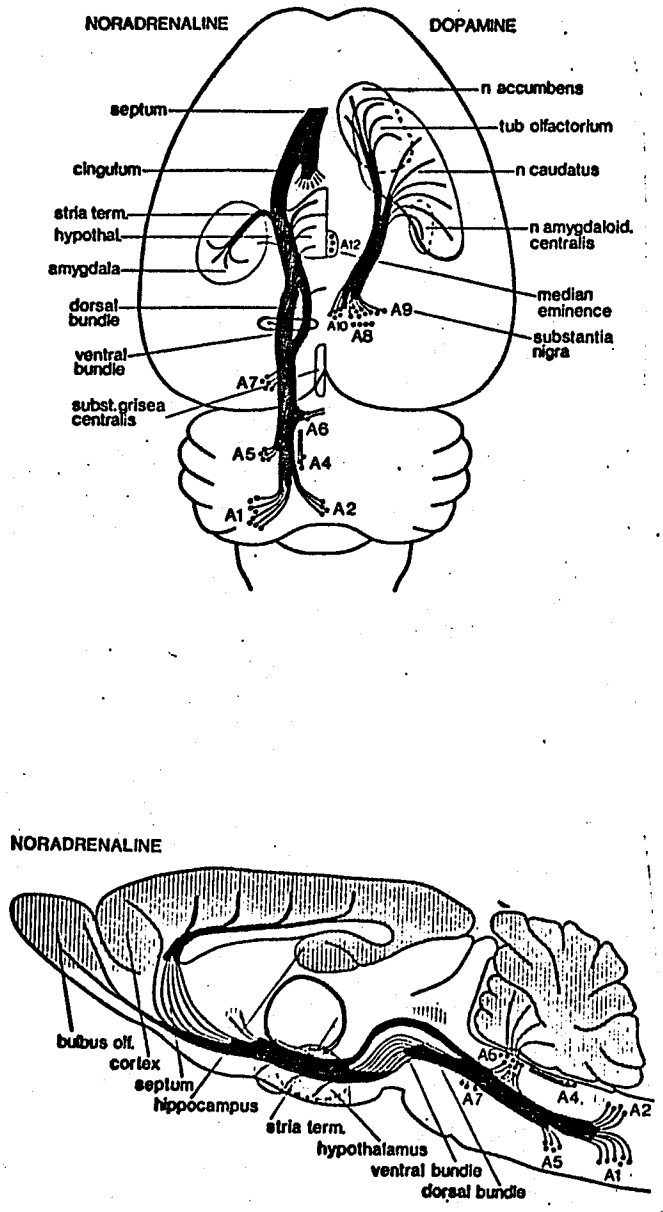

NORADRENALINE
DOPAMINE
septum
cingulum
stria term.
hypothal.
amygdala
dorsal bundle
ventral bundle
subst.grisea centralis
n accumbens
tub olfactorium
n caudatus
n amygdaloid. centralis
median eminence
substantia nigra
A12
A10
A9
A8
A7
A6
A5
A4
A1
A2
NORADRENALINE
bulbus olf.
cortex
septum
hippocampus
stria term.
hypothalamus
ventral bundle
dorsal bundle
A5
A7
A4
A2
A5
A1

FIGURE 2

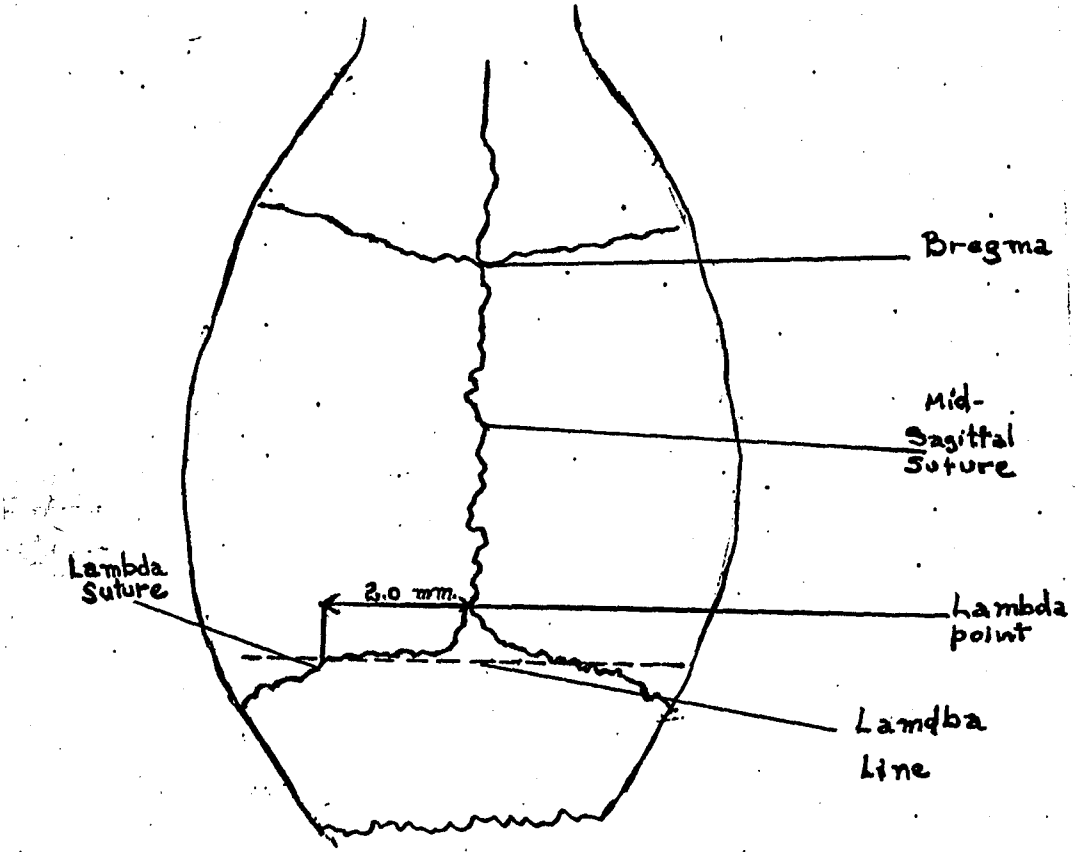

Bregma
Mid-
Sagittal
Suture
Lambda
Suture
2.0 mm.
Lambda
point
Lambda
Line

FIGURE 3

Sequence of Sleep-Drug Paradigm

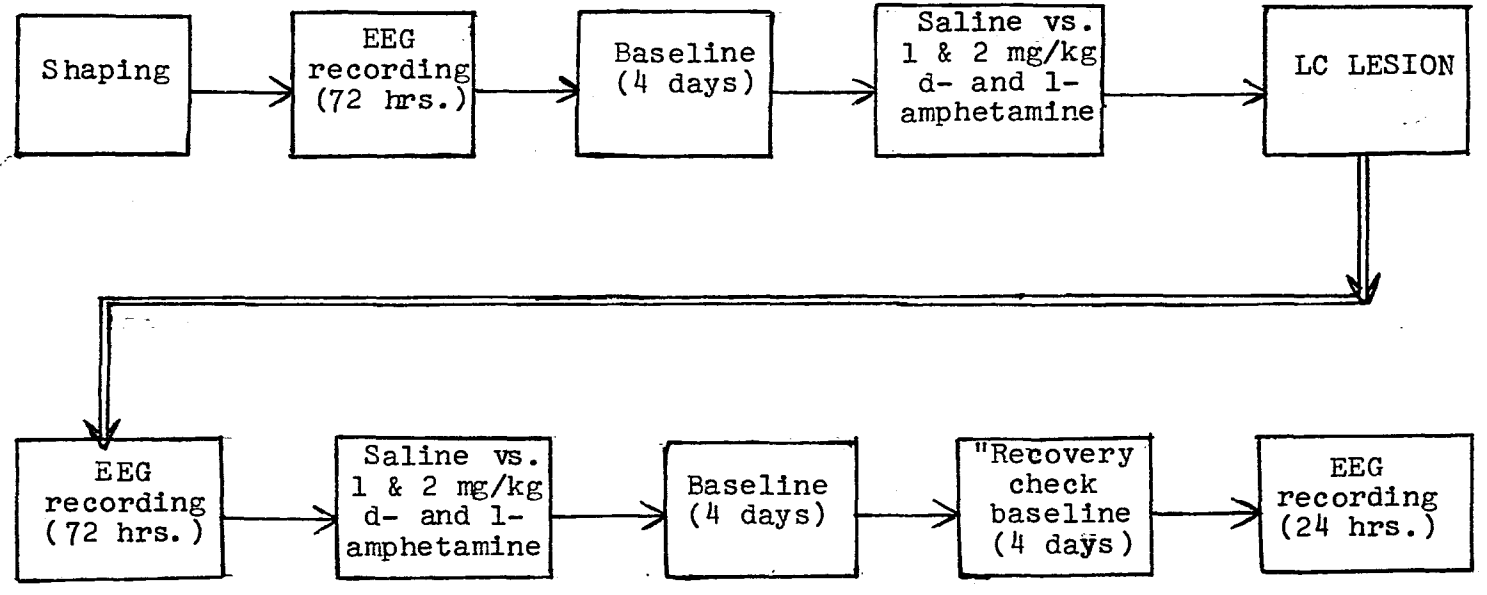


FIGURE 4

FIGURE 5

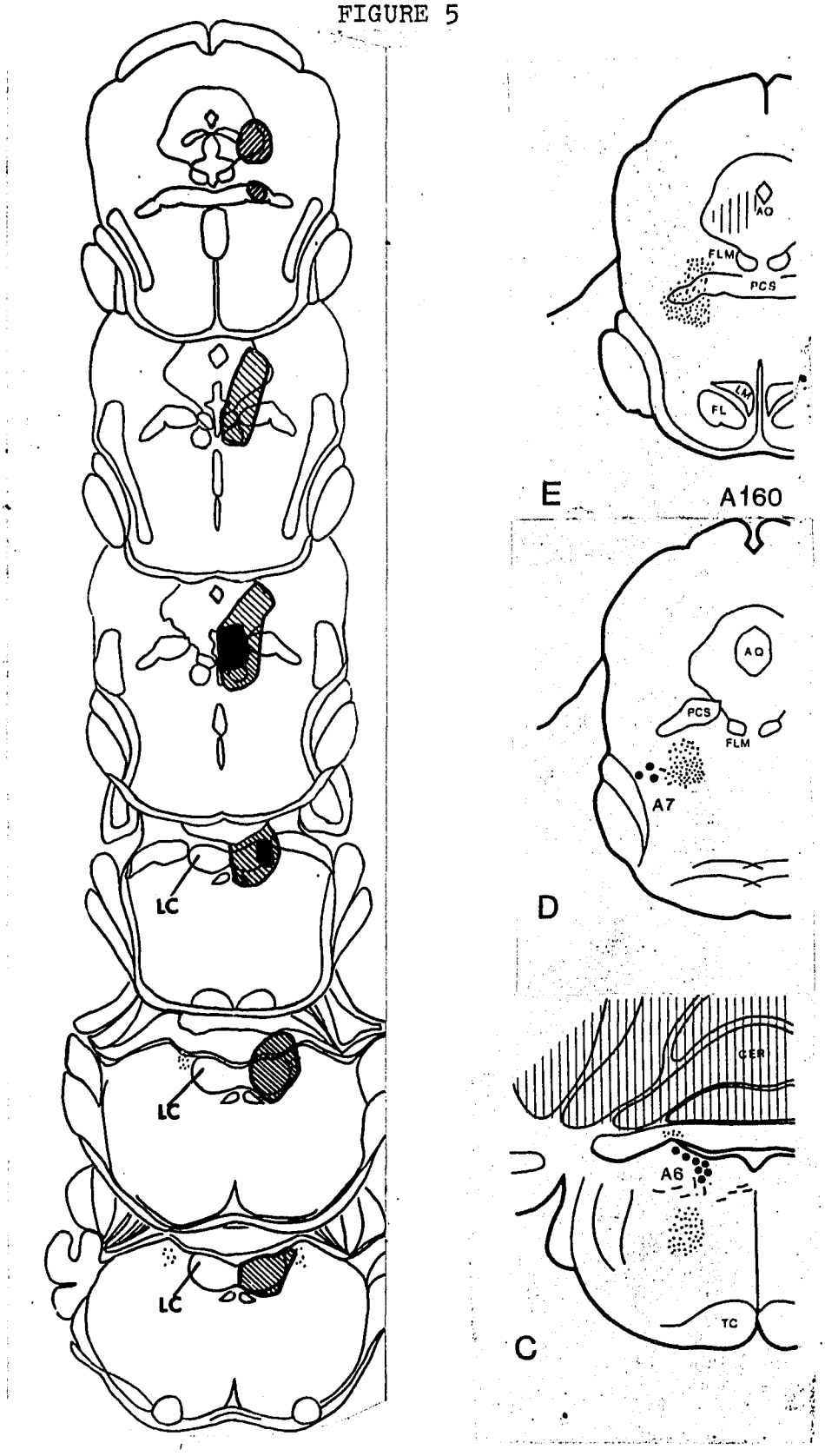


FIGURE 6

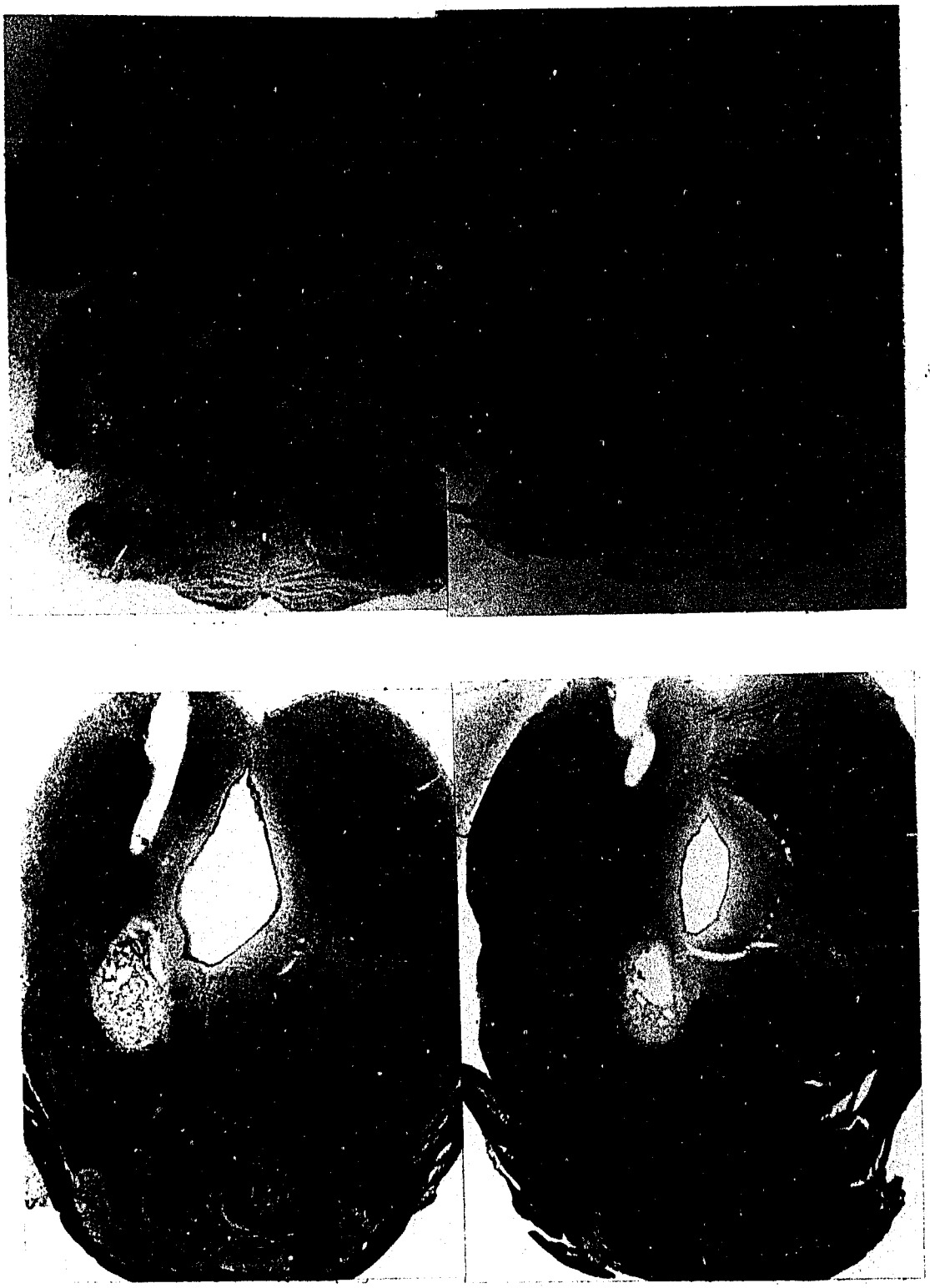


FIGURE 7

FIGURE 8

FIGURE 9

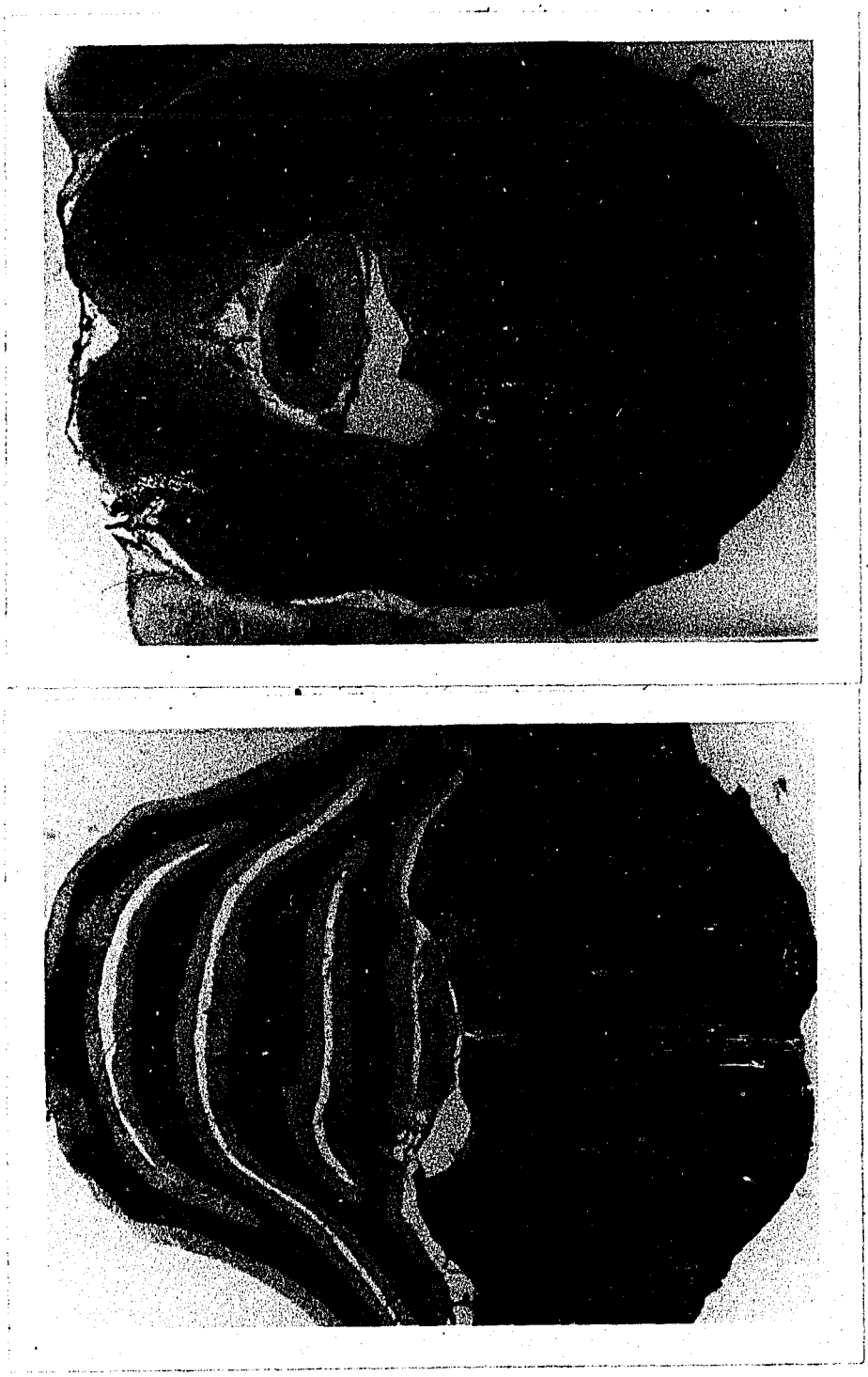


FIGURE 10

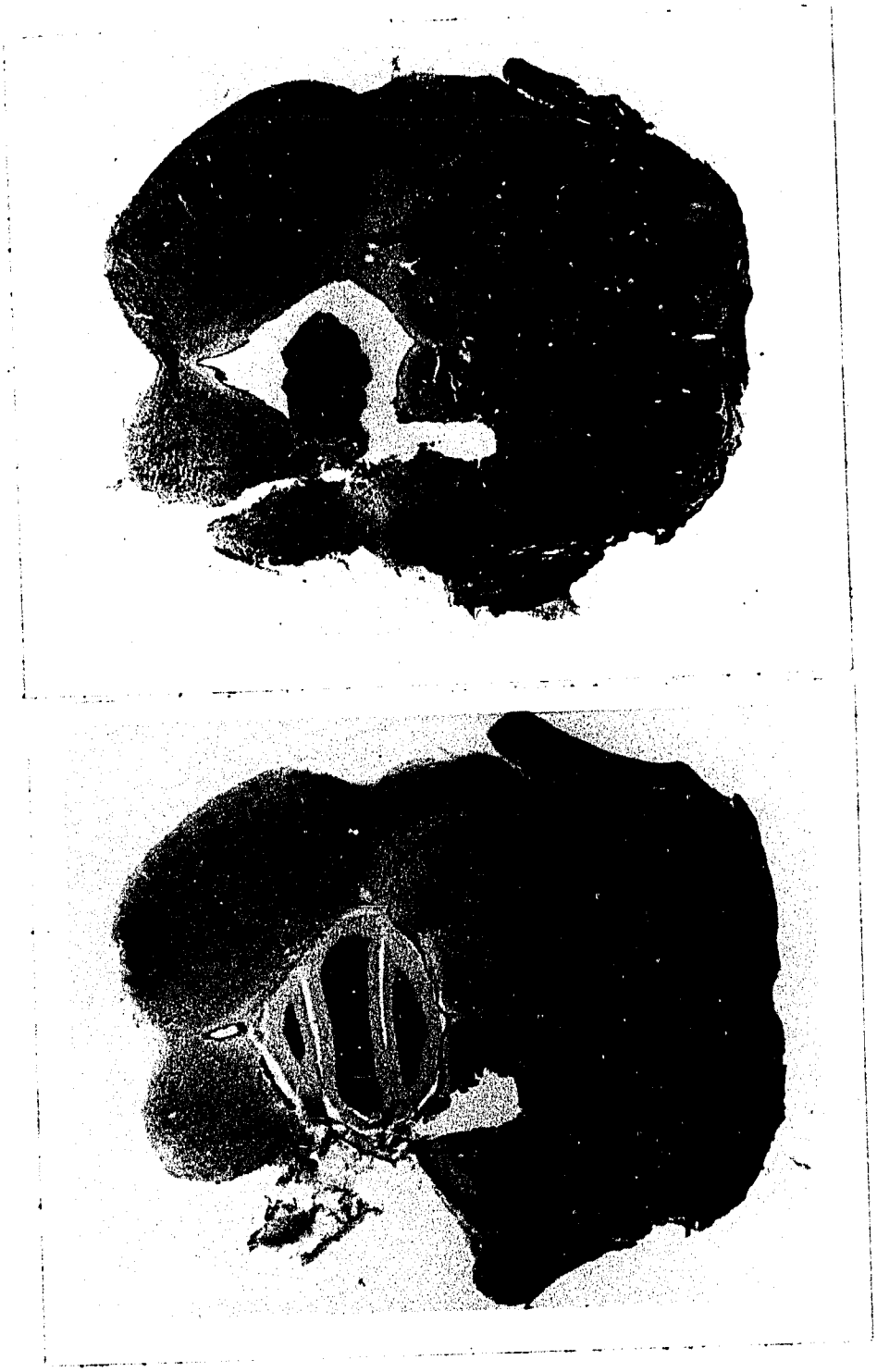


FIGURE 11

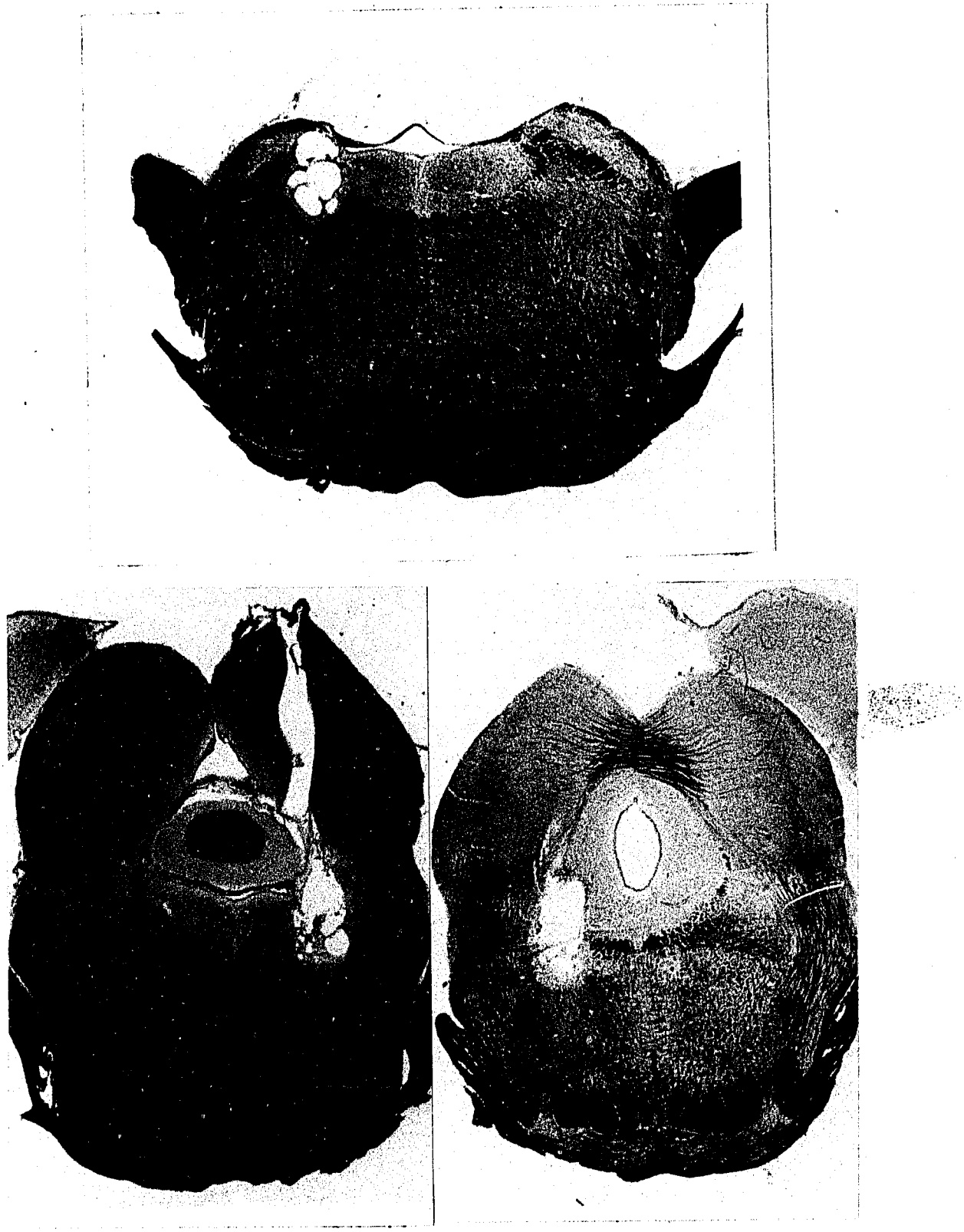


FIGURE 12

FIGURE 13

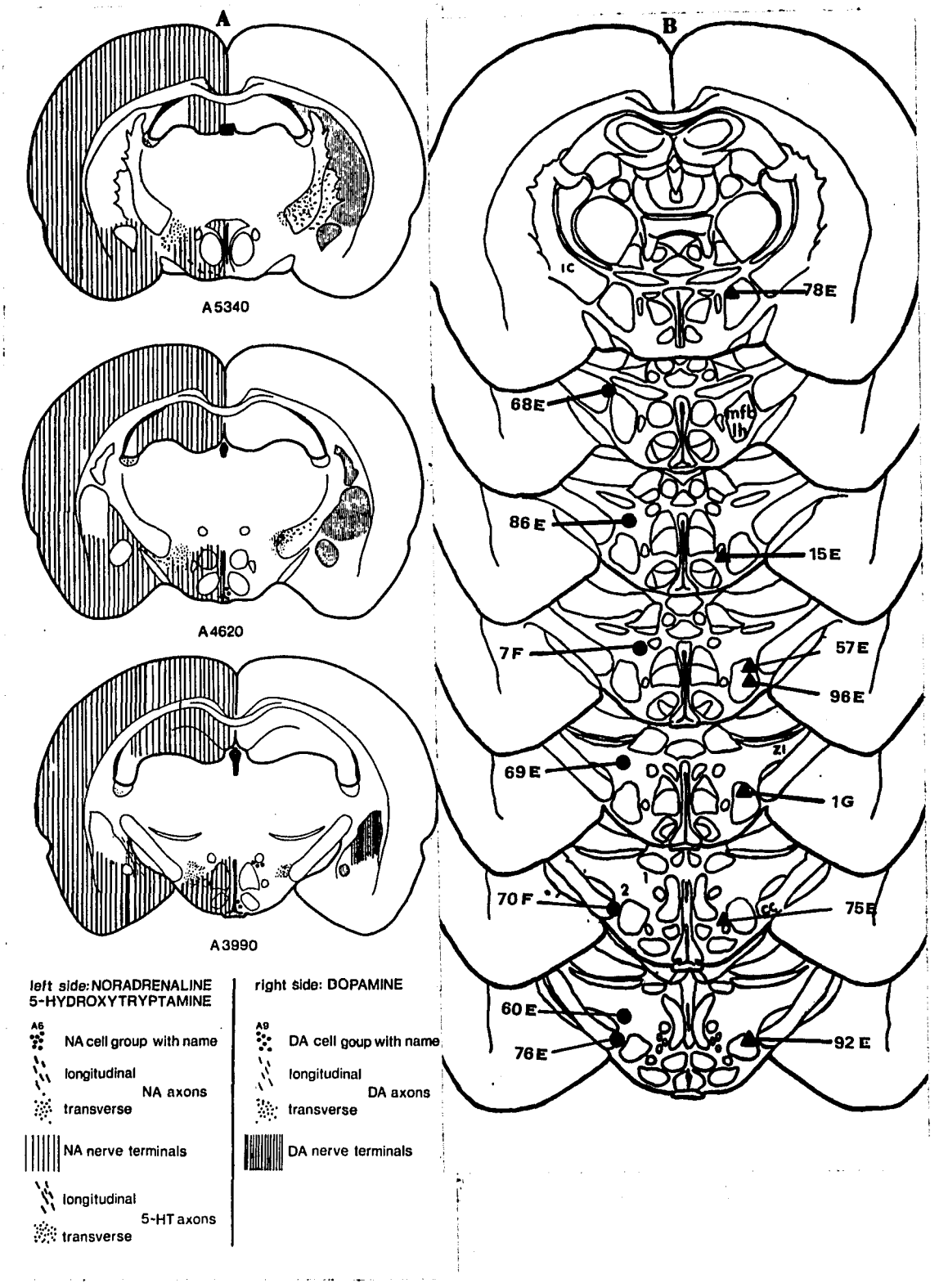

A
A5340
A4620
A3990
left side: NORADRENALINE
5-HYDROXYTRYPTAMINE
A6
NA cell group with name
longitudinal
NA axons
transverse
NA nerve terminals
longitudinal
5-HT axons
transverse
right side: DOPAMINE
A9
DA cell goup with name
longitudinal
DA axons
transverse
DA nerve terminals
B
IC
78E
68E
mfb
lh
86E
15E
7F
57E
96E
ZI
69E
D
1G
1
2
70F
75E
60E
76E
92E

FIGURE 14

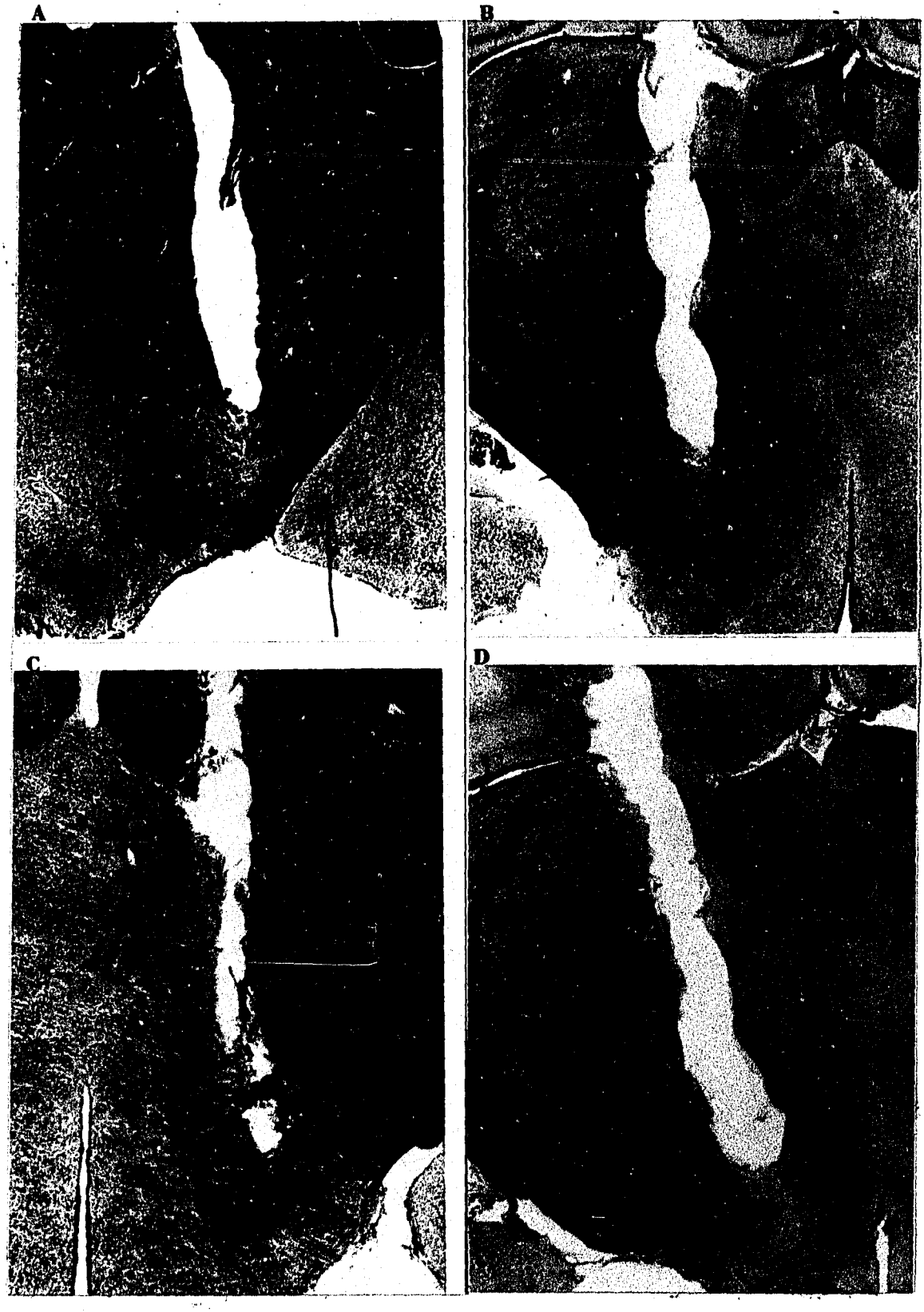


FIGURE 15

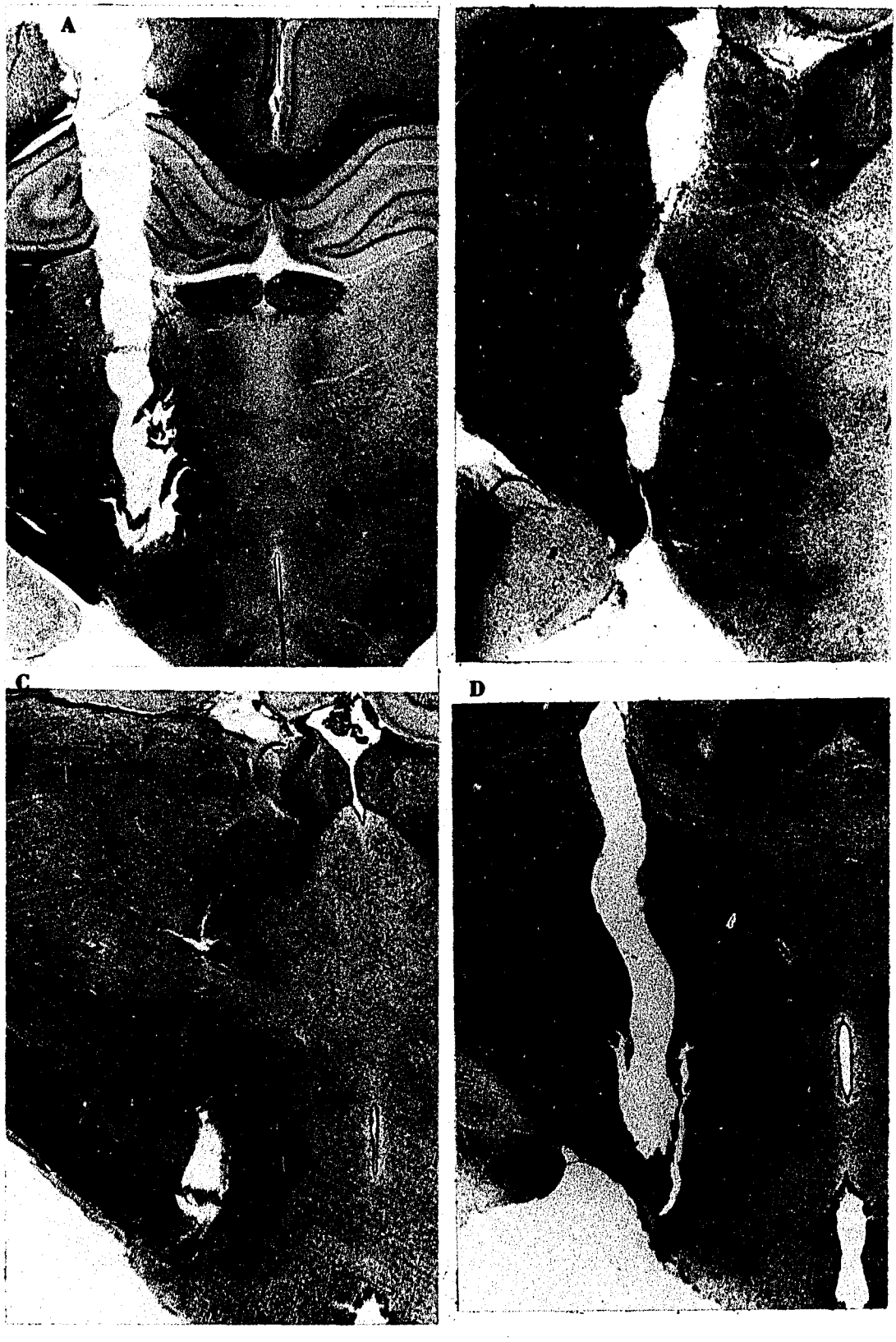


FIGURE 16

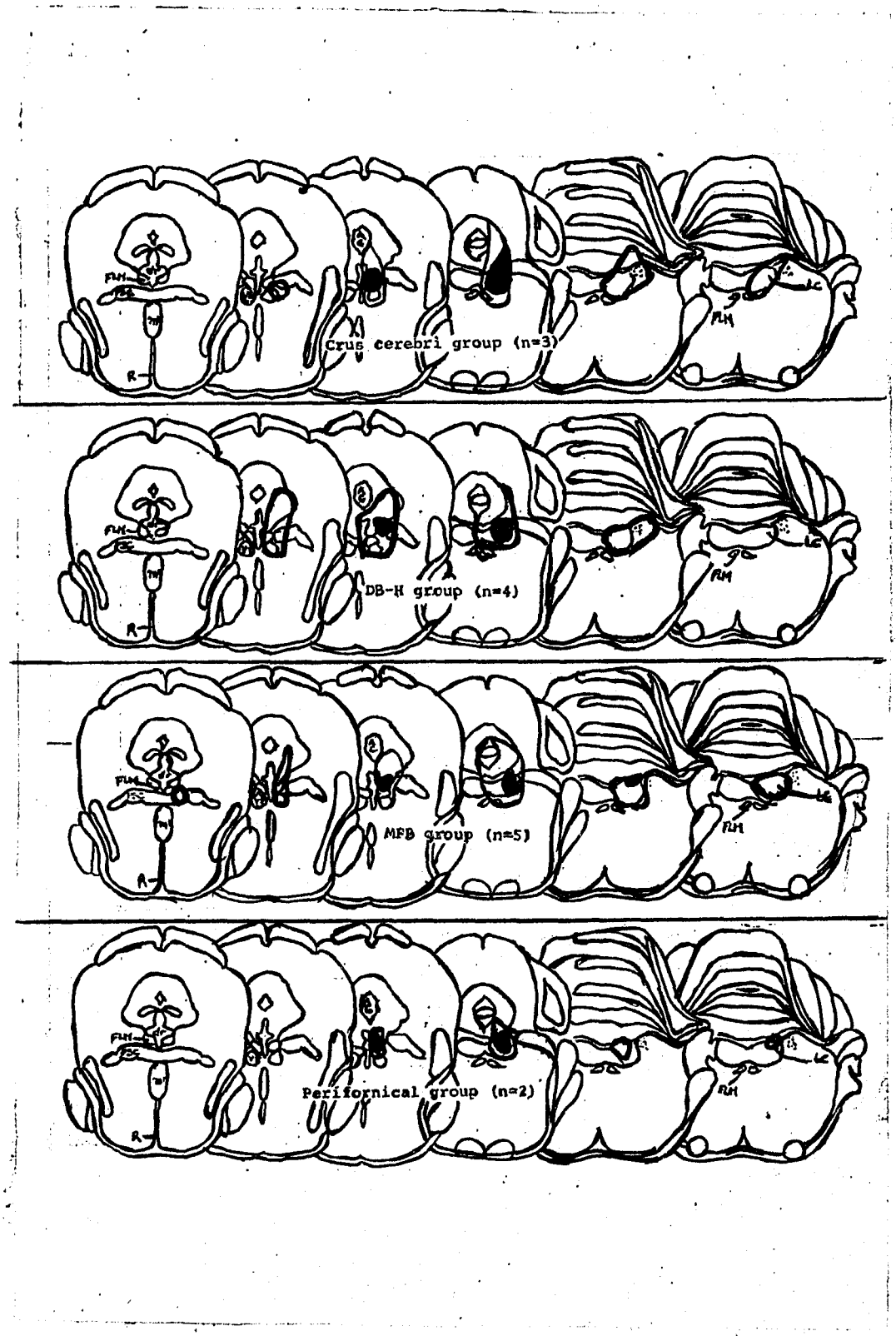

Crus cerebri group (n=3)
DB-H group (n=4)
MFB group (n=5)
Perifornical group (n=2)
FLM
LC
R

FIGURE 17

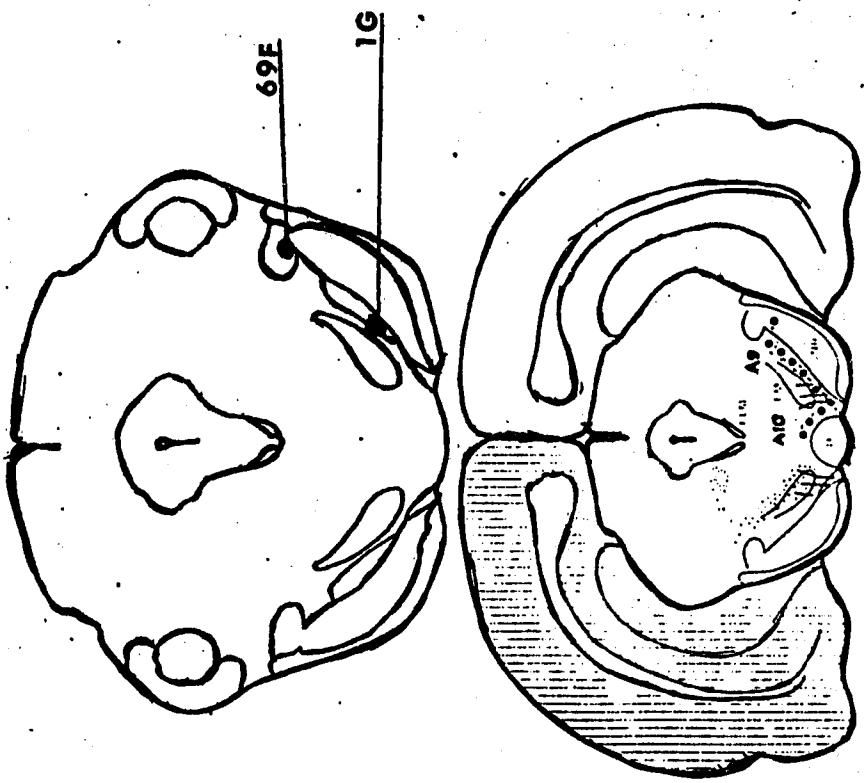


FIGURE 18

FIGURE 19

CC Group

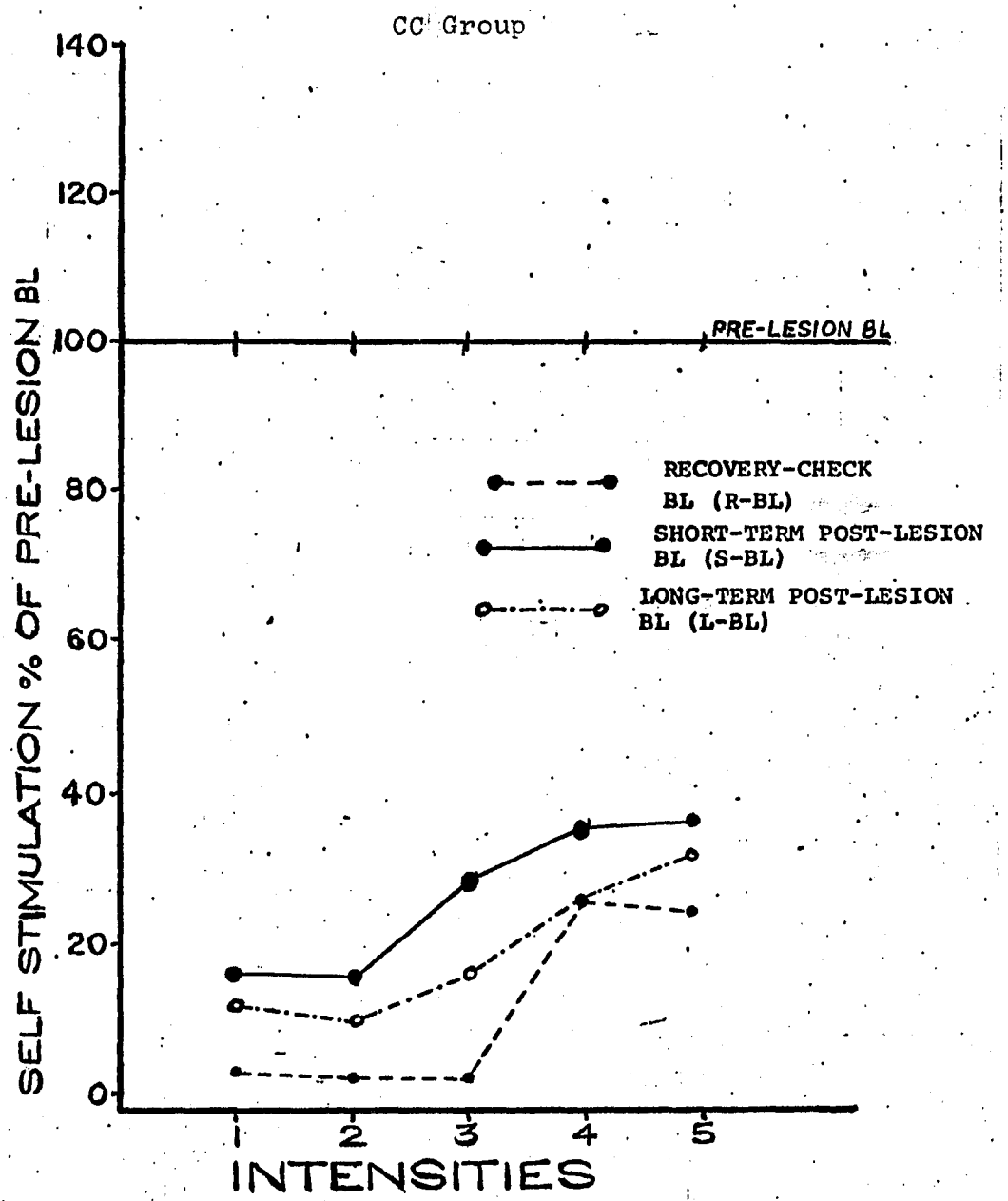
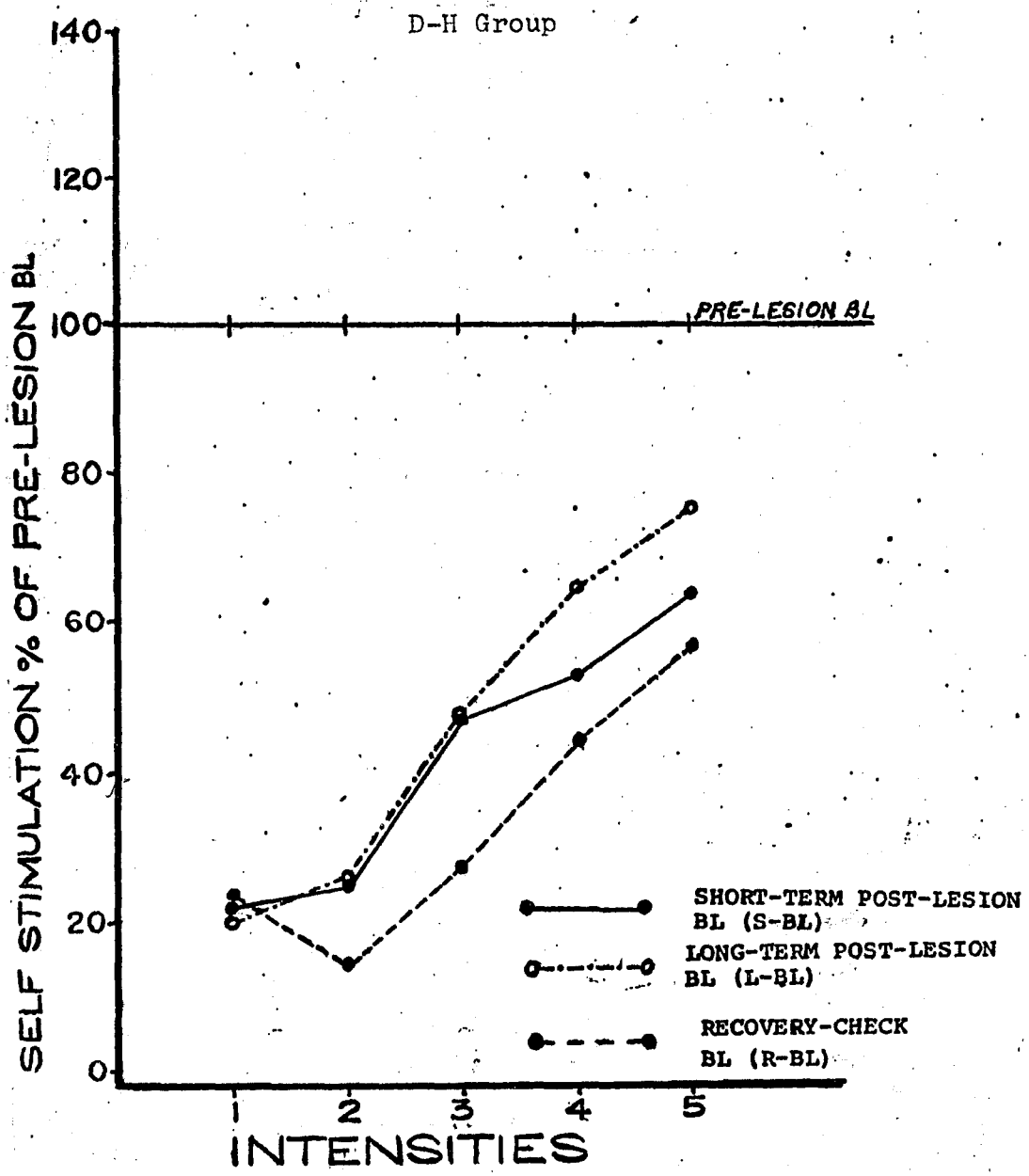


Figure 20

D-H Group



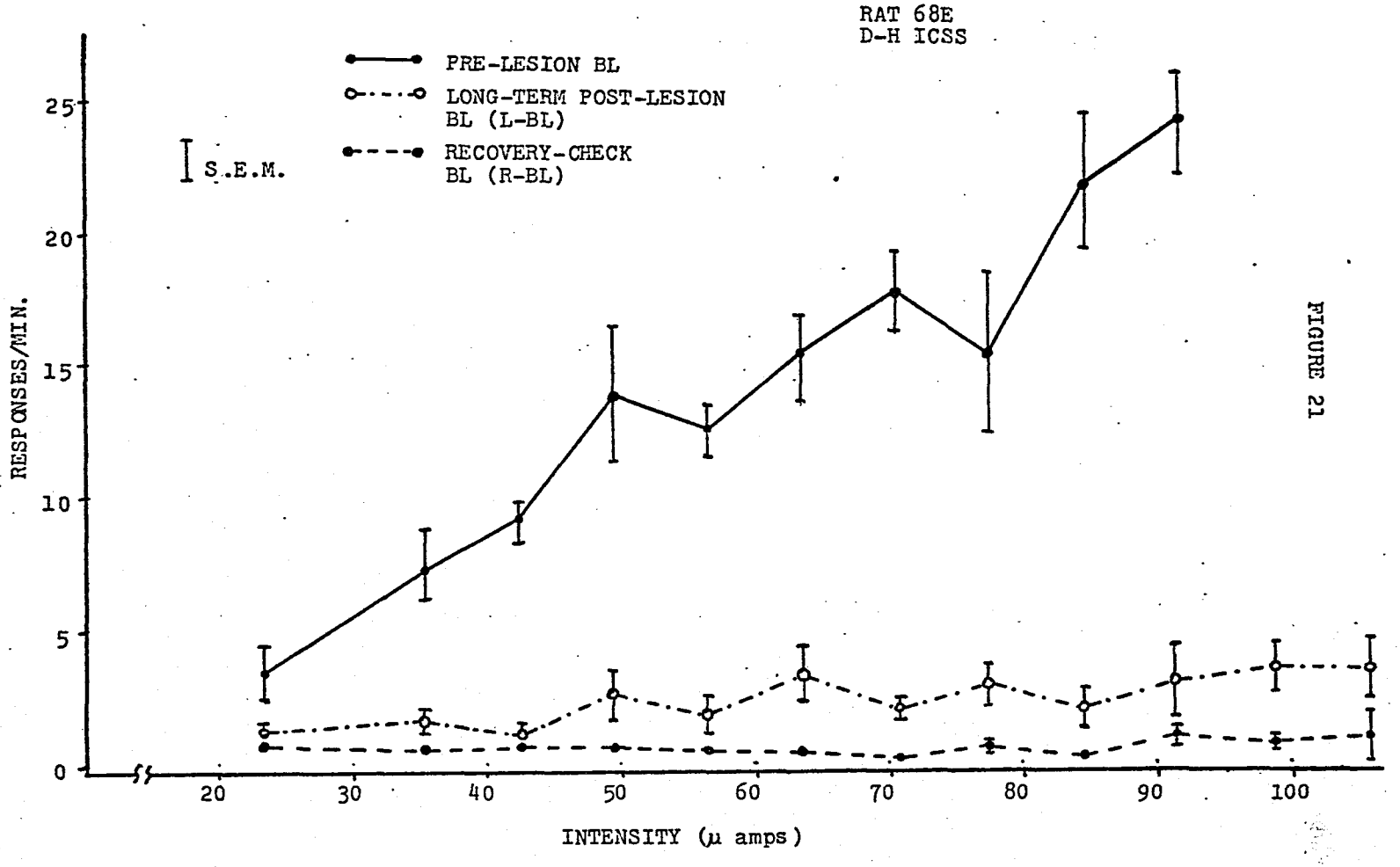

RAT 68E
D-H ICSS
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.
RESPONSES/MIN.
0
5
10
15
20
25
20
30
40
50
60
70
80
90
100
INTENSITY (μ amps)

FIGURE 21

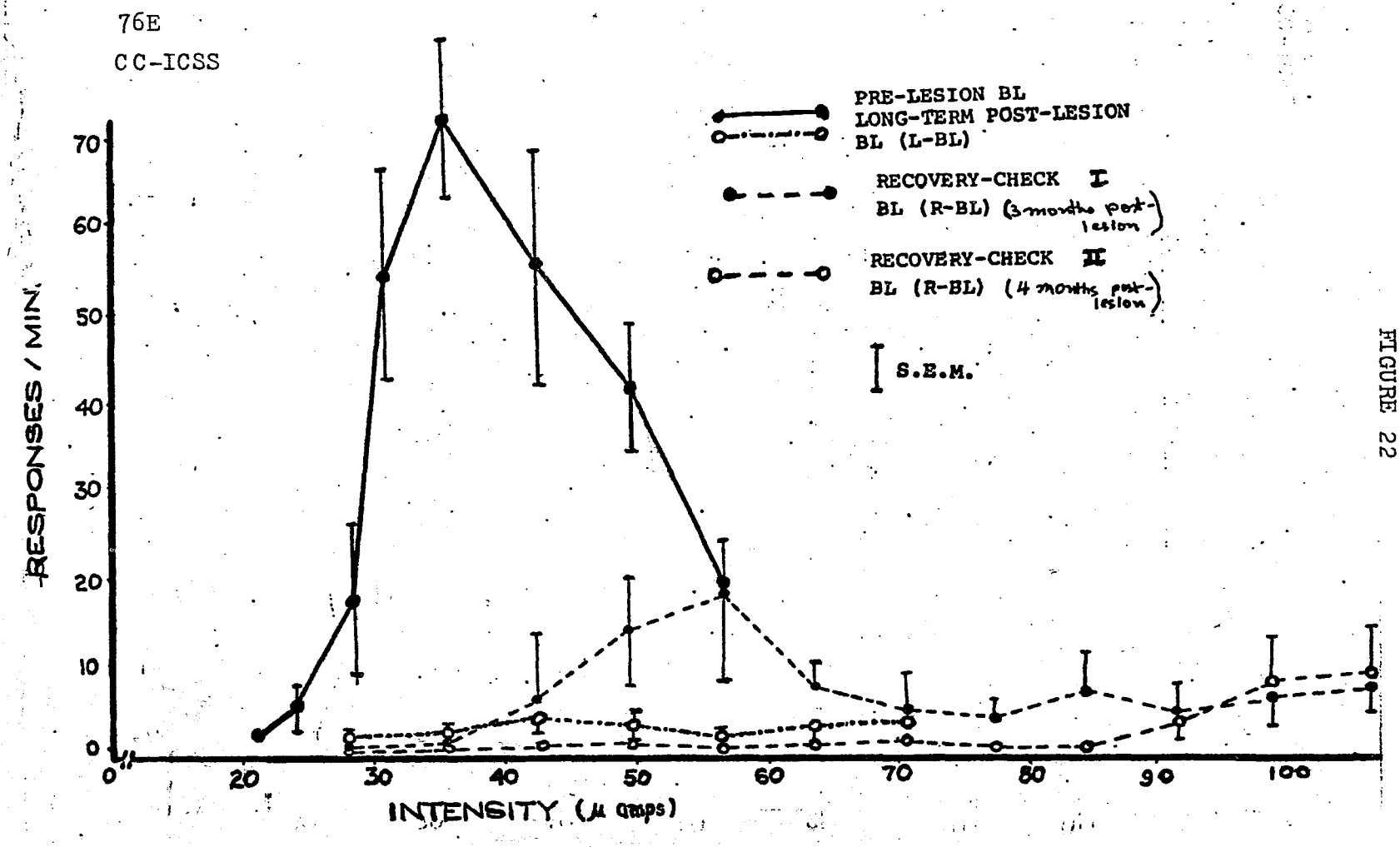

76E
CC-ICSS
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK I BL (R-BL) (3 months post-lesion)
RECOVERY-CHECK II BL (R-BL) (4 months post-lesion)
S.E.M.
RESPONSES / MIN.
INTENSITY (μ amps)
0
10
20
30
40
50
60
70
80
90
100

FIGURE 22

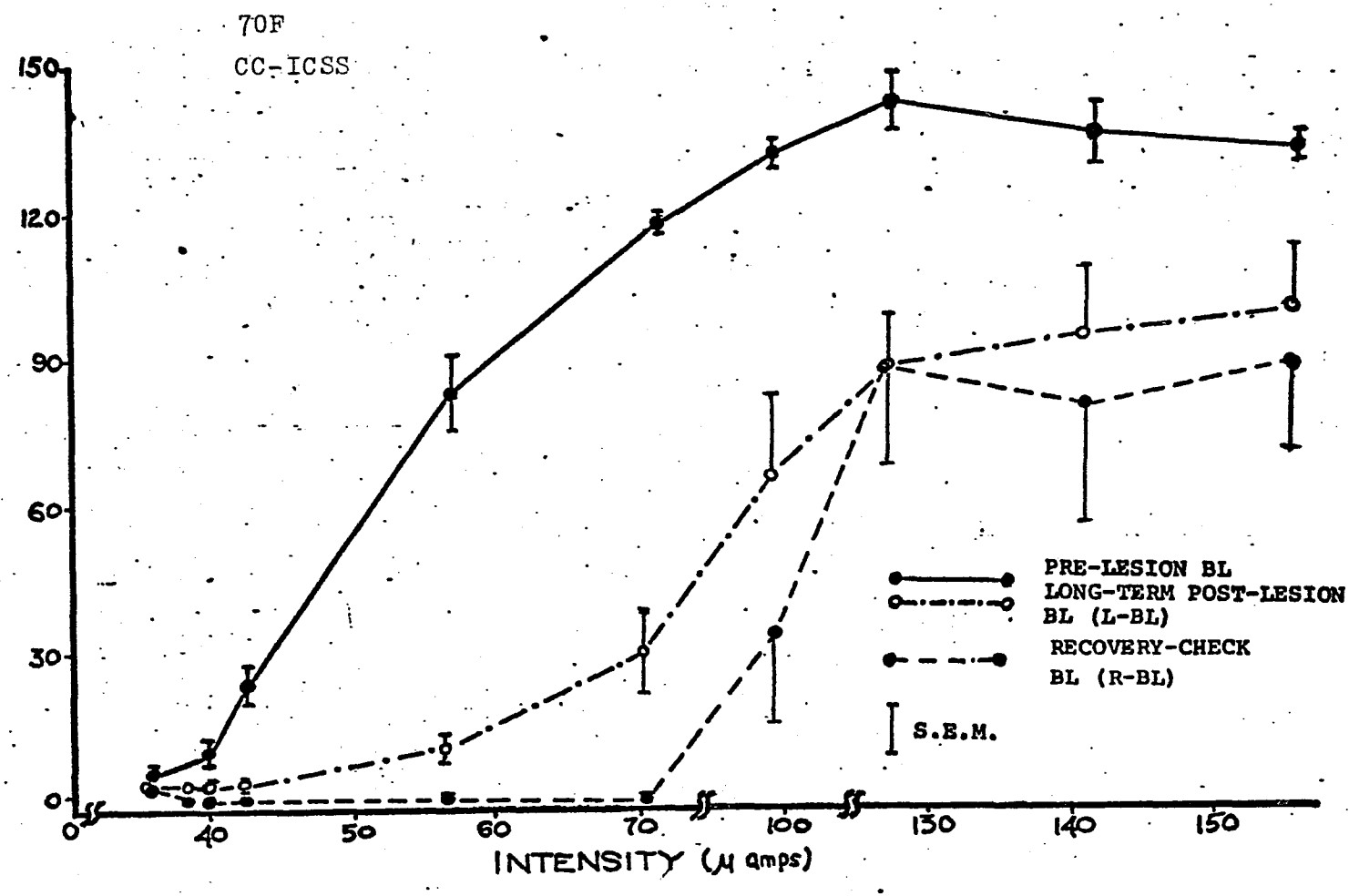

70F
CC-ICSS
150
120
90
60
30
0
0
40
50
60
70
100
130
140
150
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.

FIGURE 23

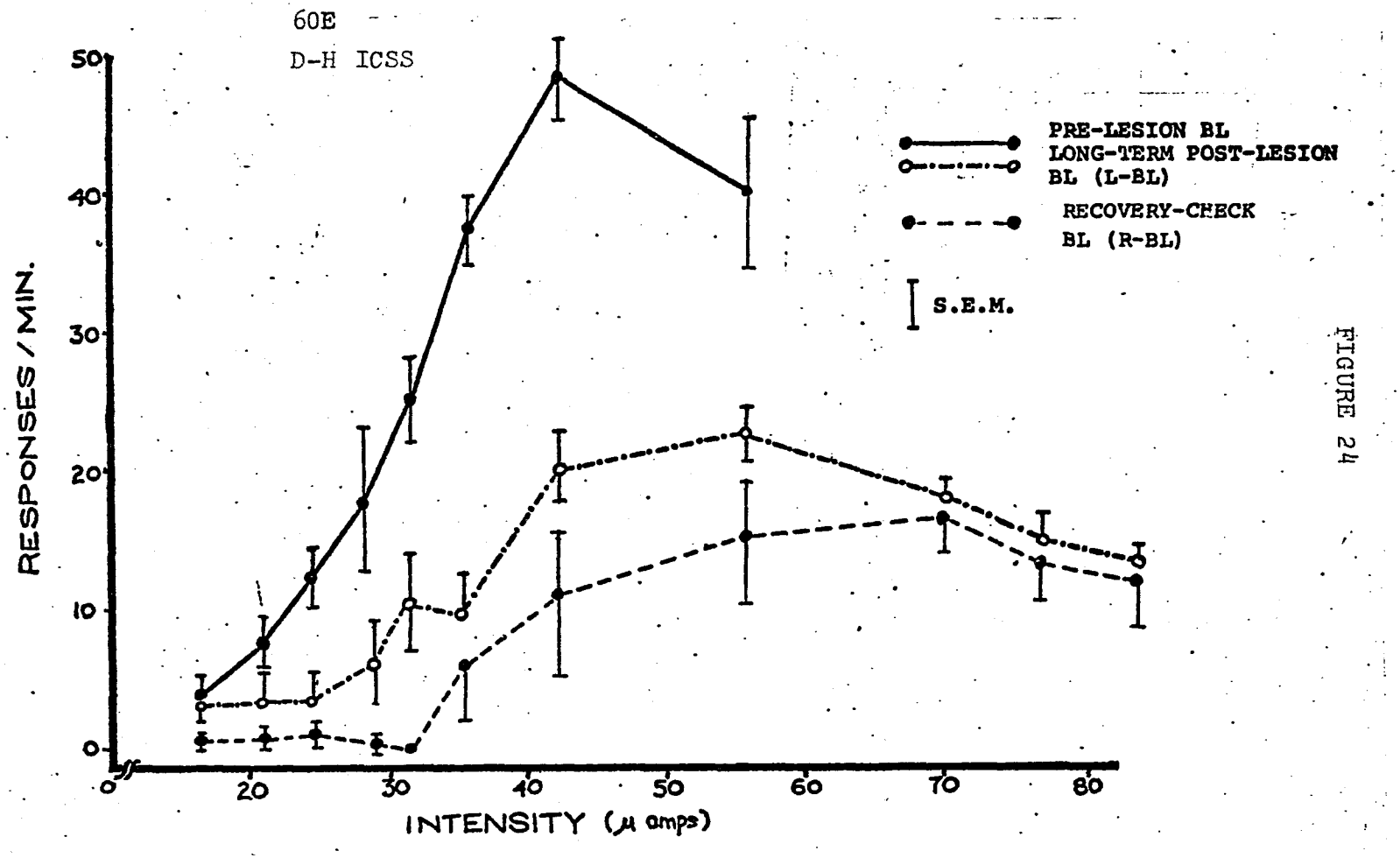

60E
D-H ICSS
RESPONSES / MIN.
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.
0
10
20
30
40
50
60
70
80

FIGURE 24

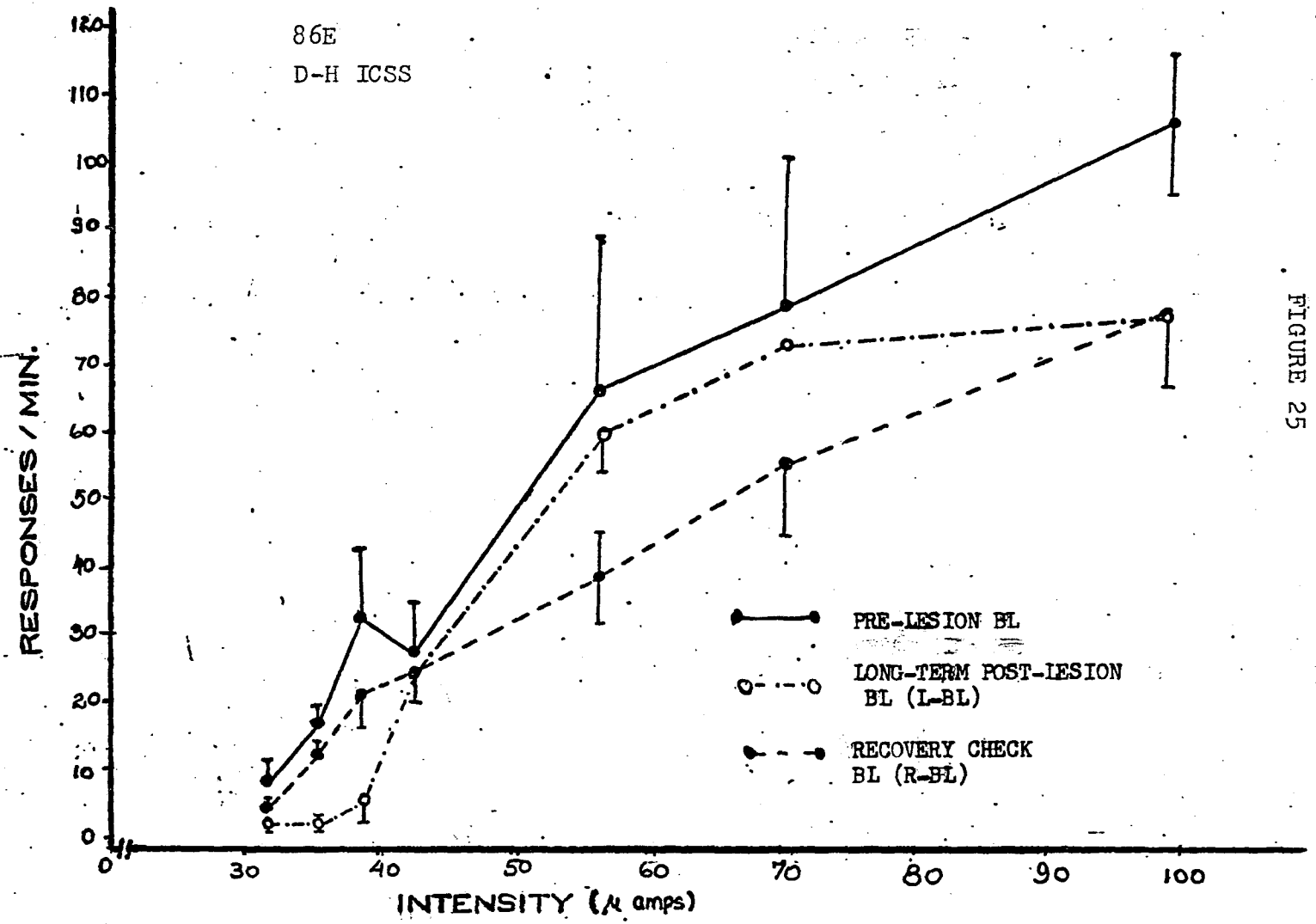

86E
D-H ICSS
RESPONSES / MIN.
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY CHECK BL (R-BL)

FIGURE 25

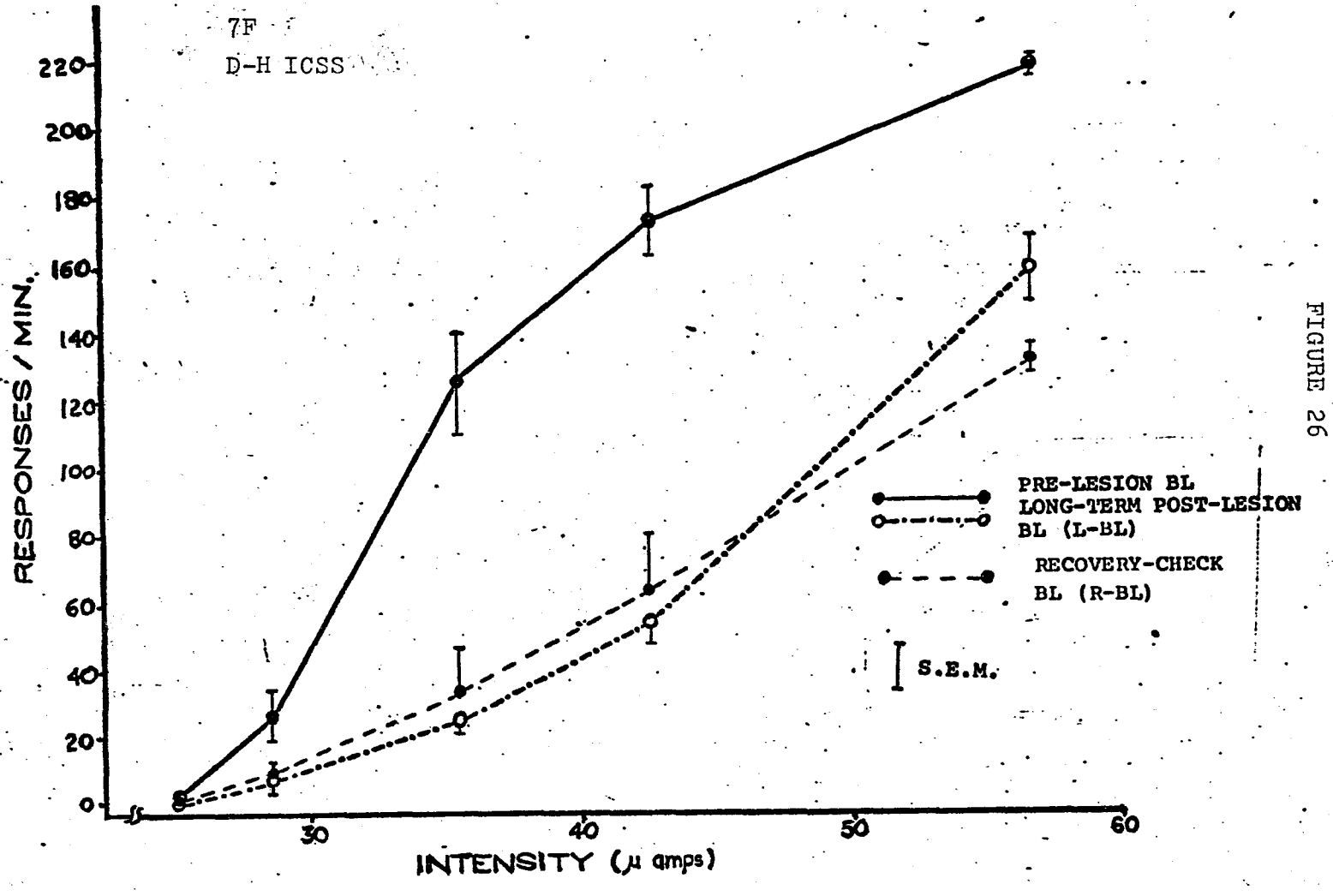

7F
D-H ICSS
RESPONSES / MIN.
220
200
180
160
140
120
100
80
60
40
20
0
30
40
50
60
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.

FIGURE 26

69F
D-H ICSS

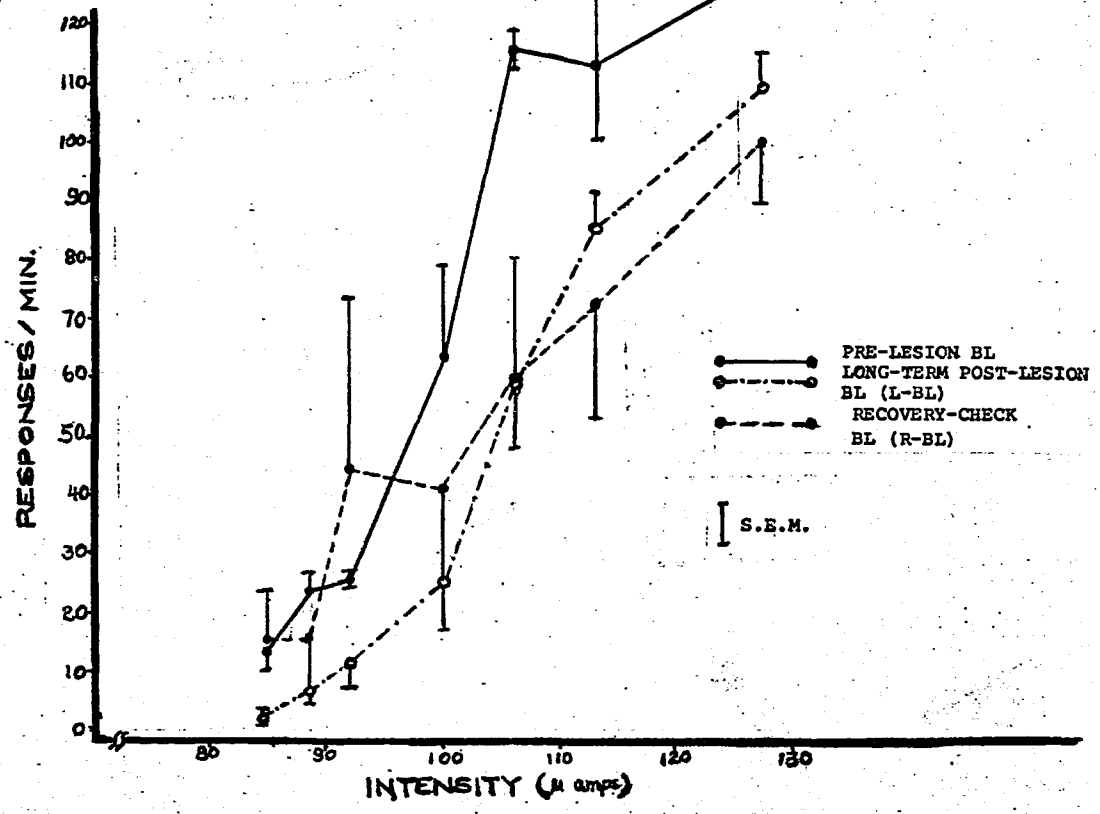


FIGURE 27

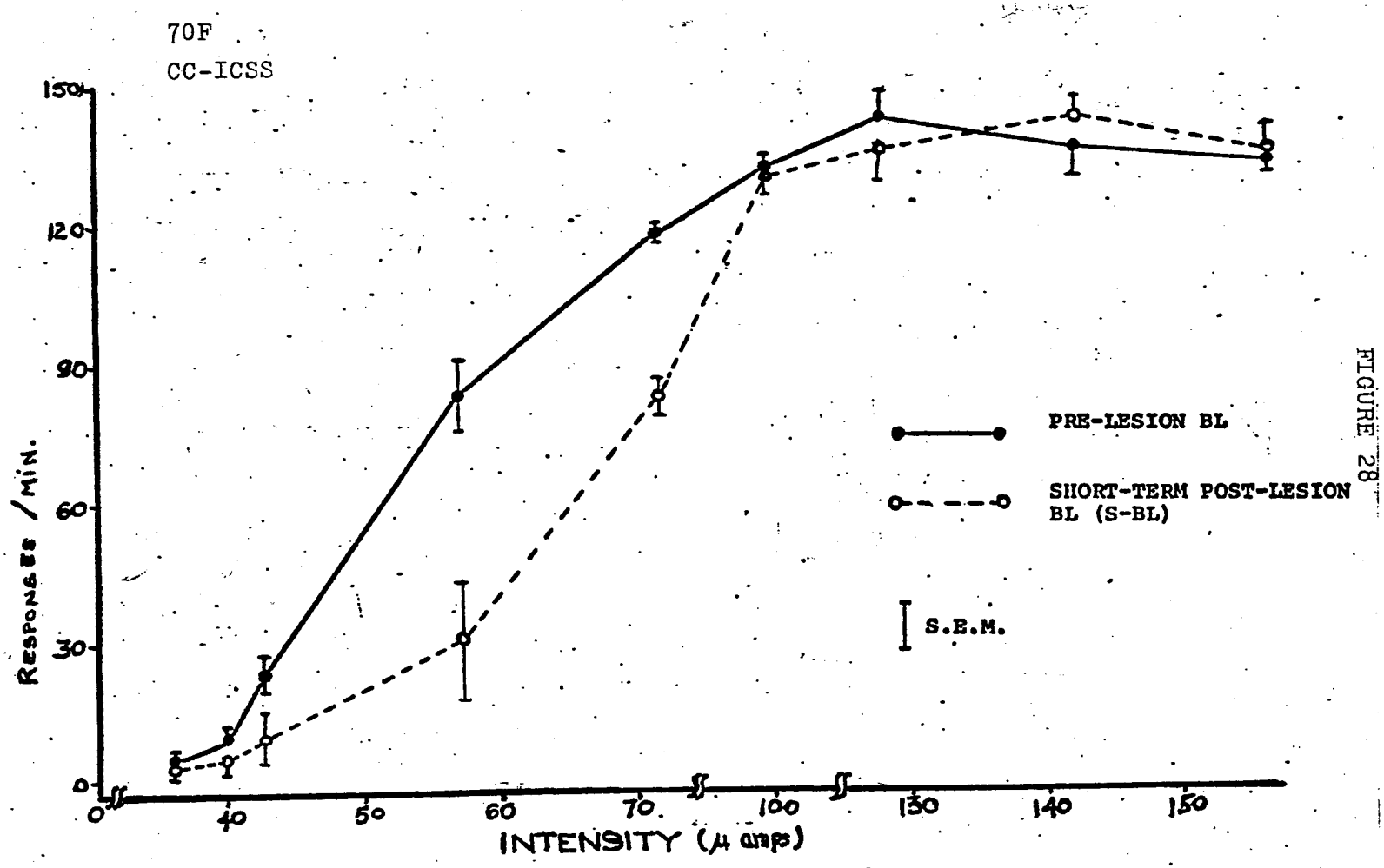

70F
CC-ICSS
150
120
90
60
30
0
RESPONSES / MIN.
0
40
50
60
70
100
130
140
150
INTENSITY (μ amps)
PRE-LESION BL
SHORT-TERM POST-LESION BL (S-BL)
S.E.M.

FIGURE 28

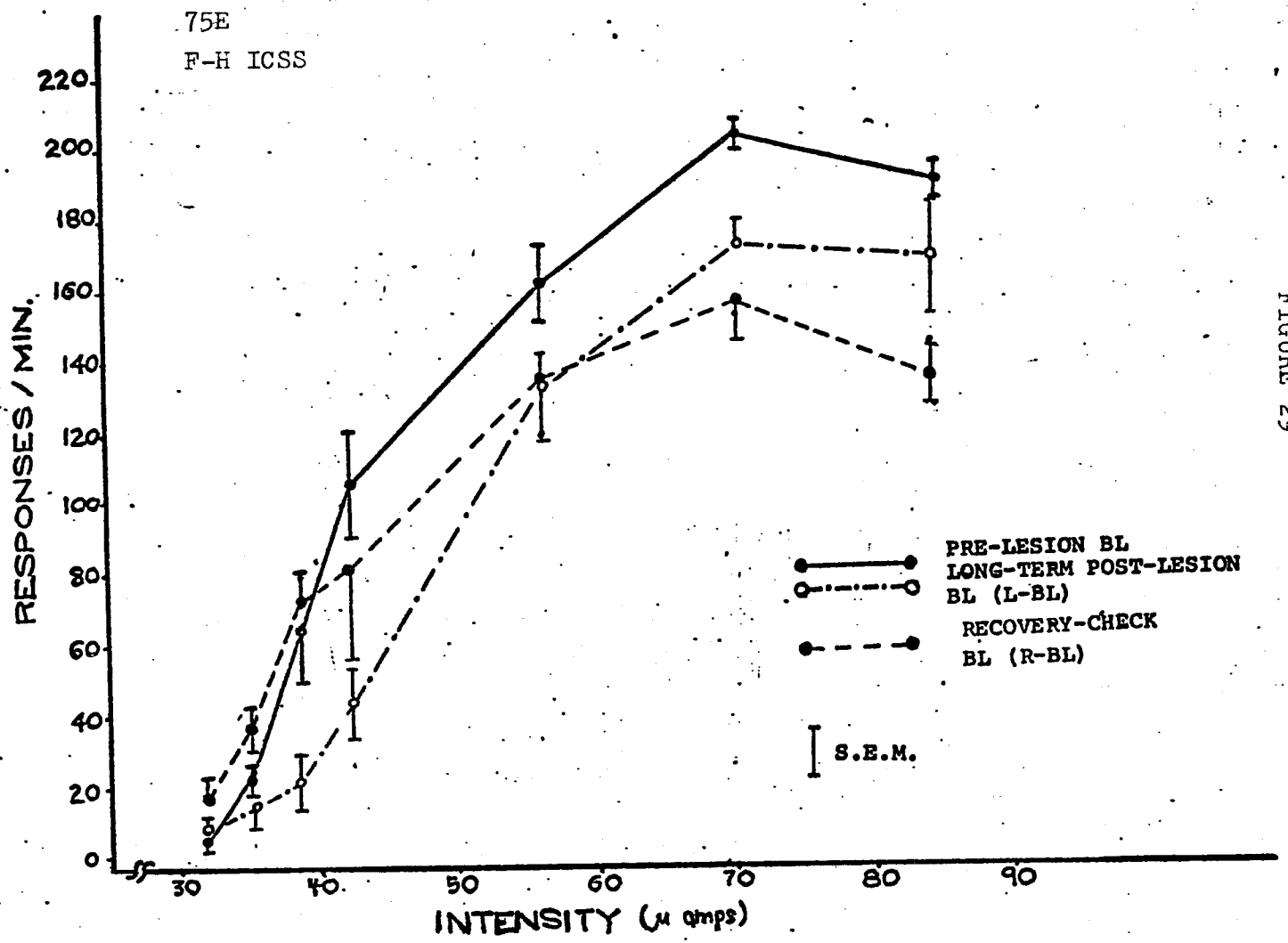
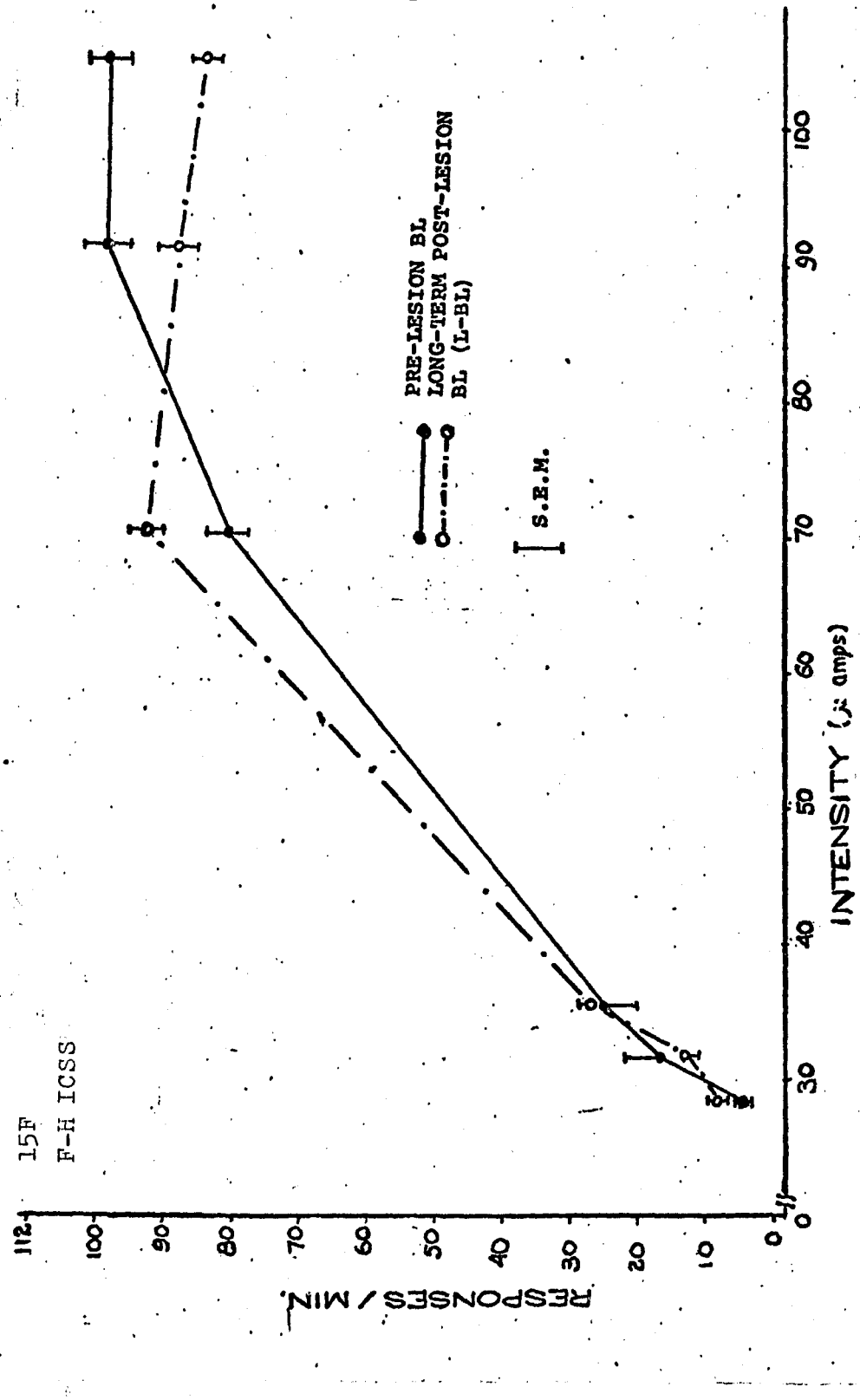

75E
F-H ICSS
RESPONSES / MIN.
220
200
180
160
140
120
100
80
60
40
20
0
30
40
50
60
70
80
90
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.

FIGURE 29

FIGURE 30


15F
F-H ICSS
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
S.E.M.
RESPONSES / MIN.
INTENSITY (μ amps)
112
100
90
80
70
60
50
40
30
20
10
0
0
30
40
50
60
70
80
90
100

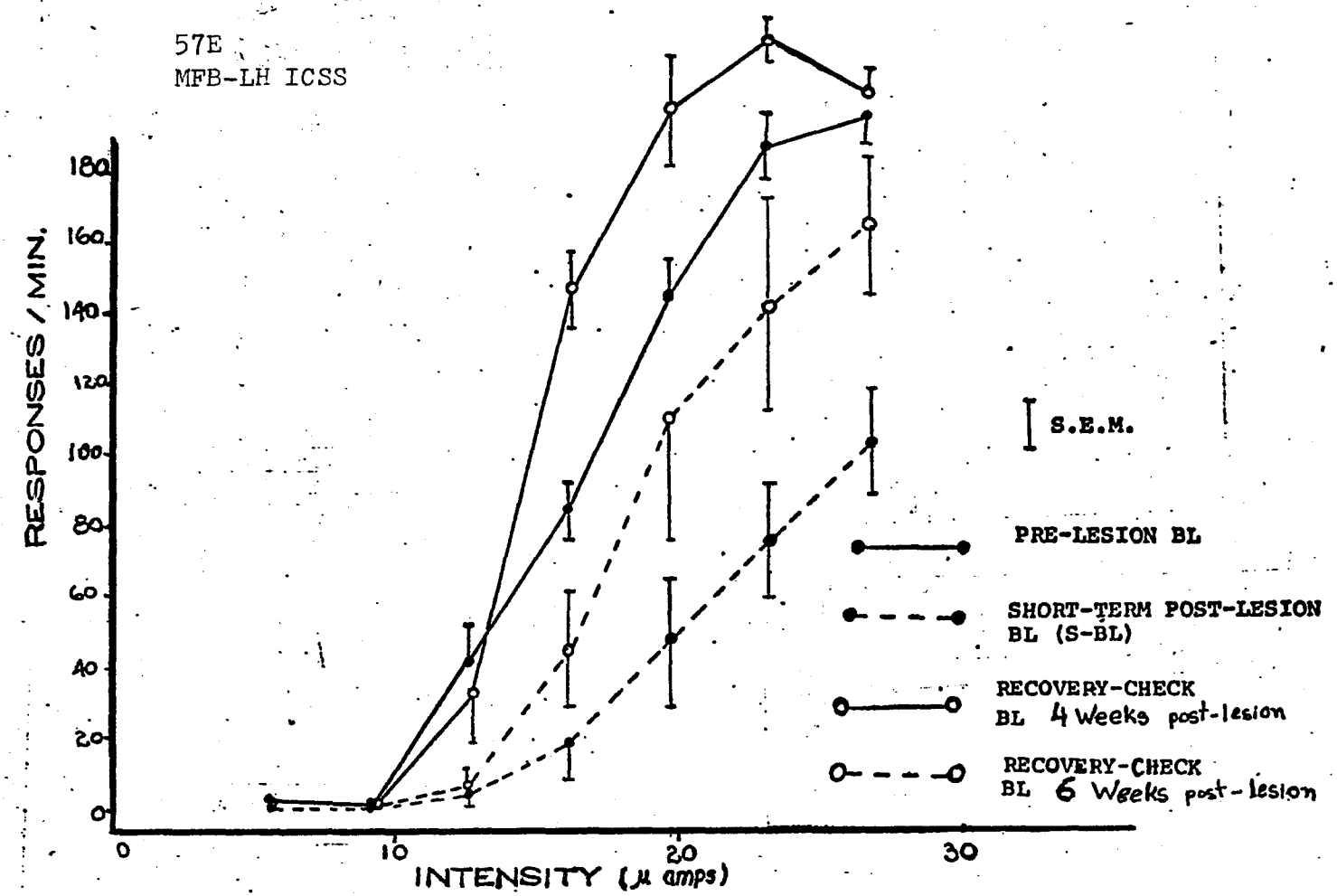

57E
MFB-LH ICSS
RESPONSES / MIN.
180
160
140
120
100
80
60
40
20
0
0
10
20
30
INTENSITY (μ amps)
S.E.M.
PRE-LESION BL
SHORT-TERM POST-LESION BL (S-BL)
RECOVERY-CHECK BL 4 Weeks post-lesion
RECOVERY-CHECK BL 6 Weeks post-lesion

FIGURE 31

78E
MFB-LH ICSS

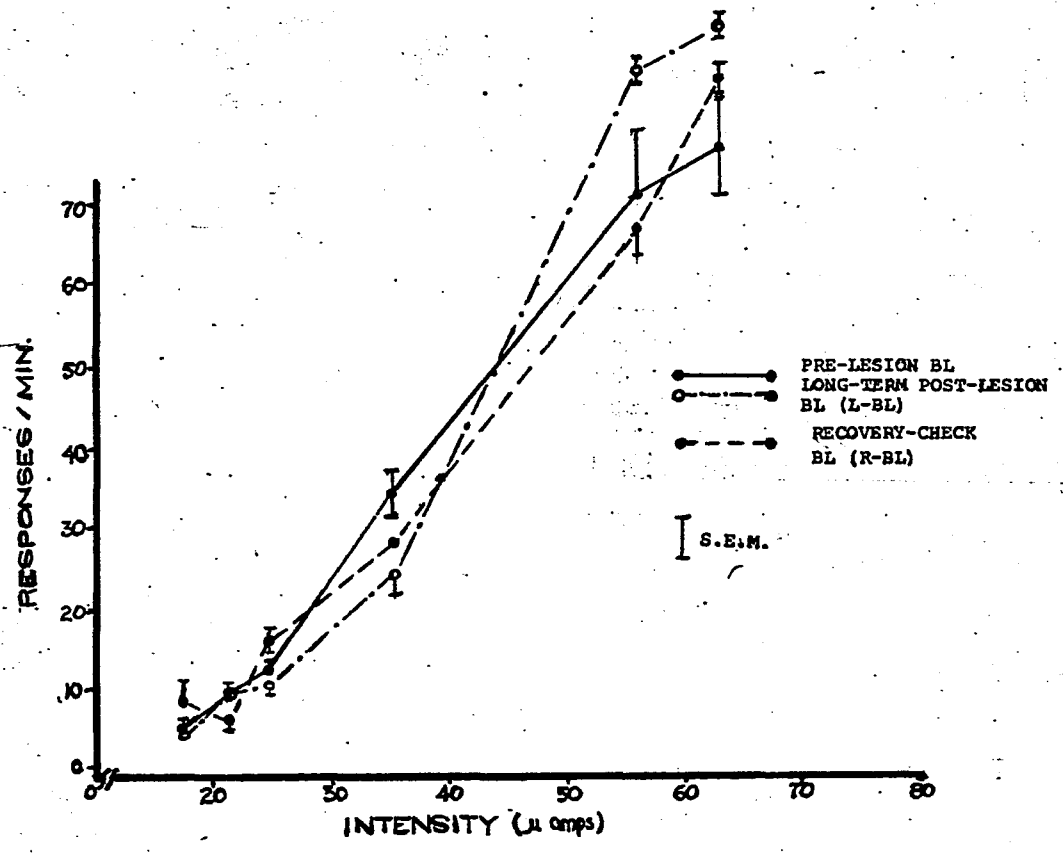


FIGURE 32

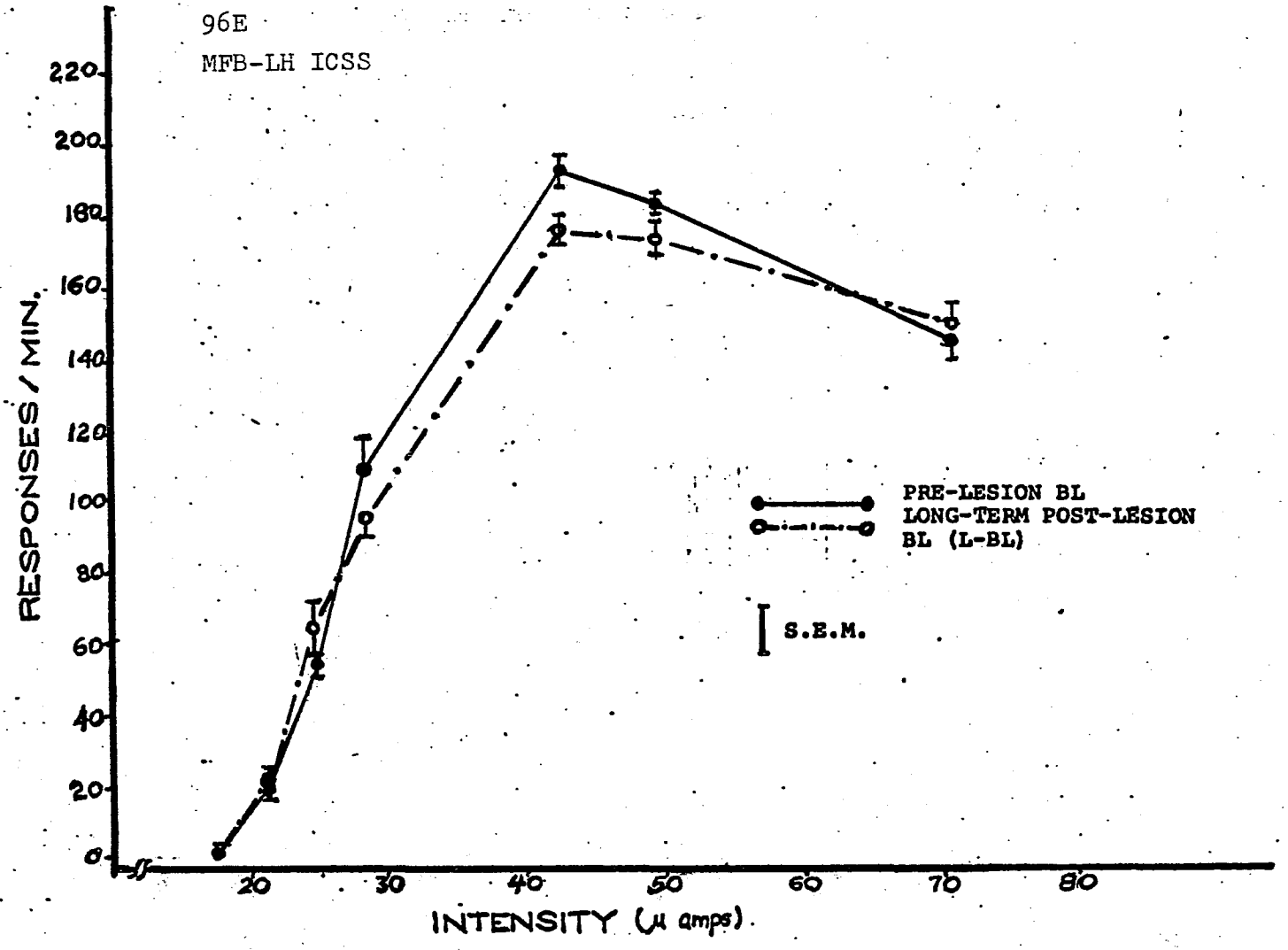

96E
MFB-LH ICSS
RESPONSES / MIN.
220
200
180
160
140
120
100
80
60
40
20
0
20
30
40
50
60
70
80
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
S.E.M.

FIGURE 33

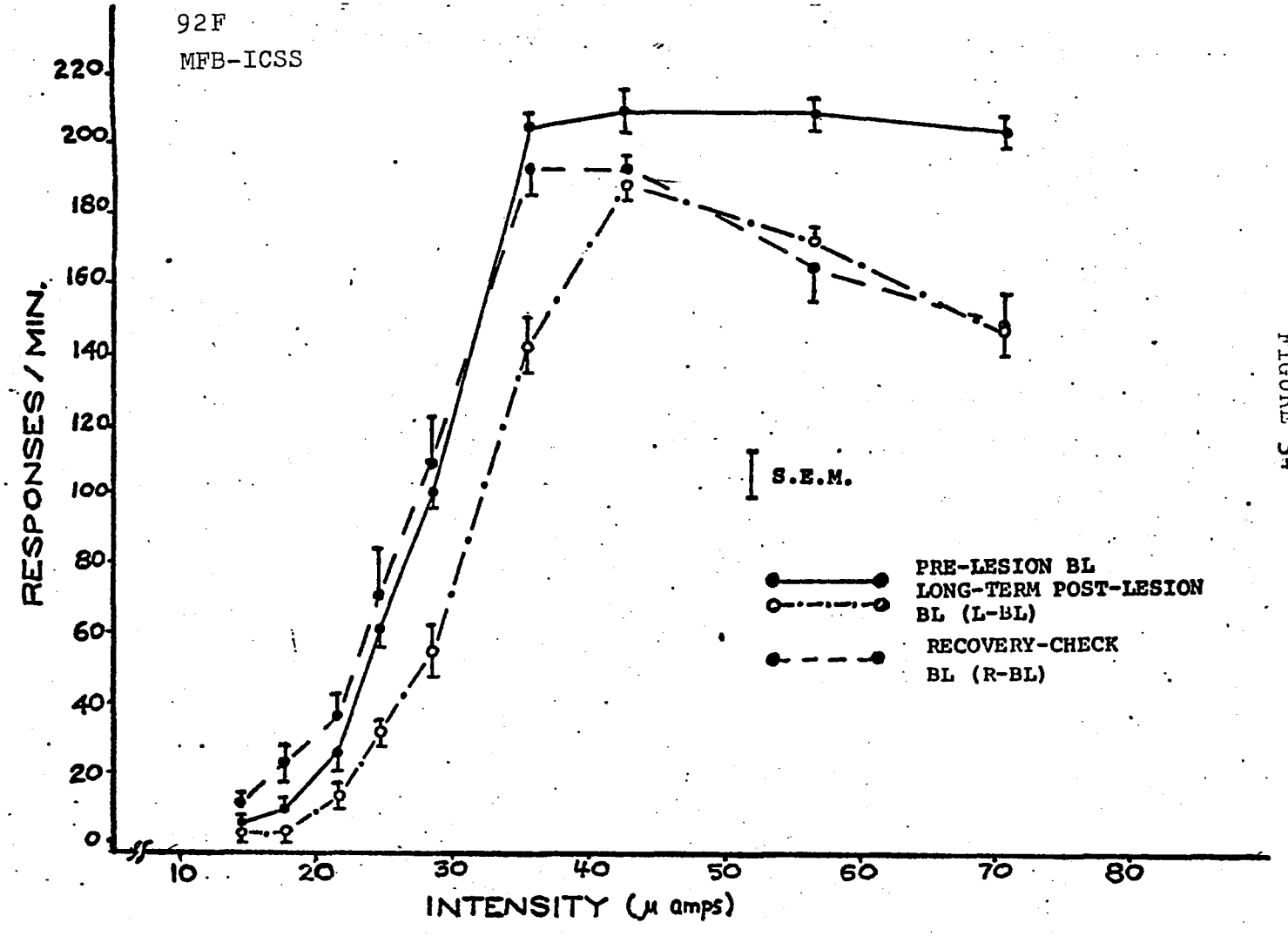

92F
MFB-ICSS
RESPONSES / MIN.
220
200
180
160
140
120
100
80
60
40
20
0
10
20
30
40
50
60
70
80
INTENSITY (μ amps)
S.E.M.
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)

FIGURE 34

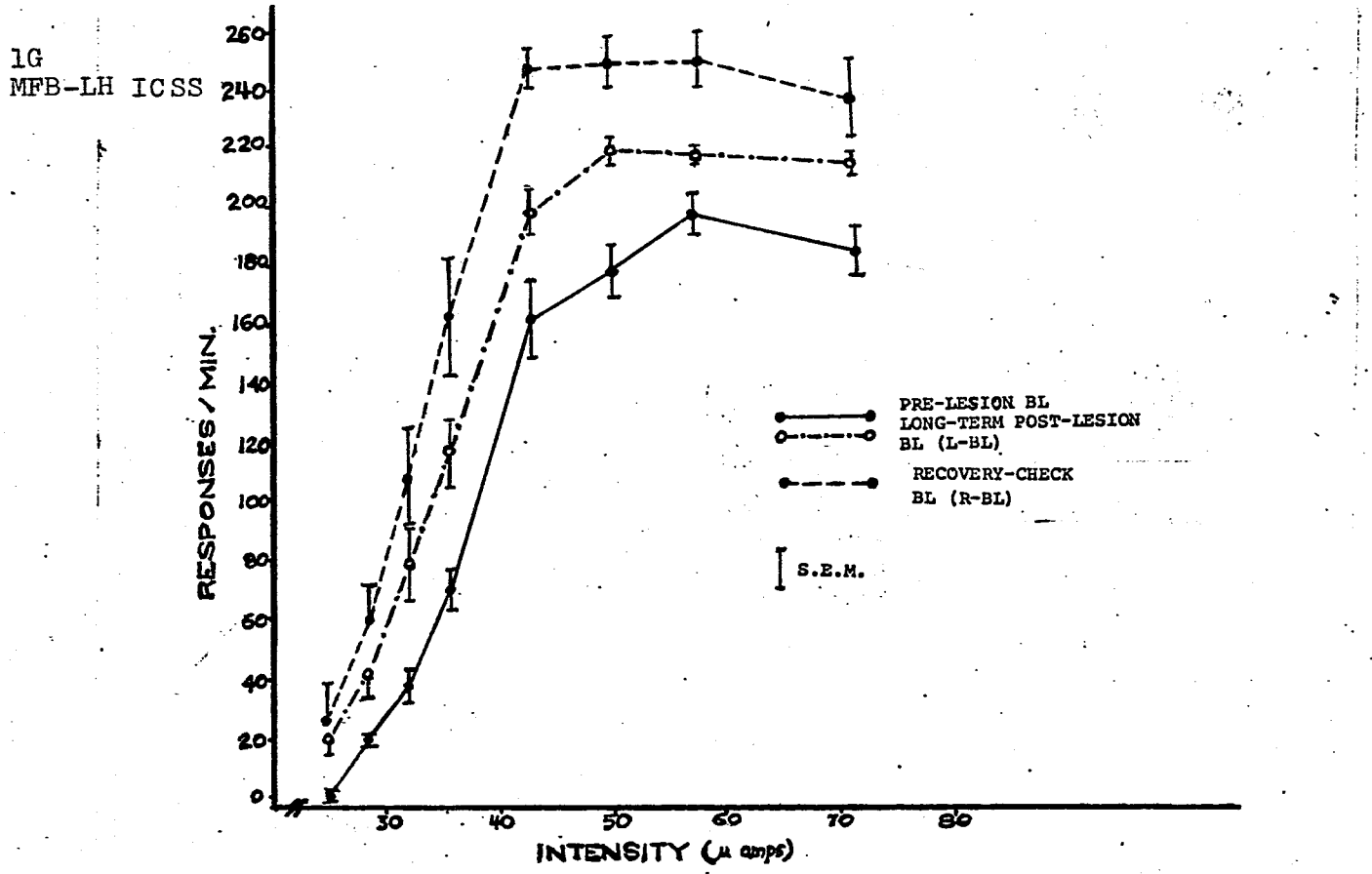

1G
MFB-LH ICSS
RESPONSES / MIN.
260
240
220
200
180
160
140
120
100
80
60
40
20
0
30
40
50
60
70
80
INTENSITY (μ amps)
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.

FIGURE 35

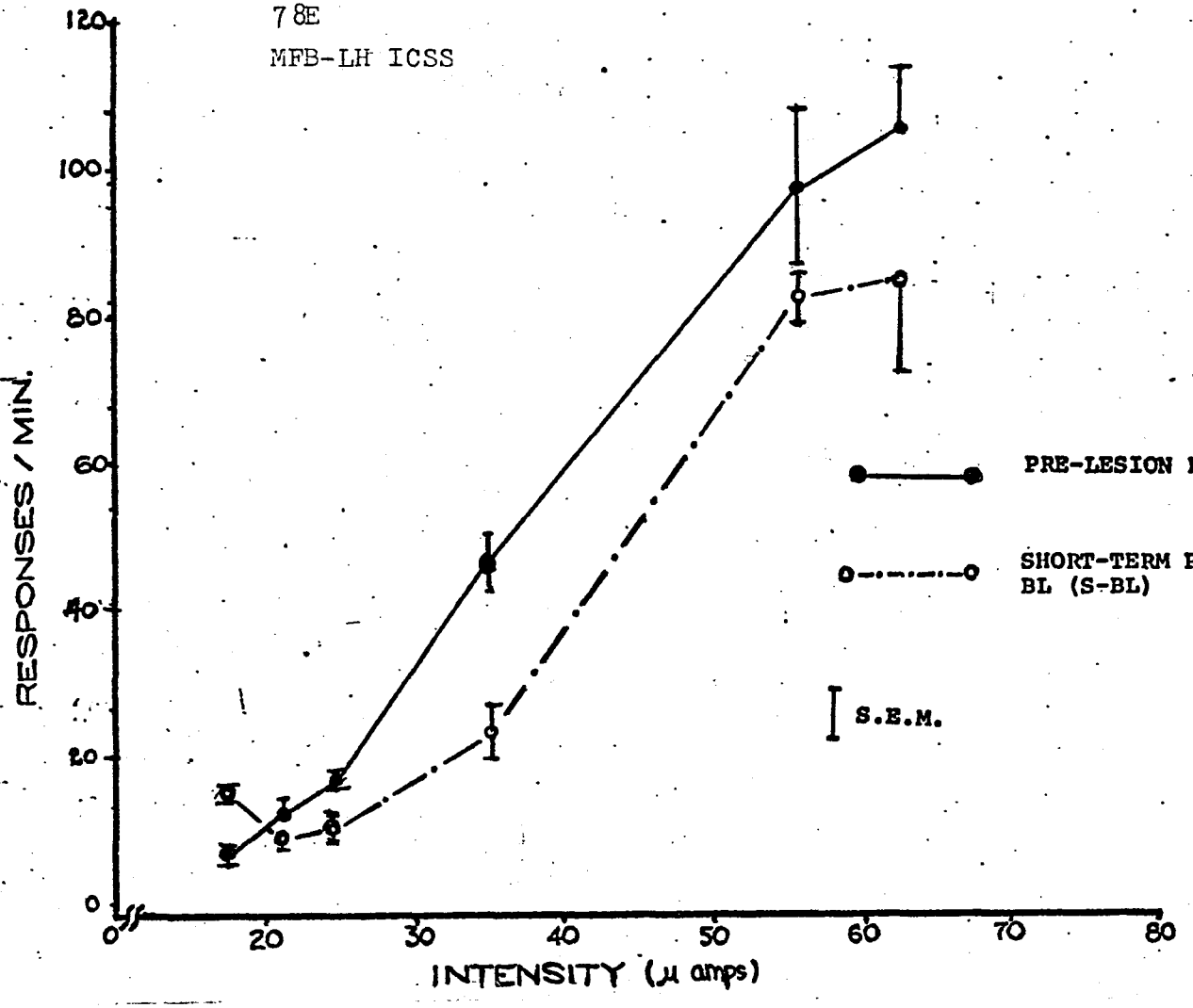

78E
MFB-LH ICSS
RESPONSES / MIN.
120
100
80
60
40
20
0
0
20
30
40
50
60
70
80
INTENSITY (μ amps)
PRE-LESION BL
SHORT-TERM POST-LESION BL (S-BL)
S.E.M.

FIGURE 36

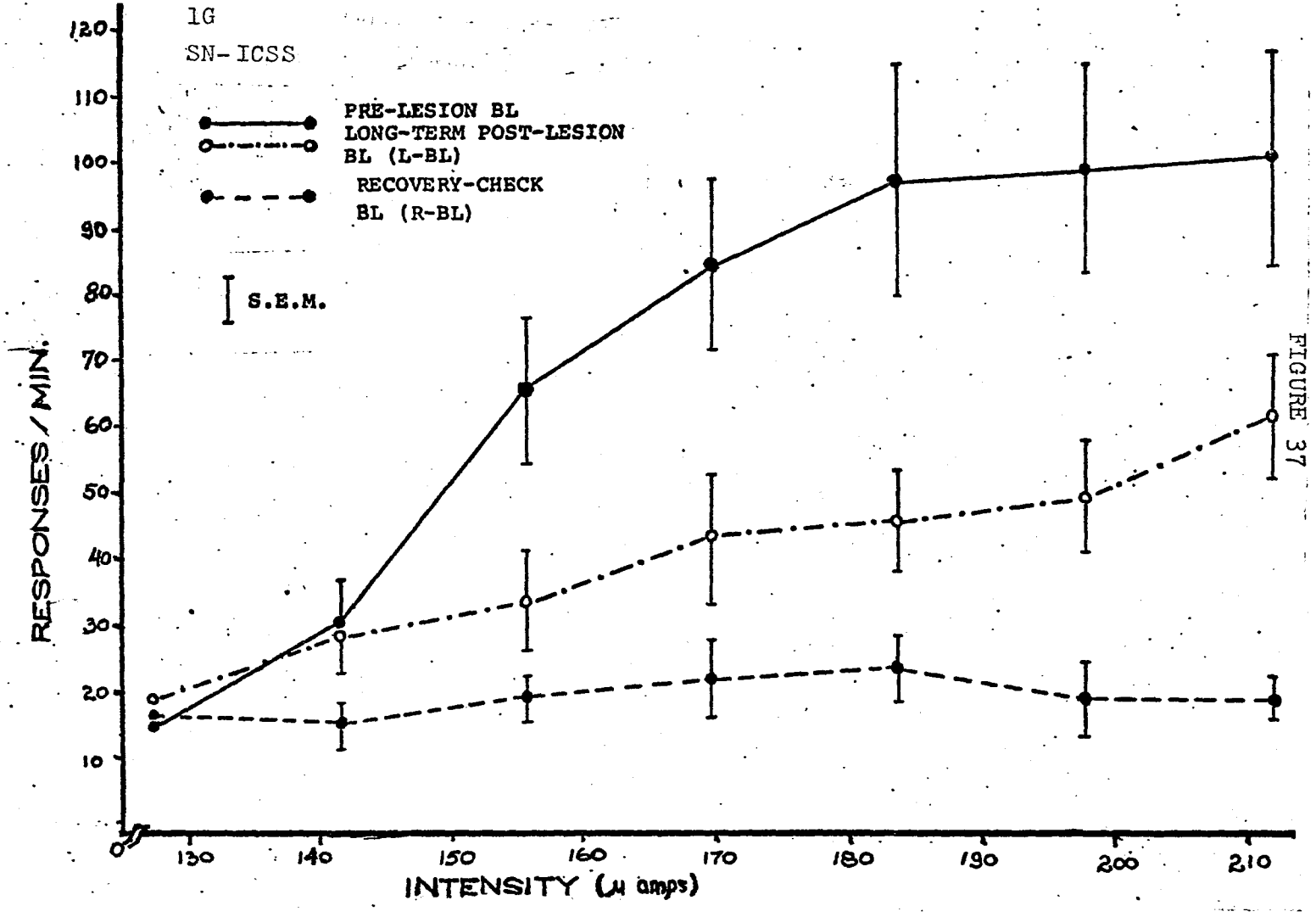

1G
SN-ICSS
PRE-LESION BL
LONG-TERM POST-LESION BL (L-BL)
RECOVERY-CHECK BL (R-BL)
S.E.M.
RESPONSES / MIN.
120
110
100
90
80
70
60
50
40
30
20
10
0
130
140
150
160
170
180
190
200
210
INTENSITY (μ amps)

FIGURE 37

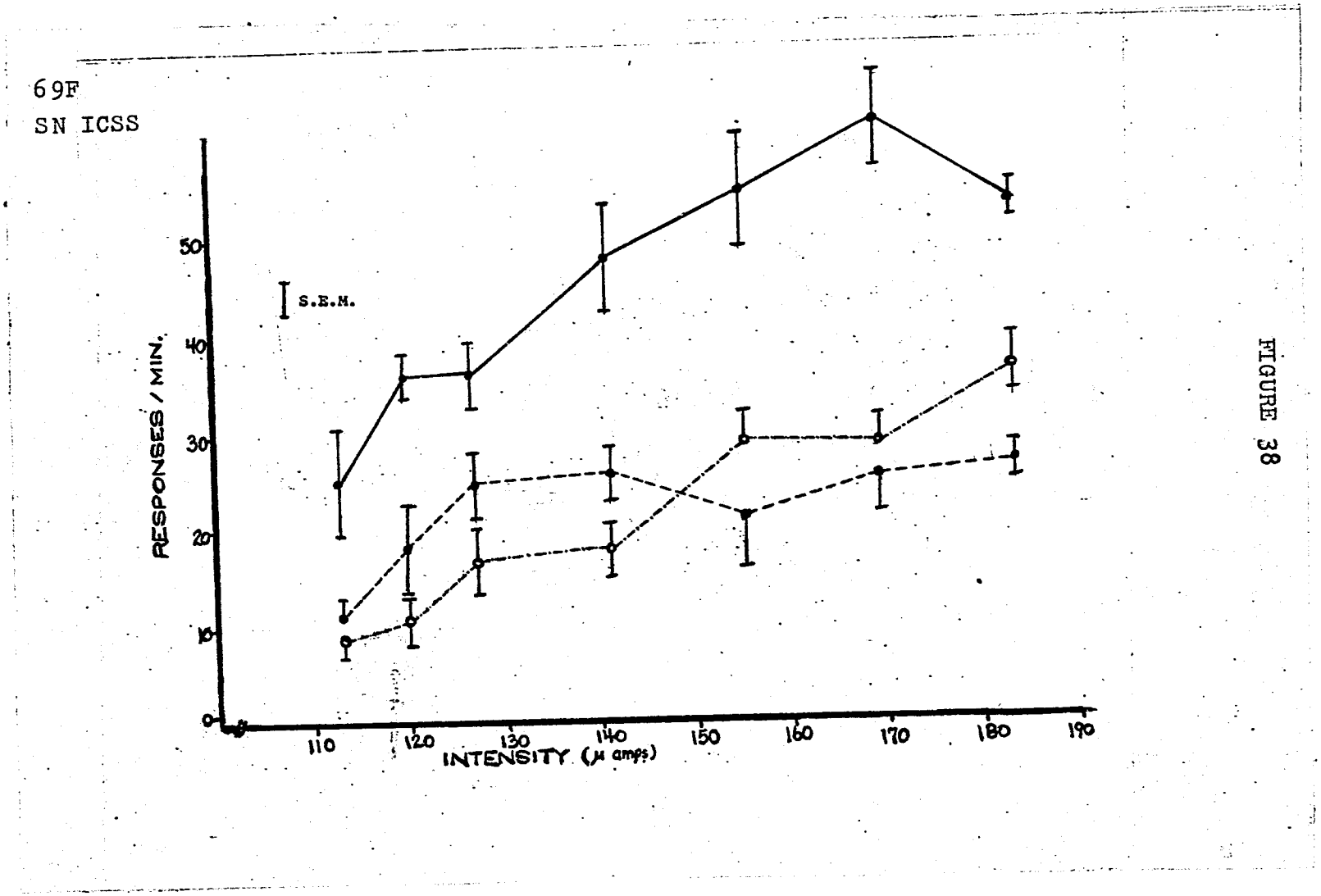

69F
SN ICSS
S.E.M.
RESPONSES / MIN.
0
15
30
45
50
110
120
130
140
150
160
170
180
190
INTENSITY (μ amps)

FIGURE 38

FIGURE 39
SN Group

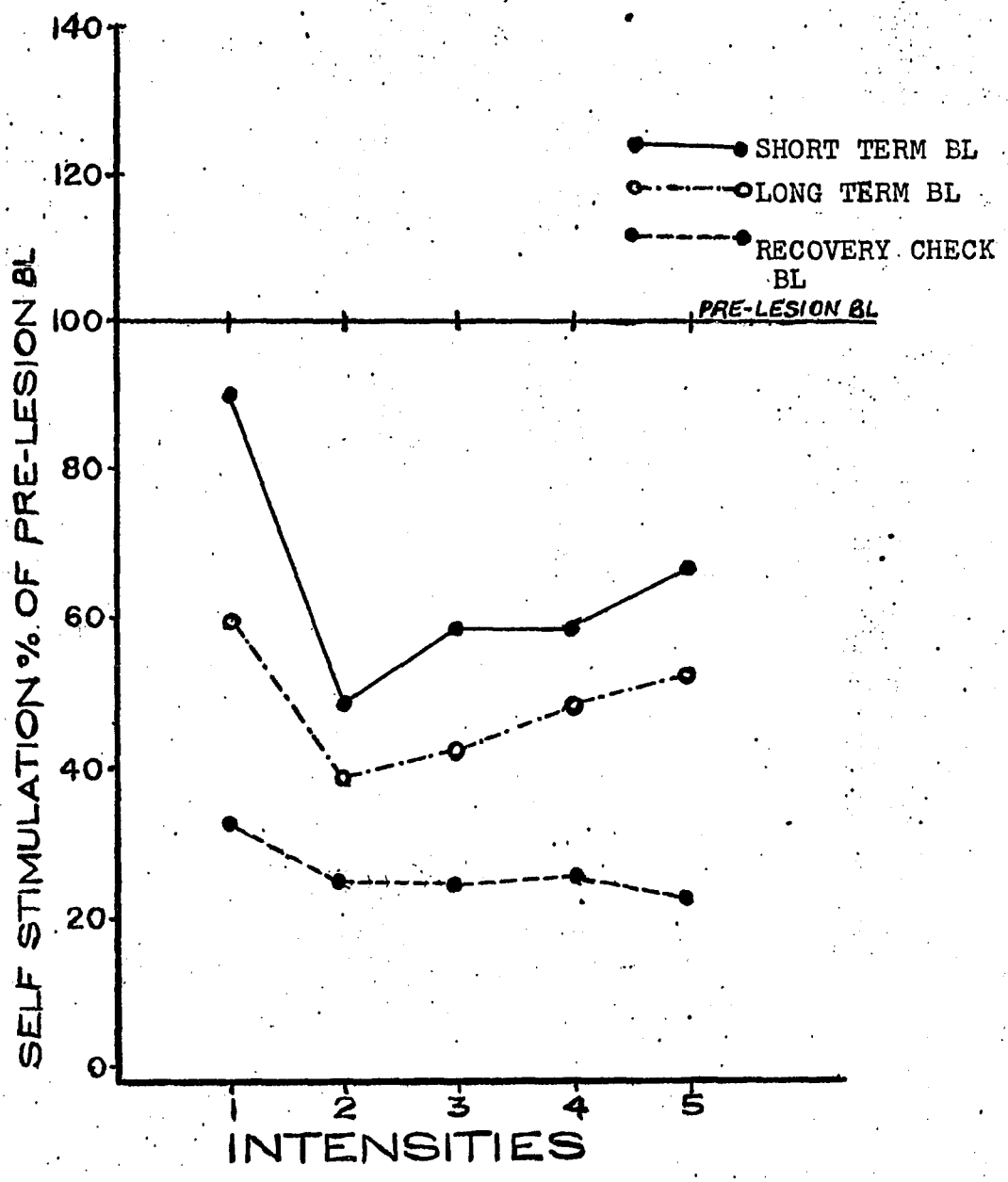


FIGURE 40

S-BL

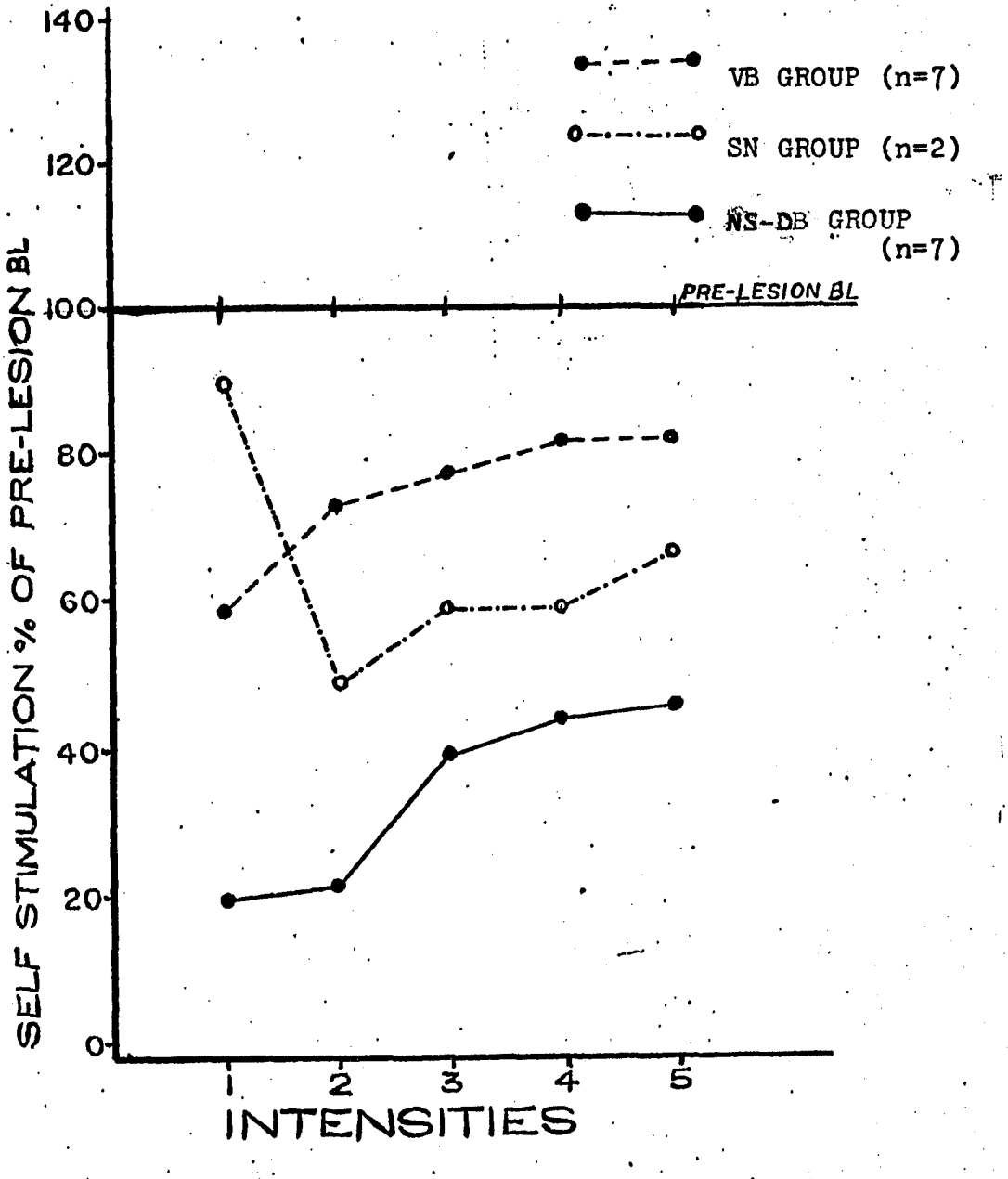


FIGURE 41

L-BL

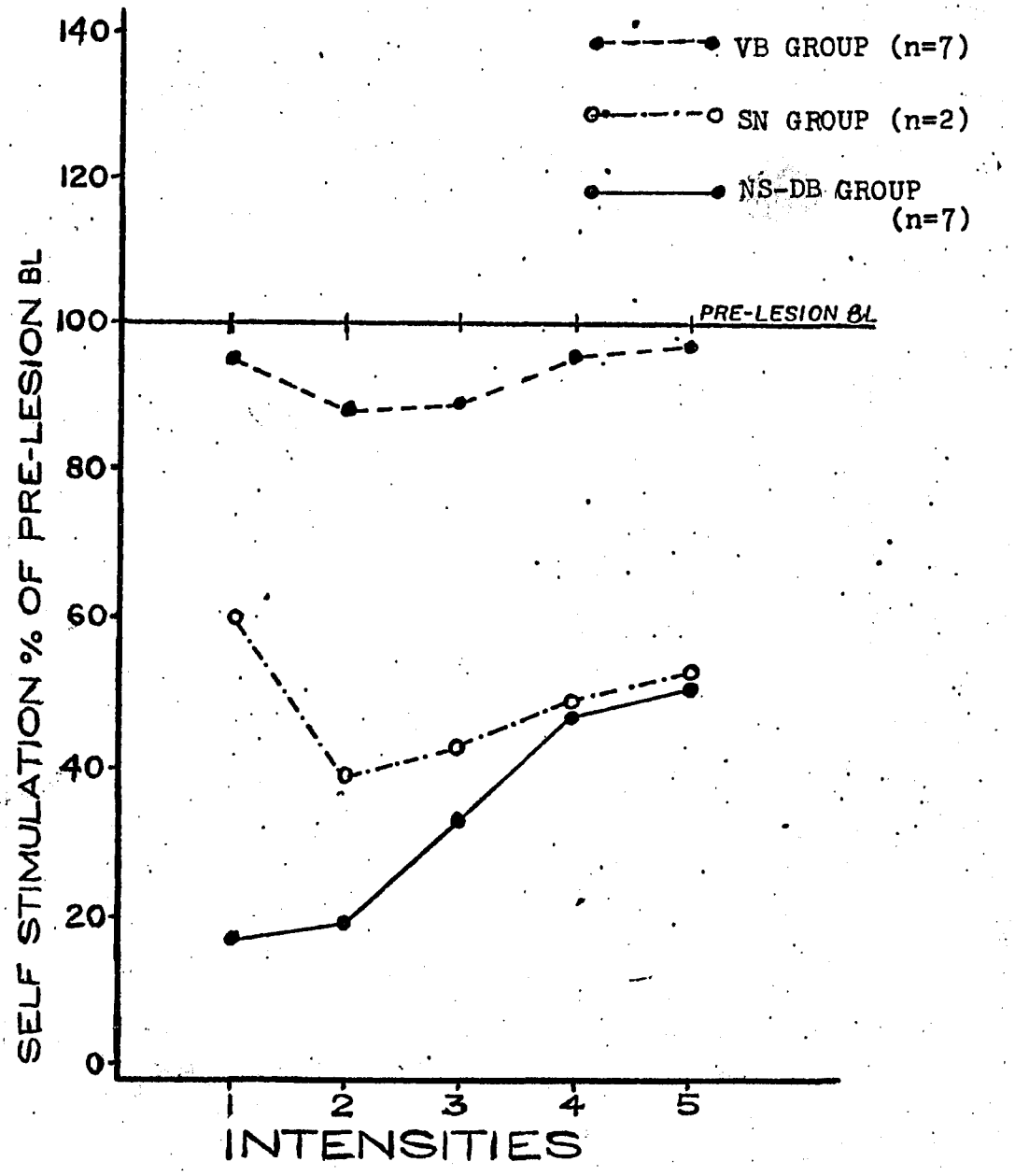


FIGURE 42

R-BL

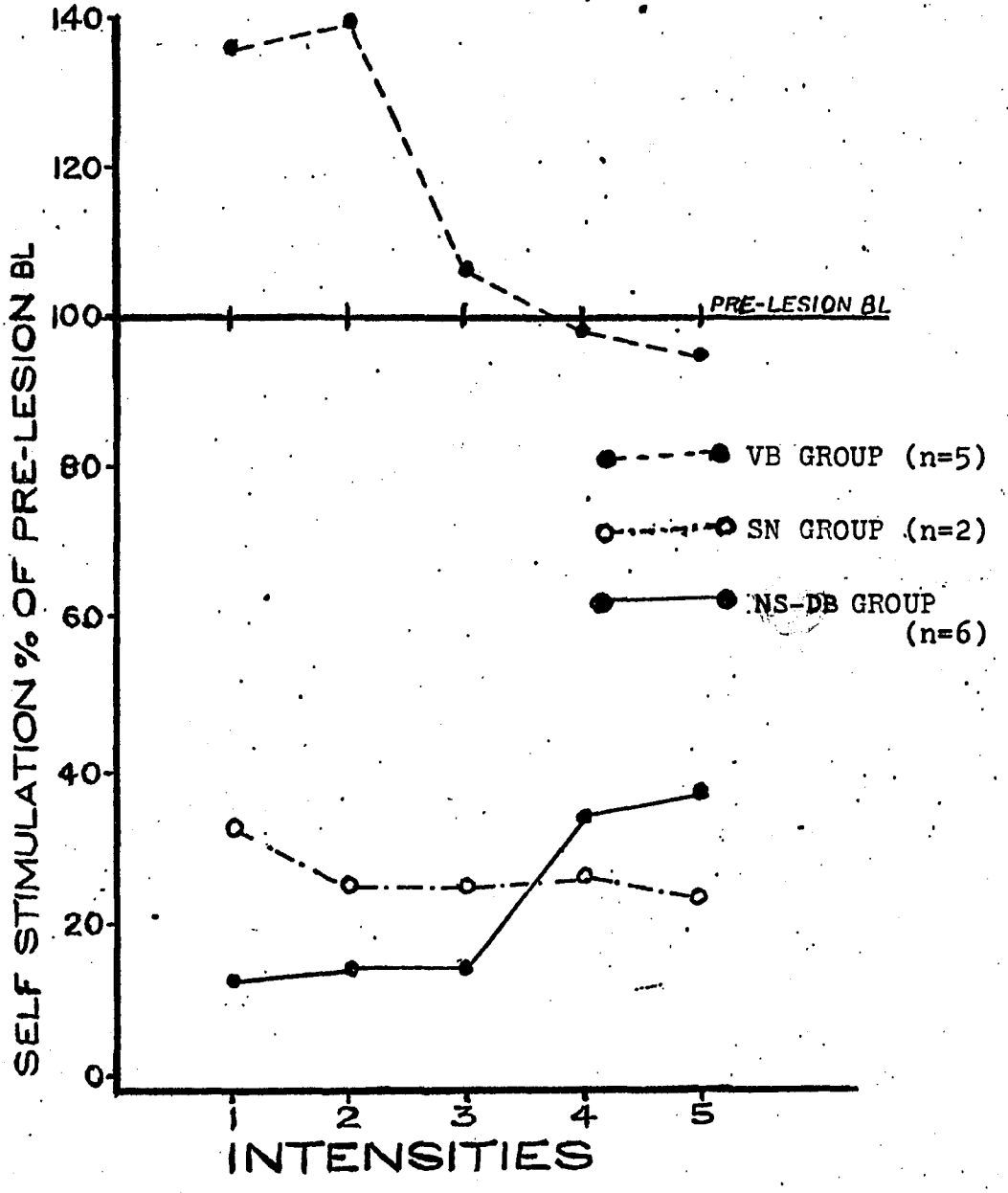


FIGURE 43

NS-DB Group

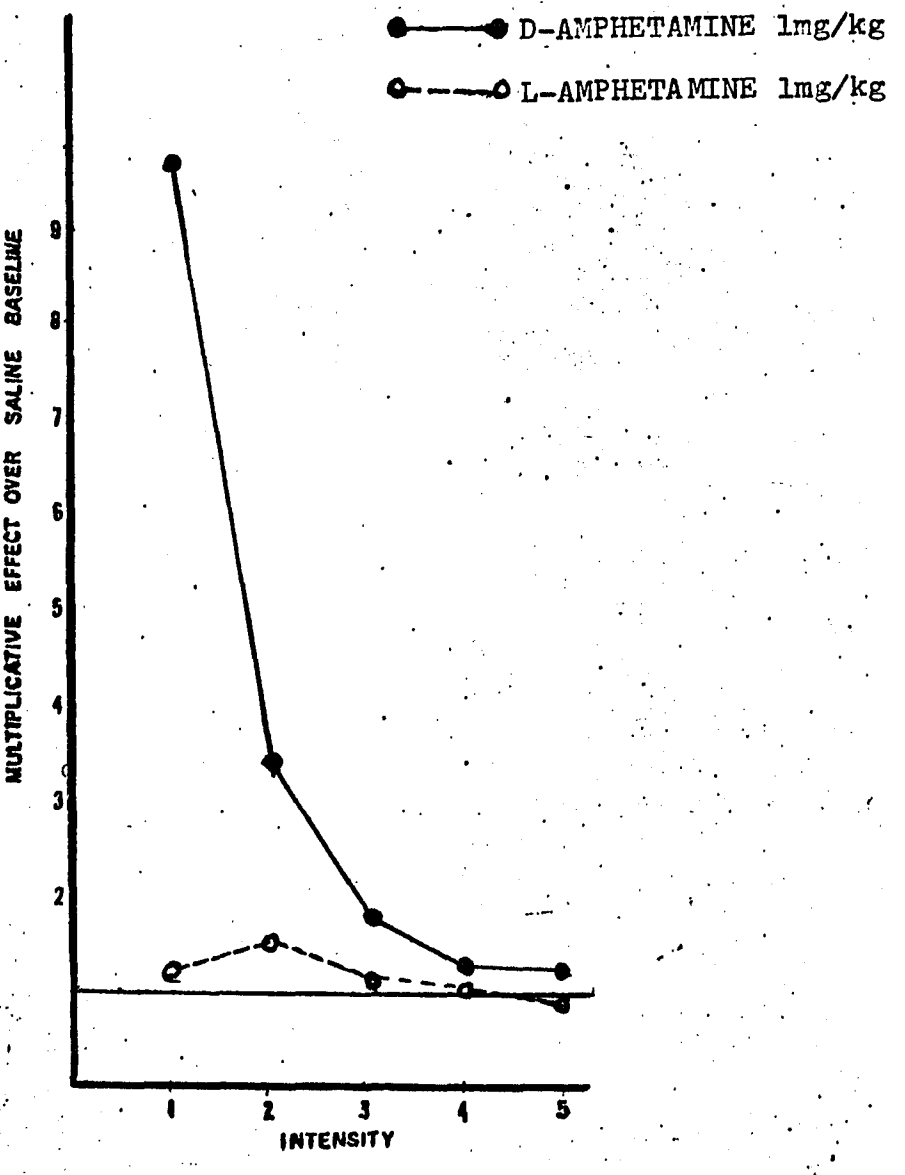


FIGURE 44

VB Group

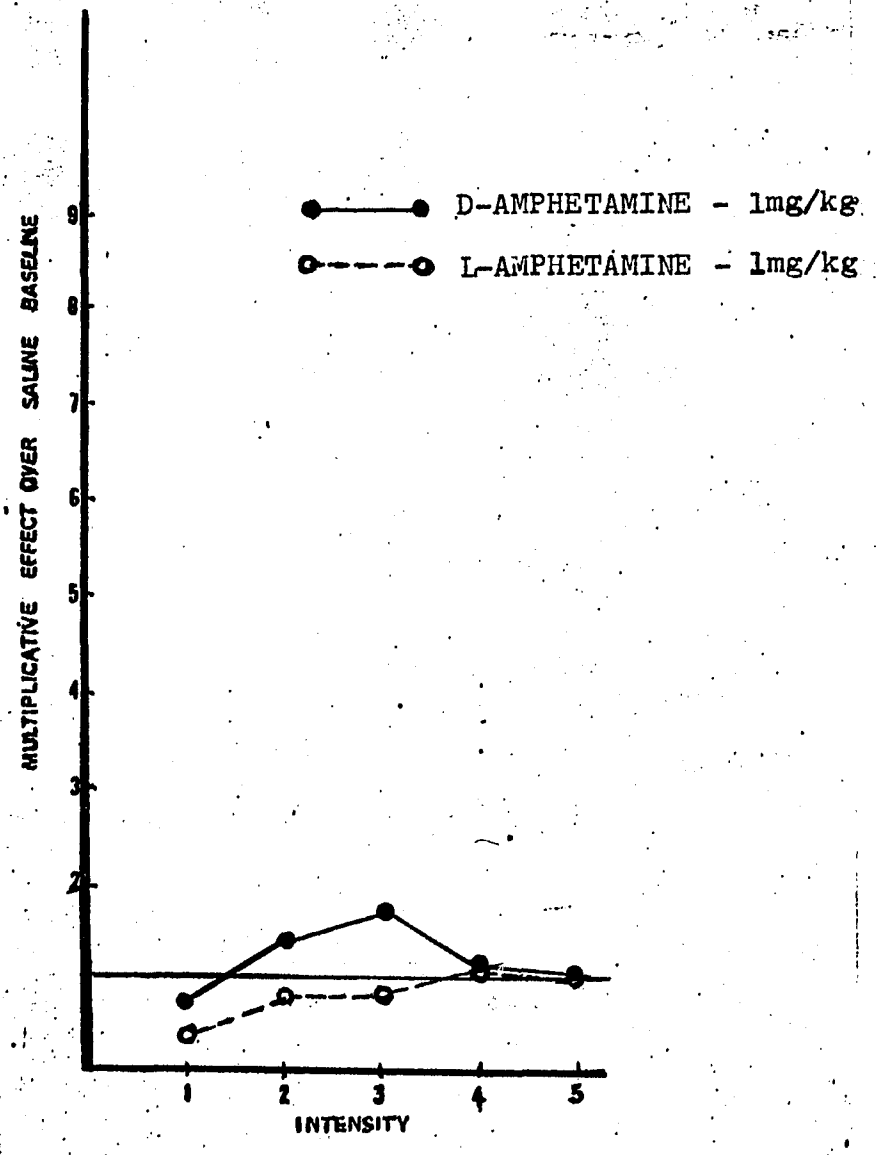


FIGURE 45

NS-DB Group

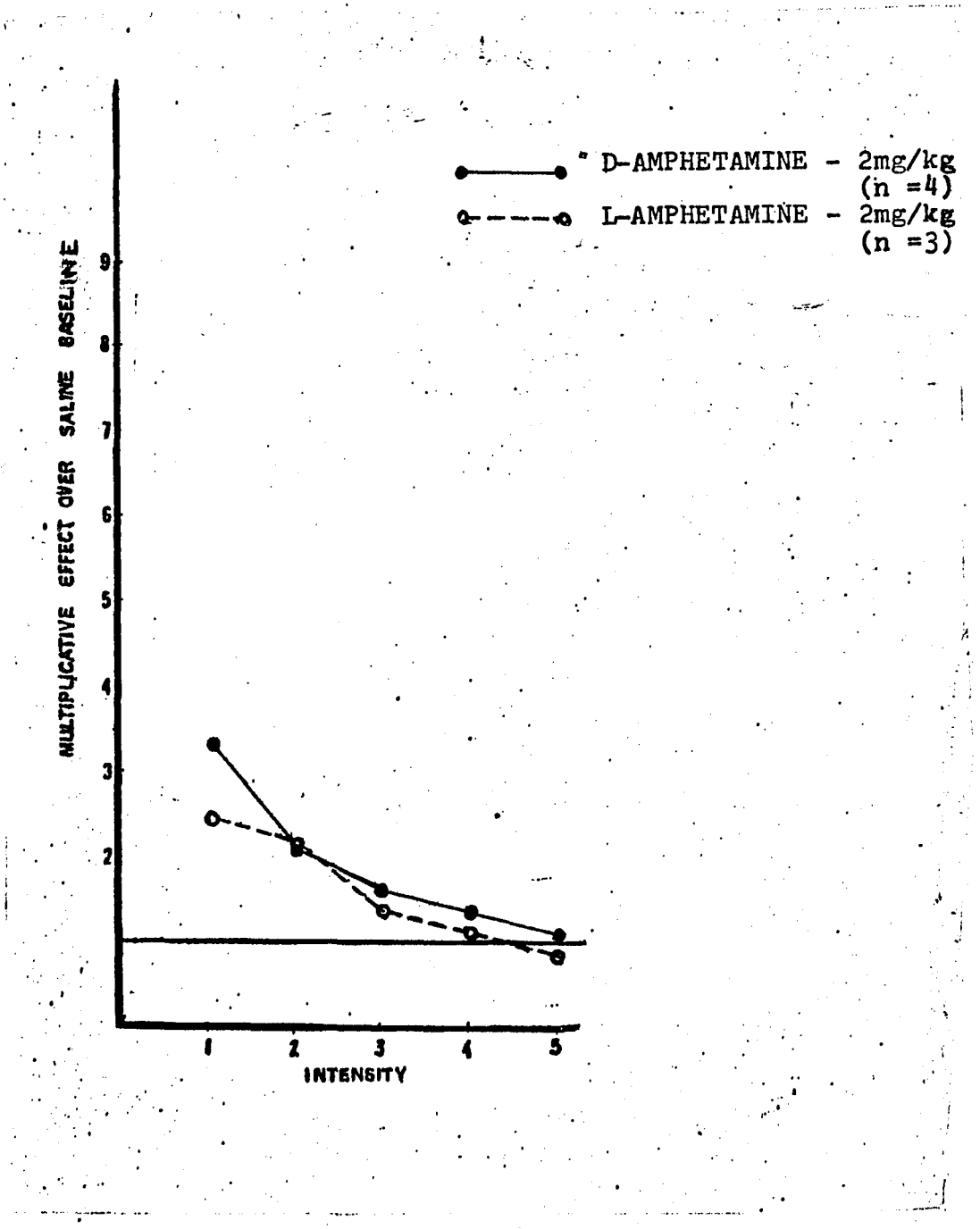


FIGURE 46

VB Group

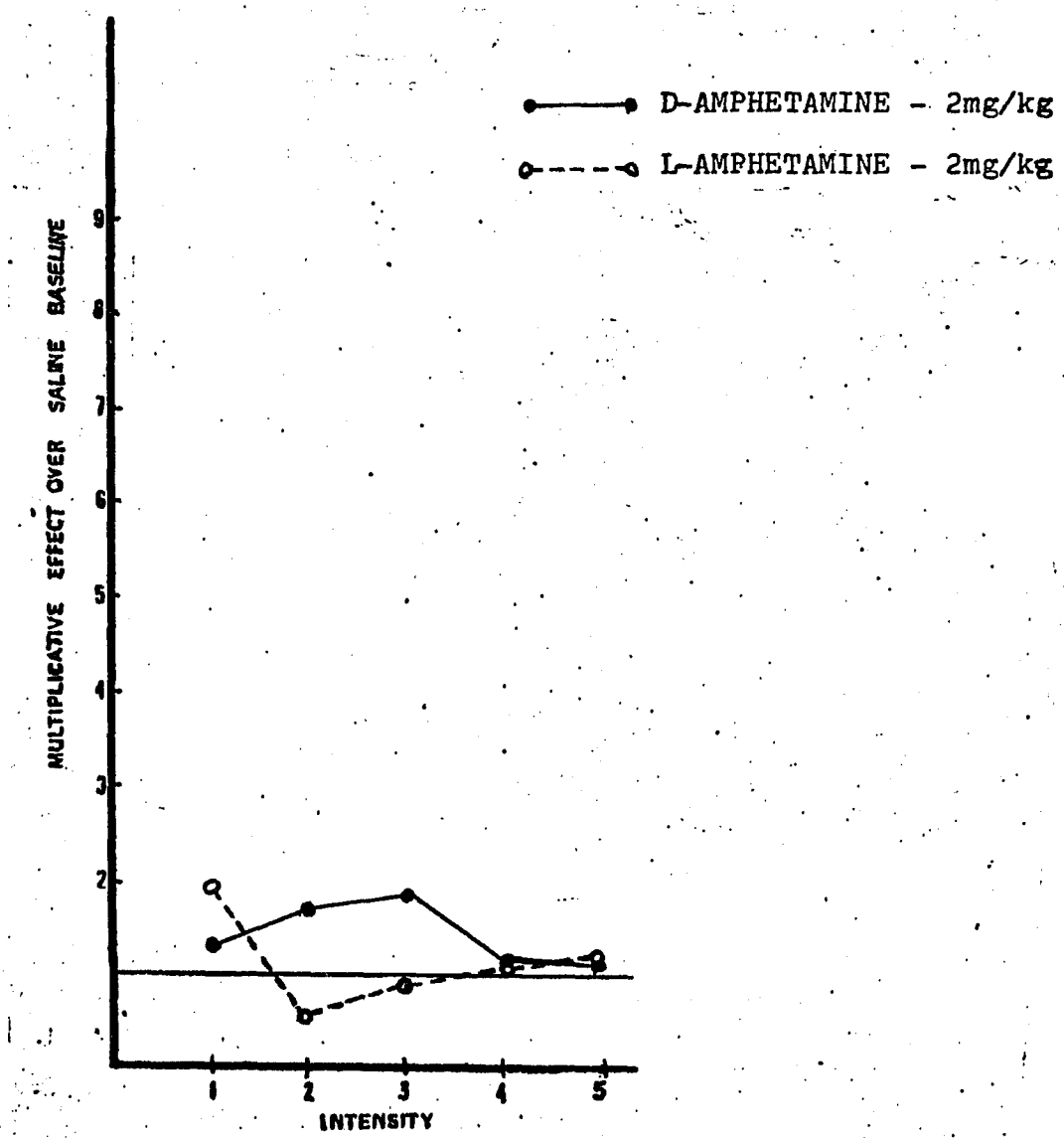
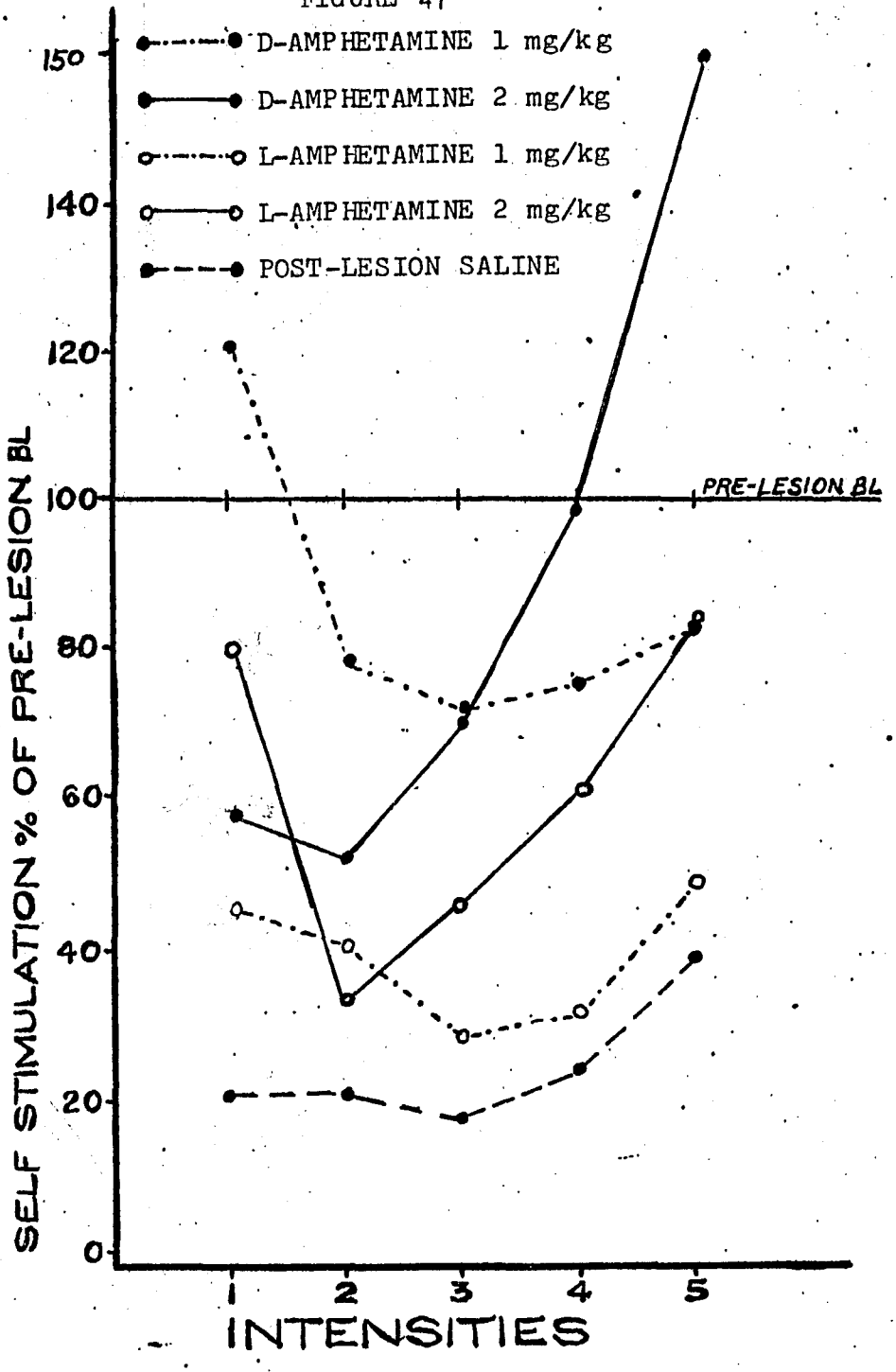


FIGURE 47


D-AMPHETAMINE 1 mg/kg
D-AMPHETAMINE 2 mg/kg
L-AMPHETAMINE 1 mg/kg
L-AMPHETAMINE 2 mg/kg
POST-LESION SALINE
PRE-LESION BL
SELF STIMULATION % OF PRE-LESION BL
150
140
120
100
80
60
40
20
0
1
2
3
4
5
INTENSITIES

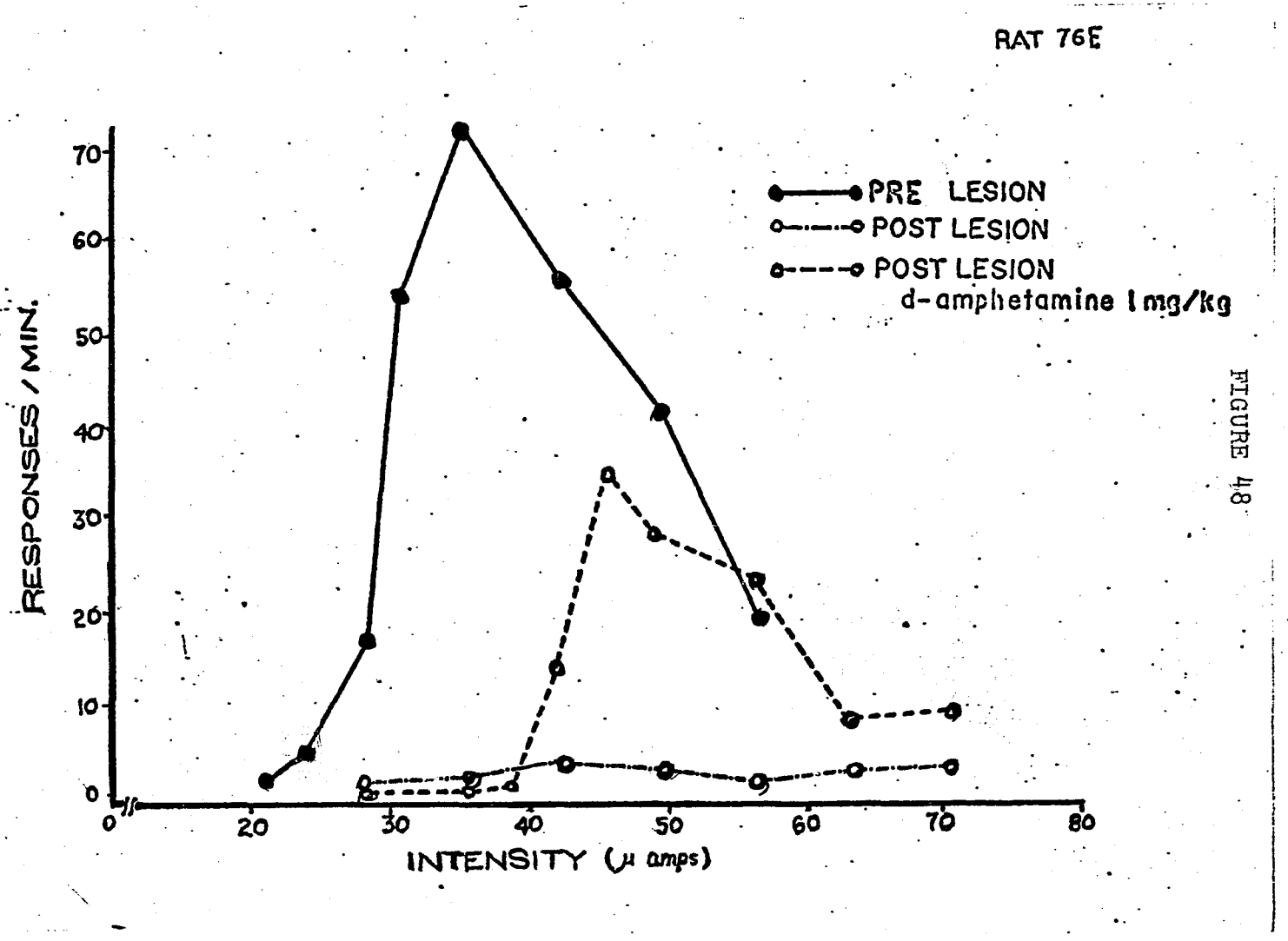
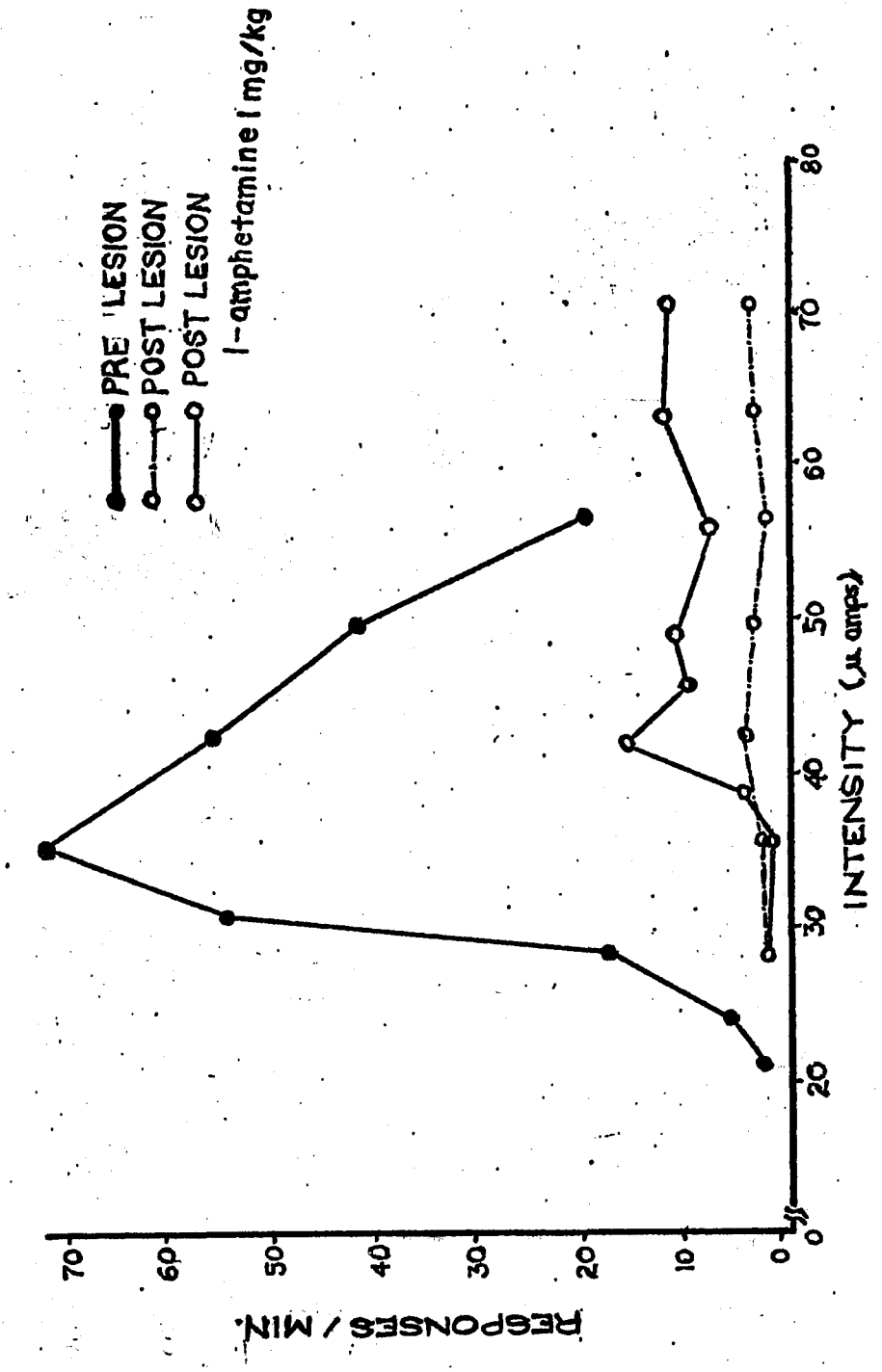

RAT 76E
PRE LESION
POST LESION
POST LESION
d-amphetamine 1 mg/kg
RESPONSES / MIN.
INTENSITY (μ amps)
0
10
20
30
40
50
60
70
80

FIGURE 48

FIGURE 49


PRE LESION
POST LESION
POST LESION
l-amphetamine l mg/kg
RESPONSES / MIN.
INTENSITY (μ amps)
0
10
20
30
40
50
60
70
80

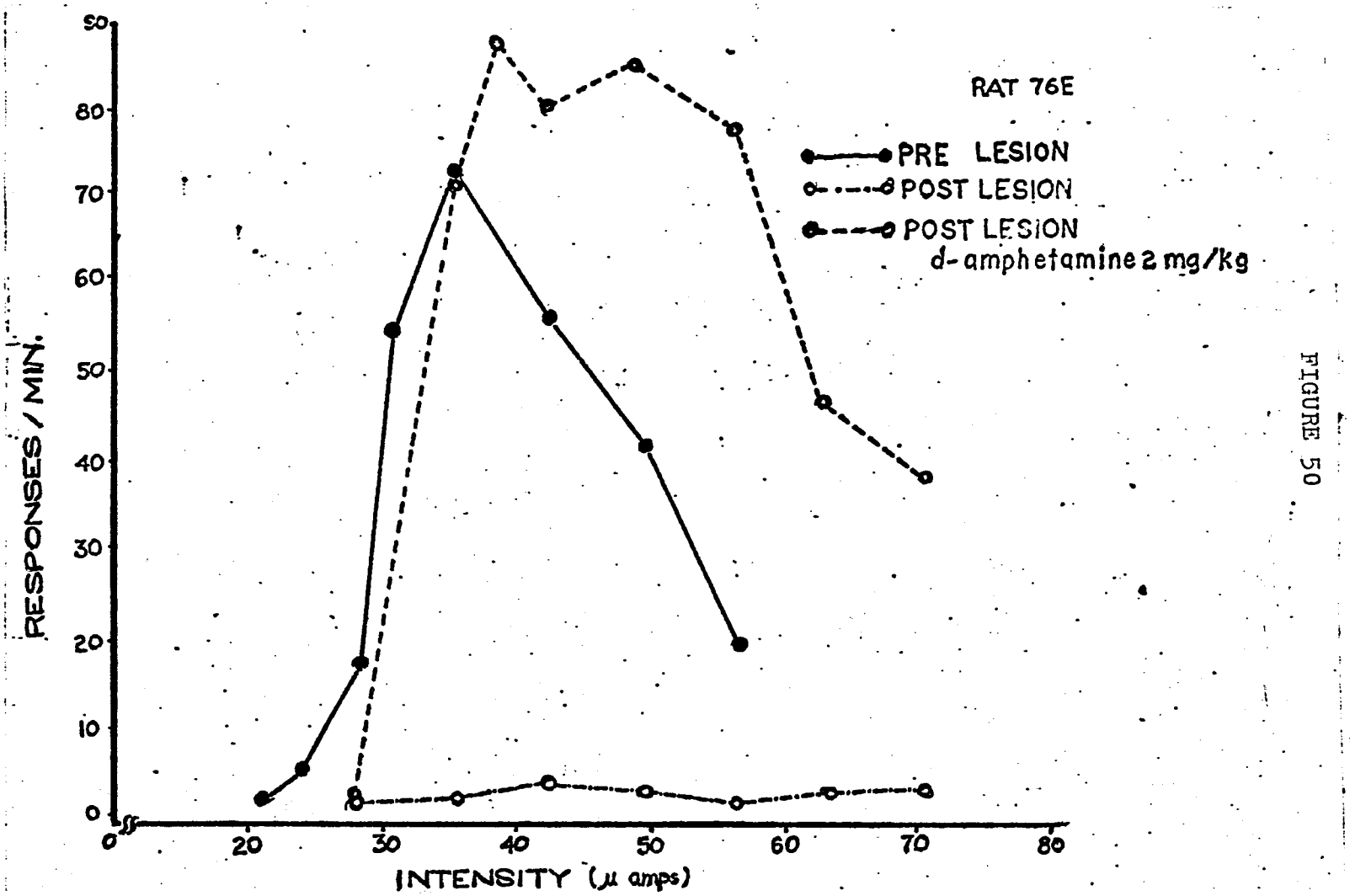

RAT 76E
PRE LESION
POST LESION
POST LESION
d-amphetamine 2 mg/kg
RESPONSES / MIN.
INTENSITY (μ amps)
0
10
20
30
40
50
60
70
80
20
30
40
50
60
70
80

FIGURE 50

FIGURE 51

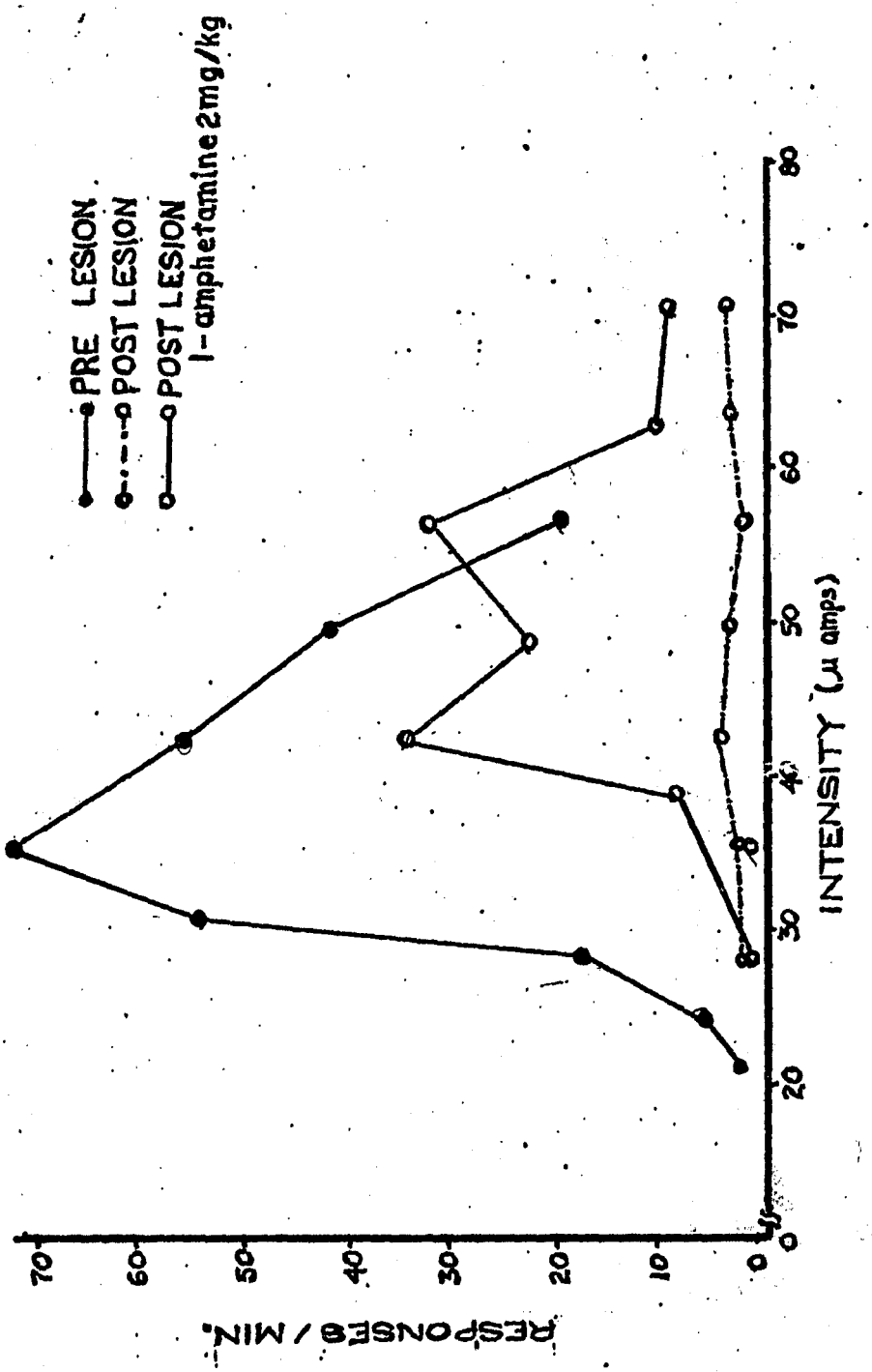

PRE LESION
POST LESION
POST LESION
l-amphetamine 2mg/kg
RESPONSES / MIN.
INTENSITY (μ amps)
0
10
20
30
40
50
60
70
80

FIGURE 52

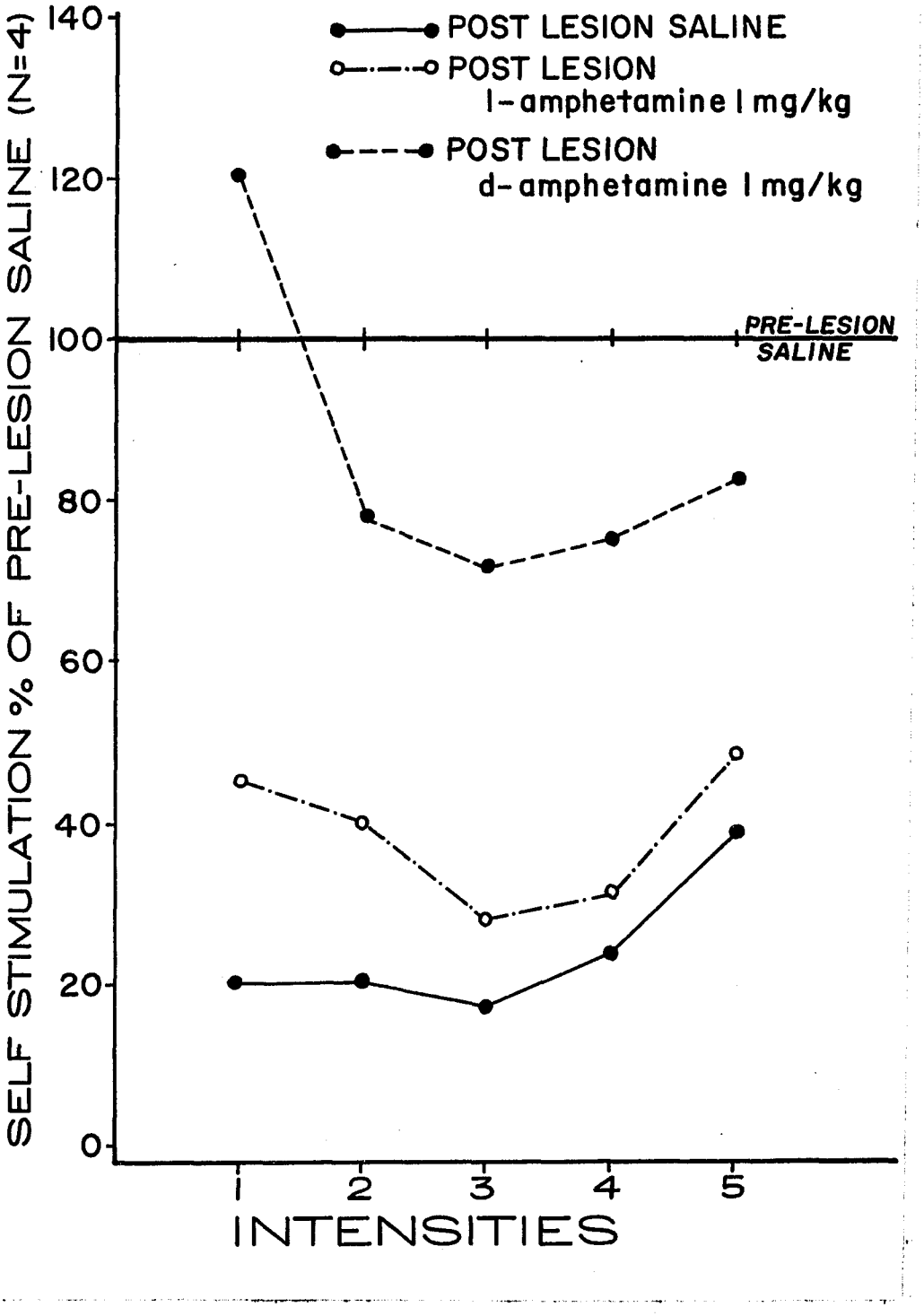

POST LESION SALINE
POST LESION
l-amphetamine l mg/kg
POST LESION
d-amphetamine l mg/kg
PRE-LESION
SALINE
SELF STIMULATION % OF PRE-LESION SALINE (N=4)
140
120
100
80
60
40
20
0
1
2
3
4
5
INTENSITIES

FIGURE 53

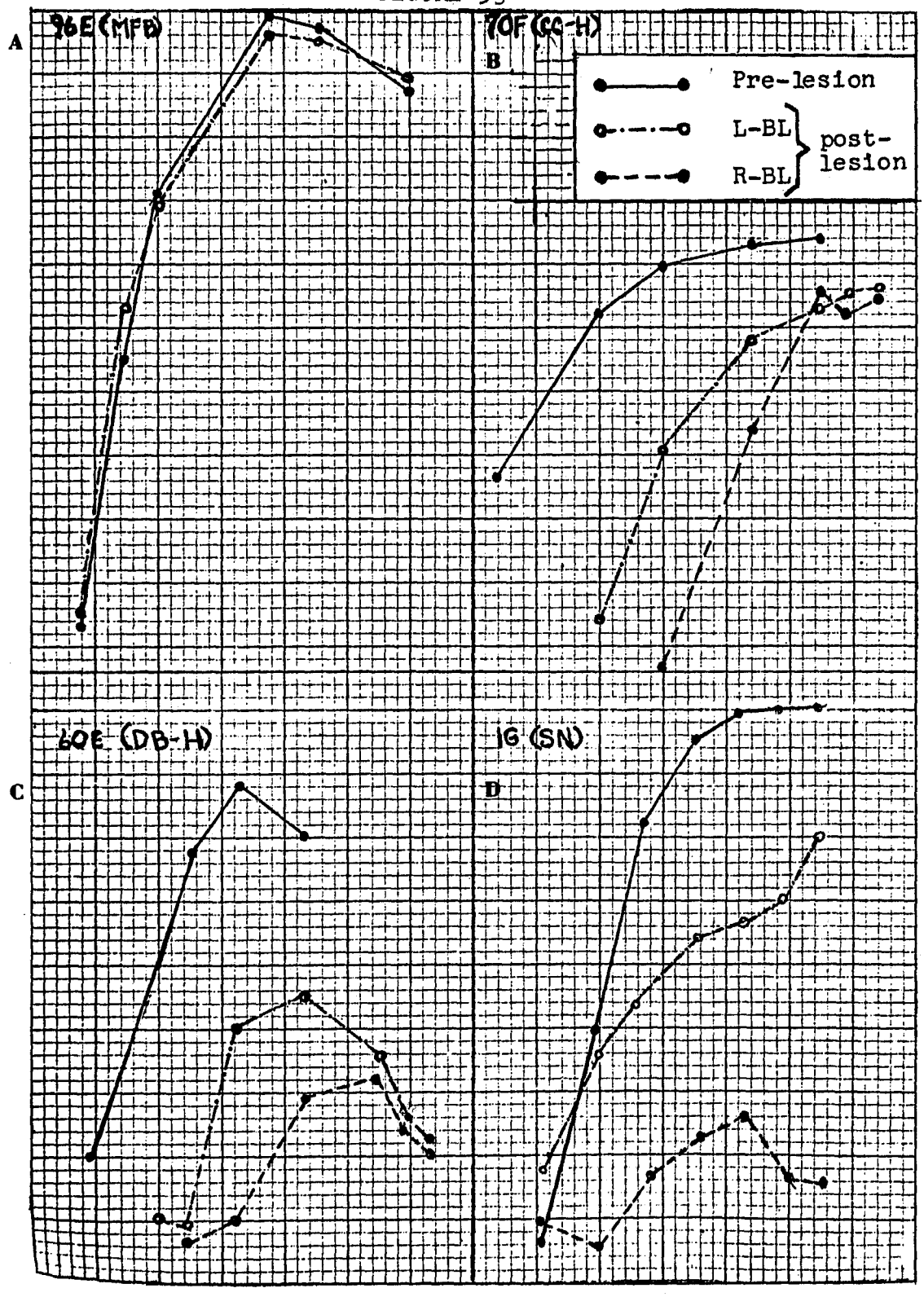
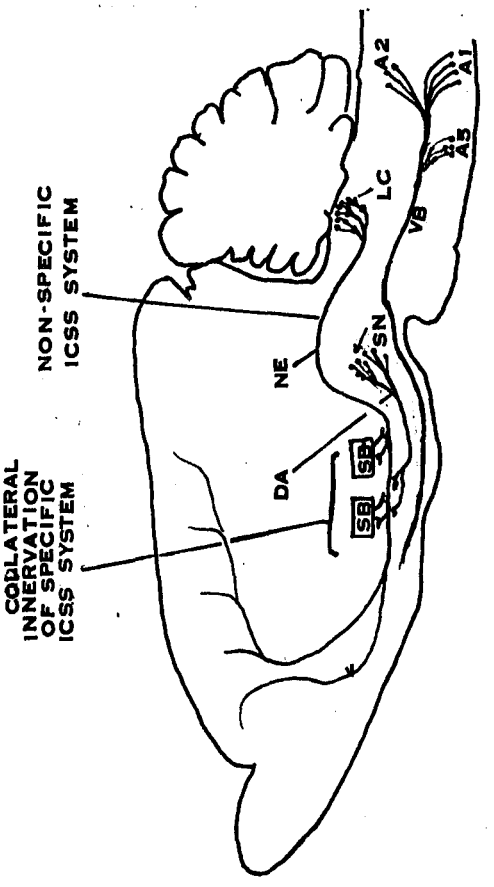

A
96E (MFB)
B
70F (CC-H)
Pre-lesion
L-BL
R-BL
post-lesion
60E (DB-H)
C
IG (SN)
D

FIGURE 54

FIGURE 55


NON-SPECIFIC
ICSS SYSTEM
COLLATERAL
INNERVATION
OF SPECIFIC
ICSS SYSTEM
NE
DA
LC
SN
VB
A2
A1
A5
SB
SB
SB