NEURONAL INTERACTION

IN THE EPILEPTIFORM AFTERDISCHARGE

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ABSTRACT

The work reported in this thesis represents part of a research program aimed at elucidating the mechanism of the epileptiform afterdischarge. The experimental preparation used was the neuronally isolated slab of cat's cerebral cortex. Stabilisation was by means of a rigidly mounted silver trough arranged so as to wholly contain the slab below the intact pia; surface stabilisation was by a matching lid which also carried stimulating and recording electrodes. Recording from single cells was by extracellular microelectrodes arranged so that recordings from two separate points could be made simultaneously. Intracellular recordings were also made on some occasions.

Epileptiform afterdischarges were induced in the slabs by repetitive electrical stimulation at the pial surface. The afterdischarge activity was recorded by the microelectrodes as typically a series of repetitive slow negative potential 'bursts' each with a superimposed train of single cell spikes. Photographic records of large numbers of these burst-spike episodes were examined from both acutely and chronically isolated slabs. Measurements were made from large numbers of individual burst-spike episodes to determine the values of certain characterising parameters. By investigating the dependences of these on time, distance, and other relevant factors, a number of qualitative and quantitative conclusions are drawn from the data obtained in this study.

The individual burst is identified as a gross integration at any moment of all cellularly developed potentials of all forms over a wide region. The associated spikes represent activity in excitable cells immediately adjacent to the microelectrode tip. The probability of spike

firing is the same for all excitable cells affected simultaneously by a burst.

It appears that the effect of stimulation is the establishment of a shell of activity, ideally spherical with the stimulated point as its centre, in which activity is maintained by continuous recirculation between the shell itself and the central region. The shell thus behaves as a focus, and from it at each recirculation a burst spreads out into the remainder of the slab as a continuous wave of activity which may or may not remain coherent. In the acute slab all activity ceases when the focal shell becomes exhausted; but in the chronic slab, perhaps because of looser interneuronal coupling resulting from degeneration, burst activity becomes independent of any single focus and may continue to reverberate for many hours.

It is recommended that further data should be obtained to supplement those already acquired; and it is suggested that profitable extensions of the work might be made along the lines already established, that complementary studies should be made of the intact cortex, and that relevant histological investigations should be undertaken. It is also stressed throughout that there is much need and scope for a parallel theoretical development, and some attempt is made to provide an elementary basis for this.

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CONTENTS

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TABLE OF SYMBOLS

X, Y, Z	Bipolar surface stimulating electrodes in lid.
A, B, C, D	Surface recording electrodes in lid.
V_S	The surface recording channel; or the potential recorded by it.
V_1	The d.c. microelectrode recording channel in parallel with V_F; or the potential recorded by it.
V_2	The d.c. microelectrode recording channel not in parallel with V_F; or the potential recorded by it.
V_F	The high gain high-pass filtered recording channel in parallel with V_1; or the potential recorded by it.
(x_0, y_0, z_0)	Reference coordinates: vernier readings when microelectrode tip is at corner of slab.
(s_p, y_p, z_p)	Probe coordinates: vernier readings before commencing probing by oil drive.
r_1	Horizontal distance anteriorly from stimulated point to tip of microelectrode recording V_1.
r_2	Horizontal distance anteriorly from stimulated point to tip of microelectrode recording V_2.
r_F	Whichever of r_1 or r_2 has the greater scalar value.
r_N	Whichever of r_1 or r_2 has the lesser scalar value.
r	Used for both r_1 and r_2 when distinction is unnecessary.
(r, θ)	Polar coordinates with pole at stimulated point and initial line extending anteriorly.
$\|r\|$	The scalar (absolute) value of r; similarly for r_F, r_N, and Δr.
$\bar{r}$	The scalar mean of r_1 and r_2; given the sign of r_F.
Δr	The scalar difference of r_1 and r_2; given the sign of r_F.
d	The burst-spike delay; measured from beginning of burst to first associated spike.
$\bar{d}$	The distribution mean of d, either overall or within a specified interval of r.

V_{MAX1}	The maximum negative amplitude of V_1 during an epileptiform burst, measured from the local inter-burst potential.
V_{MAX2}	The maximum negative amplitude of V_2 during an epileptiform burst, measured from the local inter-burst potential.
V_{MAX}	Used for both V_{MAX1} and V_{MAX2} when distinction is unnecessary.
$\bar{V}_{MAX}$	The distribution mean of V_{MAX} within a specified interval of r.
δ	The burst burst-delay; measured from the beginning of the burst recorded at r_N to the beginning of the burst recorded at r_F.
$\bar{\delta}$	The distribution mean of δ , either overall or within a specified interval of r.
Δf	Fraction of d values in interval d, $d + \Delta d$.
N	Number of observations in a specified group of data.
σ	Standard deviation.
σ_N	Standard error of the mean.

I. INTRODUCTION

The present work was undertaken in the Department of Pharmacology and Therapeutics of the University of Manitoba, mainly during the academic year 1964-1965. As part of a research program aimed principally at elucidating the fundamental mechanisms of the epileptiform afterdischarge, it was suggested that it would be of interest to determine what, if any, is the relationship between epileptiform burst-spike delay and the distance of the point of recording from the point of the initiating stimulation. It should be noted now that throughout this thesis the word 'spike' is used to denote pulsatile potential changes of the order of one millisecond duration, presumably to be identified with classical action potentials; and the word 'burst' is used to denote those slower changes in potential, of the order of some tens of milliseconds duration, upon which, in microelectrode recordings from the vicinity of a single neurone, the spikes are apparently superimposed. Such bursts evidently correspond to similar potential changes which may be recorded from the cortical surface, the electroencephalographer's 'spikes'.

The most immediate problem which arises is that the mode of generation of the burst itself has never been clearly defined. The 'burst-spike delay', of course, is the time delay, usually a few milliseconds, between the commencement of the burst and the appearance of the first spike. Since the burst and spikes are apparently in some respect interdependent, it was hoped that, by studying this parameter and identifying the factors upon which it may depend, some progress might be made towards determining the mode of generation of the burst.

It was initially hoped to record these epileptiform events intracellularly; but this was for the most part not achieved. However, extracellular recordings proved in most respects quite adequate, and in

terms of results considerably more of interest was found than had been initially anticipated. A number of parameters in addition to the burst-spike delay were analysed, and it is evident that there are still others which might also usefully be studied. Unfortunately, these potentialities did not become apparent until the experimental acquisition of data was practically completed; and some of the data are not well balanced for statistical analysis of parameters other than the burst-spike delay. Nevertheless, much useful information has emerged, and the indications for further study, particularly if a computer can be used for analysis as is hoped, are extensive. The potential application of this progress to the clinical problem of epilepsy is self-evident; and it seems by no means improbable that some further concept of the workings of the normal cortex may also be forthcoming.

II. REVIEW OF PREVIOUS WORK

1. INTRODUCTION

In a recent review of research into epilepsy, Ajmone-Marsan and Abraham (1963) have estimated that the current rate of publication of papers on this topic is equivalent to one every day; and they have suggested that this rate is really a manifestation of continued frustration in attempting to discover the basic epileptogenic mechanism. The present review is not so much historical as an attempt to outline the current state of knowledge, especially in so far as it pertains to the work recorded in this thesis; no particular attempt has been made to present material in chronological order of publication, for it was felt that in view of the immense volume of published work available, and the consequent unequal development of different aspects of the subject, to do so would inevitably result in loss of clarity. For the same reasons, the published work herein referred to represents what it is hoped may be an adequate sample of the whole, but certainly no attempt has been made to be comprehensive. Furthermore, a comprehensive historical review covering much of the same material has recently been written in this department by Reiffenstein (1964).

Experimental epileptic seizures may be produced (Ajmone-Marsan and Abraham, 1963) by direct stimulation of the cerebral cortex by means of electric current, local freezing, or locally applied drugs (such as strychnine, eserine, alumina, or penicillin), or by systemically applied drugs (convulsants). Evidently all of these means but the latter may be expected to produce that type of seizure known as 'focal'. The designation 'idiopathic', applied to clinical epileptic cases in which no origin can be found for the condition other than presumed genetic, is becoming progressively less applicable as it is realised that a wide range of aetiological

factors, biochemical and metabolic as well as physical, may contribute to the establishment of functional epileptic foci. Ajmone-Marsan and Abraham (1963) have suggested that research into seizure mechanisms may be divided into two categories, firstly studies of intrinsic local factors such as the relation of slow electrical potential changes in the cerebral cortex to the activity of single cortical neurones, and secondly studies of indirect factors such as the influence of other parts of the central nervous system. The present work falls clearly into the first of these two categories.

The particular manifestation of convulsive activity which is studied in the present work is the electrically recorded response of the cerebral cortex to repetitive electrical stimulation, the epileptiform afterdischarge. The basic characteristics and possible modes of generation of this response have been extensively studied by Burns (1958). Burns (1949, 1950) and, independently, Kristiansen and Courtois (1949) have described a method for the neuronal isolation of a slab of cerebral cortex while still retaining its nutritive blood supply intact. This method, a slight modification of which has been used in the present work, allows study of intrinsic cerebral cortical mechanisms without the confusion of effects caused by interaction between the cortex and lower centres. The epileptiform afterdischarges which may be elicited in such a slab shortly following its isolation appear virtually identical to those which may be elicited in normal intact cortex. However, much interest has centred on the finding that, in slabs which have been isolated for several weeks or months, afterdischarges once initiated may last for many minutes or even hours, instead of the 'normal' duration which is only a matter of seconds. Grafstein and Sastry (1957) and Sharpless and Halpern (1962) have followed the progress of this change from 'acute' to 'chronic' response, the latter by means of permanently implated electrodes. Spontaneous electrical

activity may be recorded from the chronic slab as little as two weeks after its isolation, as compared with the acute slab which is generally considered to be electrically silent (Burns, 1958). The slab develops decreased threshold for initiation of epileptiform afterdischarges, and the mean afterdischarge duration increases, over roughly the same period. A number of investigators (Echlin, 1959; Sharpless and Halpern, 1962; and Reiffenstein, 1964) have suggested that these characteristics of chronic isolation may be due to the development of denervation supersensitivity to chemical mediators; Sharpless and Halpern pointed out that the time taken for their appearance is approximately the same as that required for the development of denervation supersensitivity in peripheral structures. Clinical epilepsy might thus be expected to result from functional denervation of some part of the brain due to growth of scar tissue or a tumour.

An important byproduct of work on such evoked responses as the epileptiform afterdischarge is knowledge which may be acquired concerning the structure and function of the normal brain. Indeed, such knowledge must ultimately be of far more significance than that concerned specifically with the origin and treatment of epilepsy; and in fact it seems doubtful whether the latter can ever be fully comprehensive in the absence of the former. It has been frequently pointed out (e.g., Burns, 1958) that procedures such as direct electrical stimulation of the cortex must cause many cells to fire together which would never do so in the course of normal function; nevertheless, from any response it should be possible to draw at least some conclusions regarding the structure producing it, and this should be so even if the structure itself has been interfered with, providing that the nature of the interference is known. However, most published descriptions of experimental investigations of cortical physiology do not concern themselves more than incidentally with the implications of their work in this direction.

There seems, in fact, to be a fairly wide dichotomy between publications dealing primarily with specific investigations of the various evoked responses of the cortex and those dealing with the properties of the cortex as a whole. The former are largely concerned in their interpretations with effects that might be expected to arise at the level of the single cell, or as a result of interaction between large numbers of cells while still reflecting the properties of the single cell; in short, their interpretations are largely within the bounds of classical neurophysiology. Papers of the latter type, on the other hand, are often not written by physiologists at all, but by physical scientists who see in the immense number of interconnecting neurones which comprise the cortex a system which should in some way be amenable to statistical analysis. The remainder of this review is occupied for the most part in summarising knowledge which has been acquired by investigators using one or other of these two separate approaches.

Attempts to integrate these two approaches have been rather few and far between. One of the most notable experimental contributions has been the histological work of Sholl (1956); and a good statement of some of the problems involved, both the direct problems and the underlying 'mind-brain' problem, has been provided by Eccles (1953); these contributions also will be further discussed in the pages that follow. If the present work can lay any real claim to originality, it is perhaps chiefly that, while the initial intention was to remain well within the bounds of the 'single cell' approach, some of the conclusions finally drawn suggest that the 'statistical' approach, and, more important, the truly integrated approach, may also usefully be brought within the bounds of experimental physiology.

2. THE STRUCTURAL BASIS FOR CORTICAL ACTIVITY

The histology of the cerebral cortex has been widely studied, and many of the anatomical features of 'typical' individual neurones are well known. Sholl (1956) has suggested that there are really only two basic neurone types in the cortex, stellate cells and pyramidal cells. The former are most concentrated in regions concerned with the reception of impulses from sensory receptors; and it is the latter which have been most generally implicated in the genesis of evoked responses, including the epileptiform afterdischarge. The most prominent pyramidal cells have large somata in layer V from which their axons and basal dendrites project towards the underlying white matter, and their apical dendrites as branching trees towards the cortical surface.

The so-called 'neurone doctrine', the fundamental thesis of which is that the neurone is the basic structural unit of the nervous system, has, as Bullock (1959) has pointed out, come to be understood as implying that the neurone is also the basic functional unit. The time has come, Bullock suggests, when this implication must be to some extent revised. Thus there is much evidence that the axonal membrane, including probably the membrane of the axon hillock, is specialised in a manner not shared by the somatic and dendritic membranes, and that only in the axonal membrane can a regenerative action potential be established (see also Clare and Bishop, 1955; Eccles, 1957; and Grundfest, 1958). Conduction in the soma and dendrites must therefore be decremental, and this means that labile and integrative processes are not restricted to synapses as would be the case if a possible outcome of all synaptic activity were the immediate establishment in the vicinity of the synapse of a regenerative action potential.

Considerable interest has centred particularly on the role of the apical dendrites both in normal cortical function and in the genesis of

artificially evoked responses. A large area of the membrane of the apical dendritic tree is occupied by the receptor sites of axo-dendritic synapses; indeed, it has been suggested that this may be one reason why the dendritic membrane differs in behaviour from the axonal membrane (Eccles, 1957, 1964). Afferent activity in the axons may thus be expected to establish transient potential differences across the dendritic membrane at one or many sites. The manner in which such potential differences might be expected to spread by decremental conduction throughout the branching tree and to the soma has been worked out mathematically by Rall (1962, 1964), and, using Rall's calculations as a basis, has been studied in a model by Sances and Larson (1965). The basic conclusion is that transient potential differences established in the dendrites, presumably more or less pulsatile in the immediate vicinity of their synaptic origins, will become diffuse and attenuated in the course of conduction to the soma, and will combine with similar potential differences from throughout the dendritic tree to produce only slowly varying modifications of the somatic membrane potential.

Experimentally, this same general conclusion has been reached by a number of investigators. Clare and Bishop (1955) suggested that synaptic activity in the dendritic tree may result in either facilitation or inhibition, depending on the induced polarity, of activity induced in the soma by axo-somatic synapses. Bishop (1958) went on to point out that the output of one neurone is thus influenced by the integrated activity of the many other neurones whose axons form synapses with its soma and dendritic tree; and thus the single neurone is a fundamental unit of cortical integration. Similar conclusions have been reached by Chang (1959), Andersson (1965), and Wall (1965); and the latter two investigators have recorded small spike-like potentials which they have identified as individual excitatory postsynaptic potentials appearing in the dendrites. Gloor *et al.* (1961) have

implicated a similar transmission of activity via dendrites to somata in the genesis of epileptic discharges in the hippocampus. Pinsky (1965) has suggested that decrementally conducted potentials in the dendrites may still be of sufficient amplitude on reaching the soma to themselves initiate action potentials without any need for additional axo-somatic synaptic activity. Fox and O'Brien (1965), with the aid of a computer, have shown that the probability of firing of a single cell following sensory stimulation corresponds closely to the average potential recorded at the same point following the same stimulation but after destruction of the cell which had been firing. They suggest that this average potential, which thus evidently controls the probability of firing, might be a summation of electrotonically conducted somatic and dendritic postsynaptic potentials; though it might also be merely a summation of discharge potentials from other cells in the vicinity.

Investigations of the relationship between single cell activity and the electroencephalogram (EEG) recorded at the cortical surface have produced contradictory results. A number of investigators have reported finding no relationship at all (e.g., Mountcastle et al., 1957). However, Enomoto and Ajmone-Marsan (1959), Verzeano and Negishi (1960), Goldensohn and Purpura (1963), Fromm and Bond (1964), and others have all recorded increased single cell firing during surface positive EEG waves, and vice versa. This suggests that cells fire most readily when their deeper parts are depolarised and their superficial parts polarised, i.e., as might be expected, when their somata are depolarised and their apical dendrites are not. Fromm and Bond suggested that dendritic depolarisation, corresponding to negative EEG waves may actually inhibit cell firing. Brazier (1955) pointed out that the periodicity of EEG waves is of the order that might be expected from dendritic conduction times. Clare and Bishop (1955) and

Schmidt et al. (1959) likewise suggest that the EEG probably results from dendritic activity. Klee et al. (1965) have used cross-correlation analysis to show a close correlation between EEG waves and slow changes in single cell membrane potentials; they suggest that EEG waves reflect integration of membrane potential changes in both dendrites and somata.

A corollary of these concepts centring on decremental dendritic conduction is the possibility that differential depolarisation within a single neurone might result in repetitive firing of that neurone and thus provide a basis for seizure discharges. An action potential induced in the axon hillock region of the soma would be expected to cause antidromic decremental conduction in the dendrites; the resulting dendritic depolarisation would persist after the soma membrane potential had recovered, and under the influence of the dendrites the soma would again be depolarised to generate a further action potential. A mechanism of this type was proposed by Burns (1958), and studies of radial cortical potential gradients have given support to the theory (e.g., Burns, 1958; Pinsky, 1961; and O'Leary and Goldring, 1964). Ward (1961) observed that the same effects would result if the dendrites became permanently depolarised as a result of some abnormality such as deformation by astrocytic gliosis; anatomical evidence is consistent with this possibility. More recently, Atkinson and Ward (1964) have suggested that this depolarisation may extend to the soma as well as the dendrites, with the resulting repetitive activity restricted entirely to the axon. A somewhat different possibility, while still retaining the same capacity for repetitive discharge within a single neurone, is that axonal collaterals may form synapses with the dendritic tree of their own neurone; decremental conduction in the dendrites would provide the time delay necessary for recovery of the axonal membrane following each circulation of activity (Chang, 1959; Beritoff, 1965).

The present discussion has thus far been restricted to consideration of the structure of a single cortical neurone and the manner in which activity might be expected to occur in such a neurone. It is necessary also to consider briefly the manner in which such neurones interact.

Sholl (1956), from his histological studies, has related dendritic density, in terms of the number of dendrites crossing unit surface area, to distance from the soma; in general this dependence is an inverse exponential. Uttley (1955), assuming random axon growth and that if an axon and dendrite approach within a certain cortical distance a functional synapse results, has used Sholl's results to calculate the mean number of synapses to be expected between specified axonal and dendritic systems. It is possible that, in chronically isolated cortical slabs, this 'connectivity' may be greatly increased as a result of collateral sprouting from intact axons in the vicinity of degenerating neuronal structures (Sharpless, 1964). Mountcastle *et al.* (1957) found that the potential field developed around an active cell extends with significant magnitude through a sphere of more than a hundred microns diameter; they suggest that in view of the known proximity of neighbouring cells ephaptic interaction may be possible. Such interaction has been shown to occur between immediately adjacent axons (*e.g.*, Rosenblueth, 1941; and Renshaw and Therman, 1941), although Burns (1958) has estimated that potentials more than ten times those considered physiologically normal would be necessary for it to occur in the cortex. In any event, there seem to be very adequate grounds for the frequently made assertion (*e.g.*, Lashley, 1952) that every cortical cell must be indirectly connected to every other cortical cell; and that activity in any one cell may therefore be expected to influence activity in at least a very large number of other cells. This evidently provides the basis for a 'divergent' aspect of cortical

integration. There also appears to be a simple structural basis for the possibility that activity once initiated may recirculate indefinitely along so-called 'reverberating' or'self re-exciting' neuronal chains. Burns (1953) has suggested that, in view of the experimental observation (Sperry, 1947) that multiple incisions in the cortical grey matter have no evident effect on learned responses or behaviour, the only reasonable conclusion is that all intracortical pathways are duplicated by extracortical (cortico-cortical) association pathways. This does not seem entirely satisfactory; however, the matter will not be further discussed herein.

3. THE GENERATION AND TRANSMISSION OF CORTICAL ACTIVITY

General discussions of evoked cortical potentials have been provided by Bremer (1958), Burns (1958), Chang (1959), and O'Leary and Goldring (1964). On the basis of Burns' (1949, 1950) observation that a neuronally isolated slab of cerebral cortex is electrically silent, it may be argued that all cortical potentials are in fact evoked potentials. Cortical potentials may be recorded either grossly from the surface as in an EEG, or by means of a microelectrode from the vicinity of a single cell. The only sure way to record exclusively from one cell is to have the microelectrode tip inside the cell; however, much can be gained from recordings in which the microelectrode remains extracellular, and, apart from the lesser technical difficulties involved, the cell itself remains undamaged. Recordings made with surface electrodes show only slow variations in potential, of the order of tens or even hundreds of milliseconds; while microelectrode recordings show slow variations too, and also spikes which are presumably action potentials. It was mentioned in the previous subsection that some correlation has been noted between surface positive EEG waves and increased firing of single neurones. However, the primary purpose of the previous subsection was to define those modes of activity which appear potentially possible in the light of known anatomy; whereas the intention here is to consider the physiology of activity patterns which actually occur.

In general, slow potentials recorded through microelectrodes from the vicinity of single cells have been identified with postsynaptic potentials. Eccles (1953) pointed out that the durations of slow cortical potentials were often of the same order of magnitude as those of known postsynaptic potentials recorded from spinal motoneurones; and Grundfest (1958) has reported pharmacological confirmation of this identity.

Gloor et al.(1963) have attempted detailed identification of the various components of composite postsynaptic potentials observed in hippocampal neurones as a result of afferent volleys. Purpura and McMurtry (1965), in investigating the effect of applied polarisation at the cortical surface on single cell activity, found changes in presumed postsynaptic potentials which might be attributed both to the expected direct effect on the postsynaptic membrane and also to polarisation of the presynaptic terminals. Klee and Offenloch (1964) and Nacimiento et al.(1964) have recorded two depolarising shifts, one following closely after the other, in cortical neurones following electrical stimulation of thalamic nuclei. They suggest that the second of these shifts results from axo-dendritic synaptic activity more remote from the soma, where the shifts are presumed to be recorded, than that causing the first; though Klee and Offenloch point out that a similar double shift would result from separate 'fast' and 'slow' thalamo-cortical pathways.

In addition to the two depolarising shifts, which they identify as excitatory postsynaptic potentials, Nacimiento et al also observed at low frequencies of stimulation a subsequent hyperpolarisation which they consider to be an inhibitory postsynaptic potential. Similar observations have recently been made by Andersson (1965). Identification of such hyperpolarisations as inhibitory postsynaptic potentials has in fact been fairly common, especially in work on induced epileptiform afterdischarges; and such work has also provided occasion for studies on the relation of slow potential shifts to action potentials. Goldensohn and Purpura (1963), using epileptogenic lesions produced by local freezing, found that membrane hyperpolarisation was invariably accompanied by inhibition of action potential firing, whereas depolarisation might or might not potentiate such firing; they suggest that these effects result from a combination of

excitatory and inhibitory potentials. Atkinson and Ward (1964) on the other hand, studying chronic alumina-induced epileptogenic foci, found that the excitatory postsynaptic potentials recorded in normal cortex were abolished, though action potential spikes continued to occur. As mentioned in the previous subsection, they interpret this to mean that the neurone somata are permanently depolarised, perhaps due to loss of inhibitory afferents, so that activity is restricted entirely to the axons. Sawa et al.(1963) likewise relate the prolongation of afterdischarges in strychninised cortex to interference by the strychnine with inhibitory synapses.

Ralston (1958) investigated the manner in which interictal epileptiform activity in the vicinity of chronic penicillin-induced foci may develop into ictal discharges. He concluded that randomly occurring interictal epileptiform bursts do not merely become themselves coordinated into an ictal discharge, but rather that they in some way facilitate the development of such a discharge. More recently, Matsumoto and Ajmone-Marsan (1964a, 1964b) have used intracellular microelectrodes to study both interictal and ictal events in penicillin-induced foci. They refer to the individual epileptiform bursts as 'paroxysmal depolarisation shifts (PDS)', on which may or may not be superimposed individual action potentials. The interictal PDS is often followed by a hyperpolarisation, and initiation of an ictal discharge is characterised by shortening and disappearance of this hyperpolarisation and increased frequency and change of shape of the PDS. The membrane potential finally appears merely to oscillate, the amplitude of the oscillations being more or less proportional to the amplitude of a prolonged depolarisation on which they are superimposed; the amplitude of the oscillations may also be increased by applied electrical stimulation which is presumed to activate both inhibitory and excitatory synapses. Termination of an ictal discharge is apparently the result

of excessively long depolarisations developing between the oscillations; eventually the oscillations become indistinguishable from interictal PDS. Not all cells show the same activity during the course of these events, however. Some cells do not appear to take part in the ictal discharge at all, and may either remain passive or continue to undergo PDS of interictal type. While acknowledging that PDS and hyperpolarisations may correspond at least in part to excitatory and inhibitory postsynaptic potentials respectively, Matsumoto and Ajmone-Marsan do not commit themselves on this identity. Action potentials may be recorded in the absence of any apparent PDS; and the PDS themselves vary in shape over a wide range. The change in shape which occurs during an ictal discharge in the PDS recorded extracellularly is related by Matsumoto and Ajmone-Marsan (1964c) either to a transitory failure of activity to invade some part of the neuronal membrane or to a transitory neuronal swelling. Matsumoto (1964) suggests that the PDS may even be an independent all-or-none phenomenon arising as a result of some fundamental modification of membrane properties in epileptogenic cells.

Pinsky and Burns (1962) have investigated the conditions necessary for initiation of an epileptiform afterdischarge in an isolated cortical slab by repetitive electrical stimulation in the absence of any pre-existing focus. They have found that a critical minimum number of neurones, at a critical minimum neuronal density, must be put through a critical minimum number of driven responses; this results in a critical minimum level of 'exhaustion', and the afterdischarge apparently commences during recovery. On the basis of these findings, Pinsky and Burns have developed a mathematical expression for the duration of such afterdischarges. Segal and Leclercq (1965) have demonstrated that centres highly susceptible to the initiation of afterdischarges by

electrical stimulation occur in regions where the convolutions of gyri and sulci result in a high degree of cortical folding. They relate this fact to the increased neuronal density, especially of large pyramidal cells, which is histologically shown to accompany such folding.

Concerning the manner in which electrical activity, once initiated, is transmitted through the cortex, it has already been mentioned that the structural basis exists for neuronal chains and perhaps for ephaptic transmission; and there seems also some reason to suppose that neurones which are near neighbours may have a tendency to be in the same polarisation state at any one time (Cragg and Temperley, 1954; and see following subsection). The concept of neuronal chains is of course particularly obvious, and the idea that activity may recirculate in such chains has been frequently invoked as an explanation for various forms of repetitive or retained cortical activity (e.g., Lashley, 1952; Eccles, 1953; Burns, 1958; and Chang, 1959). The precise form which such self re-exciting neuronal chains must take has not in general been agreed upon. Hebb (1949) suggested that repeated use of a particular neuronal pathway might in some way cause that pathway to become more efficient for the use concerned; while continuing disuse would result in a lessening of efficiency. Beurle (1956; and see following subsection) applied the same concept to his theoretical approach. Eccles (1953) suggested the experimentally established phenomenon of post-tetanic potentiation as a possible basis for such an effect. It is evident, however, that any effect of this type would favour the establishment of precise neuronal pathways to which activity of any particular form, repetitive in the case of closed pathways, would be restricted; and there is much evidence that this is not the case. Thus Smith and Smith (1964), in analysing records of spontaneous single cell firing in the cortex, have found that action potential spikes occur in bursts of random frequency and

duration within which the frequency of the spikes themselves is also random. Applied stimulation changes the frequency of the bursts but does not affect that of the spikes within the bursts; whereas if the spike activity resulted from recirculation of activity in closed chains, it might be expected that local polarisation due to stimulation would alter the cell excitation threshold and change the firing frequency. With regard to the epileptiform afterdischarge, Burns (1958) has pointed out that a single applied shock of sufficient strength to excite all available neurones simultaneously should abolish an afterdischarge it it were due to activity in closed chains; and this does not occur.

A more satisfactory concept of the manner in which activity may appear to recirculate is perhaps provided by postulating simply that it may 'reverberate' without any implication that it necessarily does so in 'reverberating chains'. Verzeano and Negishi (1960), while acknowledging that a regularly repeating EEG pattern must result from regularly repeating activity of some sort, have pointed out also that activity which appears at a series of recording electrodes in a particular order on one occasion may subsequently appear in different and apparently quite unrelated orders. Burns and Smith (1962) found that repetitive stimulation at any one point in the cortex would modify to a greater or lesser extent the post-stimulus histogram of cells at any other point; and that the same effect resulted from physiological sensory stimulation. They suggest that activity in the normal brain is in the form of complex spatial and temporal patterns, modifiable by stimulation, and distinguishable from 'background' spontaneous activity only because of the very large number of neurones involved in each pattern. This is evidently similar to Lashley's (1958) concept of 'trace systems' and to other theoretical approaches to be summarised in the subsection following. Stefanis and

Jasper (1964) and Andersson (1965) suggest that cortical inhibition, possibly in the case of pyramidal cells by their own recurrent collaterals, may serve to give increased 'contrast' between cells which are involved in an activity pattern and their neighbours which are not.

Adrian (1936) showed that repetitive stimulation of a point on the cortical surface causes activity to spread outward from that point in a manner analogous to waves. The more prolonged the stimulation, the greater becomes the distance over which the waves spread, but the less becomes their velocity. If the stimulation should be adequate to set up an afterdischarge, Adrian found that only initially is the afterdischarge pattern referrable to the original stimulated point as 'focus'. Subsequently the activity becomes complex, and the original stimulated point loses its unique identity; Adrian found that this effect was more pronounced in the cat and monkey than in the rabbit. Burns (1953), in seeking a mechanism for 'positive afterbursts', suggested that the excitability of some cortical neurones increases with each discharge and may thus result in the establishment of multiple foci remote from the point of stimulation. Chang (1951) has shown that waves of excitation in cats' auditory cortex, having periodicities in the order of one hundred milliseconds, are preceded at a distance of about a quarter wavelength by waves of increased excitability; he suggests this may in some way be analogous to excitability changes observed in spinal neurones following stimulation. Lindsley (1952) has related Chang's observations to normal cortical excitability patterns.

It is evident that in chronically isolated cortical slabs the normal pattern of spread of activity may in several respects be modified. Eccles (1953) has observed that during chromatolysis in the spinal cord monosynaptic pathways are temporarily replaced by polysynaptic pathways;

the latter may result from collateral sprouting from intact fibres adjacent to those which are degenerating. Sharpless (1964) points out that sprouting and subsequent regeneration, both of which occur throughout the central nervous system, may result in the establishment of synapses which are functional in the strictly local sense but which are physiologically quite inappropriate. Sawa et al. (1963) suggest that loss of inhibitory synapses, such as they postulate to occur as a result of strychninisation, may facilitate the spread of activity along neuronal chains. Finally, it has already been mentioned that denervation supersensitivity to chemical mediators, which effectively implies increased synaptic efficiency, may also be of importance in facilitating the spread of activity in chronically isolated slabs.

4. THEORETICAL APPROACHES TO THE STUDY OF THE CORTEX

While the manner in which a single cortical neurone may be expected to behave under various conditions has been reasonably well established by direct experiment, the manner in which large numbers of interacting neurones may behave has remained considerably less clear. Approaches to the elucidation of this problem (Gerard, 1960) have remained mostly theoretical. Cragg and Temperley (1954) have suggested that the degree of interaction between cortical neruones may be sufficient for the cortex as a whole to behave as a cooperative assembly, i.e., that it may have properties qualitatively distinct from those which would result from a simple summation of the properties of a single neurone. The most widely known example of such a cooperative assembly is a ferromagnetic crystal in which interaction between individual atoms results in the formation of domains; at temperatures above the Curie point the interaction is sufficiently strong to cause the whole crystal to be occupied by a single domain and thereby to become a magnet. If it could be demonstrated that cortical neurones in some way exist in analogous domains, presumably in this case domains of polarisation state, the implications would clearly be of fundamental importance. Cragg and Temperley, using the histological data of Sholl (1956), estimate that the observed degree of interneuronal connectivity could hardly fail to give rise to such effects. A number of recent works have presented mathematical analyses of cooperative processes, mainly with regard to magnetism (e.g., Bates, 1961; and Mattis, 1965); more general approaches are provided in works on classical statistical mechanics (e.g., Fowler and Guggenheim, 1939).

Unless all cortical neurones are connected in closed circuits, for which there is no positive evidence and much negative, it seems

that some mechanism such as that of neuronal domains must be implicit in Lashley's (1958) concept of 'trace systems'. Lashley supposes that the same neurones in different permutations may participate in many different such systems, each system maintaining 'traces' of some particular habit or memory; the dominating system at any particular moment is a function of afferent activity. It has already been mentioned that Burns and Smith (1962) have arrived at a similar concept as the result of experimental observation. They suggest that, in order to retain specificity, the outputs from all neurones involved in any one response must somewhere converge on an individual 'detector cell'.

A comparatively early mathematical model applicable to the cerebral cortex, which in many respects remains the most attractive, is that of Beurle (1956). Beurle considered a mass of neurone-like cells connected in a statistically defined manner in accordance with the histological observations of Sholl (1956). He showed that a wave of activity initiated in such a mass will be propagated through it. However, in order for the amplitude of the wave to remain constant, a certain critically sized initiating disturbance is essential; too small a disturbance will give a wave which rapidly dies out, whereas too large a disturbance will give a wave which will increase in amplitude until it eventually involves all available cells simultaneously and is thus 'burned out'. If it can be assumed that the excitation threshold of a cell in some way decreases as the number of excitations increases, it can be shown that the mass of cells may be able to modify its response to stimulation on the basis of previous 'experience'. Lashley (1952) has suggested that, if cortical activity can be thought of in terms of waves, retained and repetitive activity may perhaps be thought of in terms of standing waves and interference patterns; somewhat

similar concepts emerge from Beurle's model. It may be noted that in the present context the terms 'wave' and 'domain' appear to be merely different expressions of the same fundamental concept that neuronal assemblies may exhibit cooperative properties.

Stahl (1965) has reviewed theories of self-reproducing automata some of which appear to be of potential application to explaining the mechanism of repetitive activity in the cortex. Of particular interest is von Neumann's 'tesselation', or cellular, model in which events occur on an infinitely large grid of squares. Each active cell (square) transmits pulses to neighbouring quiescent cells, and thus any array of activity is able continually to reproduce itself by moving through short distances. Possible explanations of the mechanism of repetitive activity arise also in 're-entry' theories of cardiac fibrillation (e.g., Moe et al., 1941; and Orias et al.,1950).

Farley (1962) has assembled simulated neurone nets within a computer and has shown that the result of stimulation depends on the nature of the 'interneuronal' coupling. In 'tightly coupled' nets, in which each element is connected only to its nearest neighbours, the predictions of Beurle (1956) were largely confirmed, i.e., the excitation either 'dies out' or 'burns out'. In 'loosely coupled' nets, however, having a significant number of longer connections, 'backfiring' of excitation may occur by conduction of impulses via these long connections from the excited wavefront to beyond the refractory area which inevitably develops immediately behind the wavefront. This gives rise to the possibility of various patterns of oscillation, the principal characterising factor being the refractory period of the individual 'neurones'.

At the level of the single cell, the work of Rall (1962, 1964)

in prediciting the mode of conduction of impulses in individual dendritic trees has already been referred to. Recent application of computers to the analysis of data recorded from single cortical neurones (e.g., Gerstein and Kiang, 1960) has opened the way to investigation of the manner in which single neurones are involved in gross activity patterns. Smith and Smith (1964, 1965) have analysed the frequency distribution of spontaneous action potential firing in single cortical neurones (see previous subsection). On the basis of their results they have developed a mathematical model (Smith and Smith, 1965) in which a neurone is gated 'on' or 'off'; firing occurs with a Poisson frequency distribution only when the neurone is 'on'.

A number of recent models have retained the basic concept of a randomly connected network while superimposing various other properties. Freeman (1964) has considered such a case in which the interneuronal connections have the properties of transmission lines; the connections terminate randomly in accordance with the histological observations of Sholl (1956), and the resulting neuronal interaction is assumed to be mainly inhibitory. An interesting outdome of this model, in accord with the experimental observations of Burns (1949, 1950), is the prediction that elimination of afferent noise in the network should result in total electrical silence. Gerstein and Mandelbrot (1964) postulated that variations in neuronal membrane potential resulting from afferent synaptic activity may be distributed as a modified random walk; they were able to demonstrate reasonable agreement between results predicted on this basis and observed frequency distributions of spontaneous cortical action potentials.

Freeman (1964) pointed out that the maintenance of stability in a large population of spontaneously active interconnected elements

presents a theoretical problem of some magnitude. Evidently any cortical model which is to be at all realistic must of necessity incorporate some solution to this problem. Ashby (1950, 1960) has considered the general case of a large number of 'dynamically active parts' connected at random and free to interact. He observes that if all the parts themselves are stable the whole can be equivalent to nothing more than a collection of the separate parts; in all other cases there is an intrinsic bias to instability which increases proportionately to the number of parts and the degree of connectivity. Nevertheless, having considered these problems in the light of observed cortical behaviour, Ashby (1960) has evolved a comprehensive mathematical model to demonstrate the capacity of such interacting systems for adaptive behaviour. Offner (1965) has shown that the maximum useful complexity of a random network which is to be adaptive is limited by the signal-to-noise ratio. A number of experimental observations which appear to have some bearing on this problem have already been referred to (Burns and Smith, 1962; Stefanis and Jasper, 1964; Andersson, 1965; and see previous subsection).

III. EXPERIMENTAL METHODS

1. PREPARATION OF NEURONALLY ISOLATED SLABS OF CEREBRAL CORTEX

(a) Acute Isolation

Cats of either sex weighing between 2.0 and 4.0 kg were used.

Anaesthesia was induced by placing the cat in a closed wooden box having a glass door for observation and a small upper compartment separated from the rest of the box by a wire gauze partition on which was placed an ether-soaked pad of cotton wool. When surgical anaesthesia was attained, the cat was transferred to the operating table and secured on its back. Anaesthesia was temporarily continued by a cone-shaped mask containing an ether-soaked pad which was held over the cat's nose and mouth. The trachea was exposed and cannulated, and anaesthesia was thereafter maintained from a variable-bypass ether bottle connected to the cannula by a short polyethylene tube. An air intake was provided at the cannula in addition to that at the ether bottle in order to reduce the effect of the dead space represented by the volume of the tube; in some experiments, a two-way respiration valve was interposed at the cannula. A suitable level of anaesthesia was estimated from the cat's reflex and respiratory behaviour, and was maintained by adjusting the ether bottle bypass valve as required.

The right femoral vein was cannulated at this stage to provide a route for subsequent administration of drugs and fluids.

The cat was then turned over and its head clamped in a Czermak holder. A midline scalp incision was made and the scalp was separated from the temporal muscle on both sides. The left temporal muscle was reflected from the skull, clamped as far laterally as possible, and the free part of it cut off. A dental burr was used to remove an approximately trapezoidal area of bone having its base along

the line of inflection which effectively indicates the posterosuperior margin of the tentorium cerebelli, its parallel but shorter top a few millimetres anterior to the coronal suture, its medial side just lateral to the midline, and its lateral side as far out as the remaining attachment of the temporal muscle would allow. Bone wax (beeswax and phenol) was used to prevent bleeding from the venous sinuses of the skull both while cutting it and on removal. During cutting, the region of operation of the burr was kept irrigated with saline at 37°F to prevent possible entry of air to the sinuses, and also, by washing away blood and debris, as an aid to visibility. The bone was removed with as little trauma as possible to the underlying dura, and the latter was then cut away with scissors; vascular attachments from below were electrocauterized, and the exposed pia was kept continuously irrigated with saline.

A slab of cerebral cortex was neuronally isolated from the exposed suprasylvian gyrus by a slight modification of the method of Burns (1949, 1950) and Kristiansen and Courtois (1949). Areas of pia at either end of the gyrus, as large as possible without infringing on the central straight part of the gyrus, were electrocauterized. The cortex from these cauterized areas was removed to a depth of a few millimetres by means of the rough tapered tip of a glass tube attached to a water tap aspirator. The posterior hole was deepened at a lesser diameter to penetrate the lateral ventricle and thus provide a drainage route for cerebrospinal fluid which might otherwise accumulate and cause the brain to swell. The slab was then cut by introducing into the posterior hole a composite knife (Fig. 1) which was pushed gently along with the rounded tips of its two prongs just visible through the pia and its flat blade as nearly as possible parallel to the pial surface.

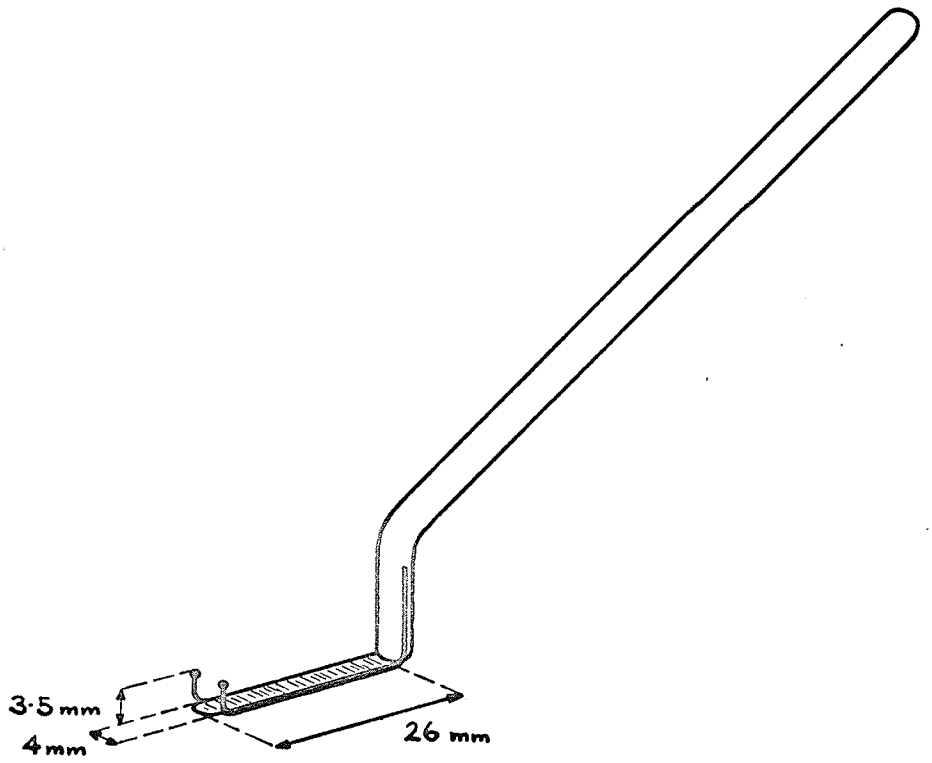


FIG. 1. COMPOSITE KNIFE USED FOR ISOLATING CEREBRAL CORTICAL SLABS. THE HANDLE IS 3/16" DIAMETER BRASS ROD, THE FLAT BLADE WHICH CUTS THE BOTTOM OF THE SLAB IS A PIECE OF STEEL RAZOR BLADE, AND THE VERTICAL PRONGS WHICH CUT THE SIDES OF THE SLAB ARE 0·028" STAINLESS STEEL WIRE. THE ANTERIOR EDGES OF THE PRONGS ARE GROUND MODERATELY SHARP, EXCEPT THAT THE TOPMOST PORTIONS, WHICH MUST BE OBSERVED THROUGH THE PIA WHILE CUTTING THE SLAB, ARE ROUNDED OFF AND MADE SMOOTH BY DIPPING IN 'EPOXY' CEMENT (BORDEN CHEMICAL CO., NEW YORK).

When the end of the knife emerged at the anterior hole, the neuronal isolation was complete; yet the blood supply to the slab, descending wholly from vessels at the pial surface, was undisturbed. The knife was gently withdrawn by the same procedure used for its insertion.

The dimensions of a slab thus isolated are determined by the distance between the anterior and posterior holes, and by the dimensions of the knife. In these experiments, the length of viable tissue between the holes was never less than 1.0 cm, and usually considerably more. The width and depth, determined by the knife, were 4.0 and 3.5 mm respectively. This depth should be quite adequate to include the whole thickness of the cortex, at least in the central part of the gyrus, since Reiffenstein (1964), using a cut depth of 4.0 mm, found on histological examination a cortex-to-slab depth ratio of seldom less than 1-to-2.

Finally, decerebration was performed by inserting a stainless steel spatula, of the pattern described by Pinsky (1957), below the cerebral hemisphere and flat against the tentorium cerebelli, and cutting the brain stem at the mid-collicular level. Immediately prior to the actual cutting, the hemisphere was gently raised a little from the tentorium by means of a broad bent spatula, and any visible vascular connections between the hemisphere and tentorium were electrocauterized. Following decerebration, anaesthesia was discontinued, the exposed cortex was temporarily covered by saline-soaked cotton wool, and the cat was transferred to the recording table.

Over the period in which results were accumulated for this thesis, about 50% of the cats prepared for use in the acute state died, or their cortices became avascular, either on the operating table or before supplying useful records. The chances of survival were

evidently much increased by minimising the total time of anaesthesia; and, of those cats which did survive the initial stages, practically all remained in tolerably good condition for periods in the order of twenty-four hours. In some cases, nutrition and fluid were provided by periodic intraperitoneal injections of 5% glucose in saline. The body temperature was maintained at 37° by means of a rectal probe, connected in early experiments to an electric heating pad and fan, and later used to control the temperature of air blown through a perforated metal plate on which the cat was supported; this modification was to reduce electrical interference in the recording area. At the termination of experiments, cats no longer required were killed by massive intravenous injection of saturated magnesium sulphate solution.

(b) Chronic Isolation

In experiments on chronically isolated slabs, cats were used in which slabs had been cut in the left suprasylvian gyrus between three and fourteen months previously. These cats were in general heavier than those used in acute preparations, the weight range extending to 5.0 kg; this was partly due to weight gained during retention in the animal colony, and partly because only large cats had been chosen for chronic preparations in the first place.

The procedure followed in initial isolation of the slab varied only slightly from that described above for acute preparations. Anaesthesia was by pentobarbital (35 mg/kg intraperitoneally), tracheostomy was not performed, and the head was clamped only very loosely to avoid injury. The scalp was shaved, opened in the midline, and reflected laterally. The left temporal muscle was not removed, but merely reflected laterally also. The area of bone removed was the minimum that permitted cutting of the slab; and the dura was left

attached and reflected medially. A minimal area of cortex was cauterized at the posterior end of the gyrus only, and a drain hole of small diameter was made to the lateral ventricle. The slab was cut by a procedure similar to that used in the acute preparation, but, there being no hole at the anterior end of the gyrus, it was necessary to isolate the anterior end of the slab by means of a single wire prong, identical to those attached on either side of the horizontal blade of the knife (Fig. 1). The prong was pushed along one side of the slab, moved laterally across to cut the end, and withdrawn along the other side. The dura, temporal muscle, and scalp were sutured back in their original positions.

These chronic isolation procedures were done under clean but not aseptic conditions, and in some cases prophylactic antibiotics were administered (see also Gorchynski, 1964; and Reiffenstein, 1964): up to 0.5 gm streptomycin, and/or up to 400,000 units penicillin, intramuscularly, the initial dose half an hour after completion of the operation, and thereafter daily for the next three to five days. The cats, if healthy, were then returned to the animal colony.

Re-exposure of a chronically isolated slab for use in an experiment was done under ether anaesthesia and by means of a tracheostomy as described for acute preparations. The main difference in this case was that the temporal muscle and dura, no longer separated by bone, were invariably found to have fused together; their removal was consequently less straightforward and more time-consuming. The exposed area of cortex, once cleared, was enlarged by rongeurs or the dental burr to the size used in acute preparations. A hole was made at the anterior end of the slab, and the original drain hole was re-opened and its upper part enlarged; often this

necessitated the use of fine pointed scissors to break up the fibrous scar tissue which had formed around it. In an initial experiment, an attempt was made to re-cut along the lines of the original isolation; but this turned out to be effectively impossible because of scar tissue. Reiffenstein (1964), in overcoming this difficulty, isolated a larger volume of tissue to include the original slab; however, this was not done in the present series of experiments.

The dimensions of the chronically isolated slabs were somewhat variable, but were in general less than those acutely isolated. This was partly due to minor variations in the original cutting procedure, and partly due to subsequent shrinkage (see also Reiffenstein, 1964).

Decerebration was performed as in the acute preparation; except that sometimes, in order to minimise the time of anaesthesia, the skull was initially opened on the previously untouched right hand side and decerebration performed from there before proceeding to expose the chronically isolated slab on the left.

Cats having chronically isolated slabs were evidently in better physical condition, or better able to withstand trauma, than those in which the isolation was acute; in the present series of experiments, only one such cat died without giving useful results.

2. STABILISATION FOR RECORDING

(a) Gross Stabilisation

The cat having been transferred to the recording table, the cut edges of the scalp were tied tightly to a 4-1/2 inch diameter steel ring supported in a horizontal plane by the same stand as that supporting the Czermak holder; the latter had remained throughout clamped to the cat's head. The steel ring was adjusted to as high a level as possible so that the exposed cortex became contained, as it were, in a cradle with sides formed by the stretched-out scalp. This 'cradle' was filled with mineral oil at 37°F, thus covering the cortex to prevent it drying out or getting cold. In some experiments the temperature of the oil was maintained by an immersed electric coil, though latterly it was found simpler to use a heating lamp directed on to the oil surface and switched on intermittently as needed. With regard to the experiments presently described, the oil temperature was not found to be particularly critical within a range of a few degrees below 37°F.

The stand supporting the Czermak holder and scalp ring, as well as those supporting other items of stabilising and electrode-holding equipment to be described below, was clamped to a heavy cast-iron base plate. The body of the cat, lying on its temperature regulating pad, was likewise supported on this base plate. Thus these simple arrangements already described provided a high degree of gross stability, quite adequate for recording from the cortical surface.

(b) Stabilisation of the Isolated Slab

In order to record with microelectrodes the activity of single units, it is necessary to stabilise not merely the head as a

whole, within which the brain is by no means a rigid structure, but also that particular local part of the brain from which it is intended to record. Movements due to respiration, pulsation of the local blood supply, and swelling of the exposed brain are all sufficient to prevent a microelectrode tip being maintained in a constant position with respect to a single cell for long enough to acquire useful records of the cell's activity; and this is particularly so in the case of intracellular recording.

As an initial step to minimising respiratory movements, transmitted to the cortex both directly and as pressure changes in the blood vascular system, the cat was immobilised by intravenous gallamine injection (5 mg/kg repeated hourly), a pneumothorax was performed, and respiration was thereafter maintained by a positive pressure pump.

A variety of techniques has been designed to achieve local stabilisation of the cortex. Many of these have used liquid filled chambers attached rigidly to the skull over the exposed area so that the cortex is stabilised by a gentle direct hydraulic pressure (e.g., Mountcastle et al., 1957; Hubel, 1959; and Mandl, 1965); the microelectrode is mounted to be driven vertically downward through the chamber. A different approach is the spring suspension designed by Burns and Robson (1960) whereby the microelectrode is rendered virtually weightless and so free to move with the cortex. Most of these methods suffer to a greater or lesser extent from the disadvantage that it is a somewhat involved procedure to change the microelectrode from one line of penetration to another. A simpler and more flexible solution is that used by Phillips (1956) in which a celluloid window, having a small hole in it for the microelectrode,

is pressed gently down on the cortical surface.

In the present study it was realised that the use of an isolated cortical slab provided opportunity for a rather different form of local stabilisation. A rectangular silver trough was made having the same cross sectional dimensions as those of the slab (Fig. 2). By means of a perspex handle attached rigidly to one end, it was possible to push the trough gently into the hole at the anterior end of the slab and along the isolating knife cuts so that the entire slab became contained within it. The handle of the trough was then clamped rigidly (Fig. 3). As in the case of the original isolation procedure, the presence of the trough caused no damage or interruption to the slab's pial blood supply, and this continued to be so for as long as the cortex as a whole remained viable. In practice, the most critical adjustment in the insertion of the trough was the initial positioning of it in its clamp (Fig. 3(i)); attempts to readjust the clamp once the trough was installed were liable to prove fatal to the whole experiment. The trough was designed to accommodate slabs up to eighteen millimetres long, which was always adequate.

By itself, the trough provided protection against movement due to swelling of the cortex and against direct mechanical movement due to respiration. In order to minimise movement due to pulsation and pressure changes in the blood supply, the trough was supplied with a lid. This was a suitably sized block of perspex (Figs. 3(iii) and 4) into which were set a number of platinum and silver electrodes for surface stimulation and recording respectively. The leads from these electrodes were conveniently led out via a hollow handle whereby also the lid was clamped rigidly in a stereotaxic manipulator (W.R. Prior Co.). In use, the lid was lowered

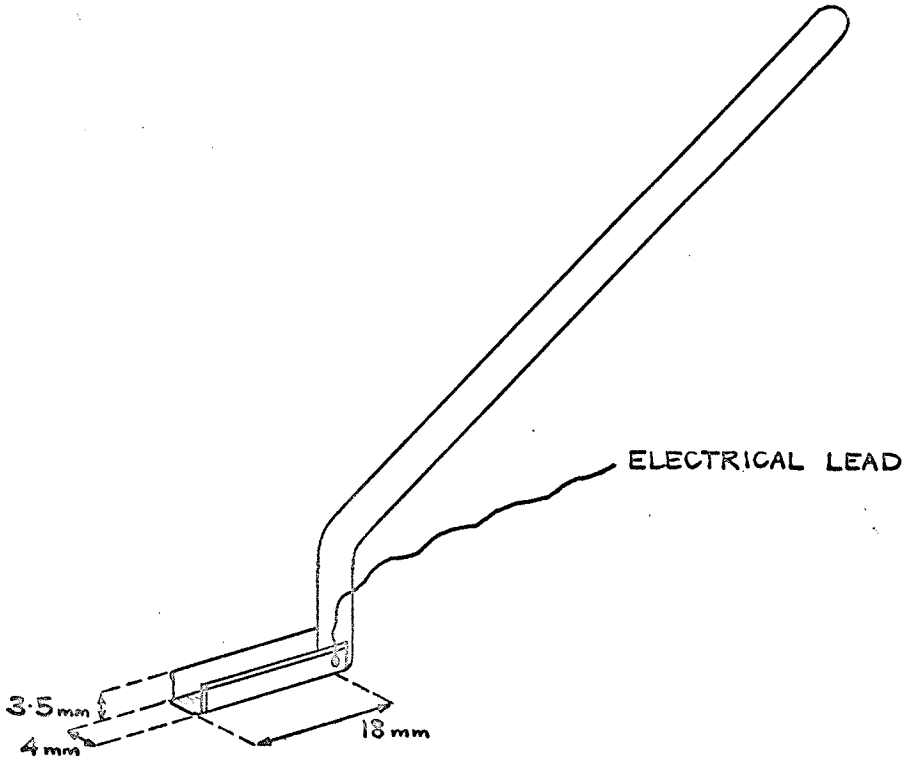


FIG. 2. STABILISING TROUGH DESIGNED TO CONTAIN SLABS CUT BY KNIFE SHOWN IN FIG. 1. THE HANDLE IS 3/16" DIAMETER PERSPEX ROD AND IS SECURED TO THE TROUGH BY A SCREW AT ITS BASE AND BY 'EPOXY' CEMENT. THE TROUGH IS MADE FROM 0·005" SHEET SILVER. THE ANTERIOR EDGE OF THE BOTTOM OF THE TROUGH IS FAIRLY SHARP; THE ANTERIOR AND UPPER EDGES OF THE SIDES ARE ROUNDED BY BEING BENT DOUBLE. AN ELECTRICAL LEAD IS PROVIDED SO THAT THE TROUGH CAN BE USED AS AN INDIFFERENT ELECTRODE.

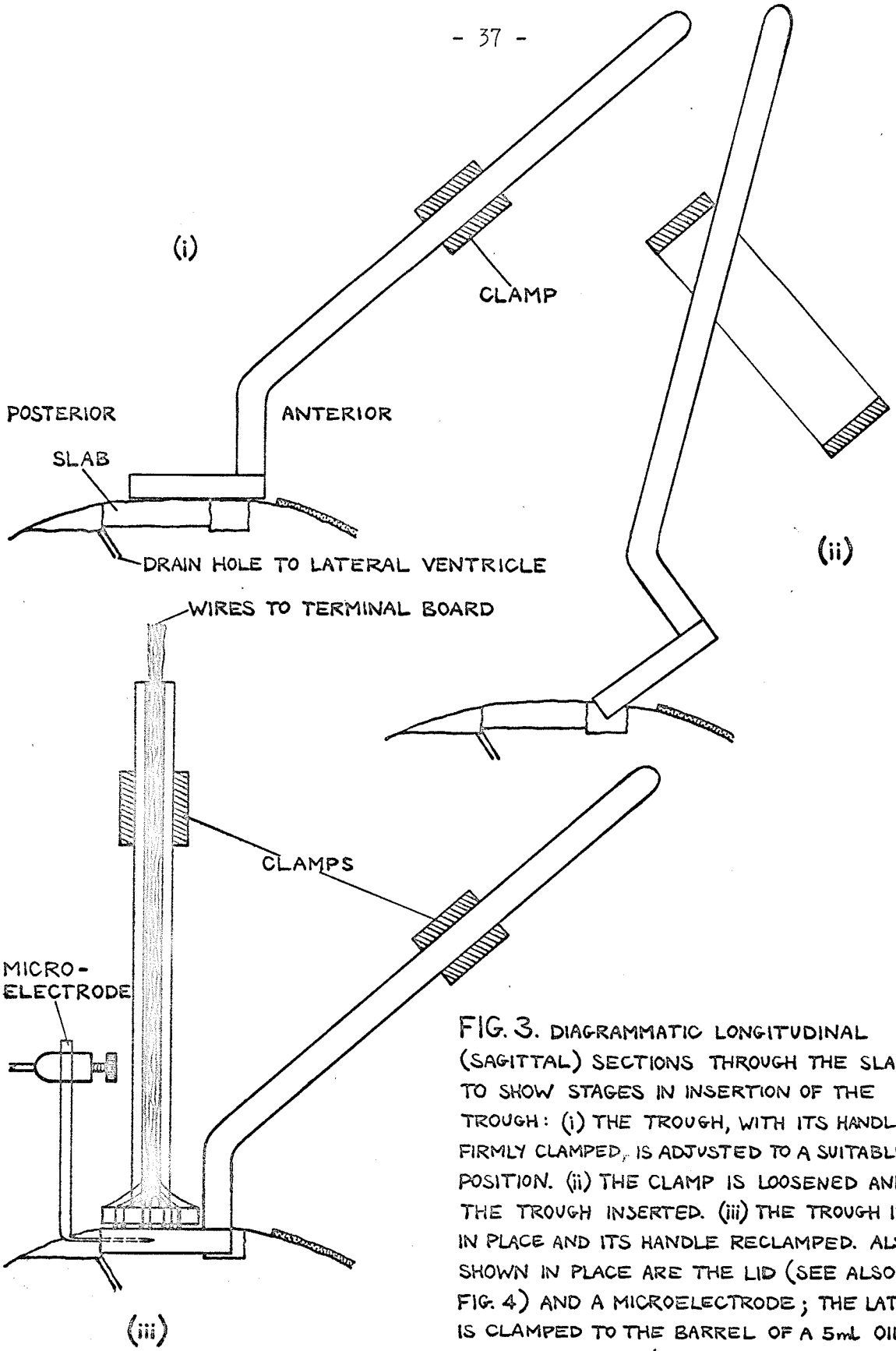


FIG. 3. DIAGRAMMATIC LONGITUDINAL (SAGITTAL) SECTIONS THROUGH THE SLAB TO SHOW STAGES IN INSERTION OF THE TROUGH: (i) THE TROUGH, WITH ITS HANDLE FIRMLY CLAMPED, IS ADJUSTED TO A SUITABLE POSITION. (ii) THE CLAMP IS LOOSENED AND THE TROUGH INSERTED. (iii) THE TROUGH IS IN PLACE AND ITS HANDLE RECLAMPED. ALSO SHOWN IN PLACE ARE THE LID (SEE ALSO FIG. 4) AND A MICROELECTRODE; THE LATTER IS CLAMPED TO THE BARREL OF A 5mL OIL-DRIVEN SYRINGE (NOT SHOWN: SEE TEXT).

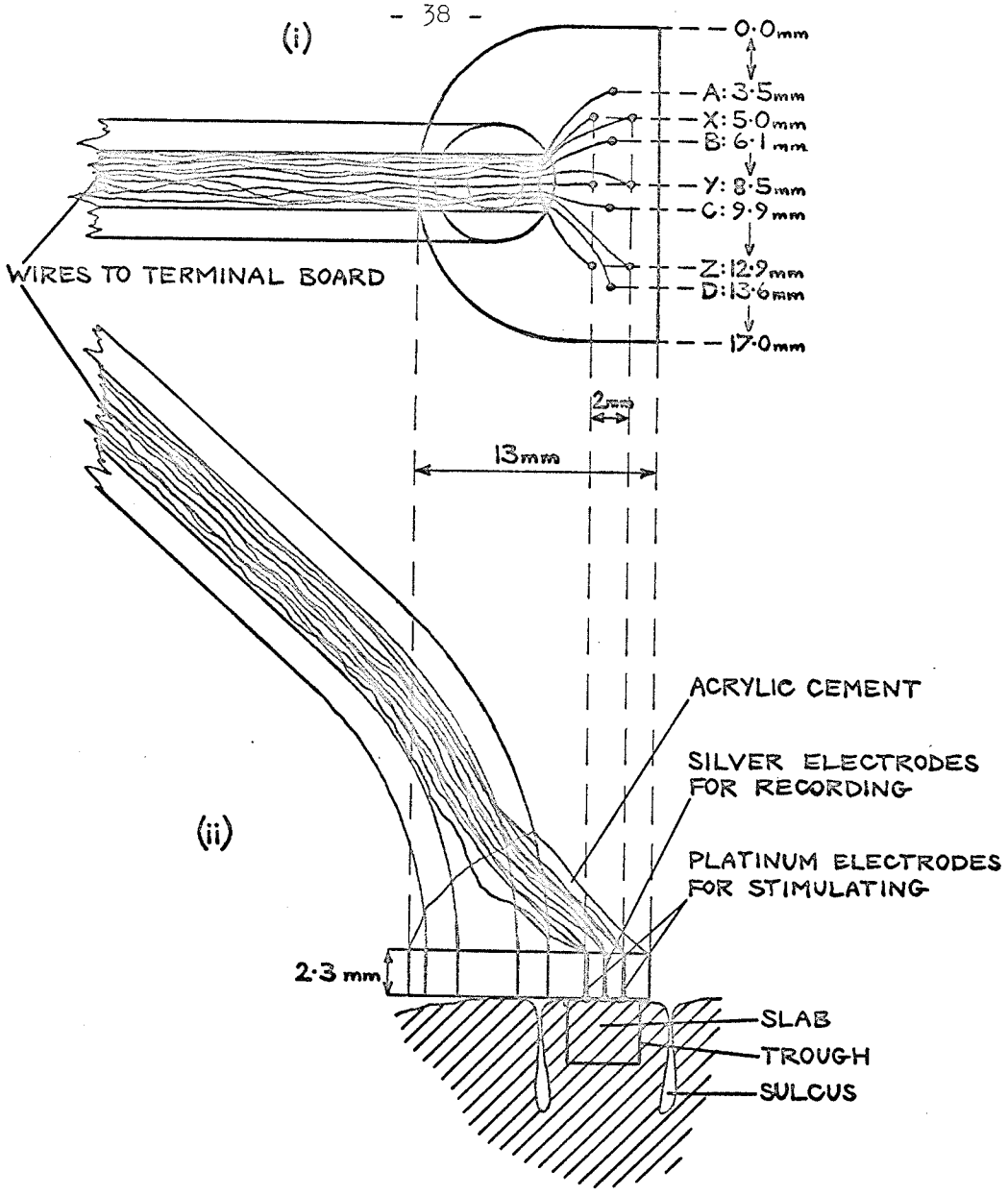


FIG. 4. STABILISING LID (USED WITH TROUGH AS IN FIG. 3): (i) PLAN VIEW SHOWING ARRANGEMENT OF ELECTRODES. (ii) TRANSVERSE (CORONAL) SECTION SHOWING LID IN POSITION ON SLAB; THE HANDLE OF THE TROUGH IS NOT SHOWN. THE LID IS MADE FROM SHEET PERSPEX AND ITS HANDLE FROM 1/4" OUTSIDE DIAMETER PERSPEX TUBE. THE RECORDING ELECTRODES (A, B, C, D) ARE 0·016" SILVER WIRE, AND THE STIMULATING ELECTRODES (X, Y, Z) ARE 0·016" 10% IRIDIUM PLATINUM WIRE. THE ELECTRODES ARE BEADED AT THEIR LOWER ENDS AND ARE SET IN THE LID SO AS TO PROJECT VERY SLIGHTLY TO ENSURE GOOD CONTACT WITH THE CORTICAL SURFACE. THE ENTIRE AREA ON TOP OF THE LID WHERE THE WIRES EMERGE FROM THE HOLLOW HANDLE AND ARE SOLDERED TO THE ELECTRODES IS COVERED FOR PROTECTION BY TRANSPARENT ACRYLIC CEMENT (PERSPEX IN ETHYLENE DICHLORIDE).

vertically on to the surface of the slab, the final stages of this operation being best observed through a binocular microscope. Provided that both lid and trough had been initially clamped in a horizontal plane, it was usually possible to press the lid gently down until the upper edges of the vertical sides of the trough were clearly visible through it, the two being then separated only by the still intact pia. The lid was then very slightly raised to prevent interruption of the pial blood supply. The presence of the lid thus applied was often directly observed to have eliminated previously visible pulsations. Final positions with respect to the slab of both lid and trough are shown in Figs. 3(iii) and 4 (ii).

In chronically isolated slabs, since the original isolation cuts were filled with scar tissue and were not re-cut, it was not possible to use the trough. However, due partly to their evidently improved blood supply and partly presumably to the incidental structural support provided by the scar tissue, these slabs seemed able to survive a somewhat greater pressure from the lid than would have been possible in acute cases. Such pressure was in fact applied, and was in general found to provide sufficient stability to compensate for the absence of the trough.

The microelectrodes used in these experiments were bent to a right angle in the region where the stem becomes drawn out to form the shaft; the bending was easily accomplished using the flame of a miniature gas burner made from a 16-gauge hypodermic needle. With the stem mounted vertically, the shaft could then be driven horizontally into the slab from the hole at its posterior end, this being allowed by the natural curvature of the gyrus (Fig. 3(iii)). The shaft, which is quite flexible, was thus effectively floating in the cortical

substance, and so this arrangement in itself provided a further contribution to stability. A further description of the microelectrode and its mounting apparatus is provided in the subsection following.

It was originally hoped that by means of the stabilising arrangements described above it would be regularly possible to obtain intracellular records. However, this did not turn out to be the case, and intracellular records were obtained on only a comparatively few occasions. The causes for this failure are probably several, but there seems no reason to suppose that they include any fundamental inadequacy in the trough-lid method of stabilisation. This method was designed primarily to eliminate movement due to the cat's own vital functions, and not that due to external disturbances which would in fact quite probably be magnified. Such disturbances should obviously be eliminated from the recording area in any case, but it is also essential that the various clamps and items of stabilising equipment, and in particular the microelectrode, should be mounted on the base plate as rigidly as possible. Inadequate attention to this point is perhaps partly to blame for the present lack of intracellular results. In addition, concerted efforts to obtain intracellular recordings were discontinued in favour of extracellular recording at a fairly early stage in the investigation; and the microelectrodes subsequently used for this latter purpose were by no means ideally suited to stable intracellular penetration (see subsection following, part (a)).

For extracellular recording, the stabilising arrangements as used seemed entirely satisfactory. It was regularly possible, on stimulating the slab surface at successive five minute intervals, to record unit activity of a remarkably constant pattern suggesting that

relative to the local cell population significant movement of the microelectrode tip did not occur.

3. STIMULATION AND RECORDING

(a) Electrical Stimulation and Recording

A block diagram of the complete electrical arrangements is given in Fig. 5; the following is intended to be read in conjunction with that diagram.

The repetitive stimulation needed to elicit an epileptiform afterdischarge was obtained from Tektronix 160-Series pulse and waveform generators; the waveform produced by each generator is shown to its right in Fig. 5. It was convenient to generate the repetitive pulses in bursts, rather than continuously, so that during the interburst silences the recording oscilloscope could be monitored for signs of commencing biological response. A Hammond 835 1:1 transformer was used to isolate the stimulus current from ground. The stimulus was applied to the cortical surface through any one or more of the three pairs of platinum electrodes provided in the lid (X,Y,Z in Fig. 4); switching from one pair to another was by means of connections made to a terminal board mounted remote from the biological preparation.

No critical study was made in these experiments of the effects of varying the stimulus parameters (see Pinsky and Burns, 1962), neither was any effect noticed in the ranges used. These ranges were:

burst interval: 1000-1300 msecs

burst duration: 500-800 msecs

pulse interval: 32 msecs

pulse duration: 2-3 msecs

pulse voltage: 20-40 volts (-these are nominal dial volts; in fact the cortex presents to the secondary of the transformer an effective load resistance sufficient to

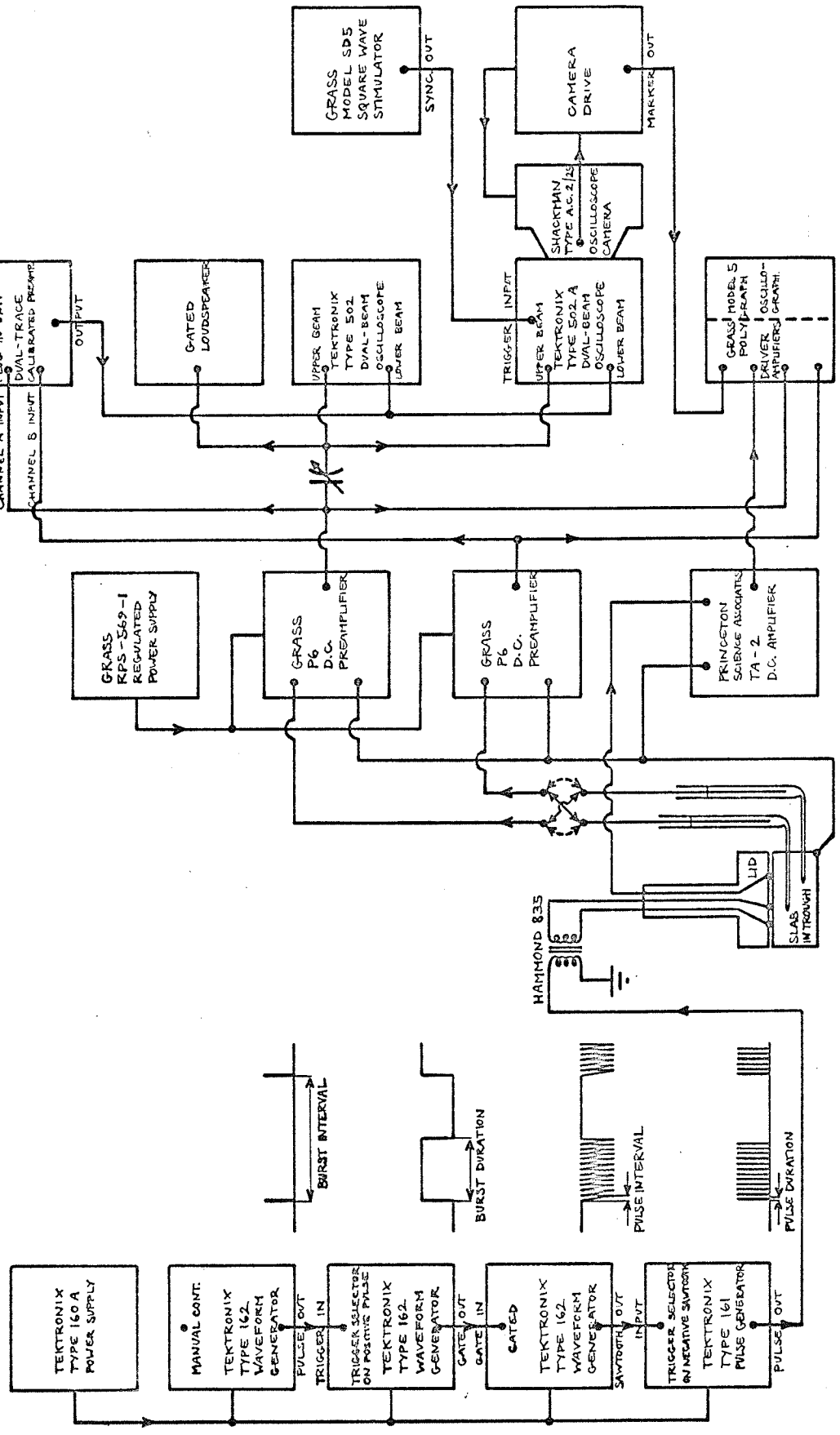


FIG. 5. BLOCK DIAGRAM OF COMPLETE ELECTRICAL ARRANGEMENTS FOR STIMULATION AND RECORDING.

reduce the actual stimulating voltage by 50% or more (by 60% according to Reiffenstein (1964) who used similar arrangements).)

Electrical recording was both from the surface by any one of the silver electrodes provided in the lid (A,B,C,D in Fig. 4) and from single units by glass microelectrodes. The microelectrodes used were mostly supplied from the Department of Physiology, McGill University, by courtesy of Dr. B.D. Burns. Outside tip diameters were 2 - 2-1/2 microns and the shafts were of constant diameter about 40 microns to within little more than 120 microns of the tip. Available shaft length for penetration into the slab was 10-14 mm. The microelectrodes were filled directly from from a syringe via polyethylene tubing (PE 20), usually with 90% saturated sodium chloride giving a tip resistance 400-700 kohms; occasionally, in attempting to record intracellularly, 2 M potassium citrate was used, giving slightly higher tip resistances up to 1 megohm. In some preliminary experiments, microelectrodes were pulled from melting point capillaries using an MI micropipette puller (Industrial Science Associates); these microelectrodes had outside tip diameters of 1 micron or less, but they were much more fragile and their use was discontinued when it was decided to concentrate on extracellular recording.

In order to record simultaneously from two different points in the cortex, two microelectrodes were used in most experiments. For both surface and microelectrodes, the indifferent electrode was provided by the silver trough itself; except that a silk wick electrode making contact with the exposed skull bone was used in chronic preparations where the trough could not be inserted. All connections to fluid electrolytes in glass electrodes were made by chlorided silver wires.

Signals from the microelectrodes were amplified by Grass P6 preamplifiers, and from the surface electrode by a Princeton TA-2 amplifier. These amplifiers have differential cathode-follower inputs. The cat, electrodes, and amplifier probes were supported in a shielded enclosure on a grounded recording table, and the cat itself was also grounded via the tooth bar of the Czermak holder. Also, most experiments were performed in a shielded room.

The amplifier outputs were applied directly to three channels of the Grass Polygraph, and those originating from the microelectrodes were applied also to the Tektronix CA dual-trace preamplifier (beam splitter) and thence to the lower beams of the 502 oscilloscopes. In addition, the amplified signal from either one interchangeably of the two microelectrodes was passed through a resistance-capacitance high-pass filter having a sufficiently short time constant (0.3 msecs) to eliminate practically all variations in potential of time course longer than that of classical action potential spikes. This filtered signal was applied to the upper beams of the 502 oscilloscopes at fairly high gain, and also to a gated loudspeaker for auditory monitoring.

The two 502 oscilloscopes were connected in parallel, one being used for visual monitoring and the other for photographic recording. In order to conserve within reasonable limits the amount of film used, the camera was turned on its side so that the direction of motion of the film was at right angles to the oscilloscope sweep. The image on the film thus appeared as successive sweeps running transversely with a gradient determined by vector addition of the film and sweep velocities; this gradient appears in the samples taken from filmed records to illustrate this thesis. In order to

avoid overlapping of the images of successive sweeps on the film, since each sweep involved three independent traces, it was found necessary to reduce the sweep frequency by triggering the camera oscilloscope externally from a Grass SD5 stimulator. This provided in effect an automatic sampling, not altogether disadvantageous, such that the equivalent of only a little more than every alternate sweep was recorded. However, in recording the chronic phases of afterdischarges from chronic preparations (see Section IV, 1) in which epileptiform burst frequency is comparatively low, this 'sampling' was dispensed with and the triggering was made recurrent. As a convenience, a connection was provided from the camera drive to a spare channel on the Polygraph whereby whenever the camera shutter was open and the film moving an indicator signal was recorded on the paper record. The film used in these experiments was Kodak Linagraph Ortho.

Principal dial settings on the various items of recording apparatus are summarised as follows:

Grass P6 D.C. preamplifiers: amplification 500; half amplitude frequencies 0 c/s, 10 kc/s.

Princeton TA-2 D.C. amplifier: amplification 1000; half amplitude frequencies 0 c/s, 3 kc/s.

Tektronix CA dual-trace preamplifier: volts/cm 0.2.

Tektronix 502 dual-beam oscilloscopes: upper beam vertical sensitivity 50 mV/cm; lower beam 1V/cm; time base 20 msecs/cm.

Grass SD5 stimulator: frequency 2.6-3.6 pulses/sec.

Grass Polygraph D.C. driver amplifiers: half amplitude high frequency 60 c/s.

Grass Polygraph oscillograph: paper speed 5-10 mm/sec during stimulation and response, otherwise 0.25 mm/sec.

In a few early experiments involving only one microelectrode, the Princeton amplifier was not used and the surface record was amplified by a Grass P6. The CA dual-trace preamplifier was not needed, and in its absence the 502 oscilloscope lower beam vertical sensitivities were set at 2 V/cm. With only two traces per sweep the SD5 was not necessary and the camera oscilloscope sweep was set to run free.

A simplified diagrammatic summary of the usual arrangement of the recording equipment is given in Fig. 6.

(b) Recording of Microelectrode Tip Position

Fine adjustment of the microelectrode in a direction parallel to its shaft was by means of an oil filled hydraulic drive consisting of two syringes connected by a length of polyethylene tubing. The microelectrode was clamped to the barrel of the larger syringe (5 ml), while the barrel of the smaller syringe (1 ml) was controlled by a micrometer and spring; such a system is described in more detail by Burns (1961). Rotation of the micrometer head through one small division (50 divisions per rotation) caused longitudinal movement of the microelectrode shaft through less than two microns. The syringe carrying the microelectrode was itself mounted on a stereotaxic manipulator which provided both the coarse longitudinal adjustment needed for penetration and the lateral and vertical adjustment needed for initial positioning.

In use, it was necessary to arrange that both the microelectrode shaft itself and its line of motion provided by one of the horizontal movements of the manipulator should be both horizontal and parallel to the sides of the slab. The microelectrode was then

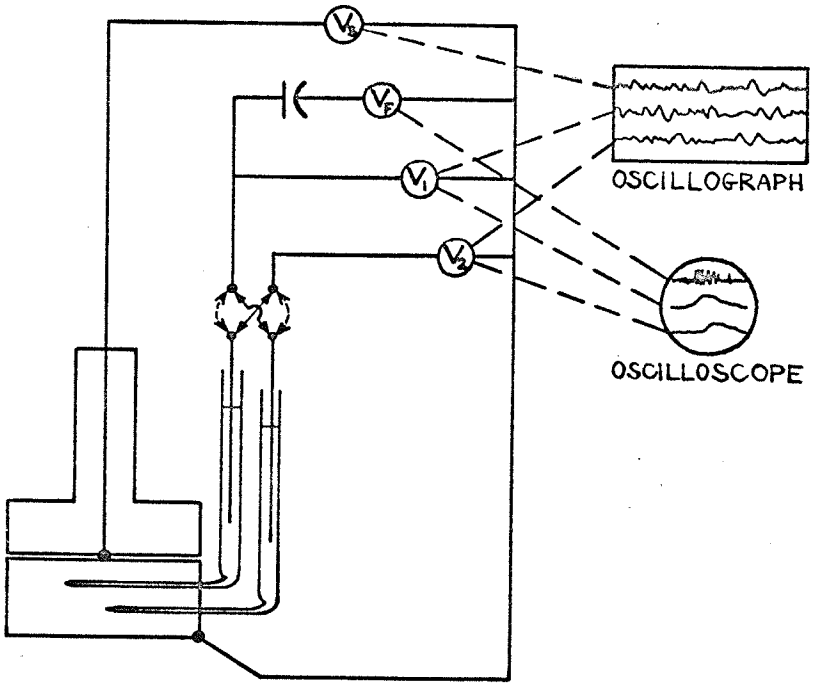


FIG. 6. DIAGRAMMATIC SUMMARY OF ELECTRICAL RECORDING ARRANGEMENTS: V_S RECORDS FROM THE SURFACE ELECTRODE IN THE LID, V_1 AND V_2 FROM THE MICROELECTRODES. V_F RECORDS AT HIGH GAIN, THROUGH A HIGH-PASS FILTER AT ITS INPUT, ACTION POTENTIAL SPIKES FROM EITHER ONE OF THE MICROELECTRODES. ALL CHANNELS SHARE THE INDIFFERENT LEAD CONNECTED TO THE TROUGH.

lowered gently into the oil until the shaft, observed through a binocular microscope, just touched the upper surface of the lid. The manipulator's vertical vernier was read, and, allowance being made for the thickness of the lid, this gave the reference coordinate, z_0 (Fig. 7). The microelectrode was then moved clear of the lid and adjusted to the point where its tip was at the medial posterior upper corner of the slab, this being arbitrarily defined as the point where the posterior edge of the lid crossed the upper edge of the medial side of the trough visible through the pia. The micrometer having previously been turned to its maximum withdrawal, i.e., 25.00 mm, the manipulator's horizontal verniers at this position gave the reference coordinates, x_0 and y_0. In experiments in which two microelectrodes were used, two independent sets of reference coordinates were established, x_{OM}, y_{OM}, z_{OM} and x_{OL}, y_{OL}, z_{OL}, the microelectrodes being temporarily distinguished as medial (M) and lateral (L).

Still using only the stereotaxic manipulator, the microelectrode was driven horizontally into the slab at some desired point in its cross section and for some desired distance. In chronic slabs, this operation was complicated by the presence of numerous obstructions in the microelectrode's path, presumably scar tissue or increased vascular tissue or both. Fortunately, these obstructions were rarely sufficiently rigid actually to break the microelectrode tip, and while it was sometimes necessary to break up the tissue at the end of the slab with fine pointed scissors, penetration was always eventually achieved. The vernier readings at this stage gave the probe coordinates, x_P, y_P, z_P (two sets for two microelectrodes, distinguished as M and L as above).

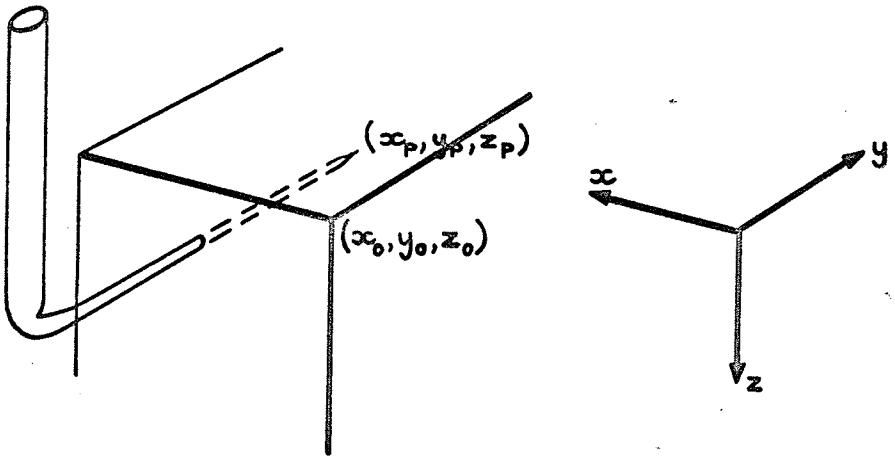


FIG. 7. ESTABLISHMENT OF COORDINATE SYSTEM FOR LOCATION OF MICROELECTRODE TIP: THE TIP IS FIRST MOVED TO THE CORNER OF THE SLAB (SEE TEXT) TO ESTABLISH REFERENCE COORDINATES (x_o, y_o, z_o) ACCORDING TO THE AXES INDICATED AT THE RIGHT, AND IS THEN DRIVEN INTO THE SLAB TO A POINT WHICH DEFINES PROBE COORDINATES (x_p, y_p, z_p). SUBSEQUENT ADJUSTMENT BY HYDRAULIC DRIVE IS SIMPLY ADDED ON TO y_p.

All further adjustment was made using the hydraulic drive, the microelectrode being driven forward being connected to the high-pass filtered recording channel so that it could be monitored both auditorily and visually for evidence of single unit activity in the vicinity of the tip. Such activity was usually manifest as abrupt discharges and spikes, often highly repetitive, presumably caused by physical disturbance of cells by movement of the microelectrode. In stimulating and recording, the oscilloscope camera drive was set in motion, and the oscillograph paper speed increased, in time to include both the stimulus artifact and a few seconds of inactive trace before it. The paper record in these experiments was used mainly as a log, and on it at each stimulation were recorded the time, the micrometer reading for each microelectrode, which microelectrode was connected to the filtered recording channel, and which surface electrodes were used for stimulation and recording (X,Y, Z and A,B,C,D, see Fig. 4). Once both microelectrodes were positioned near potentially active single units, at least six useful recordings could in theory be obtained without further adjustment; i.e., using in turn each of three pairs of stimulating electrodes, X,Y, and Z, and then repeating with the other microelectrode connected to the high-pass filtered recording channel. Using various combinations of X, Y, and Z, the number of possible recordings was increased still further; but in practice not all were usually made, even of the basic six. To avoid induction of spreading cortical depression (Burns, 1958), about five minutes was usually allowed between successive stimulations.

Once the limit of penetration imposed by either the micrometer drive or the available microelectrode shaft length had been

reached, the microelectrode was withdrawn. With the micrometer head turned back to 25.00 mm, a fresh penetration could be made elsewhere in the slab cross section, a new set of probe coordinates being established each time this was done. Provided the microelectrode was not moved relative to its mount, the original set of reference co-ordinates remained, of course, valid throughout the experiment.

IV. ANALYSIS AND RESULTS

1. INITIAL ANALYSIS OF EXPERIMENTAL RECORDS AND QUALITATIVE OBSERVATIONS

Examination of filmed records was carried out using a Dagmar Super Microfilm Reader Model 35 which projected the image directly from the film on to the surface of the work desk. The magnification was adjusted so that the image of one sweep length exactly occupied an appropriate number of divisions on a scale marked in milliseconds on squared paper; this was determined from a 60 c/s time calibration included on the film at the time of the experiment.

For each afterdischarge record, the number of sweeps during which discharge activity had actually occurred was counted and divided into ten equal parts. As is indicated in Figs. 6 and 8, each sweep consisted of three separate traces, two of them recording principally the slow epileptiform bursts at two different points in the slab, and the other recording at higher gain and with a shorter time constant the action potential spikes from the same point as one or other of the slow bursts. In general, one burst-spike episode was analysed from the first sweep of each of the ten portions of the record. The precise manner of this analysis, and the subsequent statistical analysis of the burst-spike parameters measured, are discussed in the subsection following.

In the case of chronic slabs, afterdischarges were divided somewhat arbitrarily into two parts: the 'acute phase' being the part immediately following stimulation and apparently similar to an acute slab afterdischarge; the 'chronic phase' being that subsequent part which persisted often for many minutes or even hours and which was usually characterised by bursts of high amplitude and very low frequency.

Continuous photographic recording of these prolonged afterdischarges was considered neither practical nor necessary. Instead the acute phase was recorded and then, after an interval of about five minutes, a sample of the chronic phase. The record of approximately the first ten seconds of the acute phase was divided into ten equal parts and analysed in the manner indicated above. Chronic phase bursts were of such low frequency and constant shape that usually not many more than ten consecutive burst-spike episodes were recorded, and so no sampling of the record prior to analysis was necessary.

It must be noted here that, of the five chronic slabs used, the three which were less than one year chronic (3,3, and 7 months) regularly gave afterdischarges which persisted long enough to enter the chronic phase (i.e., for analysis purposes, of duration greater than five minutes); while the two which were more than one year chronic (14 and about 18 months) most often gave shorter afterdischarges from which chronic phase data were not obtainable.

Certain qualitative characteristics of the burst-spike episodes became apparent in the course of examining in detail a large number of afterdischarge records. These, apart from a few which are intimately connected with the measurement of burst-spike parameters (see subsection following), are briefly described in the remainder of the present sub-section.

In general, a single epileptiform burst appears to develop from, and sooner or later to return to, an inter-burst potential which over times comparable to the average burst length is more or less constant (see, e.g., Plates IX(i) and XIII). Within these limits, the

shape of the burst itself may vary through a very wide range. However, there are a number of trends in burst shape which recur sufficiently often to demand attention; these may be enumerated as follows:

1. The potential most often rises to its peak (of negativity, which is represented by upward displacement in all the records from which the Plates are copied) more quickly than it afterwards returns to its inter-burst baseline (e.g., Plates VI(ii), VII(ii), XI(i), and XIV(i)); however, sometimes the reverse is true (e.g., Plate VIII).

2. Whilst the majority of bursts appear virtually monophasic negative-going (e.g., Plates VII(i) and IX(i)), many bursts occur which are more or less biphasic, most often with a positive phase preceding the negative phase (e.g., Plates VII(ii) and XIII) though sometimes with it following (e.g., Plate V(ii)). Occasionally bursts occur which are truly triphasic, with a positive phase both preceding and following the negative phase (e.g., Plate XIII(ii)). Also occasionally, bursts occur in which there is no evident negative phase at all, only a positive phase (e.g., Plate II). Sometimes it is hard to decide which part of a record represents the burst and which the baseline; and in this case, of course, the burst polarity must also remain doubtful.

3. Bursts not infrequently occur in pairs (e.g., Plates VII(i), VIII, and XI(i)), triplets (e.g., Plate VIII),or

even quadruplets; following such multiple bursts there may be a comparatively long interval before the next burst or group of bursts appear.

4. Another noticeably frequent burst shape is what may be termed the 'hump-plateau' shape. This seems to occur most often in afterdischarges from chronic slabs, particularly when in or entering the chronic phase (e.g., Plate X(ii)), and usually in such cases the 'plateau' is of far greater amplitude and duration than the 'hump'; however, bursts of this shape do occur in after-discharges from acute slabs also, most frequently towards the end (e.g., Plates VI(ii) and XIV(i)). 'Hump-plateau' bursts may perhaps be regarded as modified paired bursts in which the second burst of the pair has become the 'plateau'; Plate XI(i) perhaps represents an intermediate stage in this modification. Occasionally the hump and plateau are reversed, giving a 'plateau-hump' burst (e.g., Plate XIV(ii)).

Burst shape may remain practically constant throughout an after-discharge, or it may change slowly (e.g., Plates I and II, and V and VI), particularly in the development of biphasicity or triphasicity (e.g., Plate XIII(ii)), or, less frequently, it may change quite suddenly so that consecutive bursts are of quite different shapes (e.g., Plates IX(ii) and X(i); the latter is perhaps suggestive of two different 'populations' of burst type superimposed). To a slightly lesser extent these same remarks may be applied also to burst frequency. In the case of chronic slab

afterdischarges in the chronic phase, there is practically never any appreciable change between one burst and the next; indeed, the typical low frequency prolonged hump-plateau bursts (see paragraph 4 above) may be characterised as 'chronic type', as compared to the generally more frequent, shorter, and often better defined 'acute type' (see Plate IX(i)).

On average, when recording simultaneously from two separate microelectrodes at two different positions in the slab, the microelectrode nearer the stimulated point records bursts of greater amplitude; this observation is considered quantitatively in subsection 4 following. However, in any individual afterdischarge it is not uncommon to find that this average result does not apply. Information concerning the mode of initiation and spread of an afterdischarge may perhaps be gained by close study of the first few bursts of activity to appear, particularly having regard to development of amplitude. Plate XII shows burst activity commencing close to the stimulated point after two stimulus bursts and further away after three; after only one stimulus burst in this case (not shown in Plate), no burst activity was observed at either microelectrode.

Despite the unsuitability for intracellular recording of most of the microelectrodes used (see Section III, 2(b)), attempts were made from time to time to achieve stable intracellular penetration and recording, usually by driving the microelectrode very slowly forward by means of the oil drive during the prolonged chronic phase of a chronic slab afterdischarge. An example of a chronic phase burst recorded intracellularly following a successful penetration achieved as a result of such probing is shown in Plate XV; the recorded polarity of the burst is reversed from the usual negative-going, and the amplitude

appears considerably greater than usual. A later burst of the same afterdischarge recorded with the oil drive in the same position but with the microelectrode having presumably become extracellular is shown in Plate XVI for comparison. It must be added here that the number of records of intracellular burst-spike activity obtained was only a small fraction of the number of occasions on which a stable intracellular penetration, judged by the appearance and persistence of a presumed resting potential, was achieved while an afterdischarge was in progress.

Concerning burst-spike relations, the most usual pattern is for a train of spikes to be more or less closely correlated with the occurrence of a burst (see, e.g., Plates VI(ii), VII(i), IX(i), XI(i), XIII, and XIV). In addition, however, it is quite common to observe bursts with no apparent accompanying spikes (e.g., Plates II and VII(ii)), and conversely, rather less frequently but by no means rarely, spikes occurring independently of bursts. In the latter case several different patterns of spike activity were observed; these were as follows:

1. Spikes may occur more or less continuously, independently of the presence or absence of slow bursts; the spikes themselves may be either regular (e.g., Plate V) or irregular (e.g., Plates I, II, and III(ii)) in frequency and amplitude. Continuous spike activity of this type seems to occur particularly often at the beginning (as Plates III(ii) and V(i)) or end of an afterdischarge when the bursts give the impression of either 'building up' or 'dying down'.

2. Spikes may occur individually and apparently randomly between the burst-spike episodes of an afterdischarge (e.g., Plate I) or at some time after an afterdischarge (or, at least, epileptiform activity) has ceased (e.g., Plate III(i)); of course, the distinction between such 'individually occurring' spikes and those described as 'continuous' in paragraph 1 above might be considered to be merely a gross difference in frequency.

3. Very occasionally it seems that a discrete train of spikes, such as normally constitutes the spike activity of a burst-spike episode, may occur in the absence of any accompanying slow burst (e.g., Plate IV).

Note on Plates (including Scales)

The various plates which constitute the pages immediately following this note are copies of enlargements made directly from the 35 mm negative film used for photographic recording during the experiments. For details of the method of this recording, and for explanation of the apparent 'slope' (gradient) of the traces in the plates, see Section III, 3(a).

The direction of motion of the film in the camera at the time of recording was such that in each plate the earliest sweeps are those nearest the bottom of the plate. Each sweep in fact consists of three separate traces (see Section III, 3(a); Section IV, 1; and Figs. 6 and 8) except that in experiments where only one microelectrode was used each sweep consists of only two traces. Each individual trace in the plates is labelled for reference at its right hand end by a subscripted letter 'V' and a number. The subscripted 'V' indicates through which channel the trace was recorded (in accordance with the symbolism of Fig. 6; when only one microelectrode was used, V_2 is absent). The number separated from the 'V' by a colon, is the number of the sweep: each sweep in each acute and chronic (acute phase) afterdischarge was numbered in the course of analysis, starting with the first complete sweep after the end of stimulation as 'sweep 1'; thus separate traces belonging to the same sweep may be identified as such by their numbers even though in the plate they may be separated by one or more traces of an adjacent sweep. In chronic (chronic phase) afterdischarges, and in other cases where no stimulation appeared on the record to provide a basis for numbering, traces belonging to the same sweep are not numbered, but are labelled by a common block capital letter instead. Since the trace V_F is a recording through a

high-pass filter, it may be regarded as indicating a constant baseline against which shifts in the levels of V_1 and V_2 may be measured.

A reference is given in brackets at the end of the caption to each separate plate or part of a plate. This states whether the slab concerned was acute or chronic, and in the latter case whether the after-discharge was in the acute or chronic phase; it provides also the date of the experiment and the page number of the paper (Polygraph) record. Nearly all the enlargements from which the plates are copies have been slightly touched-up by hand to emphasise detail visible in the original negatives but of insufficient contrast for satisfactory photographic reproduction and copying.

Scales (to approximately $\pm$ 5% for time and $\pm$ 10% for potential) for all the plates are:

TIME: 1 sweep length on plate = 150 msecs.

POTENTIAL: V_1 and V_2 (d.c. microelectrode recording channels, providing records of epileptiform 'bursts') sensitivity is 1.6 mVolts per centimeter height measured vertically on plate, parallel to paper edge.

V_F (high gain high-pass filtered recording channel, providing record of action potential 'spikes') sensitivity is 58 μVolts per centimeter height on plate, measured as for V_1 and V_2.

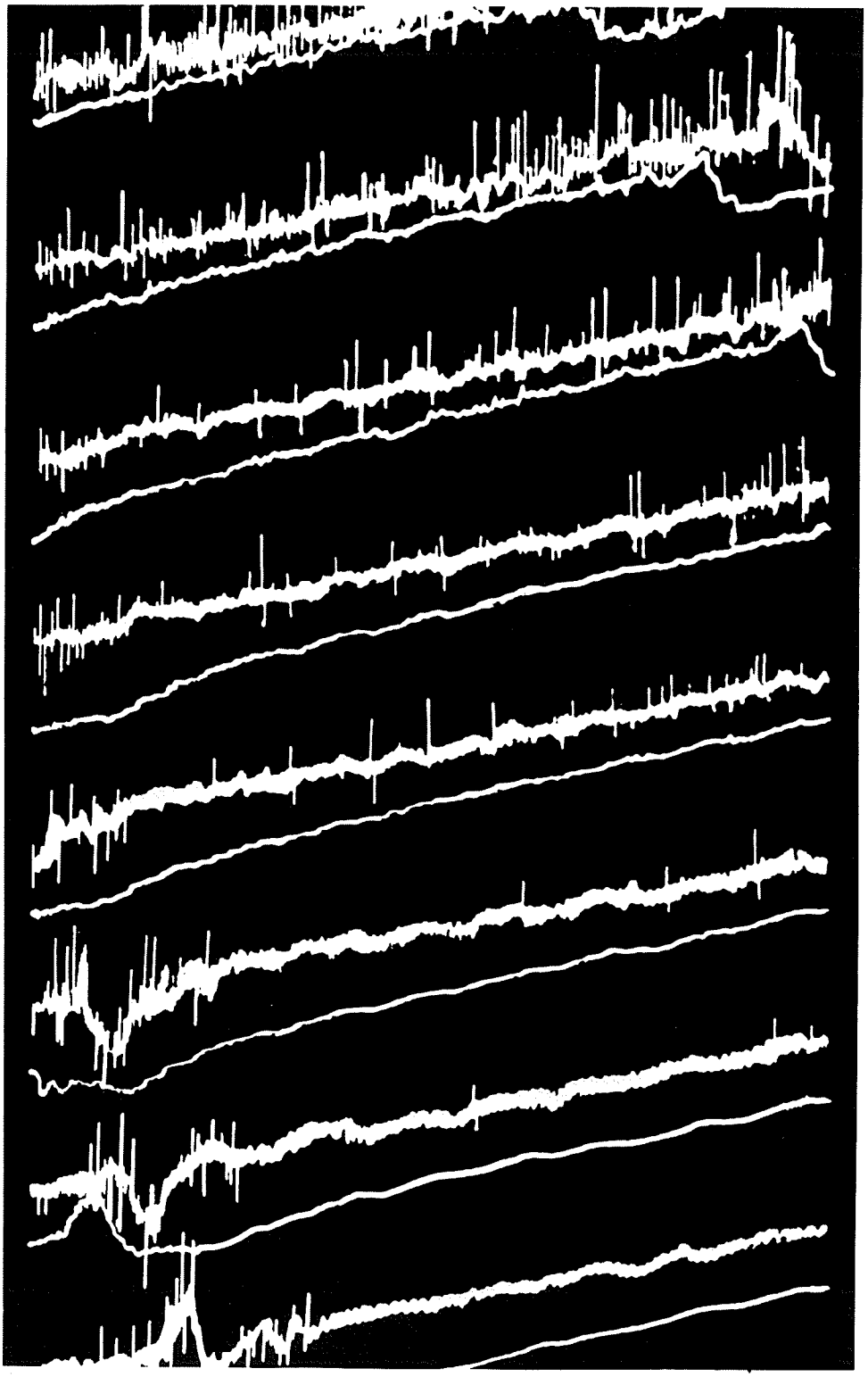


PLATE I. TRANSITION OF DISCRETE BURST-SPIKE EPISODES INTO CONTINUOUS IRREGULAR SPIKE ACTIVITY; CONTINUED IN PLATE II. [ACUTE: 21/4/65: 894]

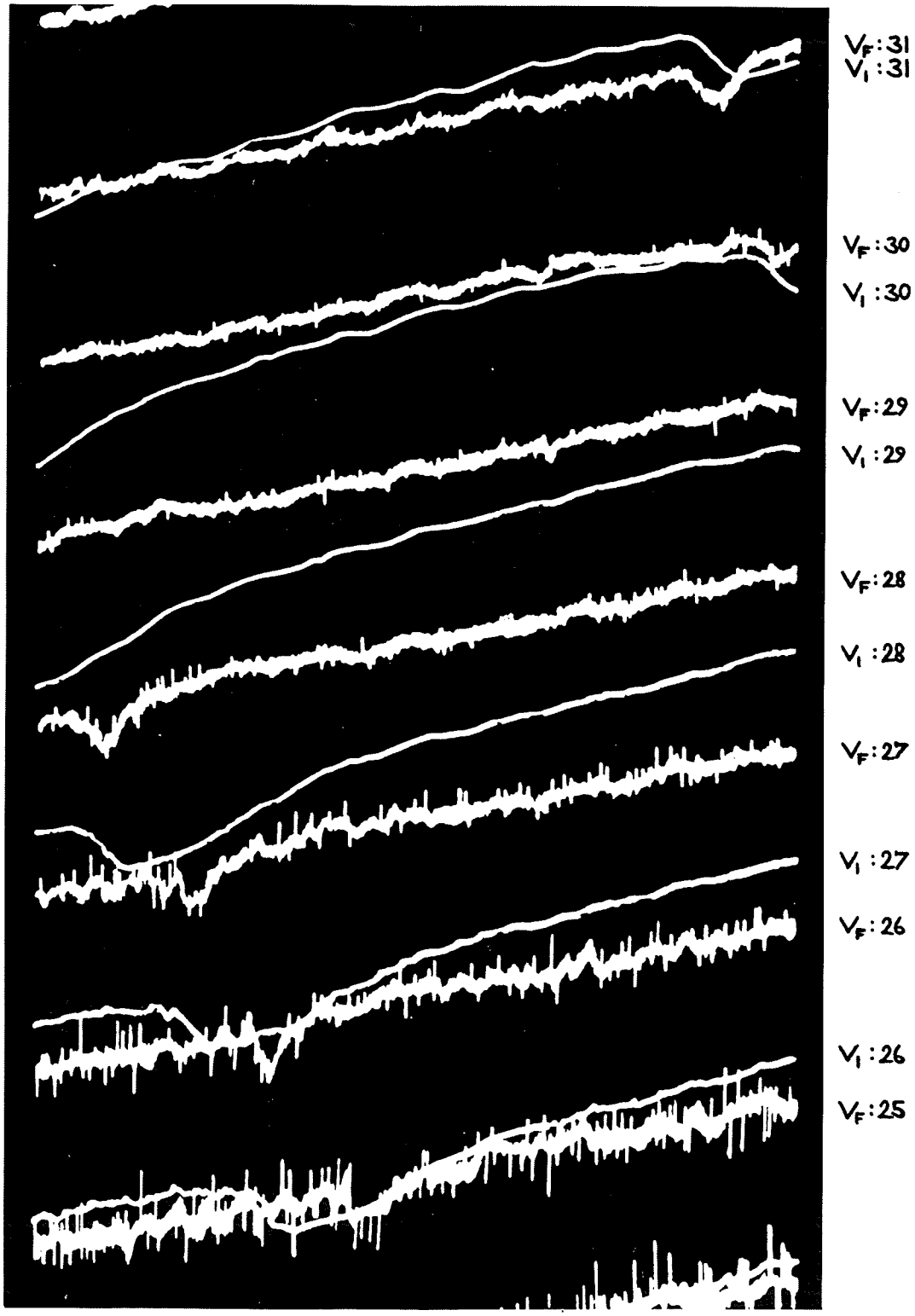
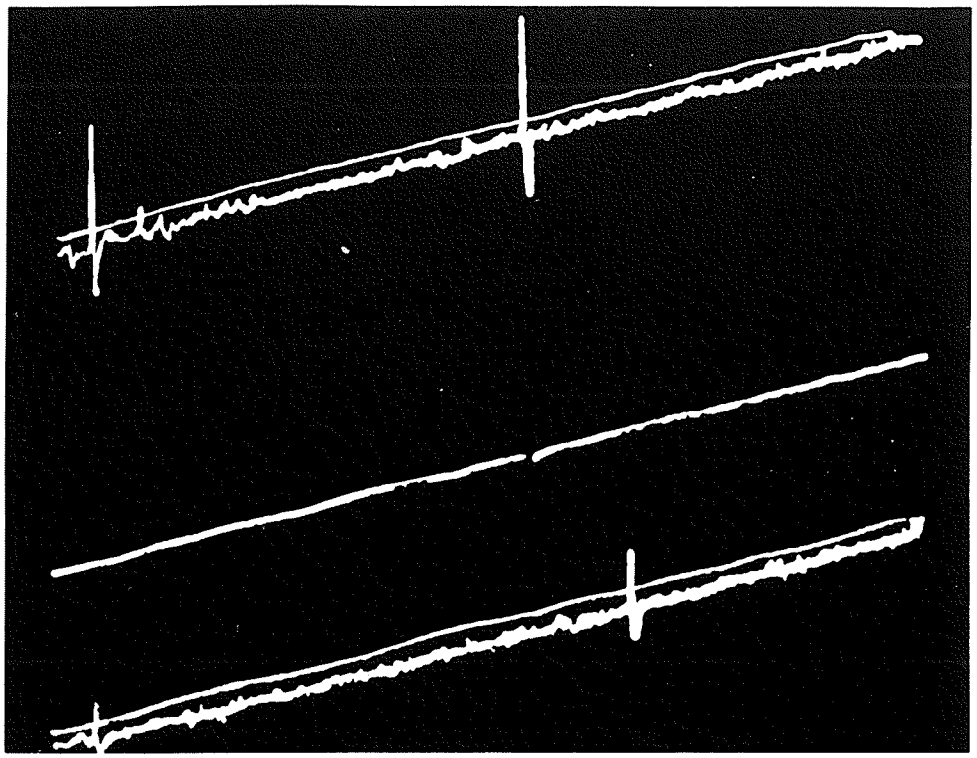


PLATE II. CONTINUED FROM PLATE I: SPIKE ACTIVITY DIES OUT, BURSTS CONTINUE, BECOMING PREDOMINANTLY POSITIVE-GOING. [ACUTE: 21/4/65: 894]

(i)



(ii)

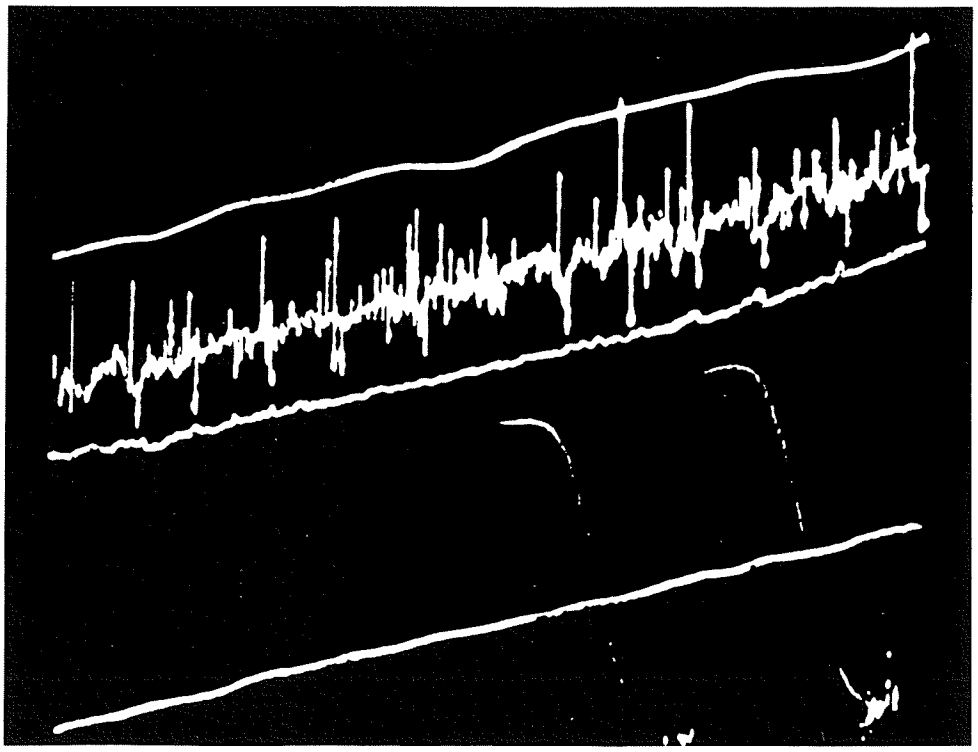


PLATE III. SPIKES WITHOUT BURSTS: (i) SPIKES OCCURRING 3½ MINUTES AFTER TYPICAL AFTERDISCHARGE (OF 10 SECS. DURATION); SUCH SPIKES CONTINUED A FURTHER ½ MINUTE. [ACUTE: 17/5/65:39-40] (ii) IRREGULAR HIGH FREQUENCY SPIKE ACTIVITY IMMEDIATELY FOLLOWING STIMULATION AND BEFORE BURSTS DEVELOP. [ACUTE: 17/5/65: 40]

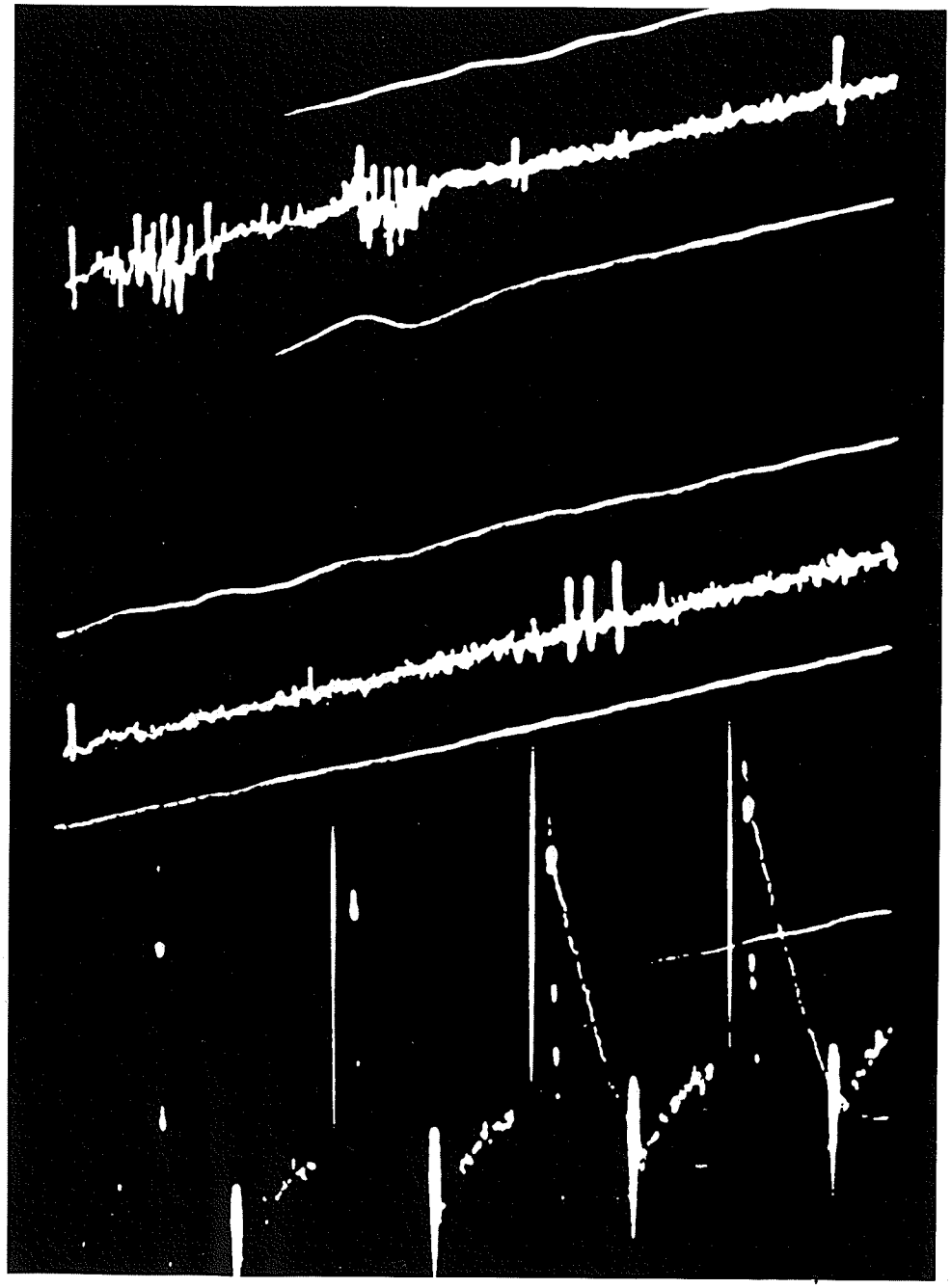
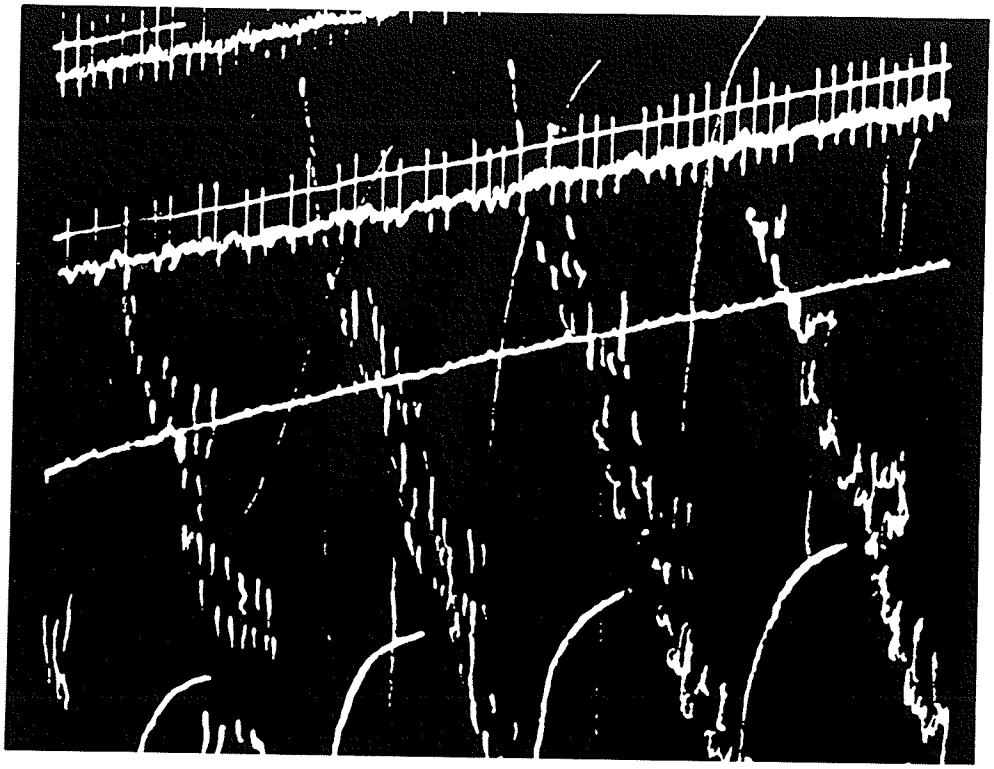


PLATE IV. 'BURST OF SPIKES' (ON V_F: 1) IN ABSENCE OF ANY CORRESPONDING SLOW BURST (ON V_1: 1); SLOW BURST ACTIVITY DEVELOPS SHORTLY AFTER (ON V_1: 2). [ACUTE: 17/5/65: 44 A]

(i)



(ii)

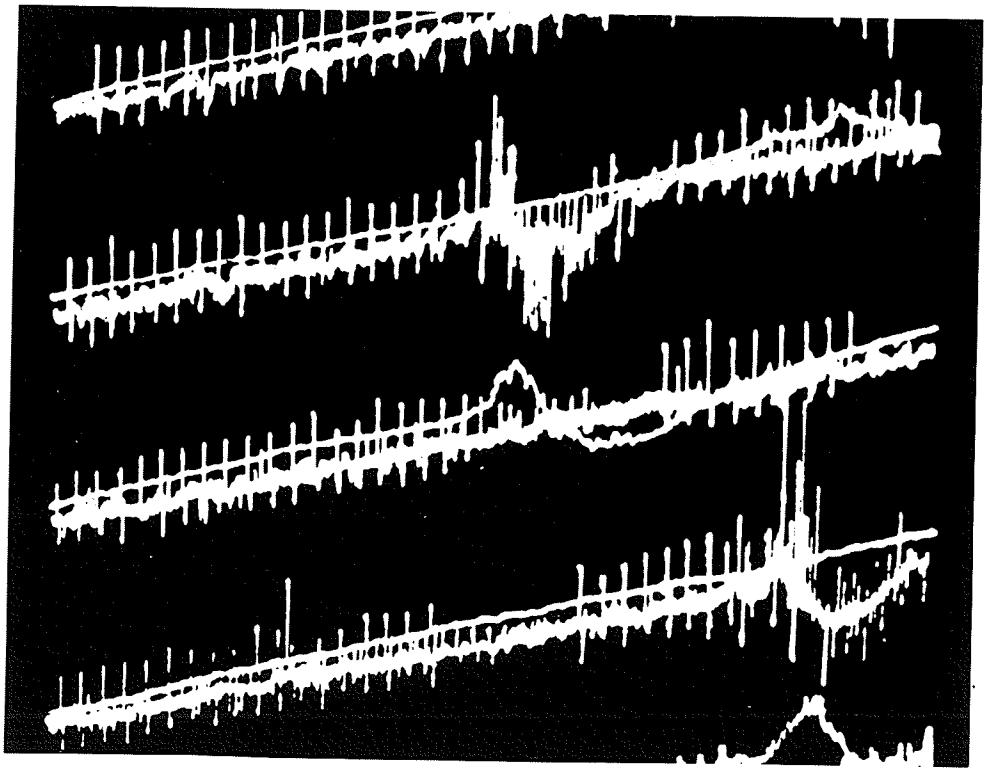
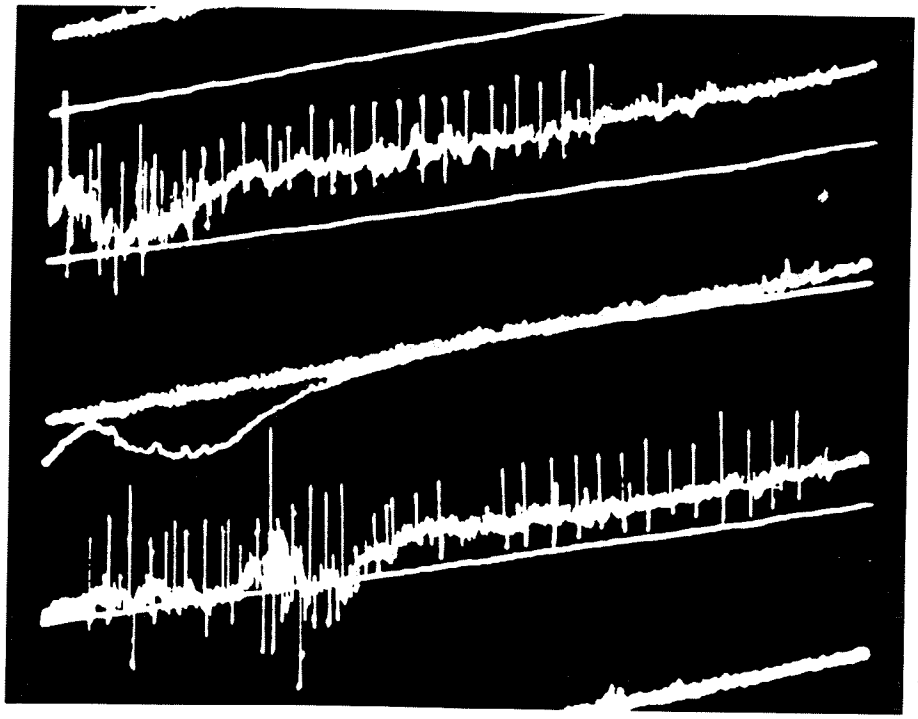


PLATE V. (i) REGULAR HIGH FREQUENCY SPIKE ACTIVITY IMMEDIATELY FOLLOWING STIMULATION AND BEFORE BURSTS DEVELOP; AND (ii) SPIKES REMAIN CONTINUOUS AFTER DEVELOPMENT OF BURSTS, 1½ SECONDS AFTER STIMULATION; CONTINUED IN PLATE VI.
[ACUTE : 21/4/65 : 926]

(i)



(ii)

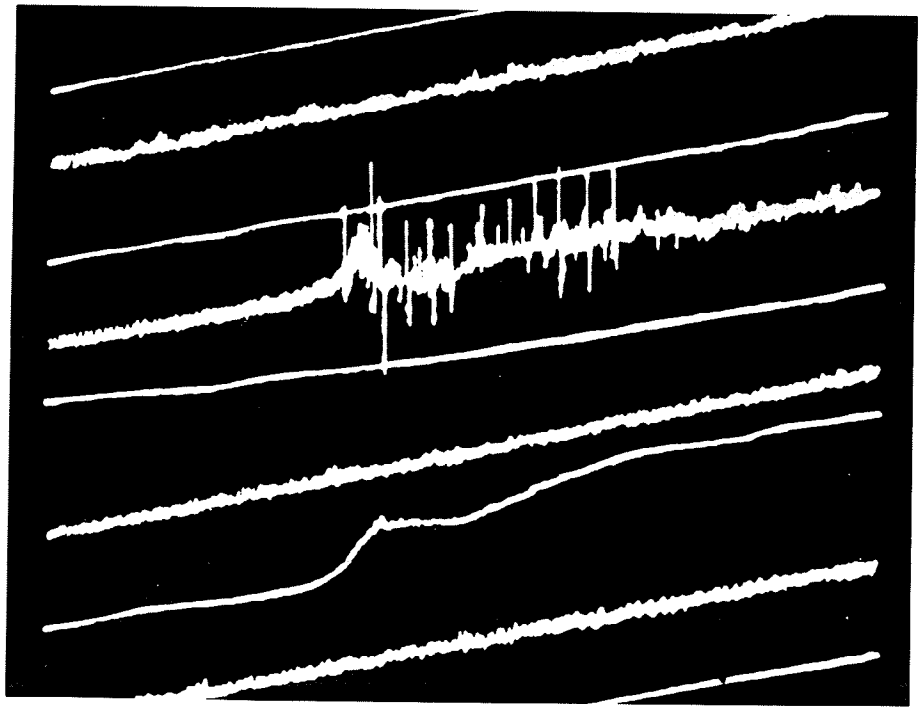
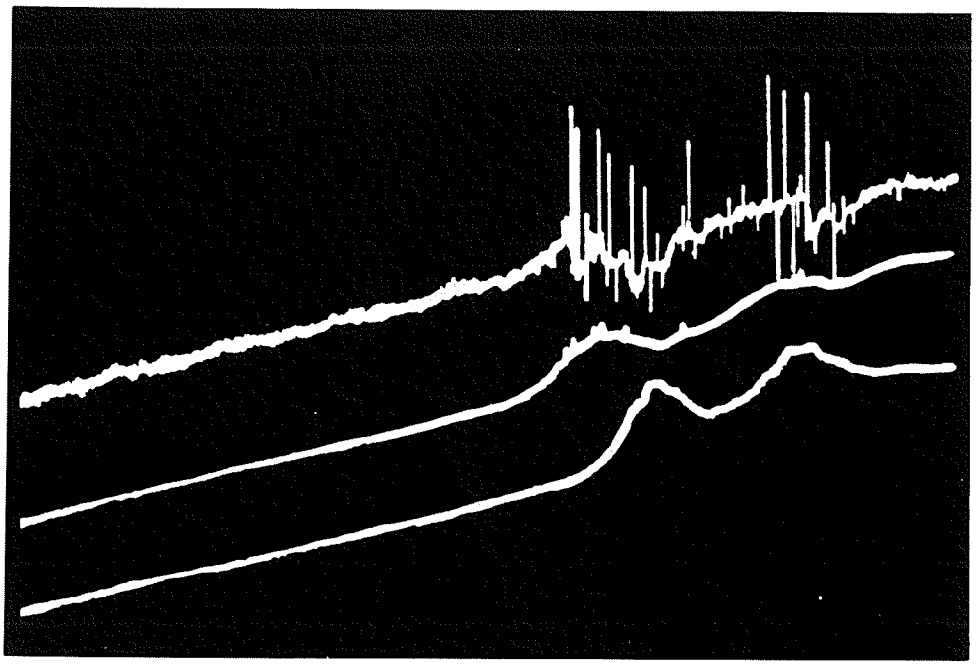


PLATE VI. CONTINUED FROM PLATE V : (i) SPIKE ACTIVITY BECOMES DISCONTINUOUS, BURST-SPIKE EPISODES DISCRETE. (ii) LAST BURST-SPIKE EPISODE, 3½ SECONDS AFTER STIMULATION; FOLLOWED ONLY BY A FEW WIDELY SEPARATED ISOLATED SPIKES (NOT ON PLATE). [ACUTE : 21/4/65 : 926]

(i)



(ii)

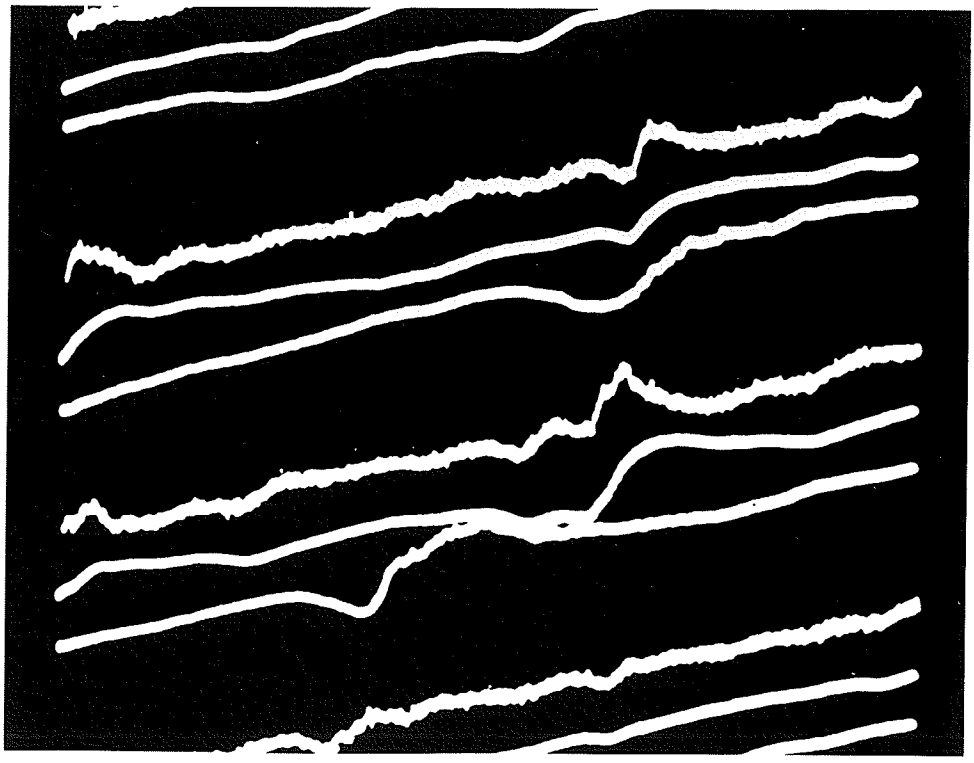


PLATE VII. (i) GOOD EXAMPLE OF BURST-SPIKE EPISODE WITH CLEARLY DEFINED d AND δ INTERVALS; BURSTS ARE 'DOUBLE' TYPE. [ACUTE : 9/6/65 : 340] (ii) BURSTS WITHOUT SPIKES, 10 SECONDS AFTER STIMULATION; NO SPIKES OCCURRED AT ANY TIME DURING THIS AFTER-DISCHARGE WHICH LASTED 5 MINUTES. [CHRONIC (ACUTE PHASE): 2/7/65 : 519 B]

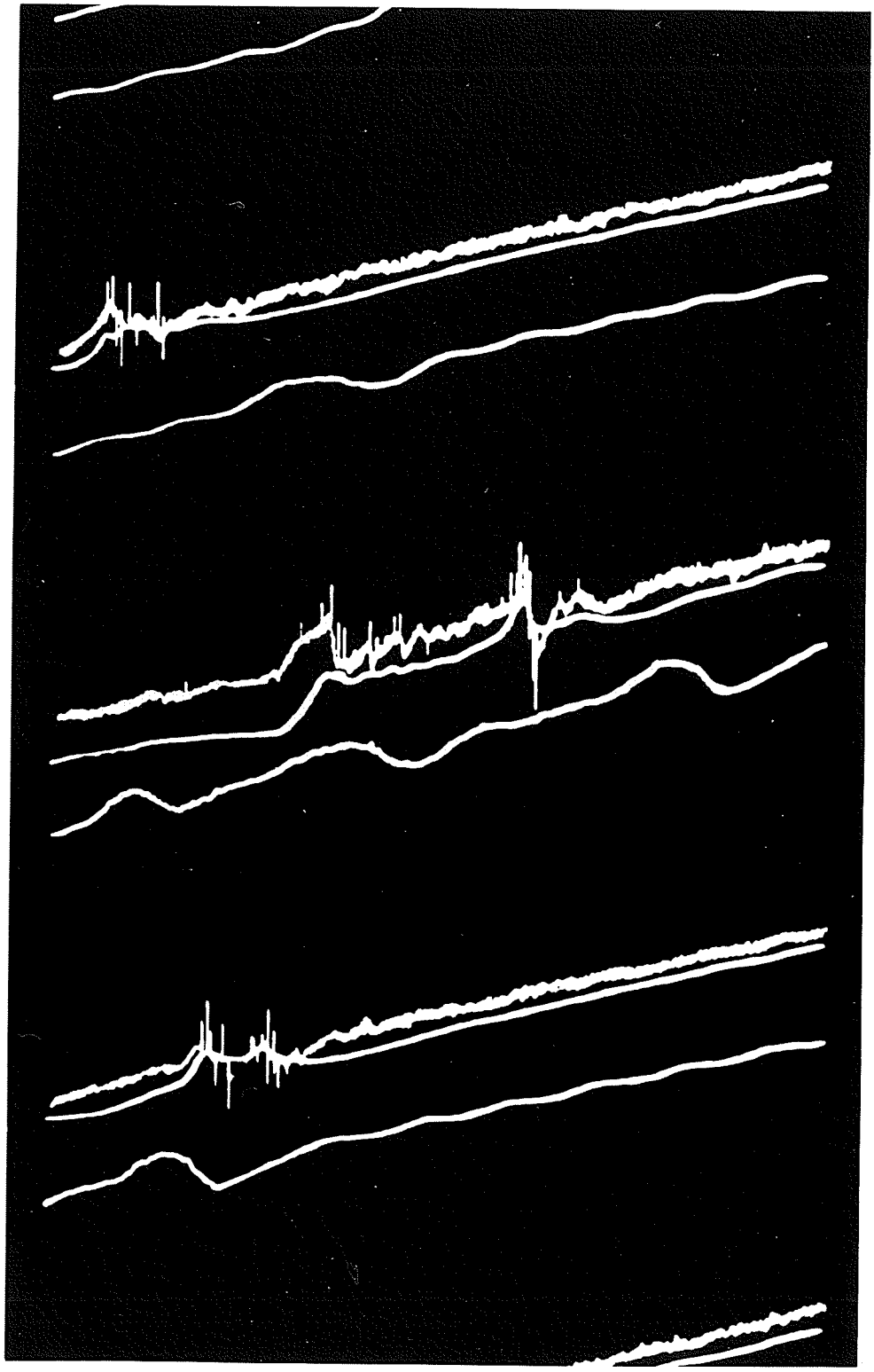
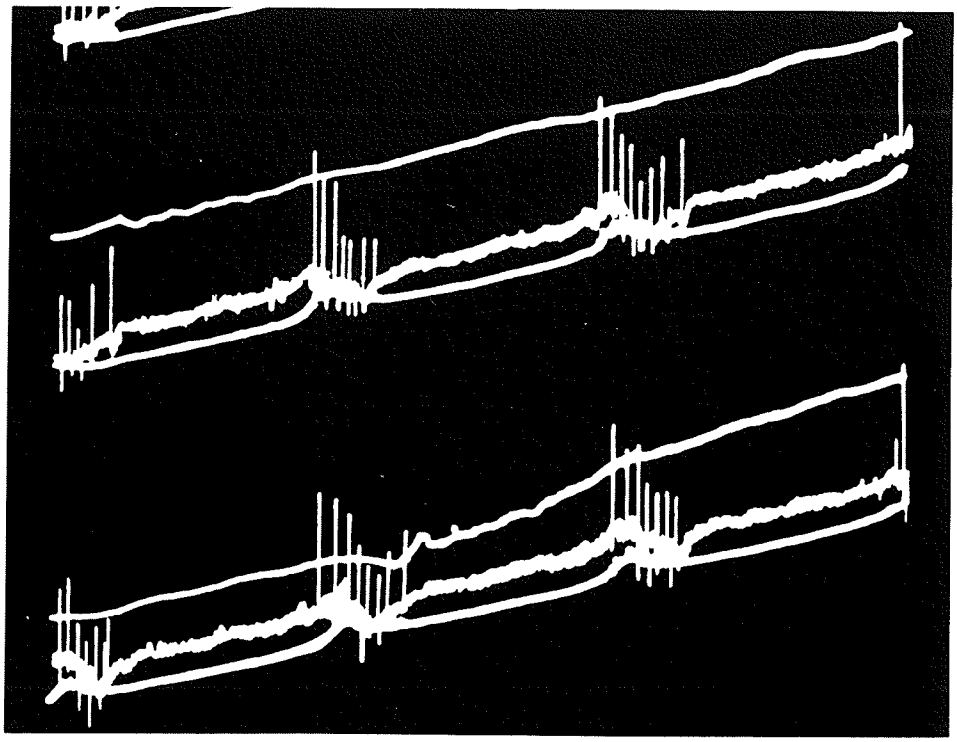


PLATE VIII. INCORRELATABLE BURSTS ON V_1 AND V_2 (SWEEP 26), 4 SECONDS AFTER STIMULATION; CORRELATION WAS DIFFICULT THROUGHOUT THIS AFTERDISCHARGE. [ACUTE : 9/6/65 : 364]

(i)



(ii)

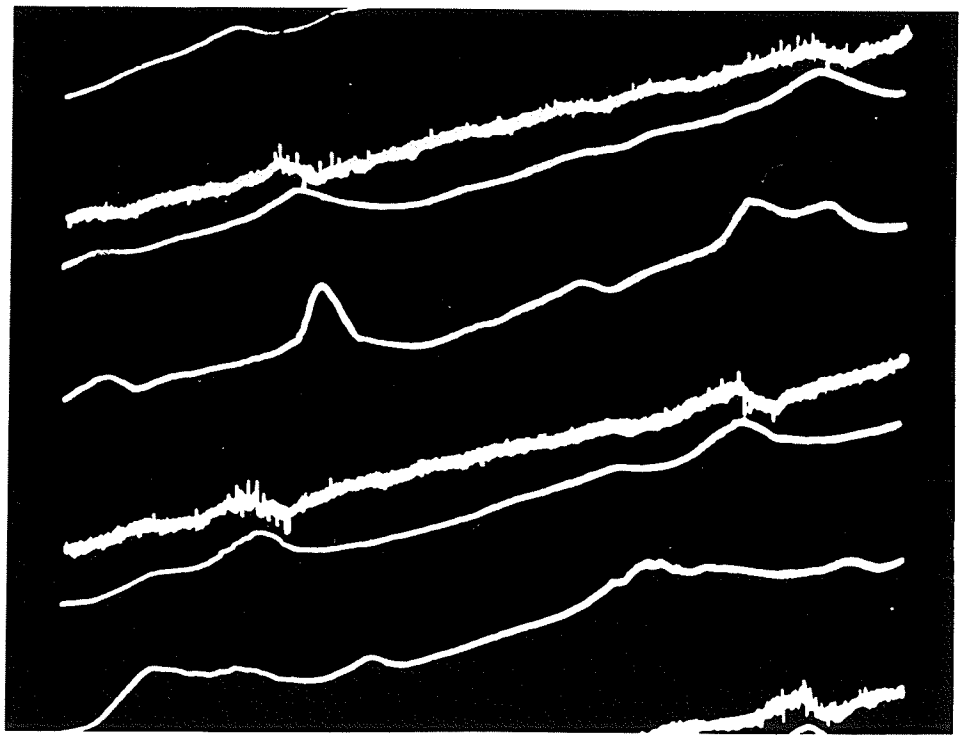
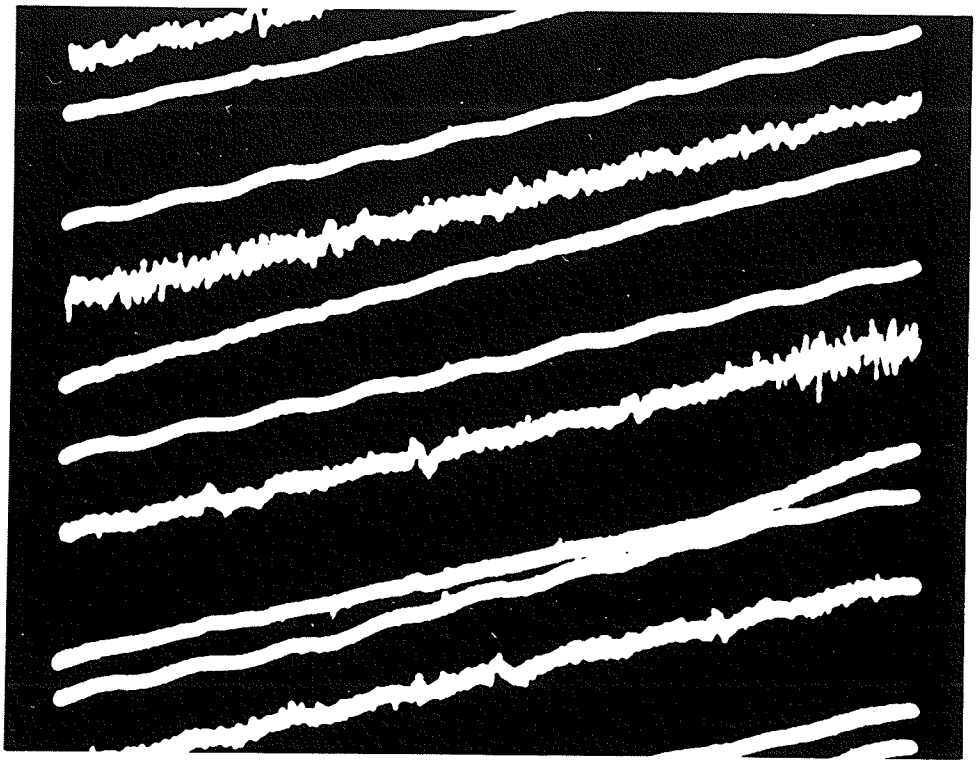


PLATE IX. (i) REGULAR 'ACUTE TYPE' BURST-SPIKE EPISODES ON V_1, 'CHRONIC TYPE' LONG SLOW BURSTS ON V_2, CORRELATION IMPOSSIBLE; V_2 SHOWED ONLY THIS PATTERN THROUGHOUT THE AFTER-DISCHARGE. [CHRONIC (ACUTE PHASE): 21/6/65 : 427] (ii) VARIATION IN SHAPE BETWEEN CONSECUTIVE BURSTS (ON V_2 : 20). [CHRONIC (ACUTE PHASE): 23/7/65 : 671]

(i)



(ii)

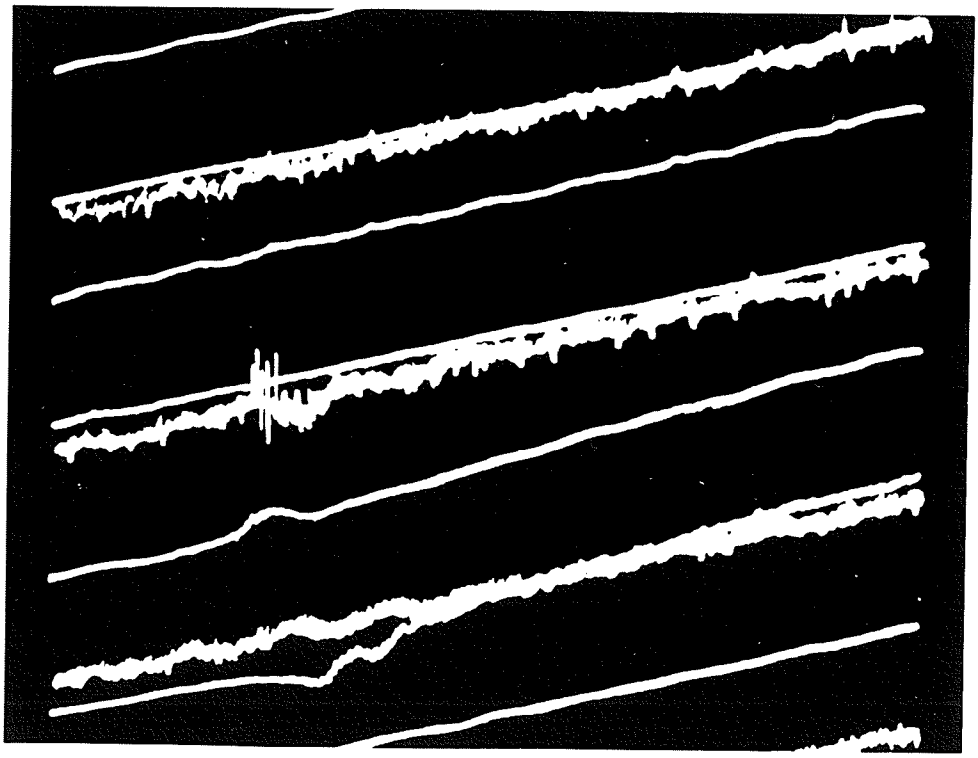
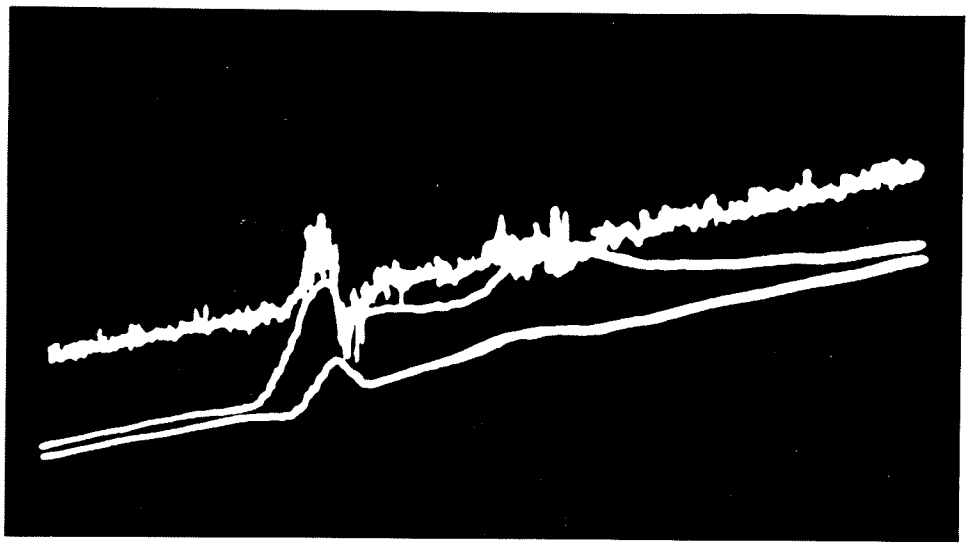


PLATE X. (i) CHRONIC TYPE BURST-SPIKE EPISODE (COMMENCING ON SWEEP B AT RIGHT) PRECEDED BY SEVERAL VERY BRIEF BURSTS OF ACTIVITY (SEEN ON V_F : B). [CHRONIC (CHRONIC PHASE) : 12/7/65 : 565] (ii) TYPICAL CHRONIC TYPE BURST-SPIKE EPISODE (COMMENCING ON SWEEP B); BURST IS REPRESENTED AS PROLONGED NEGATIVE SHIFT IN V_1 AND V_2. [CHRONIC (CHRONIC PHASE) : 25/6/65 : 471 B]

(i)



(ii)

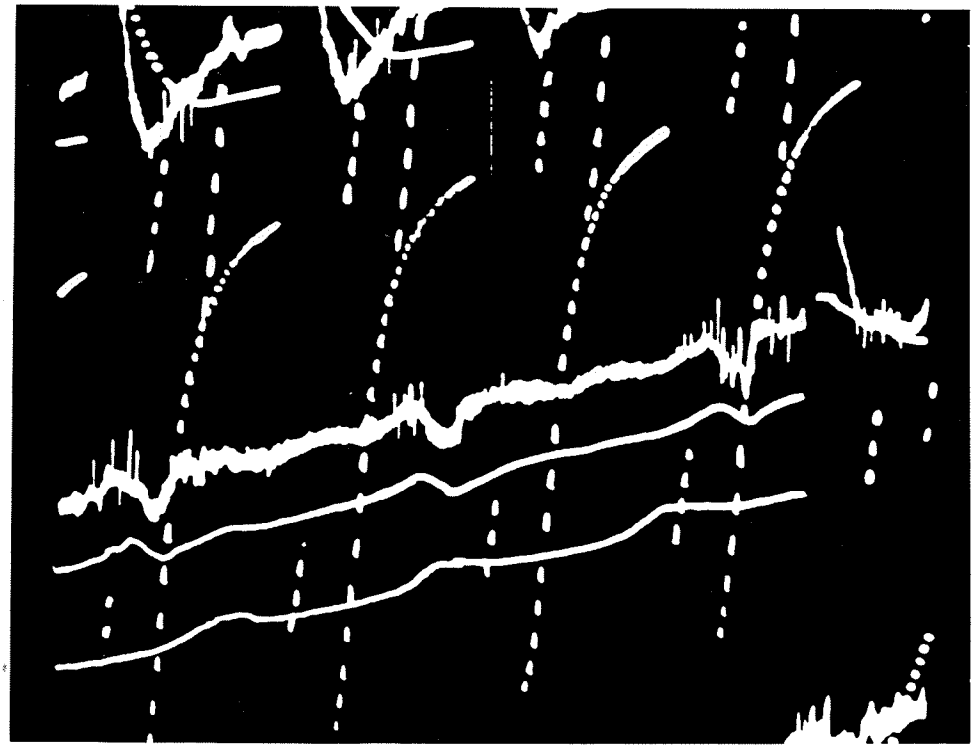
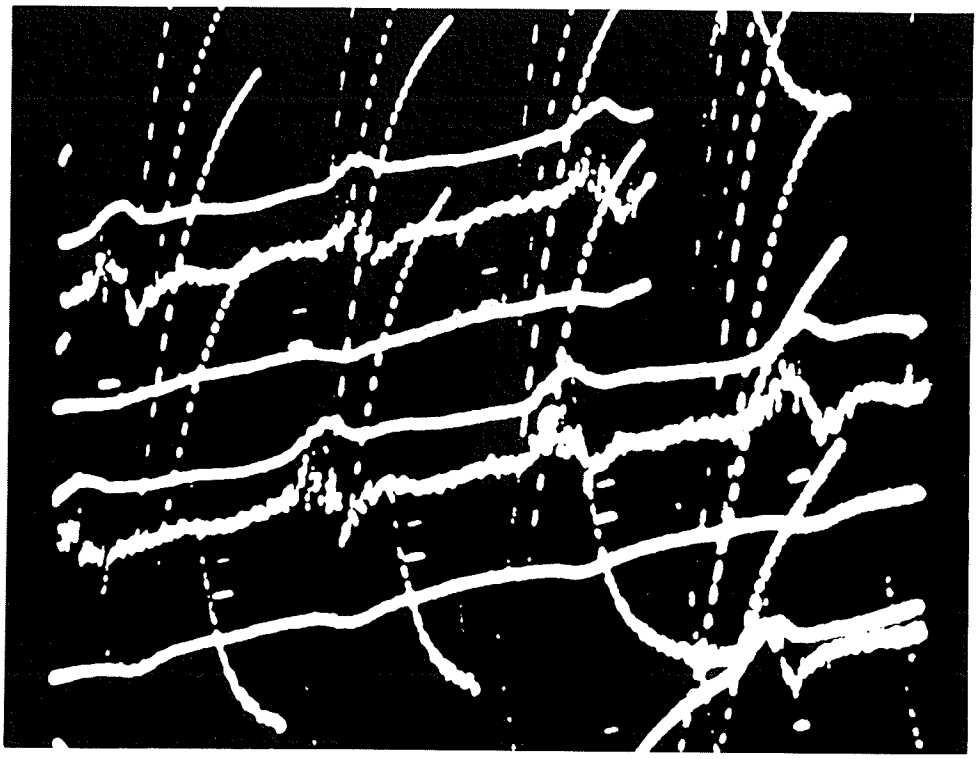


PLATE XI. (i) CLEARLY DEFINED δ INTERVAL, YET BURST MAXIMA ON V_1 AND V_2 ARE NEARLY SIMULTANEOUS; THIS PATTERN OF BURST-SPIKE EPISODE PERSISTED THROUGHOUT THE AFTERDISCHARGE. [ACUTE : 17/5/65 : 5] (ii) REVERSAL OF SIGN OF δ WITHIN ONE SWEEP; SIMILAR REVERSALS OCCURRED THROUGHOUT ACUTE PHASE. [CHRONIC (ACUTE PHASE) : 21/6/65 : 408]

(i)



(ii)

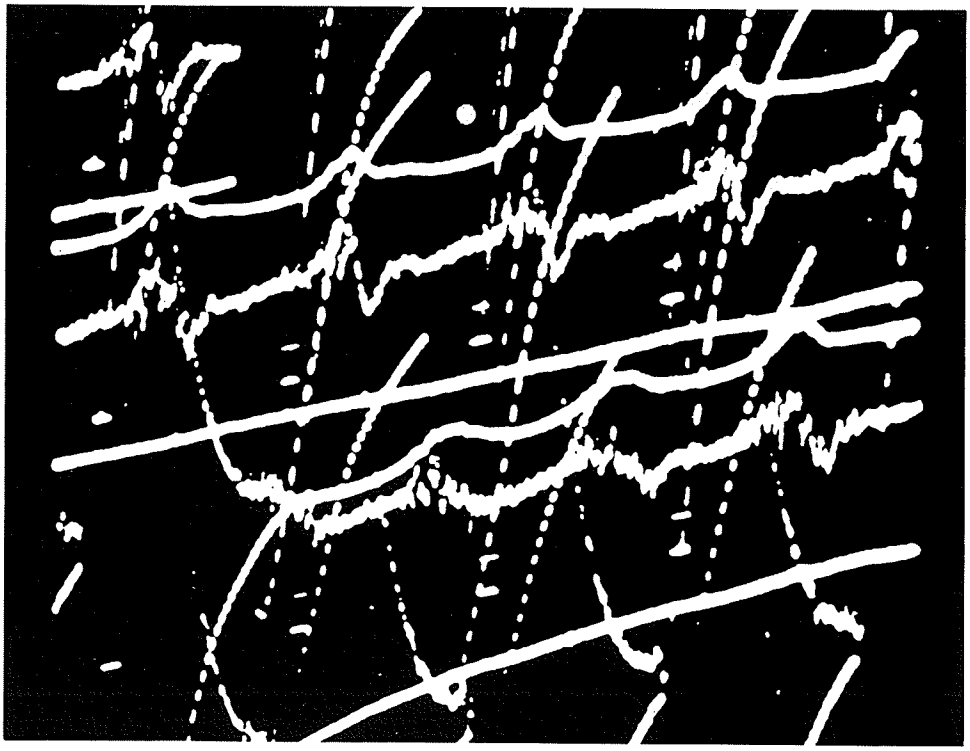
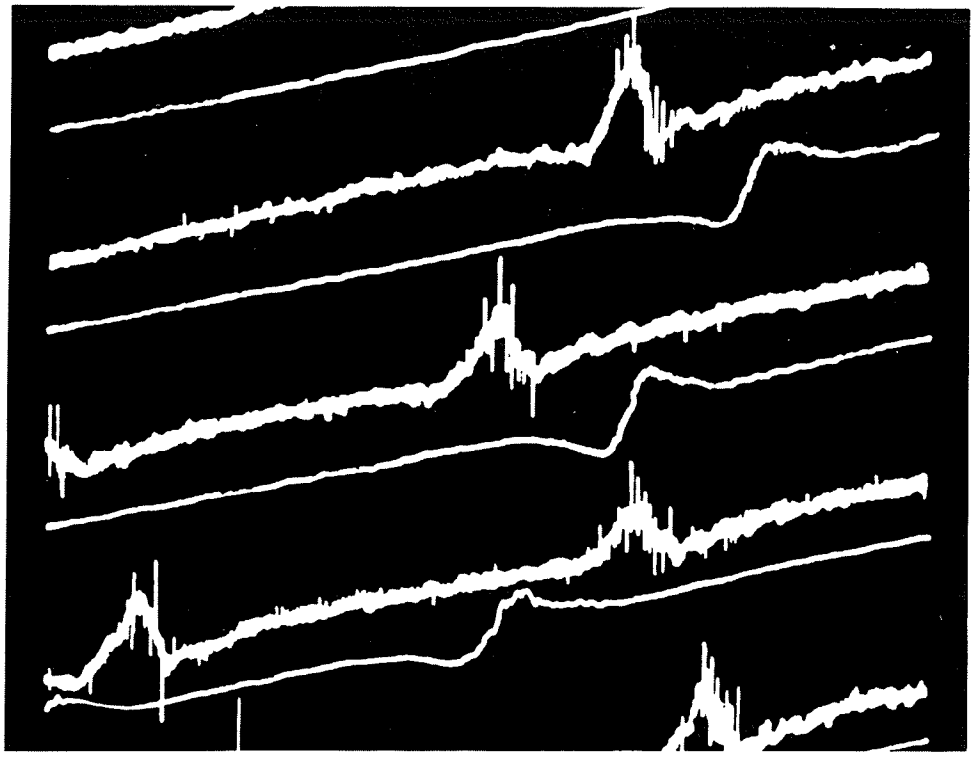


PLATE XII. DEVELOPMENT OF ACTIVITY AT DIFFERENT DISTANCES: V_1 AND V_2 WERE RECORDED 3·5 mm AND 6·8 mm POSTERIOR TO THE STIMULATED POINT RESPECTIVELY: (i) AFTER THREE STIMULUS BURSTS ACTIVITY IS CLEARLY VISIBLE IN BOTH V_1 AND V_2, WHEREAS (ii) AFTER TWO IT IS ONLY VISIBLE IN V_1. [CHRONIC (ACUTE PHASE): 2/7/65: 511 B]

(i)



(ii)

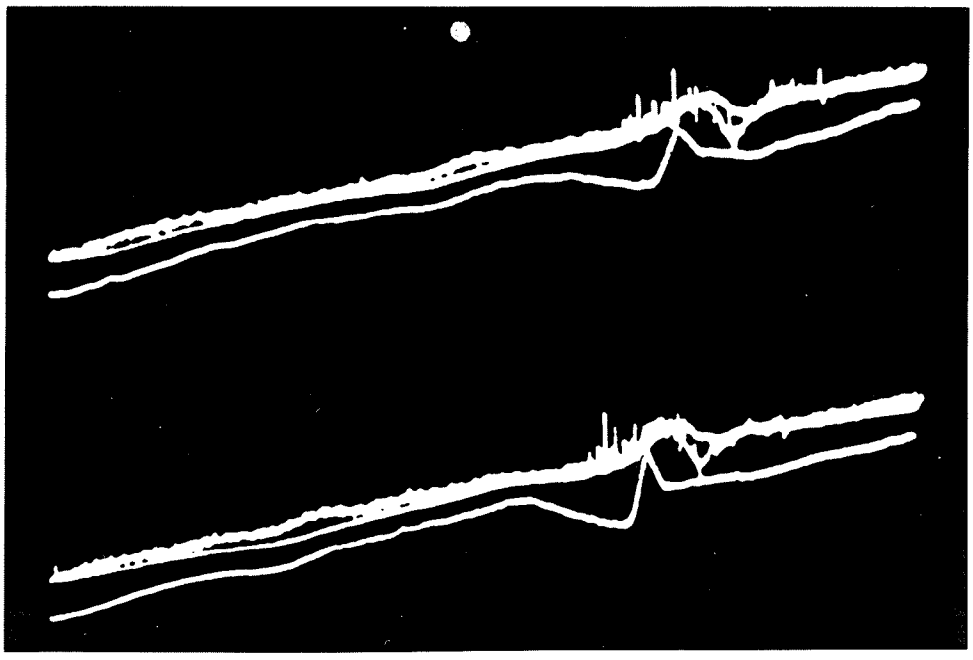
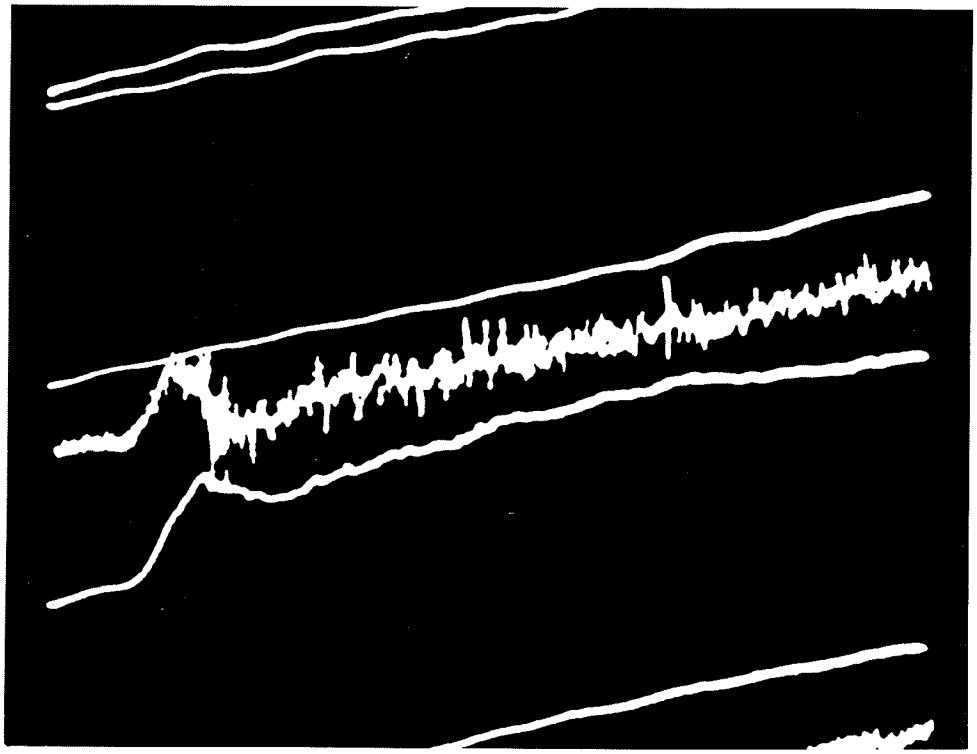


PLATE XIII. (i) BIPHASIC BURSTS WITH POSITIVE INITIAL PHASE FOLLOWED BY NEGATIVE PHASE; SPIKES (ON V_F) COMMENCE ONLY ON COMMENCEMENT OF NEGATIVE PHASE (ON V_1). [ACUTE : 21/4/65 : 931]
(ii) BIPHASIC BURST ON V_2 : 26, TRIPHASIC BURST ON V_2 : 27; BURSTS ON V_1 ARE ALMOST MONOPHASIC. [CHRONIC (ACUTE PHASE) : 25/6/66 : 487]

(i)



(ii)

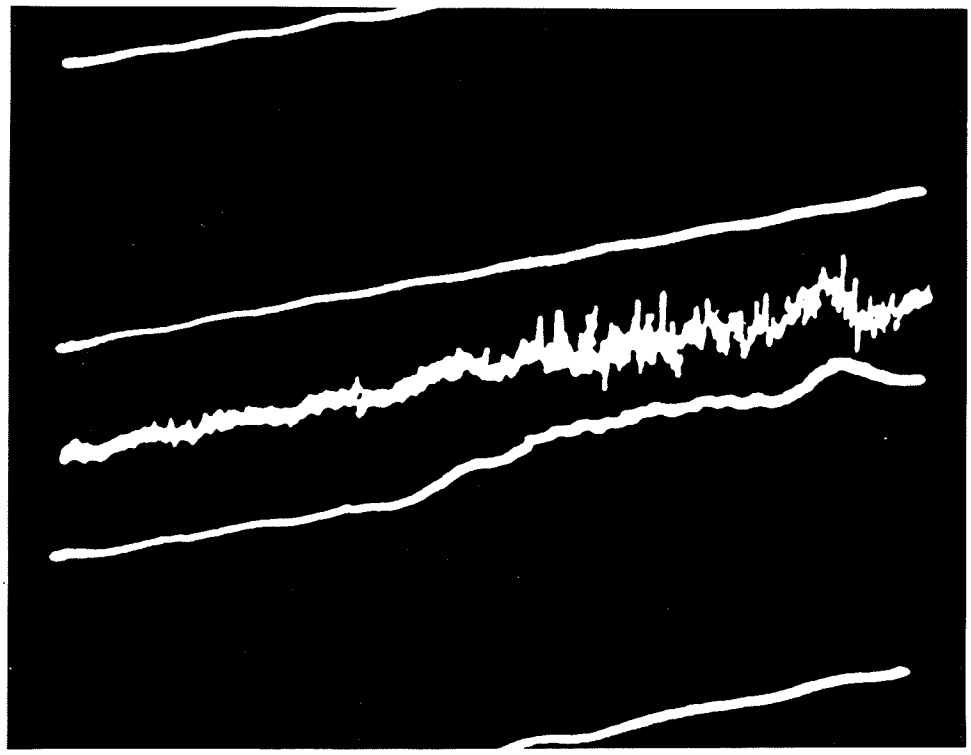


PLATE XIV. (i) 'HUMP - PLATEAU' BURST OCCURRING 8 SECONDS AFTER STIMULATION, TYPICAL OF ALL BURST-SPIKE EPISODES IN AFTERDISCHARGE EXCEPT (ii) 'PLATEAU - HUMP' BURST, 10 SECONDS AFTER STIMULATION, TYPICAL OF LAST FEW. [ACUTE : 1/6/65 : 237]

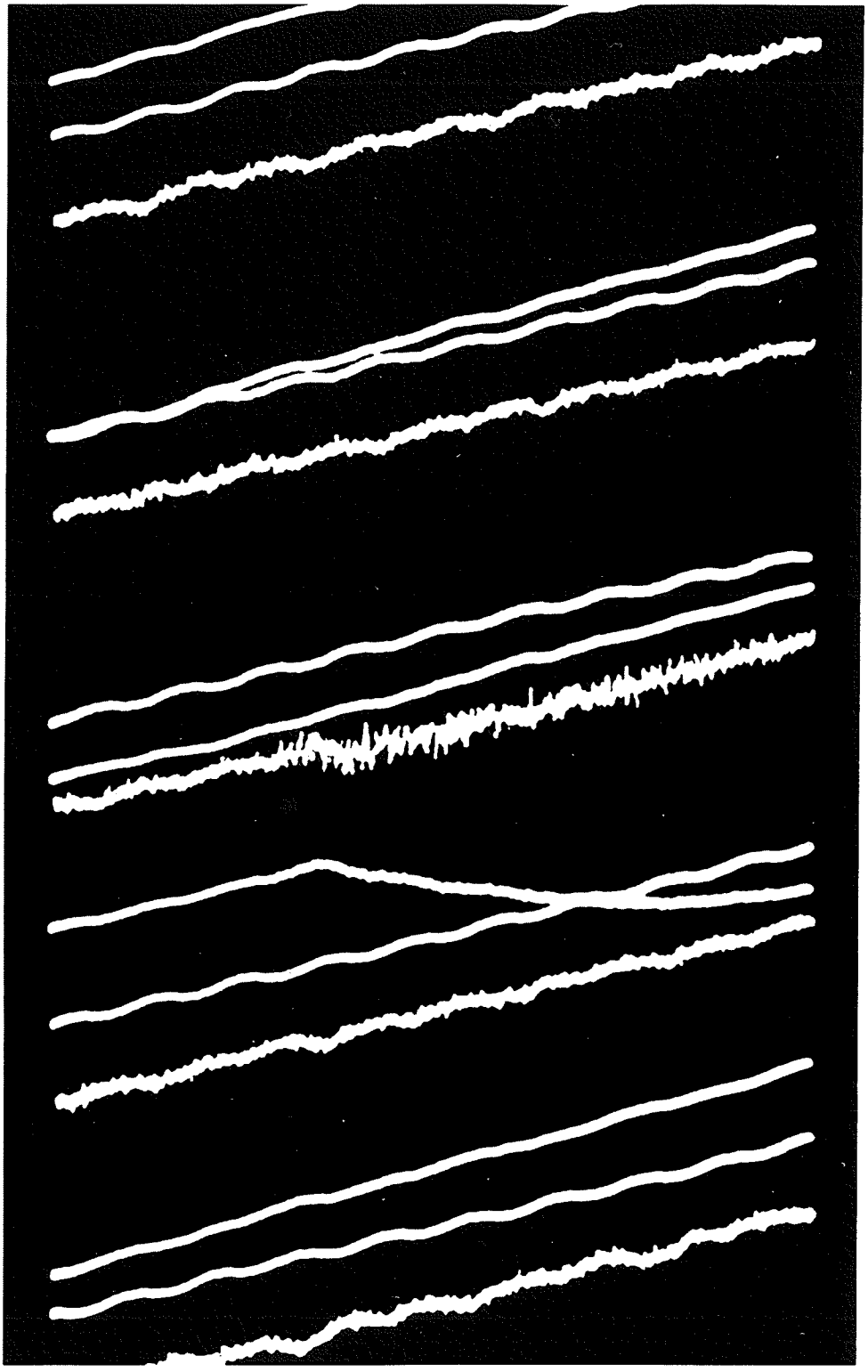


PLATE XV. PRESUMED INTRACELLULAR BURST-SPIKE EPISODE RECORDED 4 MINUTES AFTER STIMULATION IMMEDIATEY FOLLOWING ABRUPT CHANGE IN D.C. LEVEL OF V_1 REQUIRING 79 mV (ON P6 'ELECTRODE VOLTAGE') TO BALANCE: PRESUMED PENETRATION WHILE PROBING USING OIL DRIVE. D.C. LEVEL REMAINED STABLE ABOUT 1 MINUTE, THEN SLOWLY FELL. CONTINUED IN PLATE XVI.
[CHRONIC (CHRONIC PHASE): 12/7/65 : 580 B]

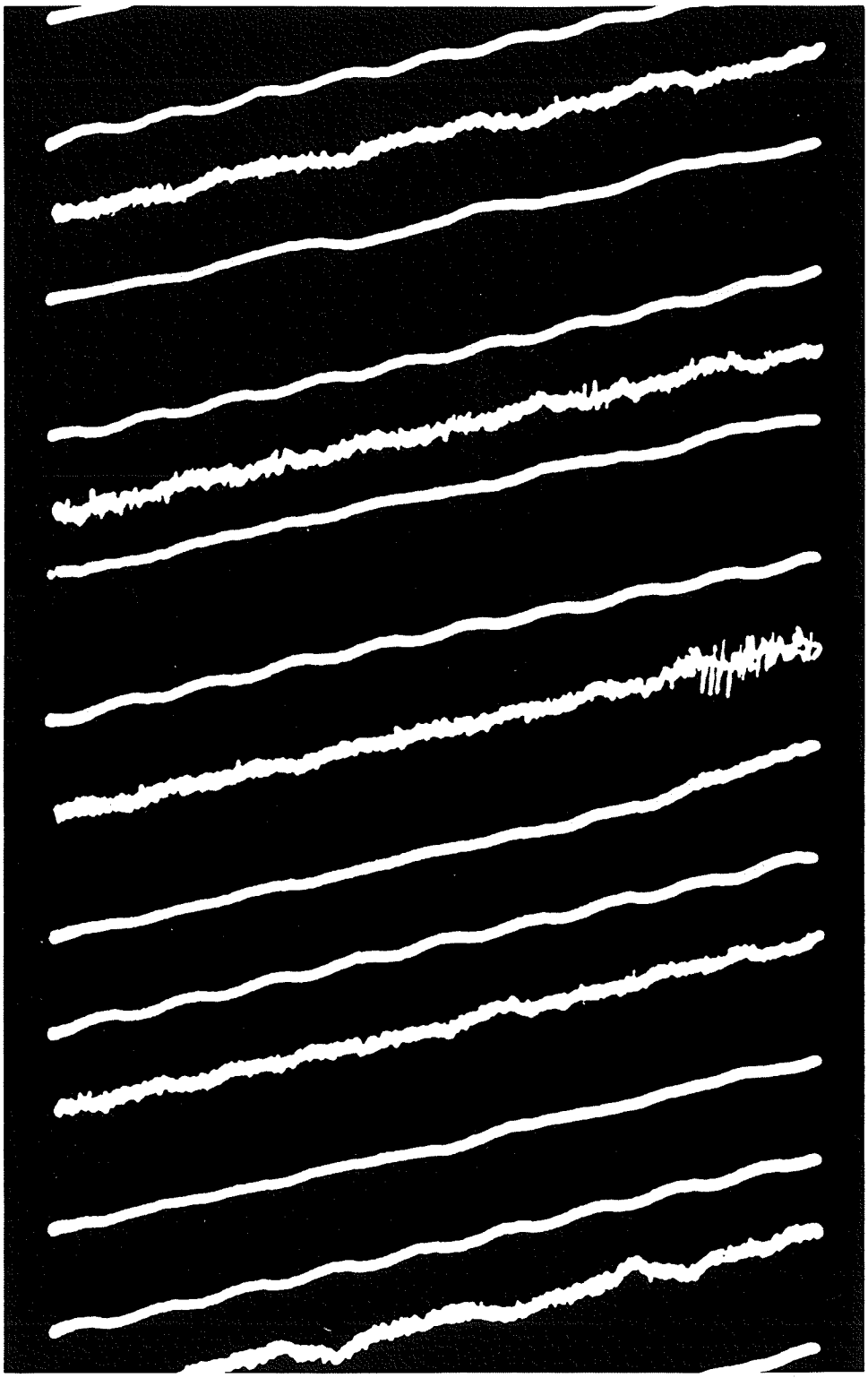


PLATE XVI. PRESUMED EXTRACELLULAR BURST-SPIKE EPISODE RECORDED 2½ MINUTES AFTER PLATE XV WITHOUT FURTHER ADJUSTMENT OF OIL DRIVE : COMMENCES NEAR END OF SWEEP 20, BURST REPRESENTED AS NEGATIVE SHIFT OF V_1:21 BY COMPARISON WITH V_1:20. [CHRONIC (CHRONIC PHASE) : 12/7/65 : 582]

2. QUANTITATIVE MEASUREMENTS AND STATISTICAL APPROACH

It is mentioned in the previous subsection that ten burst-spike episodes were chosen from the record of each afterdischarge or part of an afterdischarge, and from each of these burst-spike episodes a number of parameters were measured. These parameters, d, V_{MAX1}, V_{MAX2}, and δ, are defined diagramatically in Fig. 8, and may be seen to have clearly measurable values in, e.g., Plate VII(i). In one or two early experiments more than ten bursts per afterdischarge were analysed, and a number of additional parameters were measured, such as burst amplitude and gradient at the time of occurrence of the first spike, amplitude of the first spike, and approximate number and amplitude distribution of spikes. However, in extending this analysis to a large number of afterdischarges it became obvious that the amount of work involved in measuring all these parameters would have drastically limited the number of afterdischarges that could be analyzed. Attention was therefore confined to those parameters felt likely to be the most significant, i.e., d, V_{MAX1}, V_{MAX2} and δ.

In view of the range of variation in form of burst-spike episodes described in the previous subsection, it may be appreciated that measurement of these parameters was not always so simple as might appear from Fig. 8. The method used was to lay a transparent straight edge along what was estimated to be the mean inter-burst potential on either side of the burst being analysed (i.e., its image projected by the Dagmar viewer; see previous subsection). The burst was considered to commence at the point where the potential first appeared to deviate discernibly in the negative direction (i.e., upward in the record) from the straight edge. Many bursts develop quite gradually, however, so that often this point was somewhat arbitrary within a range of several milliseconds. In the case of

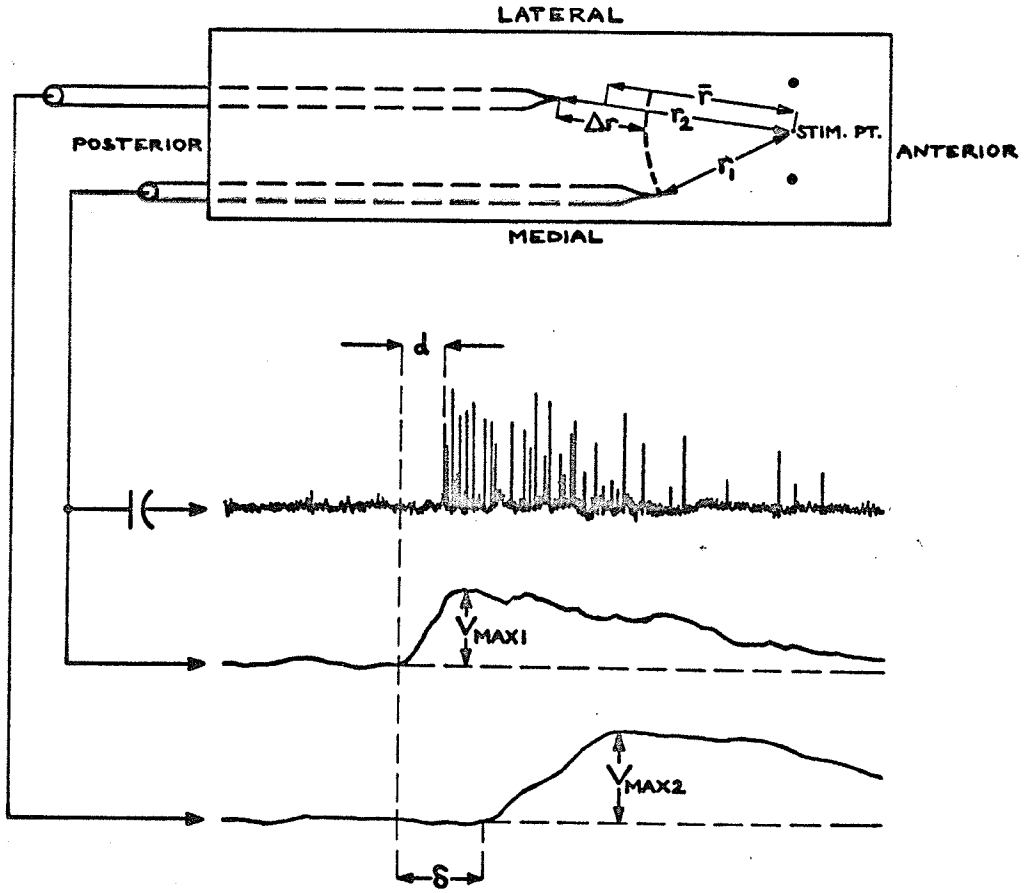


FIG. 8. DIAGRAMMATIC DEFINITION OF BURST-SPIKE PARAMETERS d, V_{MAX1}, V_{MAX2}, AND δ, AND OF HORIZONTAL DISTANCES r_1, r_2, Δr, AND $\bar{r}$. IN THE CASE SHOWN, REPRESENTING A SLAB CUT FROM THE LEFT SUPRASYLVIAN GYRUS SEEN FROM ABOVE, THE BURST-SPIKE PARAMETERS ARE ALL COUNTED POSITIVE AND THE HORIZONTAL DISTANCES ALL NEGATIVE; FOR FURTHER EXPLANATION SEE TEXT. THE 'STIMULATED POINT' IS SHOWN MID-WAY BETWEEN THE POLES OF THE SURFACE STIMULATING ELECTRODES. FOR DETAILS OF ELECTRICAL ARRANGEMENTS SEE FIGS. 5 AND 6.

bursts having an initial positive phase (downward in the record), the beginning of the burst for analysis purposes was defined as the point where the potential first became negative with respect to the inter-burst potential; it may be noted (see, e.g., Plate XIII(i) that associated spike activity seems never to commence until this point is reached. Occasionally a burst was encountered where there appeared to be only a positive phase; and in these cases the beginning of the positive phase was counted as the beginning of the burst. Conclusions drawn subsequent to analysis of the records suggest this last procedure was probably not justifiable; however, the number of occasions when it occurred were so few as to be of no significance in the net results.

The burst-spike delay, d, was measured from the beginning of the burst defined as above to the first associated spike. The spikes, of course, were recorded on the high-pass filtered channel, and the bursts on an unfiltered channel, so that measurement of d required comparison of two separate traces on the record; this was facilitated by projection of the image on to squared paper as described in the previous subsection. The 'first spike' to be counted in this context was the first spike of sufficient amplitude to be distinct from background noise and occurring in the train of spikes apparently associated with the burst. Occasionally the train of spikes commenced before the burst and in such cases d was counted as negative. The maximum burst amplitudes, V_{MAX1} and V_{MAX2}, were measured vertically from the transparent straight edge with comparatively little ambiguity, and counted as positive if representing an upward displacement of the trace (i.e., a negative-going potential change) and negative if vice-versa; conversion to millivolts was by comparison with calibrating signals included on the film at the time of experiment by

means of the calibrator on the P6 preamplifier. The interval, δ , (the 'burst-burst delay'), between commencement of apparently corresponding bursts at the two different microelectrodes, was measured in the same way as d and counted as positive when the burst appeared first at the microelectrode nearer the stimulated point (see below) and negative when vice-versa; often the sign of δ remains constant throughout an afterdischarge, but not infrequently it reverses, sometimes quite abruptly (see, e.g., Plate XI(ii)). Usually the interval between attainment of maximum burst amplitude at the two different microelectrodes appears roughly the same as δ ; however, Plate XI(i) shows a case where this interval is practically zero, clearly considerably less than δ .

Altogether, data were accumulated for roughly one thousand burst-spike episodes each from acute slabs and from chronic slabs; this represents the use of eight cats in the acute state and five in the chronic state. The number of values of any one parameter available for statistical treatment is actually somewhat less than a thousand since it was not possible to measure each parameter for every burst-spike episode analysed. Occasionally several bursts occurred with too high a local frequency for correlation between individual bursts to be possible (see, e.g., Plate VIII); and occasionally there was no evident correlation at all between bursts at the two microelectrodes (e.g., Plate IX(i)). More frequently bursts occurred at one microelectrode but not at all the other; usually, though not invariably, the microelectrode at which bursts occurred was nearer the stimulated point than that at which they did not. In all such cases no δ values could be measured. Similarly, bursts without associated spikes (e.g., Plate VII(ii)) would give values for V_{MAX1} but not for d.

For each afterdischarge, the horizontal distances, r_1 and r_2, (Fig. 8) of the microelectrode tips from the stimulated point were calculated using the values of the reference coordinates, x_0 and y_0, the probe coordinates, x_P and y_P (see Section III, 3(b)), the displacement ratio of the oil drive system, and the micrometer readings and stimulation data recorded on the paper record during the experiment. The 'stimulated point' was taken as mid-way between the poles of the surface stimulating electrodes since the flow of current was presumably symmetrical through the intervening cortex and its maximum spread may therefore be supposed to have occurred in the vertical plane containing the mid-point. The depth of the microelectrodes, which was always kept the same for both at any one time, was not combined with the horizontal distances but was calculated separately as z_0 minus z_P minus the thickness of the lid. These calculations of r_1 and r_2 and depth were not made, nor were the relevant coordinates even looked at, until after measurement of the burst-spike parameters was complete; it was felt that an effective safeguard was thereby provided against systematic subjectivity in the latter.

Since there is no reason to suppose any systematic qualitative difference between the burst-spike episode recorded at one microelectrode and that recorded at the other, the two will not in general be further distinguished in this thesis. Thus V_{MAX1} and V_{MAX2} will be referred to without distinction as V_{MAX}, and similarly r_1 and r_2 will be referred to simply as r. Investigation of relationships involving d, V_{MAX}, and δ respectively are described in the three subsections following. The remainder of the present subsection is confined mainly to discussion of the basic statistical approach and assumptions which are common to all three.

It is evident that in any one burst-spike episode, the values of d, V_{MAX} and δ might reasonably be expected to depend on any or all of the following: the scalar value of r (or, in the case of δ, of $\bar{r}$ and Δr, the scalar mean and difference respectively of r_1 and r_2, defined diagramatically in Fig. 8), the direction of r (or of $\bar{r}$ and Δr in the case of δ), the depth of recording, the position of the stimulated point, and variation (both systematic and random) between bursts within an afterdischarge, between afterdischarges, between cats, and between acute slabs and chronic slabs, and in the latter case between the acute and chronic phases of the afterdischarge.

Data from acute slab afterdischarges and from the acute and chronic phases of chronic slab afterdischarges are all treated separately in each of the following subsections. In the case of d, Table 15 in the Appendix shows that there are differences significant at the 5% level between the overall distributions of observations in these three categories. The principal difference is between acute and chronic (acute phase) data; there is no significant difference between acute and chronic (chronic phase). Between chronic (acute phase) and chronic (chronic phase) the difference is mainly in the comparatively small proportions of observations of high d values (the proportions being higher in the chronic phase).

Justification for the separate treatments of V_{MAX} in the three separate categories of data is provided directly by the differences in dependence of V_{MAX} on r (see Fig. 11, also Appendix, Tables 18 and 21). Similarly, for δ, comparison of the overall distribution means having regard to their standard errors shows significant variation between the three categories (Appendix, Tables 23,27, and 31).

No study has been made in the present work of variation between afterdischarges from a single cat or between individual cats.

Such variation, random at any rate, certainly exists, since it was sufficiently evident to be observed incidentally in the course of analysing the bursts. It is hoped, probably with some justification in the case of inter-afterdischarge variation, but with rather less in the case of inter-cat variation on account of the comparatively small number of experiments performed, that the effects of such variation have been adequately randomised out.

To determine whether there is any systematic variation between bursts within an afterdischarge, the data from each afterdischarge were divided into three equal parts, i.e., three bursts from the first third of the sampled portions of the afterdischarge were treated together, likewise three bursts each from the second and third thirds. This of course left one burst unused, since ten were usually analysed; however, in cases where no significant difference became apparent between the thirds, all ten bursts could then be used together. Recordings of chronic phase afterdischarges from chronic slabs represent only tiny fractions of the total durations of the chronic phases, and so division into thirds in these cases would have been meaningless and was not done. Sufficient work has certainly been done to give a fairly clear picture of the extent and nature of random variation between individual bursts.

No attempt has been made to investigate the effect of changes in the depth of recording or in the anatomical position of the stimulated point. No effect of these factors was particularly noted in the course of analysing the bursts, although it might certainly be expected that changes in depth should produce some effect. However, for the present purpose any influence these factors may have is presumed to be randomised out.

Possible dependence of burst-spike parameters on the direction of r was investigated by treating separately data obtained when the microelectrode tip was anterior to the stimulated point (r counted positive) and the data obtained when it was posterior (r counted negative). In other words, in terms of radial coordinates (r, θ) with the line, $\theta = 0°$, extending anteriorly from the stimulated point as origin, r values measured in the intervals $0° \leqslant \theta < 90°$ and $270° < \theta \leqslant 360°$ are counted as positive and are treated separately from r values measured in the interval $90° < \theta < 270°$ which are counted as negative (see also Fig. 8). Similarly, $\bar{r}$ and Δr are counted as positive if Δr represents an excess distance anterior to the stimulated point and negative if posterior; and values of δ having $\bar{r}$ and Δr positive are treated separately from those having $\bar{r}$ and Δr negative. Algebraically, $\bar{r} = |r_F|(|r_F| + |r_N|)/2r_F$ and $\Delta r = |r_F|(|r_F| - |r_N|)/r_F$ where r_F is the distance to whichever microelectrode is further from the stimulated point and r_N is the distance to whichever is nearer (e.g., r_2 and r_1 respectively in Fig. 8). It may be mentioned that in fact no systematic dependence of parameters on the direction of r, $\bar{r}$, or Δr was actually found; however, this investigation did form an integral part of the statistical procedure and is referred to in the subsections following. Dependence of burst-spike parameters on the scalar values of r, $\bar{r}$, and Δr, which in terms of the present paragraph are to be regarded as identical with $|r|$, $|\bar{r}|$, and $|\Delta r|$, is the subject of a major part of the subsections following.

As regards actual statistical methods, much is to be inferred from the shapes of the frequency distributions of the various parameters grouped in various manners; and these also determine to some extent the most appropriate further studies. For the sake of clarity, intervals of d, δ, r, $\bar{r}$, and Δr are specified in the following subsections

and in figures as though these quantities were measured on a continuous scale; e.g., consecutive intervals of d are $d = 0,5$ msecs, $d = 5,10$ msecs, and so on. Measurements of d and δ were made to the nearest millisecond, and of r, $\bar{r}$, and Δr to the nearest 0.1 mm (and of V_{MAX} to the nearest 0.1 mV), so that consecutive intervals should really appear, e.g., $d = 0,4$ msecs, $d = 5,9$ msecs, and so on. In the Appendix, where the various distributions and statistical tests are presented in full, this strictly correct mode of specification is followed.

In comparing groups of data with a view to detecting significant differences, only two simple non-parametric tests have been used; these are the chi-square test and the sign test, in the latter of which the numbers of increases and decreases between corresponding positions in two groups of data are regarded as the two species in a binomial sample. In addition, direct comparisons have been made of the means of grouped data having regard to their confidence distributions. All references and implied references in the following subsections to statistical significance are to be understood as referring to the 5% level except where otherwise stated.

3. STUDIES ON THE BURST-SPIKE DELAY, d

(a) Acute Slab Afterdischarges

The observed frequency distribution of all d values recorded from acute slab afterdischarges is shown in Fig. 9(a); the distribution mean is $\bar{d}$ = 4.395 msecs (see also Appendix, Table 1). It is apparent on inspection that the part of the frequency distribution lying to the right of zero, which accounts for over 92% of d values used, must be approximately enclosed by an exponential curve. Those d values lying to the left of zero; i.e., in the negative range, may not unreasonably be regarded as having only appeared negative on account of the slow commencing rise of the bursts concerned; though perhaps the higher negative values, of which there are very few, represent random spikes not directly associated with the bursts at all. In any event, it was decided justifiable in fitting a curve to the distribution to count all the negative values of d as truly belonging in the interval d = 0,5 msecs. The frequency for this interval thus becomes 437 instead of 377. It may then be simply derived (Appendix, Table 2) that the exponential equation which best describes the distribution is

$$\Delta f = 0.163 \int_{d}^{d + \Delta d} e^{-0.163\, d}\, dd \qquad (1)$$

where Δf is the fraction of the total number of observations occurring in the interval d, d + Δd. The distribution mean is thus increased to a working $\bar{d}$ = 6.135 msecs (i.e., the reciprocal of the parameter, 0.163 msecs^{-1}, in equation (1), this being a standard relationship in such exponential functions). Comparison by a chi-square test of observed and expected frequencies confirms that equation (1) is a good description of the observed distribution (see Appendix, Table 2).

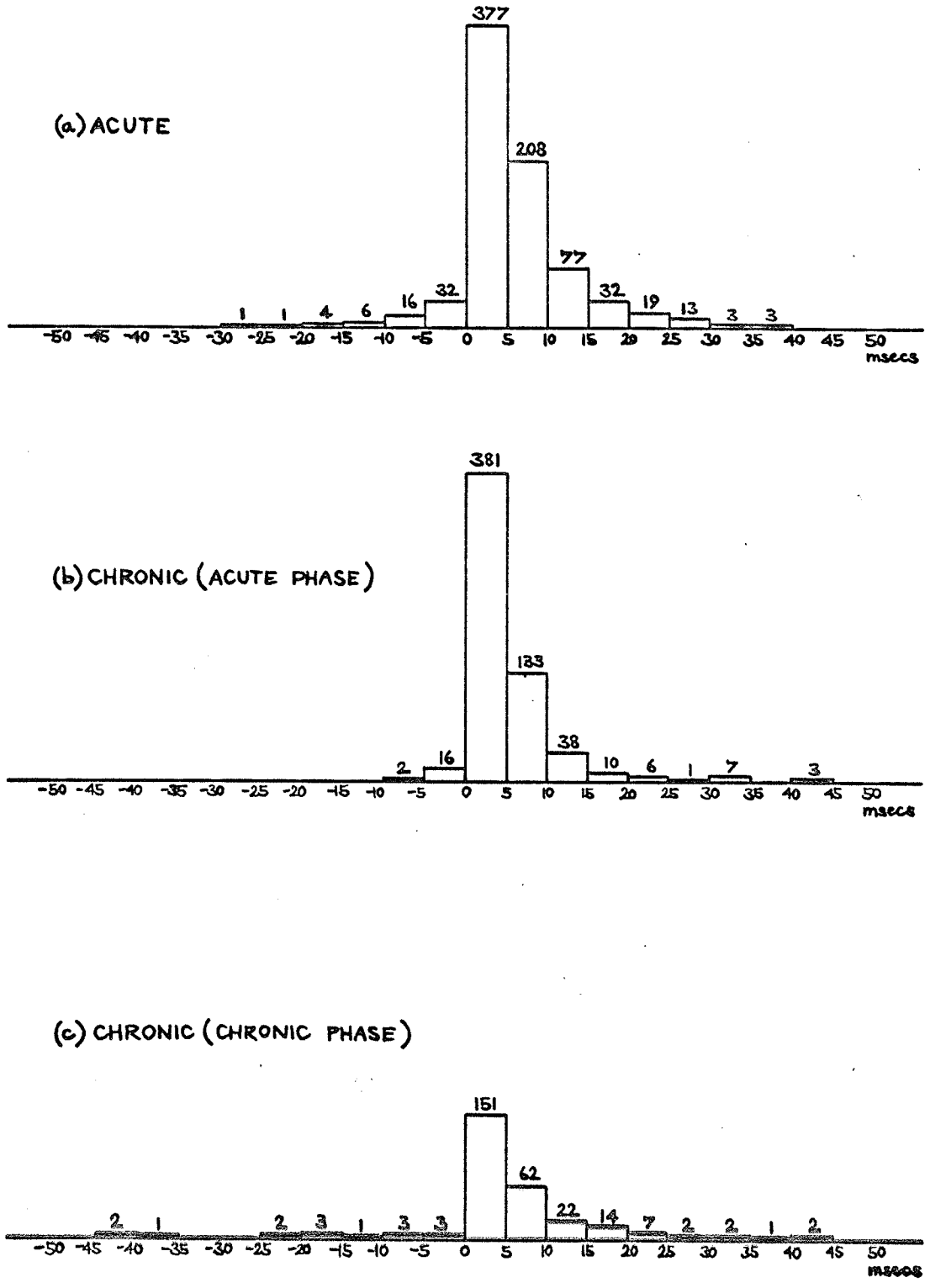


FIG. 9. DISTRIBUTIONS OF BURST-SPIKE DELAY, d, SHOWING OBSERVED FREQUENCIES IN 5msec INTERVALS. SEE ALSO APPENDIX, TABLES 1, 6, AND 11.

Possible dependences of d on time within an afterdischarge, on the direction of $\underset{\sim}{r}$, and on the scalar value of r were investigated by the means described in the previous subsection (see Appendix, Tables 3, 4 and 5). No such significant dependences were found; superficially apparent dependences on the direction and scalar value of r were due only to large contributions to chi-square from very small proportions of the data (Appendix, Tables 4 and 5; for discussion of the possible significance of the last two lines of Table 5, see part (b) below).

(b) Chronic Slab Afterdischarges; Acute Phase

The observed frequency distribution is shown in Fig. 9(b); the distribution mean is $\bar{d}$ = 3.867 msecs (see also Appendix, Table 6). It may be seen that the rate of fall off of frequency is in this case consistently greater than in the acute slab distribution. However, in the intervals d = 30,35 msecs and d = 40,45 msecs there are comparatively high frequencies which, although comprising less than 2% of the total data, are incompatible with description of the total distribution by an exponential equation. In deriving such an equation, therefore, all d values of 30 msecs or greater are disregarded. Proceeding in other respects as described above for acute slab data, the exponential equation which best describes the distribution is found, and confirmed by a chi-square test, to be (Appendix, Table 7)

$$\Delta f = 0.221 \int_{d}^{d + \Delta d} e^{-0.221\ d}\ dd \qquad (2)$$

The distribution mean is thus increased to a working $\bar{d}$ = 4.525 msecs (the reciprocal of 0.221 msecs^{-1}).

No significant dependence was found of d on time within an afterdischarge or on the direction of r (Appendix, Tables 8 and 9). However, a chi-square test did indicate significant differences between the separate d distributions for different scalar values of r, and in this case these differences could not be ascribed merely to isolated small proportions of the data. Inspection of the distribution table (Appendix, Table 10) shows that the rate of fall off of the d distributions increases at first as r increases, apparently reaching a maximum in the interval r = 3,4 mm, and then appears virtually to recycle. This observation prompted calculation of the mean value, $\bar{d}$, of d in each r interval (Appendix, Table 10) and the results are shown graphically in Fig. 10. On referring back to the corresponding acute slab data (Appendix, Table 5), although the chi-square test did not in that case show any conclusive variation of d with distance, a somewhat similar pattern of variation in the d distributions seemed apparent. The variation with r of mean d values for acute slab afterdischarges is therefore also plotted in Fig. 10, and likewise that for chronic slab afterdischarges in the chronic phase (see part (c) below and Appendix, Table 14). As some indication of the spread of individual d values contributing to these means, the band representing 68% scatter for chronic (acute phase) data is marked and shaded. The accuracy of the means themselves is indicated for chronic (acute phase) data by vertical bars representing their 95% confidence limits (i.e., $\pm$ 1.96 $\bar{d}/\sqrt{N}$, assuming that d is exponentially distributed so that $\bar{d} = \sigma$ and that the means are approximately normally distributed). To avoid confusion, corresponding confidence intervals for the other two sets of data are not marked; however, the relevant figures for all three curves are given in the last lines of Tables 5, 10, and 14 in the Appendix.

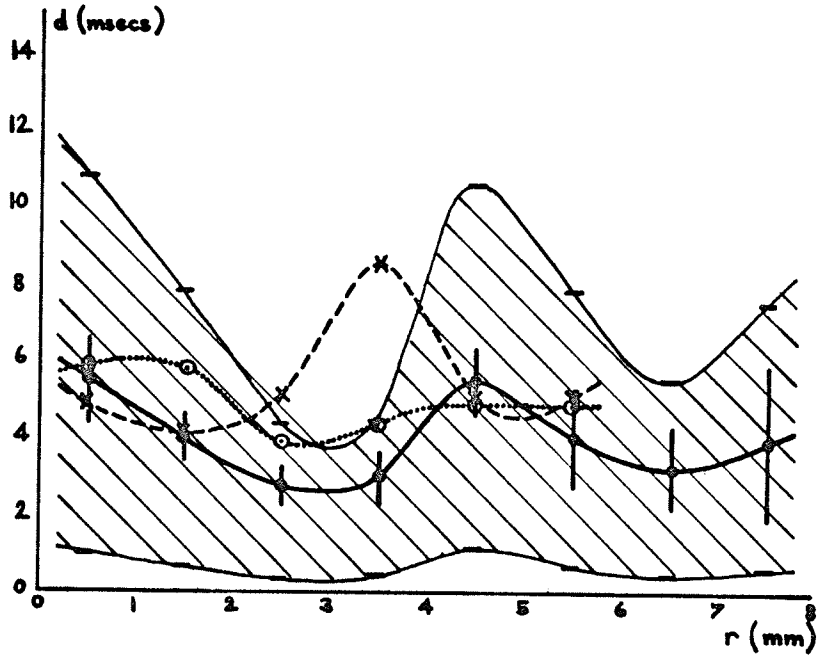


FIG. 10. DEPENDENCE OF BURST-SPIKE DELAY, d, ON DISTANCE FROM STIMULATED POINT, r. POINTS MARKED ARE MEANS, $\bar{d}$, OF ALL VALUES RECORDED IN 1mm INTERVALS OF r. DATA DISTINGUISHED THUS:

ACUTE SLAB DATA: ---×---

CHRONIC SLAB (ACUTE PHASE) DATA: ——●——

CHRONIC SLAB (CHRONIC PHASE) DATA: ……⊙……

SHADED AREA, AND HORIZONTAL BARS FOR INDIVIDUAL POINTS, REPRESENT 68% SCATTER FOR CHRONIC SLAB (ACUTE PHASE) DATA ONLY. VERTICAL BARS REPRESENT $\pm 1{\cdot}96\,\bar{d}/\sqrt{N}$ (i.e. 95% CONFIDENCE LIMITS OF MEANS, ASSUMING d EXPONENTIALLY DISTRIBUTED SO THAT $\bar{d} = \sigma$) FOR SAME. EQUIVALENT CONFIDENCE INTERVALS FOR ACUTE SLAB AND CHRONIC SLAB (CHRONIC PHASE) DATA ARE SIMILAR. SEE ALSO APPENDIX, TABLES 5, 10, AND 14.

(c) Chronic Slab Afterdischarges; Chronic Phase

The observed frequency distribution is shown in Fig. 9(c); the distribution mean is $\bar{d}$ = 3.740 msecs (see also Appendix, Table 11). Despite the lesser total quantity of data in this case, it may be seen (in Fig. 9) that the rate of fall off of frequency is intermediate between the rates for the acute and chronic (acute phase) distributions. Equation (3) below and Table 15 (Appendix) show that in fact the chronic phase distribution is quantitatively more similar to the acute distribution. As for acute phase data, in deriving an exponential equation all d values of 30 msecs or greater are disregarded. The equation which then best describes the distribution is found, and confirmed by a chi-square test, to be (Appendix, Table 12)

$$\Delta f = 0.171 \int_{d}^{d+\Delta d} e^{-0.171\, d}\, dd \qquad (3)$$

The distribution mean is thus increased to a working $\bar{d}$ = 5.848 msecs (the reciprocal of 0.171 $msecs^{-1}$).

No significant dependence was found of d on either the direction or scalar value of r (Appendix, Tables 13 and 14). However, in the latter case the mean d value in each r interval was calculated and the results are plotted in Fig. 10. There does appear to be some indication of a cyclic variation as r increases, though quite minimal compared to that seen in the acute phase data (see part (b) above).

4. STUDIES ON THE BURST AMPLITUDE, V_{MAX}

(a) Acute Slab Afterdischarges

Mean values, $\bar{V}_{MAX}$, of V_{MAX} were calculated with their standard deviations separately for successive 1 mm intervals of distance, r, from the stimulated point and in successive thirds of the afterdischarges (Appendix, Table 16). Possible dependences on the direction of r and on time within an afterdischarge were investigated by means described in subsection 2 of this Section (Appendix, Tables 17 and 18). No consistently significant dependence was found on the direction of r; however, fairly consistent differences of significant magnitude were found between data for the separate thirds of the afterdischarges. Dependence of $\bar{V}_{MAX}$ on the scalar value of r within the separate thirds is shown graphically in Fig. 11(a) (and see Appendix, Table 18); indications of confidence are provided similar to those in Fig. 10. Evidently $\bar{V}_{MAX}$ passes through a maximum in the interval r = 1,2 mm and then falls off to zero at distances greater than r = 5,6 mm; this latter is merely an expression of the direct experimental observation that no burst activity was ever found at distances greater than this. That $\bar{V}_{MAX}$ is generally greater in the second third than in the first third was also observed experimentally in most individual afterdischarges. There is also some slight indication in Fig. 11(a) that the maximum of $\bar{V}_{MAX}$ shifts slightly further from the stimulated point as an afterdischarge progresses.

(b) Chronic Slab Afterdischarges

Proceeding as described for acute slab data, significant differences were found between acute phase data recorded anterior and posterior to the stimulated point (Appendix, Tables 19 and 20(i)); in particular, in the region of $|r| = 3$ mm, $\bar{V}_{MAX}$ appears to pass through a

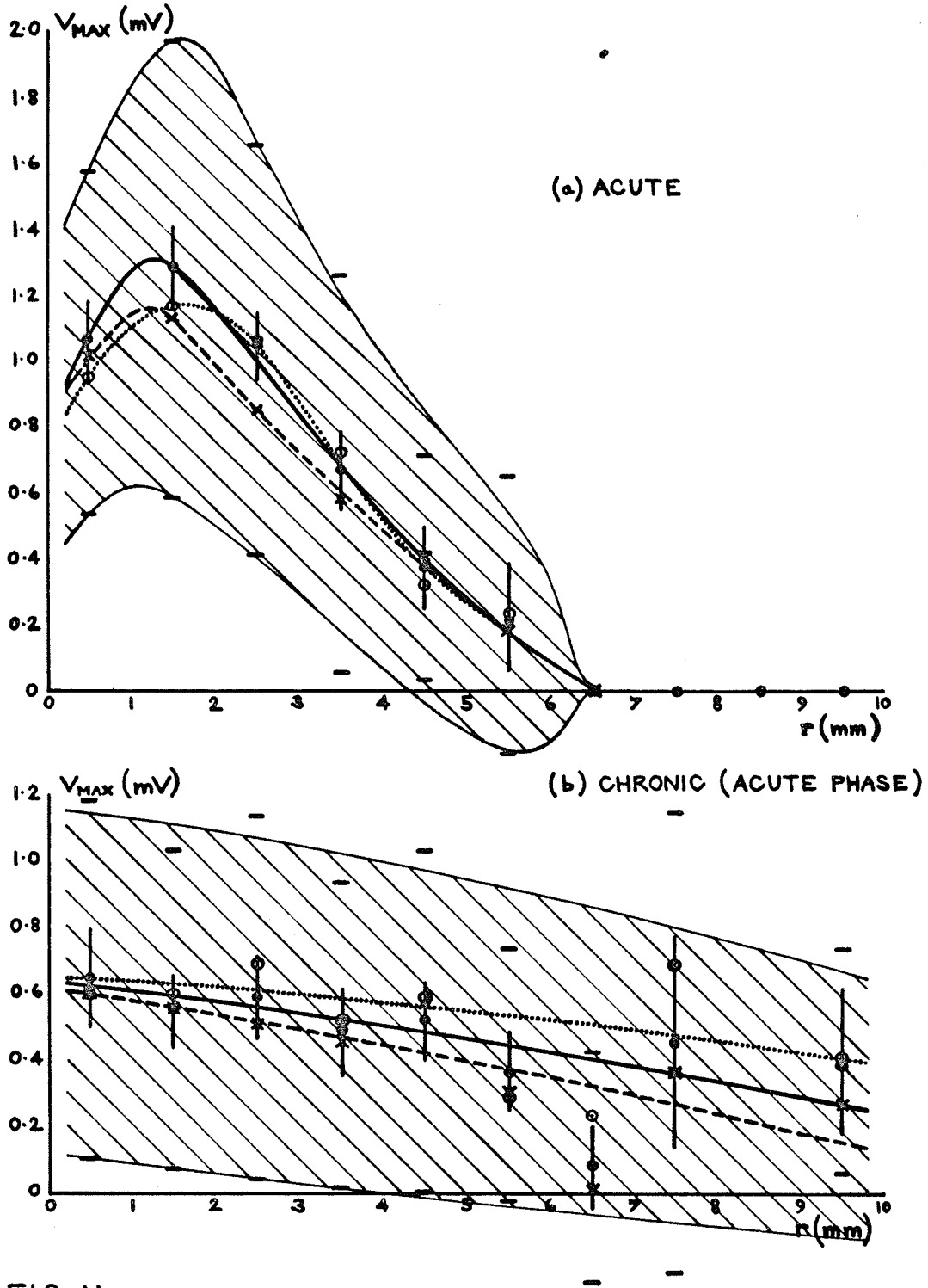


FIG. 11. DEPENDENCE OF BURST AMPLITUDE, V_{MAX}, ON DISTANCE FROM STIMULATED POINT, r. POINTS MARKED ARE MEANS, $\overline{V}_{MAX}$, OF ALL VALUES RECORDED IN 1mm INTERVALS OF r IN FIRST (--*--), SECOND (——●——), AND THIRD (·····o·····) THIRDS OF ALL AFTERDISCHARGES. SHADED AREAS, AND HORIZONTAL BARS FOR INDIVIDUAL POINTS, REPRESENT $\pm\sigma$ FOR SECOND THIRDS ONLY. VERTICAL BARS REPRESENT $\pm 1{\cdot}96\,\sigma/\sqrt{N}$ (i.e. 95% CONFIDENCE LIMITS OF MEANS) FOR SAME. EQUIVALENT CONFIDENCE INTERVALS FOR OTHER THIRDS ARE SIMILAR. SEE ALSO APPENDIX, TABLES 18 AND 21.

minimum when r is positive but a maximum when r is negative. However, particularly at higher values of $|r|$, these differences are not entirely consistent, and it has therefore been considered justifiable (below) to consider the dependence of $\bar{V}_{MAX}$ on r without further reference to direction. In the case of the chronic phase (Appendix, Tables 19 and 20(ii)), while significant differences certainly occur in individual $|r|$ intervals between data for r positive and that for r negative, the differences between the regressions of $\bar{V}_{MAX}$ on r in the anterior and posterior directions considered as a whole are not consistent at all.

Differences between data for the separate thirds of the acute phase were found not to be of significant magnitude (Appendix, Table 21); however, significant differences do occur between the acute phase and the chronic phase. Nevertheless, because a slight increase in burst amplitude was consistently observed experimentally to accompany the progress of individual acute phases, dependence of $\bar{V}_{MAX}$ on the scalar value of r is plotted separately for the separate acute phase thirds in Fig. 11(b). It is notable from Fig. 11(b) that by comparison with acute slab data (Fig.11(a)) there is no pronounced maximum near the interval $r = 1,2$ mm. On the other hand, the rate of fall of $\bar{V}_{MAX}$ as r increases is much less than in the acute case, and measurable burst activity is observed at considerably greater distances from the stimulated point. It is not certain whether any meaning can be attached to the apparent minimum (Fig. 11(b)) of $\bar{V}_{MAX}$ in the interval $r = 6,7$ mm since the numbers of observations from which $\bar{V}_{MAX}$ is computed in this and higher intervals of r are comparatively small (see Appendix, Table 21). The curves of Fig. 11(b), as distinct from the individual points, have not been drawn, therefore, to show any direct representation of this minimum.

5. STUDIES ON THE BURST-BURST DELAY, δ

(a) Acute Slab Afterdischarges

The observed frequency distribution of all δ values recorded from acute slab afterdischarges is shown in Fig. 12(a) (see also Appendix, Table 22). It is apparent on inspection that, apart from the particularly high frequency observed in the interval δ = 0,5 msecs, the distribution must be approximately enclosed by a normal curve. The mean and standard deviation of the complete distribution are $\bar{\delta}$ = 5.12 msecs and σ = 14.11 msecs, and the standard error of the mean is σ_N = 0.68 msecs. By grouping the data in intervals of 15 msecs on either side of the mean, and disregarding observations of δ less than -50 msecs or greater than 50 msecs (which gives working parameters $\bar{\delta}$ = 4.47 msecs and σ = 13.08 msecs), a normal distribution may be roughly fitted (Appendix, Table 23), though the fit is not found to be satisfactory at the 5% level when tested by chi-square.

Possible dependence of the observed distribution on time within an afterdischarge was investigated by the means described in subsection 2 of this Section (Appendix, Table 24); no such significant dependence was found.

Mean values, $\bar{\delta}$, of δ were calculated with their standard deviations separately for successive 1 mm intervals of mean distance, $\bar{r}$, from the stimulated point (see subsection 2 of this Section, also Fig. 8), and of separation, Δr, of the recording electrodes (Appendix, Table 25). Unfortunately, because the interest which might attach to studies on δ was not fully forseen at the time of most of the experiments (see Section I), there is an inbalance in the frequencies of observations in the separate $\bar{r}$ and Δr intervals which prohibits graphical representation of separate dependences of $\bar{\delta}$ on $\bar{r}$ and Δr; inspection of Table 25 suggests that

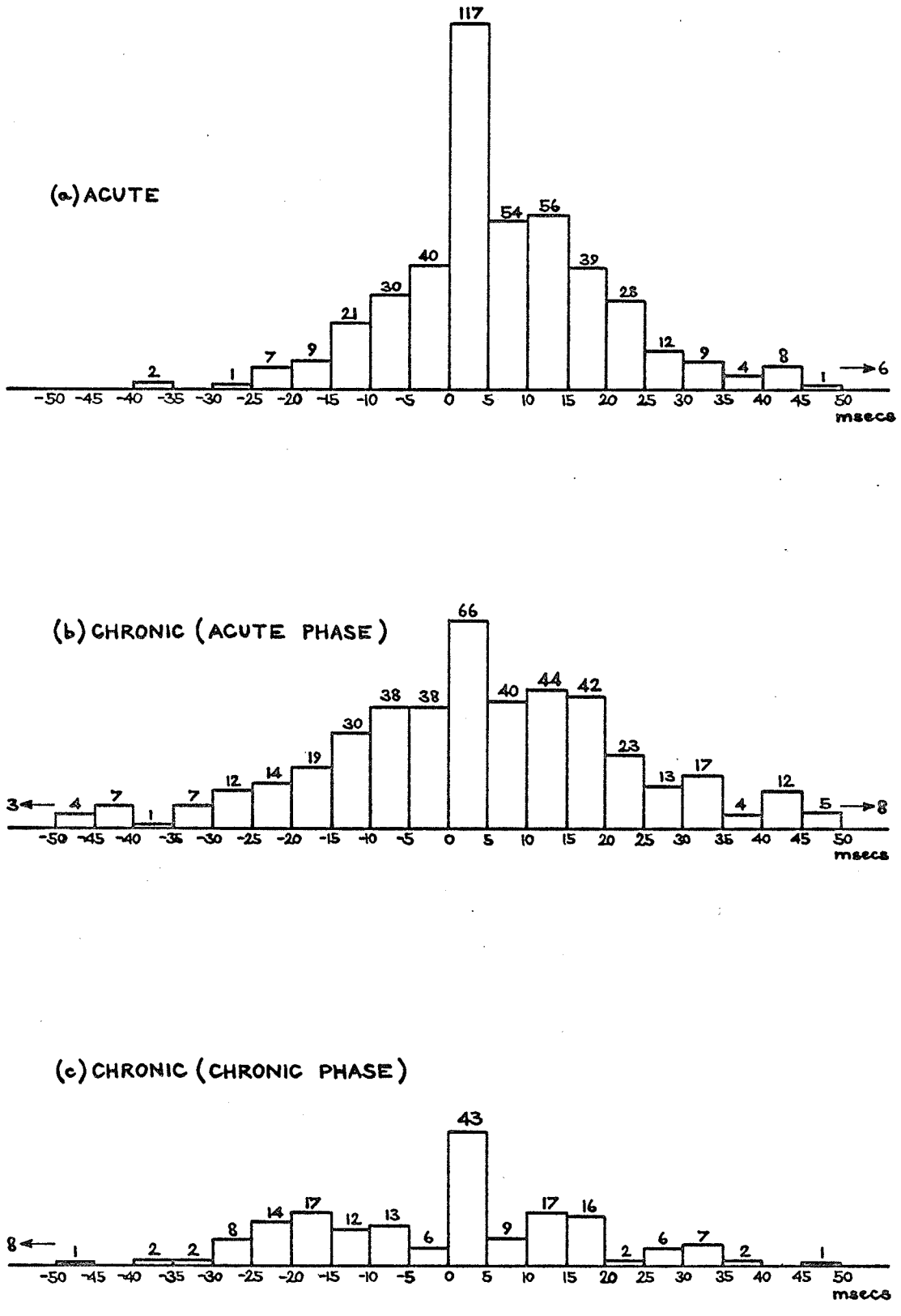


FIG. 12. DISTRIBUTIONS OF BURST - BURST DELAY, δ, SHOWING OBSERVED FREQUENCIES IN 5 msec INTERVALS. ARROWED FIGURES ARE TOTAL FREQUENCIES IN INTERVALS OUTSIDE RANGE OF DIAGRAM; FOR COMPLETE DISTRIBUTIONS, SEE APPENDIX, TABLES 22, 26, AND 30.

there are interaction effects between these dependences. In so far as could be determined by a sign test within these limitations, there is no significant dependence of $\bar{\delta}$ on the directions of $\bar{r}$ or Δr (Appendix, Table 25(i)). Dependence of $\bar{\delta}$ on the scalar values of $\bar{r}$ and Δr (Table 25(ii) and (iii)) was not found to be significant at the 5% level but is nonetheless sufficiently evident and consistent to be worthy of note. It appears that the absolute value of $\bar{\delta}$ may pass through a minimum in the region of the interval $\bar{r}$ = 1,2 mm; at smaller values of $\bar{r}$, $\bar{\delta}$ is negative, and at larger values $\bar{\delta}$ increases as $\bar{r}$ increases. The absolute value of $\bar{\delta}$ appears also to pass through a minimum in the region of the interval Δr = 1,2 mm and to increase positively on either side of this.

(b) Chronic Slab Afterdischarges: Acute Phase

The observed frequency distribution is shown in Fig. 12(b) (see also Appendix, Table 26). The mean and standard deviation of the complete distribution are $\bar{\delta}$ = 2.66 msecs and σ = 20.73 msecs, and the standard error of the mean is σ_N = 0.98 msecs. Proceeding as described above for acute slab data (which gives working parameters $\bar{\delta}$ = 2.09 msecs and σ = 18.58 msecs) a normal distribution may be fitted (Appendix, Table 27), in this case satisfactorily at the 5% level.

No significant dependence was found of the observed distribution on time within an afterdischarge (Appendix, Table 28). Within the limitations of the data obtained (see part (a) above), there appears to be no dependence of $\bar{\delta}$ on the directions or scalar values of $\bar{r}$ or Δr (Appendix, Table 29).

(c) Chronic Slab Afterdischarges: Chronic Phase

The observed frequency distribution is shown in Fig. 12(c) (see also Appendix, Table 30). The mean and standard deviation of the complete distribution are $\bar{\delta}$ = -6.02 msecs and σ = 23.02 msecs, and the standard error of the mean is σ_N = 1.69 msecs. Proceeding as described for acute slab data (which gives working parameters $\bar{\delta}$ = -2.86 msecs and σ = 17.52 msecs), a normal distribution may be fitted (Appendix, Table 31) satisfactorily at the 5% level.

Except in intervals of the scalar value of $\bar{r}$, inadequate matched data were obtained to permit very meaningful conclusions to be drawn regarding possible dependences of $\bar{\delta}$ on the directions and scalar values of $\bar{r}$ and Δr (Appendix, Table 32). No such dependences are sufficiently evident to suggest that they are present but masked by experimental variation.

V. DISCUSSION

1. THE INDIVIDUAL BURST-SPIKE EPISODE

The original intention in the work described in this thesis was, as is explained in Section I, to determine whether any definite relationship exists between the burst-spike delay, d, and the distance, r, between stimulating and recording points. Fundamental to the understanding of any such relationship, however, must be at least some understanding of the nature of the relationship between the burst and the spikes within the individual burst-spike episode; and this, therefore, may be appropriately discussed first. The possible dependence of d on r, and other relationships between the various burst-spike parameters, are discussed in the subsection following.

The commonest pattern of burst-spike episode is for a train of spikes to be clearly and comparatively closely correlated with the occurrence of a burst. Also, in well over 90% of the cases analysed in the present work, the burst was seen to have commenced before the appearance of the first spike (i.e., d counted positive; see Fig. 9). It therefore seems likely, taking the simplest interpretation of these facts possible, that the spikes are caused by the burst.

The spikes may reasonably be identified with individual action potentials generated by a cell or cells, or their axons, in the immediate vicinity of the microelectrode tip; they are much too big to be individual postsynaptic potentials. Since any initiation of action potentials normally depends on the prior application to the cell of a depolarising potential, it seems probable that this latter must somehow be provided by the burst. The intracellular correlate of the burst has in

fact been seen (Plate XV) to be a depolarising potential. Physiologically, at the level of the single cell, such a depolarising potential might be expected to arise as a postsynaptic potential, and this identity for the burst would be in accord with Eccles' (1953) general observation that most slow cortical potentials are probably postsynaptic potentials. However, it does not in fact seem that the burst as recorded extracellularly can be identified directly with a postsynaptic potential; the reasons for this, and the possible relationship of the burst to postsynaptic potentials are discussed below.

In a very large proportion, certainly more than half, of the burst-spike episodes analysed, recordings from two different and sometimes quite widely separated points in the slab show bursts of very similar shape separated by a time delay very brief in comparison with the duration of the bursts themselves. It therefore seems reasonable to regard such recordings as being in fact of the same burst which has spread or travelled from one point to the other; and so it may be assumed that any one burst might be recorded at virtually the same instant at any point within a volume of tissue large by comparison with the size of a single cell. It follows that all cells within such a volume must be affected by the burst virtually simultaneously, and the burst cannot therefore be dependent for its identity on a single cell or on only a small number of cells. It must rather be concluded that the burst represents the integrated result of all individual cellular potential changes within a large volume, and that cellular activity within such a volume is synchronised at least to an extent which distinguishes between bursts and inter-burst silences. Contributory cellular activity presumably includes action potentials as well as

excitatory and inhibitory postsynaptic potentials, and also the slow dendritic and somatic potentials which must result from synaptic activity in the manner predicted by Rall (1962, 1964). Since the theoretical amplitude limit of an excitatory postsynaptic potential is electrochemically equal to the resting potential, and assuming that the dendritic and somatic membranes are in fact inexcitable, there seems no reason why such slow potentials should not be of comparatively large amplitude even at the level of the single cell. The contribution made to the EEG by slow potential changes in single cells has been demonstrated by Klee et al (1965); and in the present work, as frequently elsewhere, direct correlation of the surface record with the visual extracellularly recorded bursts was consistently observed in the course of the experiments. This dependence of the existence of the burst on single cell activity may be summarised as representing a convergent aspect of cortical integration; whereas the manner in which the burst itself apparently regulates at least single cell spike activity, as is further discussed in the following paragraph, may be summarised as representing a divergent aspect.

The exponential distributions of burst-spike delay (d) values shown in Fig. 9 have been built up by using together individual values measured from several hundred different burst-spike episodes recorded at different times and in different experiments. Assuming that any effects of these latter and all similar variables have been adequately randomised out, the same distributions might presumably in theory be arrived at by recording simultaneously only one burst-spike episode at very many different points in the slab. The fact that the distributions are exponential may therefore be integrated to mean that within any volume within which the cells are affected by the burst equally and simultaneously, the separate cells fire

following delays which are exponentially distributed; and therefore the probability of firing must be the same for all cells within such a volume. This conclusion has already been expressed mathematically in equations (1), (2), and (3) (Section IV, 3), where Δf may in fact be regarded directly as the fraction of cells firing in a given time interval following arrival of the burst. The conclusion of Fox and O'Brien (1965) that the probability of single cell firing following sensory stimulation corresponds to the average potential recorded under the same conditions at the same site but after destruction of the cell itself is evidently closely related; since this average potential in the present work must be virtually the same as that represented by the burst. Similar, though usually less detailed, correlations between surface potentials (EEG) and single cell spike activity have been noted by a number of investigators (see Section II, 2).

The frequent recording of clearly defined bursts in the absence of any corresponding spike activity (e.g., Plates II and VII (ii)) seems hardly surprising; and similar recordings have been reported by a number of other investigators (e.g., see references below). Having regard to the postulates of the preceding paragraphs, such recordings must result whenever the microelectrode tip chances not to be in the fairly immediate vicinity of excitable structures. This may be the case either when it is in the vicinity of truly inexcitable structures such as glial cells, or when nearby excitable structures have become functionally inexcitable through exhaustion or inhibition; Goldensohn and Purpura (1963) suggest that combined excitatory and inhibitory activity may be such as to prevent spike firing yet nonetheless produce a net depolarisation. Presumably some such conditions must hold on those occasions (see Section IV, 1) when an apparently intracellular

microelectrode fails to record activity; though of course damage caused to the cell by penetration may sometimes be responsible. However, similar intracellular recordings have also been made by Matsumoto and Ajmone-Marsan (1964a, 1964b) and others using microelectrodes with much finer tips. In general, both electrotonic and volume conduction must contribute to the development of bursts recorded in the absence of spikes.

Patterns of variation in burst shape are probably worth a considerably more detailed study than has been undertaken in the present work (Section IV, 1). It seems likely that such a study might lead to a more detailed knowledge of mechanisms of cortical integration, since any variation in shape of successive bursts recorded at a single point must presumably reflect some corresponding variation in the underlying pattern of cellular activity. The basic observation that burst amplitude usually increases to its maximum more quickly than it afterwards falls off may probably be regarded as a direct correlate of the exponential distribution of d. Pinsky (1965) has shown that the 'averaged' burst shape, in falling off after its maximum, is itself approximately exponential.. If in regions of high spike activity the predominant contribution in determining burst shape is the spike activity itself, this correlation is to be expected. It would be interesting to compare burst shapes from burst-spike episodes with well defined spike activity and those from bursts unaccompanied by spikes; the latter might be found not to show the exponential fall off.

Wide variations in burst shape, particularly those in which the recorded burst appears biphasic or triphasic, may result simply from behaviour of the cortex as a volume conductor. Hyperpolarisation following excitatory depolarisation, which would be described herein as the positive phase of a biphasic burst (e.g., Plate V(ii)), has frequently been considered to

represent inhibitory synaptic activity (e.g., Nacimiento et al, 1964; and Andersson, 1965). However, there seems no particular reason why such inhibitory potentials should practically always come either immediately after or immediately before, or sometimes both after and before, excitatory burst potentials in the manner observed in the present work. Also, Plate V(ii) shows spike activity continuing throughout both the negative and positive phases of a biphasic burst, which would hardly be the case if the latter represented a true inhibitory potential.

The occurrence of bursts in close groups, usually pairs or triplets, might be due either to successive bursts of a group having travelled to the recording point by successively longer pathways or to some sort of local recirculation of burst activity. Similar double depolarisations recorded in cortical neurones following thalamic stimulation have been regarded by Klee and Offenloch (1964) and Nacimiento et al (1964) as resulting from activity in two sets of axo-dendritic synapses, one more remote from the soma than the other; functionally, this represents pathways of differing length. However, it seems unlikely that substantial burst separation of this general type could develop effectively in the comparatively homogeneous and restricted environment of a cortical slab, particularly having regard to the not infrequent occurrence of burst triplets (e.g., Plate VIII). Also, paired bursts recorded at widely separated points in a slab are often of practically the same shape and have practically the same time delay between their maxima. If the second burst of the pair had travelled by a longer pathway, it might be expected that the separation of the maxima would increase with distance travelled. It therefore seems that some more continuously effective mechanism must be responsible for maintaining the paired form. Local recirculation

might occur in a closed system of many neurones, but it might also occur within a single neurone via axon collaterals (see, e.g., Chang, 1959); and the differential repolarisation mechanism proposed by Burns (1958) might also be considered as a basic form of local recirculation. Some such local recirculation pattern might be conceived to build up synchronously throughout the volume of tissue affected by the afterdischarge; though the same recorded effect would follow if recirculation occurred only in the focal region (see subsection following). In any mechanism of this type it might be expected that the second and any subsequent bursts of a group would be of longer duration and generally more diffuse than the first; since successive recirculation would allow time for increasing loss of synchronisation. In general this is in fact observed to be the case, and when conditions are such that the synchronisation loss is maximised, combined perhaps with some amplification by recruitment in the course of recirculation, the result may be expected to be a 'hump-plateau' burst (see Section IV, 1). The occasional 'plateau-hump' form must then be accounted for as a reversal of the process, i.e., an increased synchronisation and concentration of activity. The conditions under which these changes develop would clearly be worth determining.

The occurrence of spikes in the absence of burst activity (Section IV, 1) may indicate either that the activity is too localised for bursts of significant amplitude to be generated or else that the burst generating mechanism has somehow been inactivated in such a way that spikes can still occur. Atkinson and Ward (1964), supporting the latter possibility, suggest that the neurone somata involved may become permanently depolarised. In their experiments, using chronic alumina-induced foci, this might be by loss

of inhibitory afferents. It is widely accepted that regenerative spikes occur only in the axon and axon hillock (Bullock, 1959; and see Section II, 2), so that depolarisation of the soma might well result in repetitive spike activity; though this in turn might be expected to lead quite quickly to complete exhaustion. In the present work, repetitive spike activity in the absence of bursts occurred most frequently either right at the end of an afterdischarge, perhaps representing therefore an intermediate stage in terminal exhaustion, or else near the beginning, presumably a manifestation of localised exhaustion following intense driven activity due to stimulation. In the former case burst activity often continued for some time after repetitive spiking had commenced; and in the latter spikes became discontinuous and associated with the bursts as the bursts themselves developed. It seems, therefore, that during transitional or other unstable phases (see subsection following) of an afterdischarge, not all neurones in a region pass through the various stages of activity simultaneously. This, of course, is in contrast to what is suggested above to be the situation during a well defined burst-spike episode in an established afterdischarge. Continuous trains of spikes in which spike amplitude and frequency are entirely regular are probably recorded from only a single axon; whereas simultaneous activity in many adjacent axons appears, when superimposed in a recording, to be quite irregular. The occurrence of isolated spikes and bursts of spikes is hardly unexpected in the wake of such gross activity as an afterdischarge. It seems quite possible that those patterns of neuronal activity which in many neurones synchronously are manifest as an afterdischarge may also under suitable conditions appear restricted to only one or a few neurones (e.g., Plate IV perhaps).

2. THE GENERATION AND TRANSMISSION OF THE AFTERDISCHARGE

In considering the manner in which the afterdischarge proceeds in the slab as a whole, it may first be observed that the repetitive nature of the bursts recorded at any one point, together with the usually obvious correlation between recordings from widely separated points, suggests that the spread of burst activity may in some respects be analogous to wave motion. There is, of course, nothing basically new in this suggestion; it has been made many times before (e.g., Adrian, 1936; and see Section II, 3 and 4). It does, however, seem remarkably well in accord with both the qualitative and quantitative results of the present investigation, and as a working concept it may therefore usefully be enlarged upon.

Persistent patterns of activity, in which the burst shapes and relationships remain constant, suggest stable patterns of waves; while changes from one pattern to another suggest corresponding variations in wave pattern, presumably caused by changes in the elements carrying the waves. In particular, sudden changes in burst shape and pattern such as were sometimes observed (e.g., Plate IX(ii)) suggest correspondingly sudden changes in the gross wave pattern. It does not seem likely that all the elements responsible for a particular pattern would change simultaneously, e.g., by becoming exhausted, and it therefore seems probable that changes in only a small proportion of wave-carrying elements, and presumably in the limit in even only a single element if it is playing a critical role, may cause gross changes in the entire activity pattern of the slab. Gross changes of this type in the behaviour of an assembly, prompted by only minor changes in individual elements, are well established phenomena in many physical systems. It thus seems that there may be fairly direct experimental backing, seen only at its crudest level in the changes of burst shape recorded herein, for the

postulate of Cragg and Temperley (1954) that cortical activity may be described in terms of cooperative domains.

Further correlations between present experimental observations and previous theoretical suggestions and developments (see Section II, 4) are not hard to find. However, due partly to the inadequacy of the present data and partly to the excessive generality of much of the available theory, such correlations must remain at present somewhat speculative and cannot be greatly elaborated. Nevertheless, enough has perhaps been said even in the previous paragraph (and is further suggested below) to indicate the potential value of a closely integrated theoretical and experimental approach.

Concerning the mode of initiation of the epileptiform afterdischarge, the postulate of Pinsky and Burns (1962) that a critical minimum number of neurones must be put through a critical minimum number of driven responses seems very much in accord with the present approach. The result of repetitive electrical stimulation may thus be considered to be the generation of a domain pattern of sufficient dimensions to determine the behaviour of the remainder of the slab and to be itself at least temporarily stable. As stimulation proceeds, progressively more neurones are presumably recruited into determined activity, and the point at which the minimum number necessary for establishment of an afterdischarge is achieved may be compared to the Curie point in the establishment of a magnetic domain in a ferromagnetic material. It is tempting to identify the point of stimulation as the focus corresponding to that of focal epilepsy, and in fact a number of basic concepts regarding the special role and significance of this point appear to emerge from the present work and are discussed below.

The experimental data most directly concerned with the presence and behaviour of the burst are the various distributions of V_{MAX} and δ. For the sake of clarity, discussion in the present subsection is confined to acute slab data; modifications of behaviour found in the chronic slabs are discussed in the subsection following. Fig. 11 shows that in acute slab afterdischarges $\bar{V}_{MAX}$, the mean of V_{MAX}, passes through a maximum in the region of $r = 1.5$ mm. Such results as were obtained for δ (Section IV, 5(a); and Appendix, Table 25) suggest that on average the absolute value of $\bar{\delta}$ is least, and in fact approximates to zero, in the region of $\bar{r} = 1.5$ mm; at lower values of $\bar{r}$, $\bar{\delta}$ is negative, i.e., bursts most often appear at a point further from the stimulated point before they appear at a point nearer to it. Both these results, concerning V_{MAX} and δ respectively and quite independently, suggest that the true source or 'focus' of epileptiform bursts is not at the stimulated point itself but is an annular or spherical shell of radius about 1.5 mm and having the stimulated point as its centre. Bursts originating in this shell spread as continuous waves (or domains) of activity both outwards into the remainder of the slab and inwards towards the stimulated point. The inward spread is of particular interest since it provides a sound basis for supposing that the repetitive nature of afterdischarge activity may result from a re-entry mechanism. It is mentioned in Section II, 4 that such mechanisms have been proposed as explanations of cardiac fibrillation. The basic requirement, which it is not hard to imagine satisfied, is that the outward spread of activity (i.e., towards the focal shell from the initially stimulated central region) shall not simultaneously block all inward paths. A highly schematic representation of a re-entry mechanism, in which the inward return path is represented simply as a discrete segment, is shown in Fig. 13. Fig. 14, likewise highly schematic and simplified, shows how the

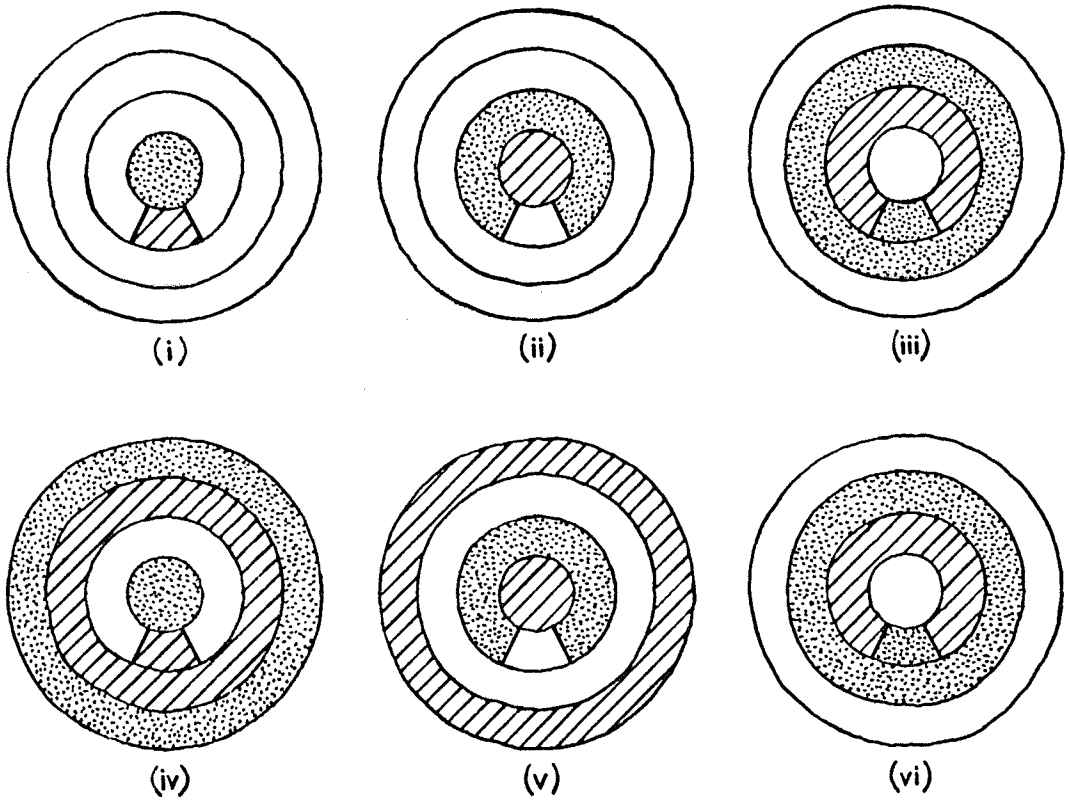
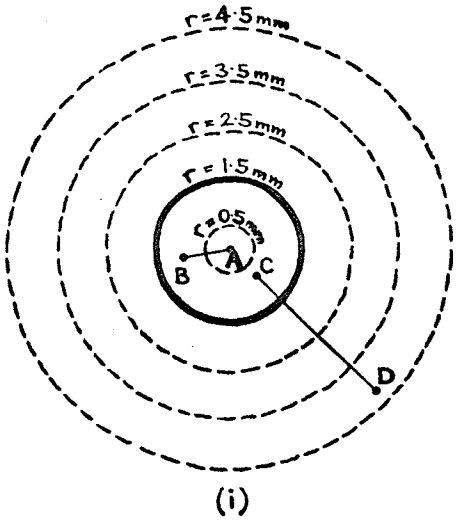


FIG. 13. DIAGRAMMATIC REPRESENTATION OF A SIMPLE REPETITIVE RE-ENTRY MECHANISM. THE REGION AVAILABLE FOR ACTIVITY IS REPRESENTED AS A SERIES OF CONCENTRIC ANNULAR (OR SPHERICAL) ZONES; ONLY THE CENTRAL FOUR OF THESE ARE SHOWN, BUT THERE MAY BE MANY MORE. DURING UNIT TIME INTERVAL, EACH ZONE MAY BE EXCITED (▒), REFRACTORY (▨), OR INACTIVE BUT AVAILABLE FOR EXCITATION IN THE FOLLOWING TIME INTERVAL (□). ALSO DURING UNIT TIME INTERVAL, ACTIVITY WILL SPREAD FROM AN EXCITED ZONE TO ANY IMMEDIATELY ADJACENT INACTIVE ZONE. ONCE A ZONE IS EXCITED, ITS STATE DURING THE TWO IMMEDIATELY FOLLOWING UNIT TIME INTERVALS IS DETERMINED AS FIRST REFRACTORY, THEN INACTIVE. TO ALLOW FOR RE-ENTRY, A SEGMENT OF THE FIRST ANNULAR ZONE IS POSTULATED TO LAG ONE STEP IN THE ACTIVITY CYCLE BEHIND THE REMAINDER OF THE ZONE; IT MAY NOT BE NECESSARY FOR THIS SEGMENT ACTUALLY TO BE INITIALLY REFRACTORY AS SHOWN. THE DIAGRAMS REPRESENT SUCCESSIVE UNIT TIME INTERVALS: (i) CENTRAL ZONE EXCITED; (ii) ACTIVITY SPREADS OUTWARD; (iii) AND (iv) ACTIVITY CONTINUES TO SPREAD OUTWARD AS CONTINUOUS WAVE, AND ALSO RE-ENTERS CENTRAL ZONE; (v) AND (vi) OUTWARD SPREAD AND RE-ENTRY ARE REPEATED; THIS WILL CONTINVE INDEFINITELY UNLESS INTERRUPTED IN THE CENTRAL OR FIRST ANNULAR ZONE (e.g. BY EXHAUSTION).



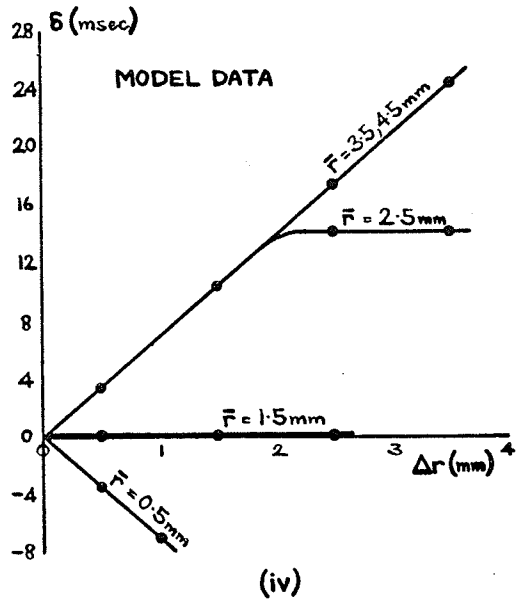
(i)

δ PREDICTED BY MODEL (msec)				
$\bar{r}$ (mm)	Δr = 0·5 mm	Δr = 1·5 mm	Δr = 2·5 mm	Δr = 3·5 mm
0·5	-3·5	[-7 WHEN Δr = 1]	—	—
1·5	0	0	0	—
2·5	3·5	10·5	14·0	14·0
3·5	3·5	10·5	17·5	24·5
4·5	3·5	10·5	17·5	24·5

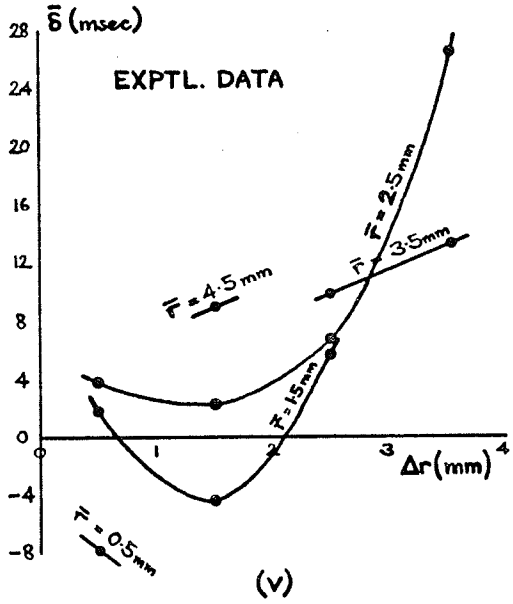
(ii)

$\bar{\delta}$ DETERMINED EXPTLY. (msec)				
$\bar{r}$ (mm)	Δr = 0·5 mm	Δr = 1·5 mm	Δr = 2·5 mm	Δr = 3·5 mm
0·5	-7·9	—	—	—
1·5	1·8	-4·3	5·3	—
2·5	3·8	2·5	6·3	26·4
3·5	—	—	10·0	13·2
4·5	—	8·9	—	—

(iii)



(iv)



(v)

FIG. 14. COMPARISON OF EXPERIMENTALLY DETERMINED DEPENDENCE OF δ ON $\bar{r}$ AND Δr WITH THAT DETERMINED BY A SIMPLE MODEL (i) CONSISTING OF A FOCAL SHELL, RADIUS 1·5 mm, FROM WHICH BURSTS SPREAD AS CONTINUOUS ACTIVITY WAVES RADIALLY INWARDS AND OUTWARDS. SUPPOSE WAVE VELOCITY = $\frac{1}{7}$ mm.msec^{-1} (SINCE THIS GIVES RESULTS DIMENSIONALLY MOST COMPARABLE WITH EXPERIMENTAL). THEN, e.g., FOR RECORDING ELECTRODES AT A AND B, $\bar{r}$ = 0·5 mm, Δr = 1·0 mm, $\delta = -(1{\cdot}0/\frac{1}{7}) = -7$ msec. δ IS COUNTED NEGATIVE SINCE WAVE REACHES ELECTRODE FURTHEST FROM CENTRE OF SYSTEM (≡ STIMULATED POINT) FIRST (i.e. B BEFORE A). SIMILARLY, FOR C AND D, $\bar{r}$ = 2·5 mm, Δr = 3·5 mm, $\delta = +(2{\cdot}0/\frac{1}{7}) = 14$ msec. FOR DEFINITIONS OF $\bar{r}$, Δr, AND δ, SEE FIG. 8 AND SECTION IV, 2. NOTE THAT NO ATTEMPT IS MADE IN THE PRESENT MODEL TO INTERPRET DIRECTIONS OF $\bar{r}$ AND Δr (i.e. AS + OR −) OR POSSIBLE DEPENDENCE OF VELOCITY ON $\bar{r}$ AND Δr. MODEL RESULTS ARE TABULATED (ii) AND GRAPHED (iv); EXPERIMENTAL RESULTS SIMILARLY, (iii) (FOR ACUTE SLAB DATA, SIMPLIFIED FROM APPENDIX, TABLE 25(i)) AND (v).

inward and outward spread of bursts from an annular (or spherical) focal shell gives a theoretical dependence of δ on $\bar{r}$ and Δr not unlike that observed experimentally (see below).

In reality, the focal shell itself may be supposed to arise as a result of the slab tissue in the immediate vicinity of and below the stimulated point becoming totally exhausted as a result of the intensive driven activity to which it is subjected on stimulation. Activity is thus confined to the periphery of the exhausted volume, and as stimulation proceeds both the latter and the active shell grow radially outwards. The critical point at which stimulation can be stopped and activity becomes self-supporting presumably corresponds to a minimum size of both the central inactive region and the active shell which becomes the focus. It seems probable that these minimum 'domain' dimensions might be theoretically determinable given adequate statistics of the neuronal population; they are not necessarily the same as those persisting through the majority of the afterdischarge (i.e., corresponding to the 1.5 mm radius determined herein) since once the afterdischarge is established its domain dimensions may be expected to be self-adjusting to equilibrating values; the latter might also be theoretically determinable. A slight increase in the presumed focal radius (V_{MAX} maximum) as the afterdischarge progresses is in fact indicated in Fig. 11(a). In addition, Fig. 13 suggests that the periodicity and duration of the bursts spreading outwards into the remainder of the slab must depend directly on the periodicity, and therefore presumably on the dimensions, of the focal re-entry mechanism; though it is not, of course, intended that the 3:1 relationship between periodicity and duration shown in Fig. 13 should be construed to have any particular quantitative bearing on reality.

The manner of spread of the bursts from the focal shell would be demonstrated clearly were it possible to plot graphically the dependence of burst velocity on r. Unfortunately, however, the ratio $\Delta r/\delta$ can only give a meaningful value for the velocity when Δr itself is very small. For much of the data obtained this condition is not satisfied and in theory, therefore, it is not possible to deduce the exact form of the dependence of velocity on r. In fact, however, a much more serious obstacle as regards the present data is the imbalance of data frequencies in the separate $\bar{r}$ and Δr intervals (see Section IV, 5(a)). The theoretical difficulties could be largely overcome by appropriate averaging if further data more suitably distributed with respect to $\bar{r}$ and Δr could be obtained.

Present conclusions concerning the dependence of burst velocity on r and Δr cannot profitably be extended beyond what is generally and for the most part quantitatively apparent from the overall trend of tabulated results (Appendix, Table 25; however, see also Fig. 14). For $\bar{r}$ greater than 1.5 mm, $\bar{\delta}$ in general increases as $\bar{r}$ increases; and therefore it seems likely that burst velocity decreases as the burst moves outward from the focal shell. Further, $\bar{\delta}$ tends in general to be least when Δr is in the interval 1,2 mm; i.e., the time taken by a burst to travel between two points is least when the points are very roughly 1.5 mm apart. A simple corollary of this is that excitation must appear less readily in the region immediately ahead of that already excited than it does rather further ahead. This might be a result either directly of histological structure (as seems quite possible, see Sholl, 1956) or of some sort of functional inhibition developed immediately ahead of the excitation. In terms of the wave analogy, the natural wavelength for burst activity in the cat's cortex is evidently about 1.5 mm (see above). This being so, it is not surprising that the radius of the

focal shell has also been found to be 1.5 mm, i.e., one 'wavelength' from the primary stimulated point.

The occurrence of activity patterns in which bursts recorded at one point cannot be correlated with those recorded at another, i.e., in which bursts evidently do not travel in an orderly manner in the region between the recording points and by inference throughout the slab, is strongly suggestive of instability analogous to turbulence. It would be of interest to determine the relationship between such activity and the regularly repetitive activity in which correlation between recordings from two separate points is quite obvious; there is perhaps some suggestion that unstable patterns occur most frequently near the beginning and end of an afterdischarge. It might also be instructive to compare the mean durations of 'regular' afterdischarges with those of afterdischarges in which instability predominates. Incorrelatable bursts do not, of course, give any meaningful value for δ; and even clearly correlatable series of bursts in which δ changes progressively and may even reverse in sign presumably represent some form of developing instability. Data from such bursts would have to be discarded in any averaging procedure for the determination of mean velocities from values of $\Delta r/\delta$; nevertheless, quite sufficient data for the latter purpose are either available or could easily be obtained from afterdischarges showing virtually constant activity relations throughout.

Closely related to factors influencing the stability of excitation patterns must be those which determine 'excitation density'. The latter term can be used only somewhat loosely at present since the balance between excitatory and inhibitory activity during afterdischarges is not known; however, it may be supposed to be related more or less directly to burst

amplitude. There is certainly evidence that not all cells in the region of a burst actually take part in it (Section IV, 1), and it is perhaps not too far-fetched to suppose that only certain levels of excitation density, envisaged as a function of the proportion of cells in an active region, are naturally stable. A region either 'over-excited' or 'under-excited' might then be expected to equilibrate itself; this concept seems to be generally in line with the suggestions of Stefanis and Jasper (1964) and Andersson (1965) that boundaries between active and inactive cortical areas are 'self-sharpening' as a result of inhibitory mechanisms.

It might be expected that the probability of firing of a single cell would be directly related to local excitation density. However, the results shown in Fig. 10 suggest that the dependence of $\bar{d}$ on r is in some way cyclical, and, taken in conjunction with the dependence of $\bar{V}_{MAX}$ on r shown in Fig. 11, this certainly does not indicate a linear dependence of d on V_{MAX}. Of course, the simple observation that spikes are sometimes recorded in the absence of bursts and vice versa shows that excitation density is probably not itself simply related to V_{MAX} (see also following subsection); and the data of Fig. 10 are in any case barely signficant. Nevertheless, the idea of a true cyclical dependence of d on r, and therefore on V_{MAX}, does not seem wholly out of keeping with what is suggested above concerning the stability of only particular excitation levels. As might be expected, Fig. 10 shows (for acute slab data) a maximum probability ($\bar{d}$ minimum) in the region of the focal shell, r = 1.5 mm; it may even be that the activity level in this region represents some sort of saturation. This in itself provides one more item of evidence for the existence of the focal shell.

3. MODIFICATIONS OF AFTERDISCHARGES IN CHRONIC SLABS

The individual bursts of an epileptiform afterdischarge recorded in a chronically isolated slab are initially similar in appearance and frequency to those recorded in an acute slab (Section IV, 1). Instead of decreasing in frequency and ceasing within a matter of seconds, however, the bursts in a chronic slab decrease in frequency to an apparently stable level and may then continue to occur with remarkable regularity for many minutes or even hours. At the same time, variations in burst shape such as commonly occur in acute slab afterdischarges and during the first few seconds (i.e., the 'acute phase') in chronic slabs also cease; throughout the remainder of the afterdischarge (the 'chronic phase') it is quite unusual for there to be any detectable change in shape between one burst and the next. Burst amplitude (V_{MAX}) increases during the acute phase and during the chronic phase is maintained at a level roughly equal to the mean burst amplitude of acute slab afterdischarges (Appendix, Tables 18 and 21). The dependence of V_{MAX} on r, however, is quite different (Fig. 11); once the chronic phase is established, burst activity can usually be recorded throughout the slab and does not remain restricted to a region around the stimulated point. The individual burst is usually of long duration with an abrupt rise to its maximum and then a long decay (i.e., a 'chronic type' burst as defined in Section IV, 1). The increase in duration by comparison with the duration of an acute slab burst is often of much the same order (roughly ten times) as the decrease in frequency; and it is interesting that this is exactly what would be expected to result in the case of a decelerated wave motion of constant wavelength.

Summarising the above-described qualitative characteristics, burst activity in a chronic slab evidently differs quite radically in nature from that in an acute slab; and in particular, in view of its frequently prolonged

persistence, it may be said to be much more firmly 'established'. In terms of the analogies of the previous subsection, the wave pattern, or dynamic domain pattern, is evidently much more stable in a chronic slab than in an acute slab. It would clearly be of interest to determine what factors, related presumably to the prolonged isolation of the slab, contribute to this increased stability. The remainder of the present subsection is concerned with aspects of this problem on which present results appear to throw some light. The simple fact of the increased excitability of chronic slabs is, of course, already well established (see Section II).

Considering first the exponential distributions of d (Section IV, 3 equations (1), (2), and (3), the chronic slab acute phase distribution is characterised by a working mean significantly lower than that of the acute slab distribution ($\bar{d}$ = 4.525 msecs and $\bar{d}$ = 6.135 msecs respectively). The chronic phase working mean is intermediate ($\bar{d}$ = 5.848 msecs), which, taken at face value, suggests that as an afterdischarge in a chronic slab develops the probability of firing of any individual cell decreases towards, though never reaches, the acute slab level. Table 15 (Appendix) shows that the difference between the d distributions for chronic (acute phase) and chronic (chronic phase) data is only marginally significant, and that between chronic (chronic phase) and acute data is not significant at all; whereas the overall difference between chronic (acute phase) and acute data is quite significant. There thus appears to be an inverse correlation during the acute phase between the decrease in firing probability and the observed (see above) increase in $\bar{V}_{MAX}$. This seems to be to some extent in contrast to the observation (see previous subsection) that in the region of the acute slab focus there is a maximum of both firing probability ($\bar{d}$ minimum) and of $\bar{V}_{MAX}$;

however the sharp fall off of $\bar{V}_{MAX}$ as r increases beyond the focus is matched by apparent cyclicity in $\bar{d}$ (Figs. 10 and 11) rather than by a steady rise as might be expected. It thus seems possible that the inverse correlation in the chronic slab acute phase referred to above may represent a genuine effect, perhaps arising from the evidently comparatively loosely coupled structure of the chronic slab (see below).

It is difficult with the present data to assess the significance of the observation (Fig. 9) that the chronic slab d distributions show higher frequencies (not used in calculating the working means, $\bar{d}$, given above; see Section IV, 3) in d intervals far removed from zero than does the acute slab distribution. The actual frequencies involved are small, and in those cases where d is negative the spikes concerned may have represented random background activity not directly associated with the burst.

The apparent cyclical dependence of $\bar{d}$ on r is both slower and better defined in the chronic slab acute phase than in the acute slab (Fig. 10). In the chronic phase, however, the cyclicity indicated by the graph (Fig. 10) is quite insignificant and $\bar{d}$ seems to be virtually independent of r. Even in the acute phase, firing probability appears to be maximum ($\bar{d}$ minimum) in the region of r = 3 mm, twice the apparent mean radius of the focal shell in acute slabs. It is postulated on this basis, and on the basis of observations discussed in the following paragraphs on the dependence of V_{MAX} and δ on r, that in the course of a chronic slab afterdischarge a focal shell is initially established by stimulation much as in an acute slab, but that the shell then quickly grows in radius and becomes more diffuse, and finally in the chronic phase loses its discrete identity entirely. This is perhaps basically equivalent to the suggestion of Burns (1958) that increased neuronal excitability developed as a result of repeated discharge activity may lead to

the establishment of multiple secondary foci; though there seems no need to postulate continuing foci at all.

It may be seen from Fig. 11 that dependence of mean burst amplitude, $\bar{V}_{MAX}$, on r is much less marked in the chronic slab acute phase than in the acute slab. Even in the first third of the acute phase, $\bar{V}_{MAX}$ remains finite throughout the range of r used; and in subsequent thirds the dependence becomes progressively less. In the chronic phase (Appendix, Table 21) there seems to be no orderly dependence at all, and variations in $\bar{V}_{MAX}$ appear virtually random throughout the entire slab.

The normal distributions (Fig. 12) of the burst-burst delay, δ, in both the acute and chronic phases of chronic slab afterdischarges, are characterised by working means, $\bar{\delta}$, nearer zero (2.09 msecs and -2.86 msecs respectively; see Section IV, 5) and standard deviations, σ, much larger (18.58 msecs and 17.52 msecs) than those of acute slab afterdischarges ($\bar{\delta}$ = 4.47 msecs and σ = 13.08 msecs). The low values of $\bar{\delta}$ may be interpreted to mean a lesser dependence of δ on Δr and $\bar{r}$, since δ is defined (Section IV, 2) so as to be positive for bursts appearing first at a smaller value of r and later at a larger value. This is confirmed by Tables 29 and 32 (Appendix), which show virtually no orderly dependence of $\bar{\delta}$ on Δr or $\bar{r}$ for chronic slab data. The high standard deviations of the δ distributions indicate comparatively greater mean travel times of burst activity between any two recording points. This correlates with the prolonged duration and greatly decreased frequency of chronic phase bursts. It also suggests that the character of burst activity at any one point in a chronic slab may be less dependent than in an acute slab on that at other points; and this itself correlates with the evident variability of $\bar{V}_{MAX}$ referred to above.

All of these various results concerning the behaviour of d, V_{MAX}, and δ combine to support the postulate expressed above that burst activity in a chronic slab becomes quickly independent of the original focus established by stimulation and in fact cannot in the chronic phase be referred to any one point or shell as focus. In an acute slab the afterdischarge apparently remains dependent throughout its duration on the persistence and continued activity of the original focal shell (see previous subsection); and it may therefore be reasonably supposed that the whole afterdischarge ceases as soon as focal activity ceases, by exhaustion or otherwise. Activity in a chronic slab, by contrast, being neither dependent on any focus nor even so closely integrated throughout the slab, may be expected to continue until either the entire slab, or at least some critical proportion of it, becomes exhausted. This critical proportion must almost certainly represent a much greater volume than is occupied by an acute slab focus; and the chronic slab must therefore be correspondingly less susceptible to functional exhaustion. Also, although the overall means of V_{MAX} are roughly the same in both chronic and acute slab activity, nowhere in a chronic slab does $\bar{V}_{MAX}$ reach the level which it reaches in the region of an acute slab focus (Fig. 11). If V_{MAX} can be taken as representing in some respect a measure of excitation density, this provides a further reason why chronic slab activity should lead less quickly to exhaustion. It is suggested that these considerations together provide the basis for a reasonable explanation of the prolonged duration of chronic slab afterdischarges.

As regards the underlying structural basis for the modified behaviour of chronic slabs, it is of considerable interest that afterdischarges in slabs isolated for less than one year appear to develop into a prolonged

chronic phase more readily than those in slabs isolated for much longer (see Section IV, 1). The expected consequence of chronic isolation is degeneration of severed neuronal processes. This may result in both axon collateral sprouting (Sharpless, 1964) and possibly also in the long term in true regeneration. Each of these processes might be expected to lead to the establishment of fresh synaptic contacts, though it seems almost certain that the original synaptic pattern, presumably the one required for normal functioning of the cortex, can never be reproduced. The afterdischarge, however, represents such a gross form of activity that regenerated synapses, even though functionally quite inappropriate, might well suffice to contribute in some way to its transmission. Since the chronic phase evidently represents a much looser coordination between events in different regions of the slab than does the acute slab afterdischarge, it may be specifically postulated that the most important fibres cut on isolation are long fibres whose normal function is integration of activity in different regions; such regeneration as occurs would not be expected to, and evidently does not, restore this integrating function. The appearance of spontaneous activity in a chronically isolated slab may thus be due not only to collateral sprouting but also to lack of overall coupling. In an acute slab, where the integrating mechanism has not had time to degenerate, activity throughout the slab is effectively quite tightly coupled under the control of the focal shell, and when activity ceases there it is unable to persist independently elsewhere; thus an acute slab afterdischarge appears much the same in form as an afterdischarge in intact cortex. In a chronic slab, whilst activity is initially generated by a focal shell and therefore appears synchronised throughout (acute phase), it is able to persist independently throughout the slab after the initial focus has ceased to function. It may finally be noted that these suggestions are

well in accord with the results of Farley (1962) on tightly and loosely coupled computer simulated neurone nets (see Section II, 4).

VI. CONCLUSIONS AND RECOMMENDATIONS

From the numerous and, in some instances speculative, conclusions of the preceding Section there emerges an overall picture of the nature of epileptiform afterdischarge activity in an isolated slab which is supported in its several aspects by most of the separate detailed conclusions independently. The effect of stimulation appears to be the establishment of a shell of activity, ideally spherical with the stimulated point as its centre, which grows radially outward until, in the acute slab, it reaches a stable equilibrium radius of roughly 1.5 mm. Activity in this shell is maintained by continuous recirculation between the shell itself and the central region (Fig. 13). The shell thus behaves as a focus, and from it at each recirculation a burst spreads out into the remainder of the slab as a continuous wave of activity which may or may not remain more or less coherent. In the acute slab all activity ceases when the focal shell becomes exhausted; but in the chronic slab, perhaps because of looser structural coupling resulting from degeneration, burst activity becomes independent of any single focus and may continue to reverberate for many hours. The relationship between the burst activity and single unit spike activity appears to be complementary, each contributing to the generation of the other. However, the burst represents a gross integration of activity to which postsynaptic and electrotonic potentials also contribute; and while the probability of spike firing is the same for all excitable cells affected by a burst, some cells are evidently inexcitable.

As is indicated above, a substantial amount of the work which has led to these conclusions could usefully be repeated with the sole object of acquiring more and better distributed data without any actual extension in scope. It is particularly desirable that further data on d and δ should be

obtained, more evenly distributed throughout the possible range of r and Δr intervals. It would then be possible to check the apparent cyclicity of d (Fig. 10) and to determine with at least some degree of accuracy the dependence of mean burst velocity on r. It would also be of interest to determine more definitely the relationship between d and V_{MAX}, especially since this must in some respects represent quantitatively the basic relationship between spikes and bursts. Comparison of increased quantities of data from only the first few and last few burst-spike episodes in each afterdischarge might be expected to reveal more clearly dependences of burst-spike parameters on time within an afterdischarge. The initial data might also show much more definite dependences on r than do those for the entire first third of an afterdischarge. Finally, an increased quantity of chronic phase data from chronic slabs would show to what extent chronic phase parameters really do tend towards acute slab values.

Over and above the need for additional confirmatory data, a number of direct extensions of the work readily suggest themselves. Several factors which might be expected to influence the nature of recorded activity but the effect of which have not been investigated are listed in Section IV, 2. In particular these include the depth of recording and the anatomical position on the cortical surface of the stimulated point. The possibility of directional transmission in the slab has been investigated to the extent that data recorded anterior to the stimulated point are treated separately from those recorded posterior; but no significant difference has emerged. It would be of interest to repeat the work, but using sensory or motor cortex where directional transmission might more definitely be expected.

The burst-spike parameters defined in Fig. 8 do not, of course, characterise all aspects of the burst-spike episode, and additional

parameters might therefore usefully be measured. For example, the rate of initial build up of the burst to its maximum amplitude might provide further information concerning the mode of development of the burst. Similarly, measurements of burst duration, and of the number, amplitude, and distribution of spikes, and determination of the interrelations between these variables and those already studied, would all certainly contribute to extending the overall picture of the processes involved. Provision of a duplicate high gain high-pass filtered recording channel would allow comparison of spike activity as well as of bursts at the two separate microelectrode recording points (see Figs. 5 and 6). Several aspects of the burst-spike episode which have so far been considered only qualitatively might profitably be studied quantitatively. These include the various patterns of burst shape listed in Section IV, 1, and the conditions conducive to spikes in the absence of bursts, bursts in the absence of spikes, and incorrelatable bursts at different points. The evident relationship between epileptiform activity recorded at the level of the single cell and that recorded at the cortical surface should also be investigated.

The various measurements of burst-spike parameters and subsequent analyses presented in this thesis were all done visually and by hand; and in fact there seems little doubt that much of value might have been overlooked had this not been the case. However, now that the pattern of the work has been established there seems no reason why some automatic analysing or computing device should not be used where possible. This would also eliminate the possibility of variable subjectivity in standards of measurement.

Rather more radical extensions of the work should include concentration on acquiring regular intracellular recordings during activity so that it can be quite clearly determined exactly what goes on in any one particular cell. There seems no reason why the trough-lid method of stabilisation

(Fig. 3) should not work well providing that the trough and lid are themselves adequately firmly mounted. Ultimately, the entire work must be extended to include complementary studies of the intact cortex; in this case, of course, some other method of stabilisation will be necessary.

Turning in another direction, some of the conclusions suggested in the previous Section imply a histological foundation which has not been demonstrated. Histological studies should therefore be made with a view to substantiating, for example, the postulates made regarding the structural basis for chronic slab behaviour, and, above all of course, with a view to demonstrating some basis for the apparent equilibrium radius of the acute slab focal shell. Some correlation should be attempted between present results and conclusions, particularly those concerning the nature of the focus, and relevant work on clinical epilepsy.

It is suggested at various points throughout this thesis that there is a need for a thoroughly integrated theoretical experimental approach to the study of the cortex. It is hoped that the present work itself provides some indication that such an approach is possible; more than that cannot be claimed for it, for its theoretical considerations in particular leave much to be desired. However, the necessary basis is available. Action potential and synaptic theory as well as core conductor theory might be applied along with single cell morphology and cortical neuronal distribution statistics to volume conductor theory in determining probable net cortical potentials. It should then be possible to see whether there is any sound theoretical basis for cooperative behaviour in the cortical neuronal population. If there is, such behaviour would be expected to modify the overall potential distribution and provide a basis for the existence of discrete waves and domains of activity. It seems quite possible that the basic complementary relationship

between gross and single cell activity suggested in this thesis may hold not only in the epileptic cortex but also for normal cortical activity patterns. In the long run, it should be possible to describe theoretically the expected response of the cortex to any specified input; and equally important to determine what input must be responsible for any observed response. The detailed realisation of all this is clearly a long way off. Much existing theory is not based on realistic anatomical premises and in this context is therefore inapplicable. However, this thesis cannot be better concluded than by reaffirming the ultimate necessity from every standpoint of matching each further experimental step by a parallel forward step in theory; and this final observation seems no less worthwhile for its manifest unoriginality.

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APPENDIX : STATISTICAL ANALYSES OF BURST-SPIKE PARAMETERS

NOTE: THROUGHOUT THE APPENDIX, VALUES OF χ^2 ARE GIVEN TO THE NEAREST HALF UNIT. ALSO, INTERVALS OF d, δ, r, $\bar{r}$, AND Δr ARE SPECIFIED ON A DISCONTINUOUS SCALE (e.g. d = 0, 4 msecs, d = 5, 9 msecs, ETC.; SEE ALSO SECTION IV, 1) SINCE ALL ACTUAL MEASURMENTS WERE TO THE NEAREST 1 msec OR 0·1 mm. MEASURMENTS OF V_{MAX} WERE TO THE NEAREST 0·1 mV.

I. STUDIES ON BURST-SPIKE DELAY, d

(a) ACUTE SLAB DATA

TABLE 1: OBSERVED FREQUENCY DISTRIBUTION:

INTERVAL OF d (msec)	OBS. FREQ.
-30,-26	1
-25,-21	1
-20,-16	4
-15,-11	6
-10,-6	16
-5,-1	32
0,4	377
5,9	208
10,14	77
15,19	32
20,24	19
25,29	13
30,34	3
35,39	3
TOTAL	792

SEE ALSO FIG. 9 (a).

ALSO, OBSERVED Σd = 3481 msecs

$\therefore \bar{d}$ = 3481/792 = 4·395 msecs.

TABLE 2: FITTING OF EXPONENTIAL EQN.:

NOT POSSIBLE USING $\bar{d}$ = 4·395 msecs; ALL NEGATIVE d MUST BE COUNTED AS ZERO.

THEN, IF $\Delta f = b\int_d^{d+\Delta d} e^{-bd}\,dd$,

$\therefore 786/792 = b\int_0^{30} e^{-bd}\,dd$

WHENCE b = 0·163 msecs^{-1}

$\therefore \Delta f = 0{\cdot}163\int_d^{d+\Delta d} e^{-0.163d}\,dd$ (1)

HENCE ARE CALCULATED EXPECTED FREQS. FOR COMPARISON WITH OBSERVED FREQS.:

INTERVAL OF d (msec)	EXP. FREQ.	OBS. FREQ.	χ^2
0,4	442	437	0
5,9	195	208	1
10,14	86	77	1
15,19	38	32	1
20,24	17	19	0
25,29	8	13	3
⩾30	6	6	0
TOTALS	792	792	6

6 DEGREES OF FREEDOM: $\chi^2 > 12\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. $\therefore$ EQN. (1) IS SATISFACTORY DESCRIPTION OF OBSERVED DISTRIBUTION.

TABLE 3: COMPARISON OF FREQUENCY DISTRIBUTIONS FOR SEPARATE THIRDS OF AFTERDISCHARGES:

INTERVAL OF d (msec)	OBS. FREQ. IN THIRDS			TOTAL FREQ.	EXP. FREQ. PER THIRD	χ^2			
	1ST	2ND	3RD			1ST	2ND	3RD	TOTAL
⩽-6	11	7	10	28	9	½	½	0	1
-5,-1	11	9	12	32	11	0	½	0	½
0,4	135	126	116	377	125	1	0	1	2
5,9	63	69	76	208	69	½	0	1½	2
10,14	23	28	26	77	26	½	0	0	½
15,19	12	12	8	32	11	0	0	1	1
⩾20	9	13	16	38	13	1	0	½	1½
TOTALS	264	264	264	792	264	3½	1	4	8½

12 DEGREES OF FREEDOM: $\chi^2 > 21$ SIGNIFICANT AT 5% LEVEL. $\therefore$ THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN THE SEPARATE THIRDS.

TABLE 4 : COMPARISON OF FREQUENCY DISTRIBUTIONS FOR AFTERDISCHARGES RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT:

INTERVAL	ANTERIOR			POSTERIOR			TOTAL	TOTAL
OF d (msec)	OBS. FREQ	EXP. FREQ	χ^2	OBS. FREQ	EXP. FREQ	χ^2	FREQ.	χ^2
≤-6	10	11	0	17	16	0	27	0
-5,-1	17	15	½	19	21	0	36	½
0, 4	157	147	½	207	217	½	364	1
5, 9	75	75	0	110	110	0	185	0
10, 14	27	23	½	29	33	½	56	1
15, 19	9	10	0	16	15	0	25	0
≥ 20	5	19	10	43	29	7	48	17
TOTALS	300	300	11½	441	441	8	741	19½

6 DEGREES OF FREEDOM: $\chi^2 > 12\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE IS APPARENTLY A SIGNIFICANT DIFFERENCE, BUT ONLY DUE TO A FEW DATA IN THE INTERVAL $d \geq 20$. NOT REGARDED AS SIGNIFICANT IN THESIS.

TABLE 5 : COMPARISON OF FREQUENCY DISTRIBUTIONS FOR AFTERDISCHARGES RECORDED AT DIFFERENT DISTANCES, |r|, FROM STIMULATED POINT:

INTERVAL	|r| = 0,0·9mm			|r| = 1,1·9mm			|r| = 2,2·9mm			|r| = 3,3·9mm			|r| = 4,4·9mm			|r| = 5,5·9mm			TOT.	TOT.
OF d (msec)	OB.FR	EX.FR	χ^2	OB.FR	EX.FR	χ^2	OB.FR	EX.FR	χ^2	OB.FR	EX.FR	χ^2	OB.FR	EX.FR	χ^2	OB.FR	EX.FR	χ^2	FR.	χ^2
≤-1	8	10	½	27	22	1	18	20	0	6	7	0	1	2	½	3	2	½	63	2½
0, 4	62	61	0	142	127	2	121	117	0	15	37	14	11	9	½	13	13	0	364	16½
5, 9	38	31	1½	51	64	2½	63	60	0	28	19	4	3	5	1	2	6	2½	185	11½
10, 14	5	9	2	23	19	1	12	18	2	6	6	0	5	2	4	5	2	4	56	13
≥15	10	12	½	14	25	3	25	24	0	22	8	18	0	2	2	2	2	0	73	23½
TOTALS	123	123	4½	257	257	9½	239	239	2	77	77	36	20	20	8	25	25	7	741	67
$\bar{d}$	4·8			4·2			5·0			8·5			5·0			5·0				
* 68% SCATTER	0·5, 8·9			0·0, 9·1			0·3, 9·4			1·5, 16·7			0·4, 11·5			-0·1, 12·5				

20 DEGREES OF FREEDOM: $\chi^2 > 31\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE ARE SIGNIFICANT DIFFERENCES, BUT ONLY DUE TO TWO INDIVIDUAL CONTRIBUTIONS TO χ^2 (14 AND 18 IN |r| = 3, 3·9mm). NOT REGARDED AS SIGNIFICANT IN THESIS.

* SEE NOTE BELOW TABLE 10. SEE ALSO FIG. 10.

(b) CHRONIC SLAB (ACUTE PHASE) DATA

TABLE 6 : OBSERVED FREQUENCY DISTRIBUTION:

INTERVAL OF d (msec)	OBS. FREQ.
-10,-6	2
-5,-1	16
0, 4	381
5, 9	133
10, 14	38
15, 19	10
20, 24	6
25, 29	1
30, 34	7
35, 39	0
40, 44	3
TOTAL	597

SEE ALSO FIG. 9(b).

ALSO, OBSERVED Σd = 2308 msecs

$\therefore \bar{d} = 2308 / 597 = 3{\cdot}867$ msecs.

TABLE 7 : FITTING OF EXPONENTIAL EQN.:

AS FOR ACUTE SLAB DATA (TABLE 2), ALL NEGATIVE d MUST BE COUNTED AS ZERO. ALSO, HIGH OBSERVED FREQS. IN d = 30, 34 msecs AND d = 40, 44 msecs CLEARLY DO NOT CONFORM TO EXPONENTIAL DISTRIBUTION. ∴ ALL DATA FOR WHICH $d \geq 30$ msecs ARE DISREGARDED, GIVING REVISED WORKING TOTAL FREQ. = 587.

[CONTINUED ON NEXT PAGE]

[TABLE 7 CONTINUED:]

$\therefore 580/587 = b\int_0^{20} e^{-bd}\,dd$

WHENCE $b = 0{\cdot}221\ \text{msecs}^{-1}$

$\therefore \Delta P = 0{\cdot}221\int_d^{d+\Delta d} e^{-0{\cdot}221d}\,dd$ (2)

HENCE ARE CALCULATED EXPECTED FREQS. FOR COMPARISON WITH OBSERVED FREQS.; SEE TABLE (RIGHT). 4 DEGREES OF FREEDOM: $\chi^2 > 9\frac{1}{2}$ IS SIGNIFICANT AT 5% LEVEL.

$\therefore$ EQN. (2) IS SATISFACTORY DESCRIPTION OF OBSERVED DISTRIBUTION.

INTERVAL OF d (msec)	EXP. FREQ.	OBS. FREQ.	χ^2
0, 4	393	399	0
5, 9	130	133	0
10, 14	43	38	$\frac{1}{2}$
15, 19	14	10	1
≥20	7	7	0
TOTALS	587	587	$1\frac{1}{2}$

TABLE 8: COMPARISON OF FREQUENCY DISTRIBUTIONS FOR SEPARATE THIRDS OF ACUTE PHASES:

INTERVAL	OBS. FREQ IN THIRDS			TOTAL	EXP. FREQ	χ^2			
OF d (msec)	1ST	2ND	3RD	FREQ.	PER THIRD	1ST	2ND	3RD	TOTAL
≤-1	9	4	5	18	6	$1\frac{1}{2}$	1	0	$2\frac{1}{2}$
0, 4	118	127	136	381	127	$\frac{1}{2}$	0	$\frac{1}{2}$	1
5, 9	49	40	44	133	44	$\frac{1}{2}$	$\frac{1}{2}$	0	1
10, 14	15	12	11	38	13	$\frac{1}{2}$	0	$\frac{1}{2}$	1
≥15	8	16	3	27	9	0	$5\frac{1}{2}$	4	$9\frac{1}{2}$
TOTALS	199	199	199	597	199	3	7	5	15

8 DEGREES OF FREEDOM: $\chi^2 > 15\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. $\therefore$ THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN THE SEPARATE THIRDS.

TABLE 9: COMPARISON OF FREQUENCY DISTRIBUTIONS FOR AFTERDISCHARGES RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT:

INTERVAL	ANTERIOR			POSTERIOR			TOTAL	TOTAL
OF d (msec)	OBS. FREQ.	EXP. FREQ.	χ^2	OBS. FREQ.	EXP. FREQ.	χ^2	FREQ.	χ^2
≤-1	14	10	$1\frac{1}{2}$	7	11	$1\frac{1}{2}$	21	3
0, 4	199	195	0	200	204	0	399	0
5, 9	66	68	0	74	72	0	140	0
10, 14	17	18	0	20	19	0	37	0
≥15	10	15	$1\frac{1}{2}$	20	15	$1\frac{1}{2}$	30	3
TOTALS	306	306	3	321	321	3	627	6

4 DEGREES OF FREEDOM: $\chi^2 > 9\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. $\therefore$ THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN AFTERDISCHARGES RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT.

TABLE 10: COMPARISON OF FREQUENCY DISTRIBUTIONS FOR AFTERDISCHARGES RECORDED AT DIFFERENT DISTANCES, |r|, FROM STIMULATED POINT:

d	|r|=0,0·9mm			|r|=1,1·9mm			|r|=2,2·9mm			|r|=3,3·9mm			|r|=4,4·9mm			|r|=5,5·9mm			|r|=6,6·9mm			|r|=7,7·9mm			TOT.	TOT.
(msec)	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	OB.F.	EX.F.	χ^2	FR.	χ^2
≤4	46	59	3	111	109	0	87	67	6	51	40	3	61	86	7	26	25	0	24	20	1	14	14	0	420	20
5,9	23	20	$\frac{1}{2}$	39	36	0	11	22	$5\frac{1}{2}$	7	13	3	41	29	5	9	9	0	5	7	$\frac{1}{2}$	5	4	0	140	$14\frac{1}{2}$
≥10	19	9	10	13	18	$1\frac{1}{2}$	2	11	7	2	7	$3\frac{1}{2}$	26	13	13	3	4	$\frac{1}{2}$	1	3	$1\frac{1}{2}$	1	2	$\frac{1}{2}$	67	$37\frac{1}{2}$
TOTALS	88	88	$13\frac{1}{2}$	163	163	$1\frac{1}{2}$	100	100	$18\frac{1}{2}$	60	60	$9\frac{1}{2}$	128	128	25	38	38	$\frac{1}{2}$	30	30	3	20	20	$\frac{1}{2}$	627	72
$\bar{d}$	5·5			4·0			2·8			2·9			5·6			4·0			3·2			3·8				
68% SC.	1·0, 10·8			0·7, 7·8			0·4, 4·3			0·5, 4·4			1·2, 10·6			0·7, 7·8			0·5, 5·5			0·6, 7·5				

[CONTINUED ON NEXT PAGE]

[TABLE 10 CONTINUED:]

14 DEGREES OF FREEDOM: $\chi^2 > 23\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE ARE SIGNIFICANT DIFFERENCES, NOT DUE ONLY TO A SMALL PROPORTION OF DATA.

* $\bar{d}$ IS CALCULATED FOR EACH $|r|$ INTERVAL AS Σ(MID PT. OF d INTERVAL × FREQ. IN THAT INTERVAL)/TOTAL FREQ. 68% SCATTER IS CALCULATED BY CUTTING 16% OF TOTAL FREQ. OFF EACH END OF DISTRIBN. SHOWN IN TABLE. EXTREME d INTERVALS ARE TAKEN AS 0,4 msecs AND 10, 14 msecs FOR CHRONIC (AC. PH.) DATA; AND SIMILARLY FOR ACUTE AND CHRONIC (CHR. PH.) DATA (TABLES 5 AND 14). IT MAY BE SHOWN THAT THIS PROCEDURE INTRODUCES NEGLIGIBLE ERROR. SEE ALSO FIG. 10.

(c) CHRONIC SLAB (CHRONIC PHASE) DATA

TABLE 11: OBSERVED FREQUENCY DISTRIBUTION

INTERVAL OF d (msec)	OBS. FREQ.
-45,-41	2
-40,-36	1
-35,-31	0
-30,-26	0
-25,-21	2
-20,-16	3
-15,-11	1
-10,-6	3
-5,-1	3
0,4	151
5,9	62
10,14	22
15,19	14
20,24	7
25,29	2
30,34	2
35,39	1
40,44	2
TOTAL	278

SEE ALSO FIG. 9(c).

ALSO, OBSERVED $\Sigma d = 1036$ msecs

$\therefore \bar{d} = 1036/278 = 3{\cdot}740$ msecs.

TABLE 12: FITTING OF EXPONENTIAL EQN.:

AS FOR ACUTE SLAB DATA (TABLE 2), ALL NEGATIVE d MUST BE COUNTED AS ZERO. ALSO, AS FOR ACUTE PHASE DATA (TABLE 7), OBSERVED FREQS. IN HIGH d INTERVALS DO NOT CONFORM TO EXPONENTIAL DISTRIBUTION; ∴ DATA FOR WHICH $d \geq 30$ msecs ARE DISREGARDED, GIVING REVISED WORKING TOTAL FREQ. = 273.

$\therefore 264/273 = b\int_0^{20} e^{-bd}\,dd$

WHENCE $b = 0{\cdot}171$ msecs^{-1}

$\therefore \Delta f = 0{\cdot}171\int_d^{d+\Delta d} e^{-0{\cdot}171d}\,dd$ (3)

HENCE ARE CALCULATED EXPECTED FREQS. FOR COMPARISON WITH OBSERVED FREQS.:

INTERVAL OF d (msec)	EXP. FREQ.	OBS. FREQ.	χ^2
0,4	157	166	$\frac{1}{2}$
5,9	67	62	$\frac{1}{2}$
10,14	28	22	$1\frac{1}{2}$
15,19	12	14	$\frac{1}{2}$
≥20	9	9	0
TOTALS	273	273	3

4 DEGREES OF FREEDOM: $\chi^2 > 9\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ EQN. (3) IS SATISFACTORY DESCRIPTION OF OBSERVED DISTRIBUTION.

TABLE 13: COMPARISON OF FREQUENCY DISTRIBUTIONS FOR AFTERDISCHARGES RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT:

INTERVAL	ANTERIOR			POSTERIOR			TOTAL	TOTAL
OF d (msec)	OBS. FREQ.	EXP. FREQ.	χ^2	OBS. FREQ.	EXP. FREQ.	χ^2	FREQ.	χ^2
≤-1	5	5	0	5	5	0	10	0
0,4	78	70	1	55	63	1	133	2
5,9	27	27	0	25	25	0	52	0
10,14	10	11	0	10	9	0	20	0
≥15	7	14	$3\frac{1}{2}$	20	13	$3\frac{1}{2}$	27	7
TOTALS	127	127	$4\frac{1}{2}$	115	115	$4\frac{1}{2}$	242	9

4 DEGREES OF FREEDOM: $\chi^2 > 9\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE IS NO SIGNIFICANT DIFFERENCE.

TABLE 14 : COMPARISON OF FREQUENCY DISTRIBUTIONS FOR AFTERDISCHARGES RECORDED AT DIFFERENT DISTANCES, |r|, FROM STIMULATED POINT :

INTERVAL	|r| = 0,0·9mm			|r| = 1,1·9mm			|r| = 2,2·9mm			|r| = 3,3·9mm			|r| = 4,4·9mm			|r| = 5,5·9mm			TOT.	TOT.
OF d (msec)	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	FR.	χ^2
≤4	13	15	½	35	40	½	21	18	½	19	17	0	32	29	½	23	24	0	143	2
5, 9	7	6	0	15	15	0	7	6	0	5	6	0	7	11	1	11	8	1	52	2
≥10	6	5	0	18	13	2	2	6	3	4	5	0	11	10	0	6	8	½	47	5½
TOTALS	26	26	½	68	68	2½	30	30	3½	28	28	0	50	50	1½	40	40	1½	242	9½
$\bar{d}$	5·7			5·7			3·8			4·3			4·9			4·9				
* 68% SCATTER	1·1, 11·0			1·1, 11·5			0·6, 7·5			0·7, 9·0			0·8, 10·9			0·9, 9·3				

10 DEGREES OF FREEDOM : $\chi^2 > 18\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE ARE NO SIGNIFICANT DIFFERENCES.

* SEE NOTE BELOW TABLE 10. SEE ALSO FIG. 10.

(d) TABLE 15

(i) COMPARISON OF OBSERVED OVERALL FREQUENCY DISTRIBUTIONS FOR ACUTE, CHRONIC (ACUTE PHASE), AND CHRONIC (CHRONIC PHASE) DATA :

INTERVAL	ACUTE			CHRONIC (AC. PH.)			CHRONIC (CHR. PH.)			TOTAL	TOTAL
OF d (msec)	OB. FR.	EX. FR.	χ^2	OB. FR.	EX. FR.	χ^2	OB. FR.	EX. FR.	χ^2	FREQ.	χ^2
≤4	437	476	3	399	359	4½	166	167	0	1002	7½
5, 9	208	192	1½	133	144	1	62	67	½	403	3
10, 14	77	65	2	38	49	2½	22	23	0	137	4½
15, 19	32	26	1½	10	20	5	14	10	1½	56	8
≥20	38	33	1	17	25	2½	14	11	1	69	4½
TOTALS	792	792	9	597	597	15½	278	278	3	1667	27½

8 DEGREES OF FREEDOM : $\chi^2 > 15\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE ARE SIGNIFICANT DIFFERENCES; HOWEVER, INSPECTION OF TABLE SHOWS SIGNIFICANCE OF χ^2 IS DUE ALMOST ENTIRELY TO DIFFERENCE BETWEEN ACUTE AND CHRONIC (ACUTE PHASE) DATA.

(ii) SEPARATE COMPARISONS OF ACUTE AND CHRONIC (CHRONIC PHASE) DATA AND OF CHRONIC (ACUTE PHASE) AND CHRONIC (CHRONIC PHASE) DATA :

INTERVAL	ACUTE			CHRONIC (CHR. PH.)			TOT.	TOT.
OF d (msec)	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	FR.	χ^2
≤4	437	447	0	166	156	½	603	½
5, 9	208	200	½	62	70	1	270	1½
10, 14	77	73	0	22	26	½	99	½
15, 19	32	34	0	14	12	½	46	½
≥20	38	38	0	14	14	0	52	0
TOTALS	792	792	½	278	278	2½	1070	3

INTERVAL	CHRONIC (AC. PH.)			CHRONIC (CHR. PH.)			TOT.	TOT.
OF d (msec)	OB.FR.	EX.FR.	χ^2	OB.FR.	EX.FR.	χ^2	FR	χ^2
≤4	399	386	½	166	179	1	565	1½
5, 9	133	133	0	62	62	0	195	0
10, 14	38	41	0	22	19	½	60	½
15, 19	10	16	2	14	8	4½	24	6½
≥20	17	21	1	14	10	1½	31	2½
TOTALS	597	597	3½	278	278	7½	875	11

4 DEGREES OF FREEDOM EACH : $\chi^2 > 9\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN ACUTE AND CHRONIC (CHRONIC PHASE) DATA. THERE IS A SIGNIFICANT DIFFERENCE BETWEEN CHRONIC (ACUTE PHASE) AND CHRONIC (CHRONIC PHASE) DATA; BUT DUE ONLY TO A FEW DATA FOR WHICH $d \geq 15$ msecs.

2. STUDIES ON BURST AMPLITUDE, V_{MAX}

(a) ACUTE SLAB DATA

TABLE 16 : MEAN VALUES, $\bar{V}_{MAX}$, IN SEPARATE THIRDS OF AFTERDISCHARGES AND AT DIFFERENT DISTANCES, r, FROM STIMULATED POINT: ΣV_{MAX}, ΣV^2_{MAX}, AND N (TOTAL FREQ.) WERE COMPUTED DIRECT FROM INDIVIDUAL DATA BY CALCULATING MACHINE AND FROM THEM $\bar{V}_{MAX}$ ($= \Sigma V_{MAX}/N$) AND σ (STANDARD DEVIATION, $= \sqrt{(\Sigma V^2_{MAX}/N - \bar{V}^2_{MAX})}$) ARE CALCULATED:

r (mm)	FIRST THIRD					SECOND THIRD					THIRD THIRD				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{MAX}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{MAX}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{MAX}$ (mV)	σ (mV)
0, -0·9	39·5	55·9	33	1·20	0·62	36·2	44·9	33	1·10	0·40	30·7	41·7	33	0·93	0·63
-1, -1·9	57·4	101·2	51	1·13	0·85	65·8	114·3	51	1·29	0·76	57·1	86·9	51	1·12	0·67
-2, -2·9	66·4	85·7	86	0·77	0·63	86·3	127·5	86	1·00	0·69	85·3	127·6	86	0·99	0·71
-3, -3·9	47·4	56·0	81	0·59	0·58	53·9	68·6	81	0·67	0·64	59·9	91·1	81	0·74	0·76
-4, -4·9	7·6	6·7	15	0·51	0·43	5·9	4·2	15	0·39	0·25	5·3	5·1	15	0·35	0·46
-5, -5·9	5·2	3·0	29	0·18	0·27	6·4	6·7	29	0·22	0·43	6·8	6·2	29	0·23	0·40
-6, -6·9	0	0	36	0	0	0	0	36	0	0	0	0	36	0	0
0, 0·9	22·8	25·9	29	0·79	0·53	28·8	40·3	29	0·99	0·64	27·8	37·7	29	0·96	0·62
1, 1·9	61·0	96·6	55	1·11	0·74	70·2	112·0	55	1·28	0·64	65·8	98·2	55	1·20	0·60
2, 2·9	29·1	38·0	27	1·08	0·49	30·5	37·1	27	1·13	0·31	32·2	45·2	27	1·19	0·51
3, 3·9	7·5	5·1	14	0·54	0·28	8·5	6·1	14	0·61	0·25	8·8	6·5	14	0·63	0·26
4, 4·9	4·4	2·9	14	0·31	0·33	4·7	3·0	14	0·34	0·32	4·0	2·2	14	0·29	0·27
5, 5·9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
6, 6·9	0	0	3	0	0	0	0	3	0	0	0	0	3	0	0

TABLE 17 : COMPARISON OF DATA RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT : DATA OF TABLE 16 COMBINED FOR SEPARATE THIRDS :

|r| (mm)	ANTERIOR (r POSITIVE)					POSTERIOR (r NEGATIVE)				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)
0, 0·9	79·4	103·9	87	0·91	0·60	106·4	142·5	99	1·07	0·53
1, 1·9	197·0	306·8	165	1·20	0·66	180·3	302·4	153	1·18	0·76
2, 2·9	91·8	120·3	81	1·13	0·44	238·0	340·8	258	0·92	0·69
3, 3·9	24·8	17·7	42	0·59	0·27	161·2	215·7	243	0·66	0·67
4, 4·9	13·1	8·1	42	0·31	0·31	18·8	16·0	45	0·42	0·42
5, 5·9	–	–	–	–	–	18·4	15·9	87	0·21	0·37
6, 6·9	0	0	9	0	0	0	0	108	0	0
TOTALS	406·1	556·8	426	0·93	0·63	723·1	1033·3	993	0·73	0·71

N.B. IN TABLE 17 AND FOLLOWING SIMILAR TABLES, 'TOTALS' FOR $\bar{V}_{MAX}$ AND σ ARE NOT ARITHMETIC TOTALS BUT ARE CALCULATED FROM TOTALS FOR ΣV_{MAX}, ΣV^2_{MAX}, AND N. TOTALS OF $\bar{V}_{MAX}$ ARE NOT DIRECTLY COMPARABLE BECAUSE N IN EACH INTERVAL OF |r| IS NOT SAME FOR r POSITIVE AS FOR r NEGATIVE. FOR MAX. PROBABILITY 5% THAT REGRESSION OF V_{MAX} ON |r| IS INDEPENDENT OF SIGN OF r, CONFIDENCE DISTRIBUTIONS FOR SEPARATE REGRESSION LINES FOR r POSITIVE AND r NEGATIVE MUST OVERLAP BY NOT MORE THAN 22 % ($= 0.22 \approx \sqrt{0.05}$). A NET 22 % OVERLAP WILL RESULT IF THE CONFIDENCE DISTRIBUTIONS CUT EACH OTHER AT 89%, $\approx \pm 1.6\sigma/\sqrt{N}$. USING 'TOTALS' FROM TABLE, THIS GIVES APPROX. $\pm$ 0·05 mV FOR r POSITIVE AND $\pm$0·04 mV FOR r NEGATIVE. $\therefore$ SEPARATIONS $\geq$ APPROX. $\pm$ 0·09 mV ARE SIGNIFICANT AT 5% LEVEL. INSPECTION OF TABLE SHOWS GREATER SEPARATIONS DO OCCUR ; BUT EXCESS IS NOT CONSTANT IN DIRECTION AND IS COMPARATIVELY SMALL. NOT REGARDED AS SIGNIFICANT IN THESIS.

TABLE 18: COMPARISON OF DATA FOR SEPARATE THIRDS OF AFTERDISCHARGES: DATA OF TABLE 16 COMBINED FOR r POSITIVE AND r NEGATIVE:

|r| (mm)	FIRST THIRD					SECOND THIRD					THIRD THIRD				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)
0, 0·9	62·3	81·8	62	1·01	0·56	65·0	85·2	62	1·05	0·52	58·5	79·4	62	0·94	0·62
1, 1·9	118·4	197·8	106	1·12	0·83	136·0	226·3	106	1·28	0·70	122·9	185·1	106	1·16	0·64
2, 2·9	95·5	123·7	113	0·84	0·62	116·8	164·6	113	1·03	0·62	117·5	172·8	113	1·04	0·67
3, 3·9	54·9	61·1	95	0·58	0·56	62·4	74·7	95	0·66	0·60	68·7	97·6	95	0·72	0·71
4, 4·9	12·0	9·6	29	0·41	0·42	10·6	7·2	29	0·37	0·34	9·3	7·3	29	0·32	0·34
5, 5·9	5·2	3·0	29	0·18	0·27	6·4	6·7	29	0·22	0·43	6·8	6·2	29	0·23	0·40
6, 6·9	0	0	39	0	0	0	0	39	0	0	0	0	39	0	0
TOTALS	348·3	477·0	473	0·74	0·68	397·2	564·7	473	0·84	0·70	383·7	548·4	473	0·81	0·71

PROCEEDING AS FOR TABLE 17, 89% CONFIDENCE LIMITS FOR SEPARATE REGRESSION LINES FOR SEPARATE THIRDS ARE CALCULATED TO BE ± 0·05 mV IN EACH CASE. ∴ SEPARATIONS ≥ ±0·1 mV ARE SIGNIFICANT AT 5% LEVEL. INSPECTION OF TABLE SHOWS SUCH SEPARATIONS DO OCCUR; ALSO INCREASE OF AMPLITUDE, PARTICULARLY FROM FIRST TO SECOND THIRD, WAS CONSISTENTLY OBSERVED EXPERIMENTALLY. VARIATION BETWEEN THIRDS IS THEREFORE REGARDED AS SIGNIFICANT. SEE ALSO FIG. 11(a).

(b) CHRONIC SLAB DATA

TABLE 19: MEAN VALUES, $\bar{V}_{MAX}$, IN SEPARATE THIRDS OF ACUTE PHASE AND IN CHRONIC PHASE, AND AT DIFFERENT DISTANCES, r, FROM STIMULATED POINT: COMPILED AS FOR TABLE 16:

r (mm)	AC. PH.: 1ST THIRD					AC. PH.: 2ND THIRD					AC. PH.: 3RD THIRD					CHRONIC PHASE				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)
0, -0·9	16·4	16·4	31	0·53	0·50	17·3	22·7	31	0·56	0·65	14·7	16·4	31	0·47	0·55	25·0	23·4	35	0·71	0·40
-1, -1·9	23·6	19·4	48	0·49	0·40	26·9	26·3	48	0·56	0·48	31·1	36·1	48	0·65	0·58	58·8	92·6	70	0·84	0·79
-2, -2·9	19·7	16·1	33	0·60	0·36	22·5	21·1	33	0·68	0·42	25·8	33·1	33	0·78	0·63	35·9	74·4	20	1·80	0·70
-3, -3·9	16·8	18·9	30	0·56	0·56	18·2	18·0	30	0·61	0·48	17·3	19·0	30	0·58	0·55	24·5	27·8	48	0·51	0·57
-4, -4·9	14·7	9·9	38	0·39	0·30	16·2	15·0	38	0·43	0·46	19·0	16·8	38	0·50	0·44	-0·7	14·3	30	-0·02	0·69
-5, -5·9	7·7	5·0	27	0·29	0·32	8·9	6·1	27	0·33	0·36	7·8	5·3	27	0·29	0·34	23·7	29·4	20	1·18	0·26
-6, -6·9	-1·2	5·4	24	-0·05	0·47	1·0	3·0	24	0·04	0·35	4·0	5·4	24	0·17	0·44	—	—	—	—	—
-7, -7·9	-1·5	0·8	6	-0·25	0·16	-2·2	1·7	6	-0·37	0·39	-1·2	0·7	6	-0·20	0·28	-5·4	3·2	10	-0·54	0·17
-8, -8·9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
-9, -9·9	0	0	3	0	0	0	0	3	0	0	0	0	3	0	0	—	—	—	—	—
0, 0·9	13·5	11·6	18	0·75	0·29	14·1	11·6	18	0·78	0·18	14·9	15·3	18	0·83	0·41	-11·5	8·4	20	-0·58	0·30
1, 1·9	31·8	37·1	59	0·59	0·53	31·5	30·5	59	0·53	0·48	32·1	34·0	59	0·54	0·53	83·0	158·2	66	1·26	0·90
2, 2·9	16·4	18·4	39	0·42	0·54	19·8	25·7	39	0·51	0·63	24·1	27·9	39	0·62	0·58	24·1	37·6	20	1·21	0·65
3, 3·9	4·6	2·7	18	0·26	0·29	4·9	3·3	18	0·27	0·33	7·5	5·9	18	0·42	0·39	8·7	9·3	10	0·87	0·41
4, 4·9	29·7	32·2	39	0·76	0·50	24·1	26·8	39	0·62	0·55	26·6	30·5	39	0·68	0·56	57·6	69·0	60	0·96	0·48
5, 5·9	4·7	3·3	14	0·36	0·35	5·9	5·2	14	0·42	0·44	4·1	3·1	14	0·29	0·37	45·7	69·3	50	0·91	0·74
6, 6·9	1·6	1·0	3	0·53	0·22	1·2	0·5	3	0·40	0·08	2·3	2·0	3	0·77	0·28	—	—	—	—	—
7, 7·9	8·3	6·4	12	0·69	0·24	10·5	10·7	12	0·88	0·35	13·7	21·0	12	1·14	0·67	—	—	—	—	—
8, 8·9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9, 9·9	2·4	1·1	6	0·40	0·15	3·6	2·5	6	0·60	0·22	3·6	2·3	6	0·60	0·14	3·0	1·1	10	0·30	0·14

TABLE 20: COMPARISON OF DATA RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT:

(i) ACUTE PHASE: DATA OF TABLE 19 COMBINED FOR SEPARATE THIRDS:

|r| (mm)	ANTERIOR (r POSITIVE)					POSTERIOR (r NEGATIVE)				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)
0, 0·9	42·5	38·5	54	0·79	0·30	48·4	55·5	93	0·52	0·56
1, 1·9	98·4	101·6	177	0·56	0·52	81·6	81·8	144	0·57	0·50
2, 2·9	60·3	72·0	117	0·52	0·59	68·0	70·3	99	0·69	0·49
3, 3·9	17·0	11·9	54	0·31	0·35	52·3	55·9	90	0·58	0·53
4, 4·9	80·4	89·5	117	0·69	0·54	49·9	41·7	114	0·44	0·42
5, 5·9	14·7	11·6	42	0·35	0·39	24·4	16·4	81	0·30	0·34
6, 6·9	5·1	3·5	9	0·57	0·26	3·8	13·8	72	0·05	0·44
7, 7·9	32·5	38·1	36	0·90	0·51	-4·9	3·2	18	-0·27	0·33
8, 8·9	—	—	—	—	—	—	—	—	—	—
9, 9·9	9·6	5·9	18	0·53	0·21	0	0	9	0	0
TOTALS	360·5	372·6	624	0·58	0·51	323·5	338·6	720	0·45	0·52

PROCEEDING AS FOR TABLE 17, 89% CONFIDENCE LIMITS FOR SEPARATE REGRESSION LINES FOR r POSITIVE AND r NEGATIVE ARE CALCULATED TO BE ± 0·03 mV IN BOTH CASES. ∴ SEPARATIONS ≥ ± 0·06 mV ARE SIGNIFICANT AT 5% LEVEL. INSPECTION OF TABLE SHOWS SUCH SEPARATIONS DO OCCUR; IN PARTICULAR, IN THE REGION OF \|r\| = 3 mm, $\bar{V}_{MAX}$ APPEARS TO PASS THROUGH A MINIMUM WHEN r IS POSITIVE BUT A MAXIMUM WHEN r IS NEGATIVE.

(ii) CHRONIC PHASE: FOR DEPENDENCE ON \|r\|, SEE TABLE 19; WHENCE TOTALS:

	ANTERIOR (r POSITIVE)					POSTERIOR (r NEGATIVE)				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)
TOTALS	210·6	352·9	236	0·89	0·84	161·8	265·1	233	0·69	0·81

89% CONFIDENCE LIMITS ARE ± 0·09 mV FOR r POSITIVE AND ± 0·08 mV FOR r NEGATIVE. ∴ SEPARATIONS ≥ 0·17 mV ARE SIGNIFICANT AT 5% LEVEL. INSPECTION OF TABLE 19 SHOWS SUCH SEPARATIONS DO OCCUR, THOUGH QUITE UNSYSTEMATICALLY; VARIATION IN $\bar{V}_{MAX}$ SHOWS NO ORDERLY DEPENDENCE ON VARIATION IN \|r\|.

TABLE 21: COMPARISON OF DATA FOR SEPARATE THIRDS OF ACUTE PHASE AND FOR CHRONIC PHASE: DATA OF TABLE 19 COMBINED FOR r POSITIVE AND r NEGATIVE:

|r| (mm)	AC.PH.: 1ST THIRD					AC.PH.: 2ND THIRD					AC.PH.: 3RD THIRD					CHRONIC PHASE				
	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)	ΣV_{max} (mV)	ΣV^2_{max} (mV^2)	N	$\bar{V}_{max}$ (mV)	σ (mV)
0, 0·9	29·9	28·0	49	0·61	0·45	31·4	34·3	49	0·64	0·54	29·6	31·7	49	0·60	0·59	13·5	31·8	55	0·25	0·72
1, 1·9	58·4	56·5	107	0·55	0·48	58·4	56·8	107	0·55	0·48	63·2	70·1	107	0·59	0·55	141·8	250·8	136	1·04	0·88
2, 2·9	36·1	34·5	72	0·50	0·48	42·3	46·8	72	0·59	0·55	49·9	61·0	72	0·69	0·61	60·0	112·0	40	1·50	0·74
3, 3·9	21·4	21·6	48	0·45	0·50	23·1	21·3	48	0·48	0·46	24·8	24·9	48	0·52	0·50	33·2	37·1	58	0·57	0·56
4, 4·9	44·4	42·1	77	0·58	0·46	40·3	41·8	77	0·52	0·52	45·6	47·3	77	0·59	0·51	56·9	83·3	90	0·63	0·73
5, 5·9	12·4	8·3	41	0·30	0·33	14·8	11·3	41	0·36	0·38	11·9	8·4	41	0·29	0·35	69·4	98·7	70	0·99	0·66
6, 6·9	0·4	6·4	27	0·01	0·49	2·2	3·5	27	0·08	0·35	6·3	7·4	27	0·23	0·47	—	—	—	—	—
7, 7·9	6·8	7·2	18	0·38	0·51	8·3	12·4	18	0·46	0·69	12·5	21·7	18	0·69	0·85	-5·4	3·2	10	-0·54	0·17
8, 8·9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9, 9·9	2·4	1·1	9	0·27	0·22	3·6	2·5	9	0·40	0·34	3·6	2·3	9	0·40	0·31	3·0	1·1	10	0·30	0·14
TOTALS	212·2	205·7	448	0·47	0·48	224·4	230·7	448	0·50	0·51	247·4	278·8	448	0·55	0·56	372·4	618·0	469	0·79	0·83

[CONTINUED ON NEXT PAGE]

[TABLE 21 CONTINUED:]
PROCEEDING AS FOR TABLE 17, 89% CONFIDENCE LIMITS FOR THE FIRST, SECOND, AND THIRD THIRDS OF THE ACUTE PHASE AND FOR THE CHRONIC PHASE ARE CALCULATED TO BE ±0·04 mV, ±0·04 mV, ±0·04 mV, AND ±0·06 mV RESPECTIVELY. ∴ SEPARATIONS ≥ ±0·08 mV BETWEEN THE SEPARATE THIRDS OF THE ACUTE PHASE, AND ≥ 0·10 mV BETWEEN THESE AND THE CHRONIC PHASE, ARE SIGNIFICANT AT 5% LEVEL. INSPECTION OF TABLE SHOWS SUCH SEPARATIONS DO OCCUR, ESPECIALLY BETWEEN ACUTE PHASE THIRDS AND CHRONIC PHASE; ALSO INCREASE OF AMPLITUDE DURING ACUTE PHASE WAS CONSISTENTLY OBSERVED EXPERIMENTALLY. VARIATION BETWEEN ACUTE PHASE THIRDS AND CHRONIC PHASE IS THEREFORE REGARDED AS SIGNIFICANT. RE. ACUTE PHASE THIRDS, SEE ALSO FIG. 11 (b).

3. STUDIES ON BURST - BURST DELAY, δ

(a) ACUTE SLAB DATA

TABLE 22 : OBSERVED FREQUENCY DISTRIBUTION :

INTERVAL OF δ (msec)	OBS. FREQ.
-40, -36	2
-35, -31	0
-30, -26	1
-25, -21	7
-20, -16	9
-15, -11	21
-10, -6	30
-5, -1	40
0, 4	117
5, 9	54
10, 14	56
15, 19	39
20, 24	28
25, 29	12
30, 34	9
35, 39	4
40, 44	8
45, 49	1
50, 54	4
55, 59	1
60, 64	1
TOTAL	444

SEE ALSO FIG. 12(a).

TABLE 23 : FITTING OF NORMAL DISTRIBUTION :

OBSERVED DISTRIBUTION HAS PARAMETERS THUS :

$\Sigma\delta = 2273$ msecs, $\Sigma\delta^2 = 100151$ msecs^2, $N = 444$

$\therefore \bar{\delta} = 5{\cdot}12$ msecs, $\sigma = 14{\cdot}11$ msecs, $\sigma_N = 0{\cdot}68$ msecs.

IN FITTING A NORMAL DISTRIBUTION, DATA FOR WHICH $\delta \leq -51$ msecs OR $\delta \geq 50$ msecs ARE DISREGARDED ; THIS GIVES REVISED WORKING PARAMETERS THUS :

$\Sigma\delta = 1958$ msecs, $\Sigma\delta^2 = 83526$ msecs^2, $N = 438$

$\therefore \bar{\delta} = 4{\cdot}47$ msecs, $\sigma = 13{\cdot}08$ msecs.

HENCE ARE CALCULATED, USING STANDARD PUBLISHED TABLES OF AREAS BELOW THE NORMAL CURVE, EXPECTED FREQS. FOR COMPARISON WITH OBSERVED FREQS. GROUPED IN INTERVALS OF 15 msecs SYMMETRICALLY (TO NEAREST 5 msecs) ABOUT THE MEAN.

INTERVAL OF δ (msec)	EXP. FREQ.	OBS. FREQ.	χ^2
≤ -11	59	40	6
-10, 4	167	187	2½
5, 19	161	149	1
20, 34	47	49	2½
≥ 35	4	13	
TOTALS	438	438	12

3 DEGREES OF FREEDOM : $\chi^2 > 8$ SIGNIFICANT AT 5 % LEVEL. ∴ NORMAL DISTRIBN. IS NOT SATISFACTORY DESCRIPTION OF OBSERVED DISTRIBN. (BUT IS SATISFACTORY AT 0·5 % LEVEL).

TABLE 24 : COMPARISON OF FREQUENCY DISTRIBUTIONS FOR SEPARATE THIRDS OF AFTERDISCHARGES :

INTERVAL	OBS. FREQ. IN THIRDS			TOTAL	EXP. FREQ	χ^2			
OF δ (msec)	1ST	2ND	3RD	FREQ.	PER THIRD	1ST	2ND	3RD	TOTAL
≤ -16	5	7	7	19	6	0	0	0	0
-15, -11	6	10	5	21	7	0	1½	½	2
-10, -6	10	8	12	30	10	0	½	½	1
-5, -1	14	14	12	40	14	0	0	½	½
0, 4	45	35	37	117	39	1	½	0	1½
5, 9	18	21	15	54	18	0	½	½	1
10, 14	19	18	19	56	18	0	0	0	0
15, 19	13	10	16	39	13	0	1	1	2
20, 24	6	10	12	28	9	1	0	1	2
≥ 25	12	15	13	40	14	½	0	0	½
TOTALS	148	148	148	444	148	2½	4	4	10½

18 DEGREES OF FREEDOM : $\chi^2 > 29$ SIGNIFICANT AT 5% LEVEL. ∴ THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN THE SEPARATE THIRDS.

TABLE 25 : MEAN VALUES, $\bar{\delta}$, IN DIFFERENT INTERVALS OF MEAN DISTANCE, $\bar{r}$, FROM STIMULATED POINT AND OF SEPARATION, Δr, BETWEEN RECORDING ELECTRODES : COMPILED AS FOR TABLE 16 : NOTE THAT THE SIGN OF Δr IS ALWAYS THE SAME AS THAT OF $\bar{r}$:

$\bar{r}$ (mm)	$\lvert\Delta r\rvert$ = 0, 0·9 mm					$\lvert\Delta r\rvert$ = 1, 1·9 mm					$\lvert\Delta r\rvert$ = 2, 2·9 mm					$\lvert\Delta r\rvert$ = 3, 3·9 mm				
	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)
0, -0·9	-71	653	9	-7·9	3·2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
-1, -1·9	180	4692	24	7·5	11·8	-170	5558	36	-4·7	11·5	360	15302	51	7·1	15·8	—	—	—	—	—
-2, -2·9	205	5151	63	3·3	8·3	171	10275	69	2·5	12·0	91	1331	24	3·8	6·4	—	—	—	—	—
-3, -3·9	—	—	—	—	—	—	—	—	—	—	175	4287	18	10·0	11·8	238	3510	18	13·2	4·5
-4, -4·9	—	—	—	—	—	80	1300	9	8·9	8·1	—	—	—	—	—	—	—	—	—	—
0, 0·9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1, 1·9	-104	4604	18	-5·8	14·9	-25	143	9	-2·8	2·9	-41	457	9	-4·6	5·6	—	—	—	—	—
2, 2·9	105	875	18	5·8	3·8	15	325	6	2·5	6·9	266	9586	33	8·1	15·0	794	32100	30	26·4	19·2
3, 3·9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4, 4·9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

INSPECTION OF TABLE SUGGESTS THAT THERE ARE INTERACTION EFFECTS WHICH, BECAUSE OF UNEQUAL FREQUENCIES (N) IN DIFFERENT $\bar{r}$ AND Δr INTERVALS, WOULD INVALIDATE COMPARISONS OF DATA COMBINED FOR EQUAL $\bar{r}$ OR Δr. HOWEVER, DATA MAY BE ROUGHLY COMPARED BY TREATING PAIRED GROUPS OF DATA AS BINOMIAL SAMPLES (i.e. BY SIGN TEST):

(i) COMPARISON OF DATA RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT: IN INTERVALS OF $\lvert\bar{r}\rvert$ AND $\lvert\Delta r\rvert$, NUMBER OF INTERVALS HAVING $\{\bar{\delta}_{rNEG} > \bar{\delta}_{rPOS}$ IS $2\frac{1}{2}$; $\bar{\delta}_{rPOS} > \bar{\delta}_{rNEG}$ IS $3\frac{1}{2}\}$ WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL. ∴ DATA OF TABLE 25 MAY BE COMBINED FOR $\bar{r}$ POSITIVE AND $\bar{r}$ NEGATIVE :

$\lvert\bar{r}\rvert$ (mm)	$\lvert\Delta r\rvert$ = 0, 0·9 mm					$\lvert\Delta r\rvert$ = 1, 1·9 mm					$\lvert\Delta r\rvert$ = 2, 2·9 mm					$\lvert\Delta r\rvert$ = 3, 3·9 mm				
	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)
0, 0·9	-71	653	9	-7·9	3·2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1, 1·9	76	9298	42	1·8	14·8	-195	5701	45	-4·3	10·4	319	15759	60	5·3	15·3	—	—	—	—	—
2, 2·9	310	6026	81	3·8	7·7	186	10600	75	2·5	11·6	357	10917	57	6·3	12·3	794	32100	30	26·4	19·2
3, 3·9	—	—	—	—	—	—	—	—	—	—	179	4287	18	10·0	11·8	238	3510	18	13·2	4·5
4, 4·9	—	—	—	—	—	80	1300	9	8·9	8·1	—	—	—	—	—	—	—	—	—	—

(ii) COMPARISON OF DATA RECORDED IN DIFFERENT INTERVALS OF $\lvert\bar{r}\rvert$: NUMBER OF CONSECUTIVE PAIRS OF $\lvert\bar{r}\rvert$ INTERVALS FOR WHICH, AT CONSTANT $\lvert\Delta r\rvert$, $\{\bar{\delta}\uparrow$ AS $\lvert\bar{r}\rvert\uparrow$ IS 6; $\bar{\delta}\downarrow$ AS $\lvert\bar{r}\rvert\uparrow$ IS 1$\}$ WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL (WHICH WOULD REQUIRE 7 : 0 CONTRAST) ; BUT NEVERTHELESS IS NOTED IN THESIS.

(iii) COMPARISON OF DATA RECORDED IN DIFFERENT INTERVALS OF $\lvert\Delta r\rvert$: NUMBER OF CASES FOR WHICH, AT CONSTANT $\lvert\bar{r}\rvert$, $\{\bar{\delta}$(do.) $(\lvert\Delta r\rvert = 0,0\text{·}9) > \bar{\delta}(\lvert\Delta r\rvert = 1,1\text{·}9)$ IS 2; $<\bar{\delta}$(do.) IS 0; $(\lvert\Delta r\rvert = 1,1\text{·}9) > \bar{\delta}(\lvert\Delta r\rvert = 2,2\text{·}9)$ IS 0; $<\bar{\delta}$(do.) IS 2; $(\lvert\Delta r\rvert = 2,2\text{·}9) > \bar{\delta}(\lvert\Delta r\rvert = 3,3\text{·}9)$ IS 0; $<\bar{\delta}$(do.) IS 2$\}$ WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL (WHICH WOULD REQUIRE 3 X 3:0 CONTRASTS); BUT NEVERTHELESS IS NOTED IN THESIS.

(b) CHRONIC SLAB (ACUTE PHASE) DATA

TABLE 26: OBSERVED FREQUENCY DISTRIBUTION:

INTERVAL OF δ (msec)	OBS. FREQ.
-70, -66	2
-65, -61	1
-60, -51	0
-50, -46	4
-45, -41	7
-40, -36	1
-35, -31	7
-30, -26	12
-25, -21	14
-20, -16	19
-15, -11	30
-10, -6	38
-5, -1	38
0, 4	66
5, 9	40
10, 14	44
15, 19	42
20, 24	23
25, 29	13
30, 34	17
35, 39	4
40, 44	12
45, 49	5
50, 54	2
55, 59	0
60, 64	5
65, 79	0
80, 84	1
TOTAL	447

SEE ALSO FIG. 12 (b).

TABLE 27: FITTING OF NORMAL DISTRIBUTION:

OBSERVED DISTRIBUTION HAS PARAMETERS THUS:

$\Sigma\delta = 1187$ msecs, $\Sigma\delta^2 = 195732$ msecs^2, $N = 447$

$\therefore \bar{\delta} = 2{\cdot}66$ msecs, $\sigma = 20{\cdot}73$ msecs, $\sigma_N = 0{\cdot}98$ msecs.

DISREGARDING $\delta \leq -51$ msecs AND $\delta \geq 50$ msecs (AS IN TABLE 23), THESE BECOME:

$\Sigma\delta = 912$ msecs, $\Sigma\delta^2 = 152307$ msecs^2, $N = 436$

$\therefore \bar{\delta} = 2{\cdot}09$ msecs, $\sigma = 18{\cdot}58$ msecs.

HENCE, AS IN TABLE 23:

INTERVAL OF δ (msec)	EXP. FREQ.	OBS. FREQ.	χ^2
≤-31	18	19	0
-30, -16	59	45	3½
-15, -1	121	106	2
0, 14	132	150	2½
15, 29	77	78	0
≥30	29	38	3
TOTALS	436	436	11

5 DEGREES OF FREEDOM: $\chi^2 > 11$ SIGNIFICANT AT 5% LEVEL. ∴ NORMAL DISTRIBUTION IS SATISFACTORY DESCRIPTION OF OBSERVED DISTRIBUTION.

TABLE 28: COMPARISON OF FREQUENCY DISTRIBUTIONS FOR SEPARATE THIRDS OF ACUTE PHASES:

INTERVAL	OBS. FREQ. IN THIRDS			TOTAL	EXP. FREQ.	χ^2			
OF δ (msec)	1ST	2ND	3RD	FREQ.	PER THIRD	1ST	2ND	3RD	TOTAL
≤-21	10	19	19	48	16	2	½	½	3
-20, -16	7	6	6	19	6	0	0	0	0
-15, -11	11	12	7	30	10	0	½	1	1½
-10, -6	13	8	17	38	13	0	2	1	3
-5, -1	17	14	7	38	13	1	0	3	4
0, 4	25	25	16	66	22	½	½	1½	2½
5, 9	15	13	12	40	13	½	0	0	½
10, 14	17	11	16	44	15	½	1	0	1½
15, 19	11	15	16	42	14	½	0	½	1
20, 24	9	5	9	23	8	0	1	0	1
≥25	14	21	24	59	19	1½	0	1½	3
TOTALS	149	149	149	447	149	6½	5½	9	21

20 DEGREES OF FREEDOM: $\chi^2 > 31\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN THE SEPARATE THIRDS.

TABLE 29: MEAN VALUES, $\bar{\delta}$, IN DIFFERENT INTERVALS OF MEAN DISTANCE, $\bar{r}$, FROM STIMULATED POINT AND OF SEPARATION, Δr, BETWEEN RECORDING ELECTRODES: COMPILED AS FOR TABLE 25:

$\bar{r}$ (mm)	$\lvert\Delta r\rvert$ = 0, 0·9 mm					$\lvert\Delta r\rvert$ = 1, 1·9 mm					$\lvert\Delta r\rvert$ = 2, 2·9 mm					$\lvert\Delta r\rvert$ = 3, 3·9 mm					$\lvert\Delta r\rvert$ = 4, 4·9 mm					$\lvert\Delta r\rvert$ = 5, 5·9 mm					$\lvert\Delta r\rvert$ = 6, 6·9 mm				
	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)
-1, -1·9	61	853	18	3·4	6·0	208	4174	12	17·3	6·9	-65	1425	9	-7·2	10·3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-2, -2·9	150	4738	18	8·3	13·9	-138	15382	45	-3·1	18·2	-	-	-	-	-	30	1450	9	3·3	12·5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-3, -3·9	-65	4625	21	-3·1	14·5	-	-	-	-	-	-46	1310	18	-2·6	8·1	-70	5525	18	-3·9	17·1	12	3804	9	1·3	20·5	-	-	-	-	-	-	-	-	-	-
-4, -4·9	-	-	-	-	-	300	10200	9	33·3	4·2	-	-	-	-	-	-	-	-	-	-	-35	525	3	-11·7	6·0	-	-	-	-	-	-	-	-	-	-
-5, -5·9	-	-	-	-	-	-12	12664	27	-0·4	21·6	-	-	-	-	-	155	8475	18	8·6	19·9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1, 1·9	-150	10118	18	-8·3	22·2	-	-	-	-	-	-40	900	9	-4·4	8·6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2, 2·9	150	15450	18	8·3	28·1	266	9042	18	14·8	16·8	419	24208	24	17·5	26·6	-104	20878	30	-3·5	26·2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3, 3·9	-	-	-	-	-	275	15325	24	11·5	22·5	90	1200	12	7·5	6·6	-	-	-	-	-	34	626	6	5·7	8·5	-30	1250	9	-3·3	11·3	-109	1943	9	-12·1	8·3
4, 4·9	-	-	-	-	-	-	-	-	-	-	130	1950	9	14·4	2·9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-305	17025	18	-16·9	25·6
8, 8·9	-	-	-	-	-	-52	654	9	-5·8	6·3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

PROCEEDING AS FOR TABLE 25:

(i) COMPARISON OF DATA RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT:

IN INTERVALS OF $\lvert\bar{r}\rvert$ AND $\lvert\Delta r\rvert$, NUMBER OF INTERVALS HAVING $\left\{\begin{array}{l}\bar{\delta}_{r_{NEG}} > \bar{\delta}_{r_{POS}} \text{ IS } 2\tfrac{1}{2} \\ \bar{\delta}_{r_{POS}} > \bar{\delta}_{r_{NEG}} \text{ IS } 4\tfrac{1}{2}\end{array}\right\}$ WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL. ∴ DATA OF TABLE 29 MAY BE COMBINED FOR $\bar{r}$ POSITIVE AND $\bar{r}$ NEGATIVE:

$\lvert\bar{r}\rvert$ (mm)	$\lvert\Delta r\rvert$ = 0, 0·9 mm					$\lvert\Delta r\rvert$ = 1, 1·9 mm					$\lvert\Delta r\rvert$ = 2, 2·9 mm					$\lvert\Delta r\rvert$ = 3, 3·9 mm					$\lvert\Delta r\rvert$ = 4, 4·9 mm					$\lvert\Delta r\rvert$ = 5, 5·9 mm					$\lvert\Delta r\rvert$ = 6, 6·9 mm				
	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)
1, 1·9	-89	10971	36	-2·5	14·1	208	4174	12	17·3	6·9	-105	2325	18	-5·8	9·7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2, 2·9	300	20188	36	8·3	22·1	128	24424	63	2·0	19·6	419	24208	24	17·5	26·6	-74	22348	39	-1·9	23·8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3, 3·9	-65	4625	21	-3·1	14·5	275	15325	24	11·5	22·5	44	2510	30	1·5	9·0	-70	5525	18	-3·9	17·1	46	4430	15	3·1	16·9	-30	1250	9	-3·3	11·3	-109	1943	9	-12·1	8·3
4, 4·9	-	-	-	-	-	300	10200	9	33·3	4·2	130	1950	9	14·4	2·9	-	-	-	-	-	-35	525	3	-11·7	6·0	-	-	-	-	-	-305	17025	18	-16·9	25·6
5, 5·9	-	-	-	-	-	-12	12664	27	-0·4	21·6	-	-	-	-	-	155	8475	18	8·6	19·9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8, 8·9	-	-	-	-	-	-52	654	9	-5·8	6·3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(ii) COMPARISON OF DATA RECORDED IN DIFFERENT INTERVALS OF $\lvert\bar{r}\rvert$:

NUMBER OF CONSECUTIVE PAIRS OF $\lvert\bar{r}\rvert$ INTERVALS FOR WHICH, AT CONSTANT $\lvert\Delta r\rvert$, $\left\{\begin{array}{l}\bar{\delta}\uparrow \text{ AS } \lvert\bar{r}\rvert\uparrow \text{ IS } 6 \\ \bar{\delta}\downarrow \text{ AS } \lvert\bar{r}\rvert\uparrow \text{ IS } 8\end{array}\right\}$ WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL. ∴ THERE IS NO APPARENT DEPENDENCE ON $\lvert\bar{r}\rvert$.

[CONTINUED ON NEXT PAGE]

[TABLE 29 CONTINUED:]

(iii) COMPARISON OF DATA RECORDED IN DIFFERENT INTERVALS OF $|\Delta r|$:

NUMBER OF CASES FOR WHICH, AT CONSTANT $|\bar{r}|$,

$\bar{\delta}(|\Delta r| = 0,0{\cdot}9) > \bar{\delta}(|\Delta r| = 1,1{\cdot}9)$ IS 1; VICE VERSA IS 2
$\bar{\delta}(|\Delta r| = 1,1{\cdot}9) > \bar{\delta}(|\Delta r| = 2,2{\cdot}9)$ IS 3; VICE VERSA IS 1
$\bar{\delta}(|\Delta r| = 2,2{\cdot}9) > \bar{\delta}(|\Delta r| = 3,3{\cdot}9)$ IS 2; VICE VERSA IS 0
$\bar{\delta}(|\Delta r| = 3,3{\cdot}9) > \bar{\delta}(|\Delta r| = 4,4{\cdot}9)$ IS 0; VICE VERSA IS 1
$\bar{\delta}(|\Delta r| = 4,4{\cdot}9) > \bar{\delta}(|\Delta r| = 5,5{\cdot}9)$ IS 1; VICE VERSA IS 0
$\bar{\delta}(|\Delta r| = 5,5{\cdot}9) > \bar{\delta}(|\Delta r| = 6,6{\cdot}9)$ IS 1; VICE VERSA IS 0

} WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL. ∴ THERE IS NO APPARENT DEPENDENCE ON $|\Delta r|$.

(c) CHRONIC SLAB (CHRONIC PHASE) DATA

TABLE 30: OBSERVED FREQUENCY DISTRIBUTION:

INTERVAL OF δ (msec)	OBS. FREQ.
-120,-116	1
-115,-81	0
-80,-76	3
-75,-71	0
-70,-66	1
-65,-61	0
-60,-56	3
-55,-51	0
-50,-46	1
-45,-41	0
-40,-36	2
-35,-31	2
-30,-26	8
-25,-21	14
-20,-16	17
-15,-11	12
-10,-6	13
-5,-1	6
0,4	43
5,9	9
10,14	17
15,19	16
20,24	2
25,29	6
30,34	7
35,39	2
40,44	0
45,49	1
TOTAL	186

SEE ALSO FIG. 12(c).

TABLE 31: FITTING OF NORMAL DISTRIBUTION:

OBSERVED DISTRIBUTION HAS PARAMETERS THUS:

$\Sigma\delta = -1119$ msecs, $\Sigma\delta^2 = 105327$ msecs^2, $N = 186$

$\therefore \bar{\delta} = -6{\cdot}02$ msecs, $\sigma = 23{\cdot}02$ msecs, $\sigma_N = 1{\cdot}69$ msecs

DISREGARDING $\delta \leq -51$ msecs AND $\delta > 50$ msecs (AS IN TABLE 23), THESE BECOME:

$\Sigma\delta = -509$ msecs, $\Sigma\delta^2 = 56027$ msecs^2, $N = 178$

$\therefore \bar{\delta} = -2{\cdot}86$ msecs, $\sigma = 17{\cdot}52$ msecs.

HENCE, AS IN TABLE 23:

INTERVAL OF δ (msec)	EXP. FREQ.	OBS. FREQ.	χ^2
≤-21	29	27	0
-20,-6	51	42	1½
-5, 9	57	58	0
10, 24	31	35	½
≥25	10	16	3½
TOTALS	178	178	5½

4 DEGREES OF FREEDOM: $\chi^2 > 9\frac{1}{2}$ SIGNIFICANT AT 5% LEVEL. ∴ NORMAL DISTRIBUTION IS SATISFACTORY DESCRIPTION OF OBSERVED DISTRIBUTION.

TABLE 32: MEAN VALUES, $\bar{\delta}$, IN DIFFERENT INTERVALS OF MEAN DISTANCE, $\bar{r}$, FROM STIMULATED POINT AND OF SEPARATION, Δr, BETWEEN RECORDING ELECTRODES: COMPILED AS FOR TABLE 25:

$\bar{r}$ (mm)	$\lvert\Delta r\rvert$ = 0, 0·9 mm					$\lvert\Delta r\rvert$ = 1, 1·9 mm					$\lvert\Delta r\rvert$ = 2, 2·9 mm					$\lvert\Delta r\rvert$ = 3, 3·9 mm				
	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)
-1, -1·9	-35	1575	10	-3·5	12·0	345	9725	20	17·2	13·8	–	–	–	–	–	–	–	–	–	–
-2, -2·9	-610	49300	8	-76·2	18·7	-65	1575	10	-6·5	10·7	75	1025	8	9·4	6·3	150	4598	20	7·5	13·2
-4, -4·9	–	–	–	–	–	-100	9150	20	-5·0	20·8	–	–	–	–	–	–	–	–	–	–
-5, -5·9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10	250	10	1·0	4·9
1, 1·9	25	4575	10	2·5	21·3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2, 2·9	–	–	–	–	–	–	–	–	–	–	-240	5900	10	-24·0	4·0	-89	2829	20	-4·4	11·0
3, 3·9	–	–	–	–	–	-435	10675	20	-21·7	7·9	–	–	–	–	–	–	–	–	–	–
5, 5·9	-15	125	10	-1·5	3·2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
7, 7·9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	-135	4025	10	-13·5	14·9

PROCEEDING AS FOR TABLE 25:

(i) COMPARISON OF DATA RECORDED ANTERIOR AND POSTERIOR TO STIMULATED POINT: IN INTERVALS OF $\lvert\bar{r}\rvert$ AND $\lvert\Delta r\rvert$, NUMBER OF INTERVALS HAVING $\begin{cases}\bar{\delta}_{rNEG} > \bar{\delta}_{rPOS} \text{ IS } 2\\ \bar{\delta}_{rPOS} > \bar{\delta}_{rNEG} \text{ IS } 1\end{cases}$

WHICH IS NOT A SIGNIFICANT CONTRAST; THERE ARE INADEQUATE DATA FOR MEANINGFUL CONCLUSIONS TO BE DRAWN. DATA OF TABLE 32 ARE COMBINED FOR $\bar{r}$ POSITIVE AND $\bar{r}$ NEGATIVE:

$\lvert\bar{r}\rvert$ (mm)	$\lvert\Delta r\rvert$ = 0, 0·9 mm					$\lvert\Delta r\rvert$ = 1, 1·9 mm					$\lvert\Delta r\rvert$ = 2, 2·9 mm					$\lvert\Delta r\rvert$ = 3, 3·9 mm				
	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)	$\Sigma\delta$ (ms)	$\Sigma\delta^2$ (ms^2)	N	$\bar{\delta}$ (ms)	σ (ms)
1, 1·9	-10	6150	20	-0·5	17·5	345	9725	20	17·2	13·8	–	–	–	–	–	–	–	–	–	–
2, 2·9	-610	49300	8	-76·2	18·7	-65	1575	10	-6·5	10·7	-165	6925	18	-9·2	17·3	61	7427	40	1·5	13·6
3, 3·9	–	–	–	–	–	-435	10675	20	-21·7	7·9	–	–	–	–	–	–	–	–	–	–
4, 4·9	–	–	–	–	–	-100	9150	20	-5·0	20·8	–	–	–	–	–	–	–	–	–	–
5, 5·9	-15	125	10	-1·5	3·2	–	–	–	–	–	–	–	–	–	–	10	250	10	1·0	4·9
7, 7·9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	-135	4025	10	-13·5	14·9

(ii) COMPARISON OF DATA RECORDED IN DIFFERENT INTERVALS OF $\lvert\bar{r}\rvert$:

NUMBER OF CONSECUTIVE PAIRS OF $\lvert\bar{r}\rvert$ INTERVALS FOR WHICH, AT CONSTANT $\lvert\Delta r\rvert$, $\begin{cases}\bar{\delta}\uparrow \text{ AS } \lvert\bar{r}\rvert\uparrow \text{ IS } 2\\ \bar{\delta}\downarrow \text{ AS } \lvert\bar{r}\rvert\uparrow \text{ IS } 5\end{cases}$ WHICH IS NOT A SIGNIFICANT CONTRAST AT 5% LEVEL.

∴THERE IS NO APPARENT DEPENDENCE ON $\lvert\bar{r}\rvert$.

(iii) COMPARISON OF DATA RECORDED IN DIFFERENT INTERVALS OF $\lvert\Delta r\rvert$:

NUMBER OF CASES FOR WHICH, AT CONSTANT $\lvert\bar{r}\rvert$, $\begin{cases}(\lvert\Delta r\rvert = 0, 0\cdot9) > \bar{\delta}(\lvert\Delta r\rvert = 1, 1\cdot9) \text{ IS } 0\\ (\quad\text{do.}\quad) < \bar{\delta}(\quad\text{do.}\quad) \text{ IS } 2\\ (\lvert\Delta r\rvert = 1, 1\cdot9) > \bar{\delta}(\lvert\Delta r\rvert = 2, 2\cdot9) \text{ IS } 1\\ (\quad\text{do.}\quad) < \bar{\delta}(\quad\text{do.}\quad) \text{ IS } 0\\ (\lvert\Delta r\rvert = 2, 2\cdot9) > \bar{\delta}(\lvert\Delta r\rvert = 3, 3\cdot9) \text{ IS } 0\\ (\quad\text{do.}\quad) < \bar{\delta}(\quad\text{do.}\quad) \text{ IS } 1\end{cases}$

WHICH IS NOT A SIGNIFICANT CONTRAST; THERE ARE INADEQUATE DATA FOR MEANINGFUL CONCLUSIONS TO BE DRAWN.