ON THE ELECTRICAL PATTERNS OF SPONTANEOUS AND EVOKED RHYTHMIC WAVES IN THE DEPTHS OF THE CEREBRAL CORTEX OF THE CAT

by

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INTRODUCTION

Since the original description of spontaneous electrocortical waves by Berger (12) and the decisive confirmation of these findings by Adrian and Mathews (5), the study of electroencephalography has been of enormous clinical and scientific usefulness. However, the nature of the changes which produce these surface potentials has been a singularly refractory problem to the generation of neurophysiologists who have followed. Because of its regularity and reproducibility, the alpha rhythm has been studied the most completely of all the cortical rhythms and it is generally felt that the understanding of this waveform represents the logical first objective in the experimental analysis of the neuronal mechanisms underlying the electroencephalogram. As an approach to an understanding of the alpha rhythm, much attention has been devoted to the spontaneous spindle bursts which appear in experimental animals during barbiturate anesthesia (32), various types of coma and in animals with mesencephalic lesions (the cerveau isolé preparation of Bremer (14). The spindle bursts are periodically appearing trains of large amplitude cortical waves which have the same frequency as the alpha rhythm i.e. 8-12/sec.

Most explanations which have been offered for the basic mechanism underlying any of these 8-12/sec. phenomena are based upon one or the other of two basic concepts: a) autorhythmicity or b) reverberation through closed chains of thalamo-cortical neurons. The idea of autorhythmicity had its origin in Adrian's early comparison between human alpha waves and the rhythmic potential fluctuations which can be recorded from isolated invertebrate ganglia (1). The fact that these latter waves can be recorded from extremely small pieces of invertebrate nervous tissue favors the origin of these waves in a fundamental tendency of neurons for automatic and synchronized beating.

The concept of the reverberating circuit was first used in neurophysiology by Lorente de No in his studies of spinal cord interneurons (52). The application of this hypothesis to spontaneous cortical rhythmic waves in terms of thalamo-cortical reverberation was based upon 1) the demonstration of anatomical connections from the sensory cortex back to the ventrolateral thalamic nuclei, thereby completing a thalamo-cortico-thalamic circuit (33) and 2) the observation that cortical waves were abolished or made abnormal by experimental interruption of the thalamo-cortical radiations (33, 29). The cortico-thalamo-cortical reverberation theory gained stature when Dempsey and Morison were able to produce what appeared to be evoked "equivalents" of the barbiturate bursts by 8-12/sec. stimulation of the diffusely projecting thalamic nuclei. These waves were the now familiar recruiting responses. Critics of the idea of thalamo-cortical reverberation as the sole explanation for the rhythmicity of spontaneous brain waves have pointed out that 8-12/sec. waves are found in very widely separated regions of the nervous system. Furthermore, the number of synaptic delays necessary to account for 8-12/sec. rhythms in terms of reverberating circuits is enormous (16). Finally there have been a number of demonstrations that isolation of the cortex from the thalamus does not completely abolish cortical 8-12/sec. waves (15, 43). Findings such as these led Bremer to postulate a type of thalamic dynamogenic influence which he described as tonus cortical (15).

It must be pointed out that these two fundamental explanations of cortical rhythmicity are not mutually exclusive. Most investigators concede the possibility that both mechanisms may operate in the normal situation and that thalamo-cortical volleys may trigger autorhythmic phenomena.

Classification of evoked repetitive cortical waves. The fact that Dempsey and Morison were able to evoke waves which were similar to the spontaneous cortical barbiturate bursts by repetitive thalamic stimulation has been of tremendous value in the experimental analysis of thalamocortical relations. Because they are evoked waves rather than spontaneously occurring events, it has been possible to isolate, subcategorize and to analyze them in a highly controlled fashion.

In their original contributions (28, 29, 30, 31, 58), Dempsey and Morison classified the kinds of cortical waves which could be evoked by 8-12 sec. stimulation of the thalamus and other subcortical structures into two distinct groups: 1) the recruiting response which is evoked by repetitive stimulation of the diffusely projecting thalamic nuclei and 2) the augmenting response which is evoked by repetitive stimulation of the sensory relay nuclei and the nuclei which project directly to the association cortices. On the basis of appearance, distribution, and interaction studies they concluded that the recruiting response was the evoked equivalent of the spontaneous barbiturate bursts and that the augmenting response was the equivalent of 1) the repetitive after-discharge associated with the primary response and 2) the so-called projection activity which was found in the sensory projection areas of their nembutalized animals.

The overall trend of subsequent literature has been consistent with these relationships and the general idea that the recruiting response is the evoked equivalent of spontaneous barbiturate bursts has been extended to include also those spindles which can be seen in other preparations. This confirmation has been based upon observations in a number of different laboratories. 1) The similarity in the surface distribution and appearance of recruitment and spindling has been corroborated (39, 26). 2) More elaborate interaction studies have also tended to confirm the equivalence of these two waveforms (26). 3) The ease with which tripped spindles may be produced by single shocks to the diffuse thalamic system has been repeatedly demonstrated (39, 42). 4) Similarities in the behavior of single cortico-spinal units during cortical recruitment and spindling in the pyramidal cat have been described (11, 75). 5) Microelectrode studies have revealed striking analogies in the cortical depth distribution of recruiting and spindle waves (47). 6) Penicillin injections into the diffuse thalamic projection system have been found to produce remarkable alterations in cortical barbiturate spindles (67).

Interpretation of the surface electrical changes in recruitment. Partly because of these many similarities to spindling, considerable effort has been directed toward the analysis of the potential components of the individual recruiting waves. Attempts to delineate the relative roles of cortical vs. subcortical structures in the production of the waves have been markedly influenced by the changing interpretations which have been applied to other cortical responses. For example, Adrian's (3) original idea that the positive-negative sequence recorded at the cortical surface in response to a sensory stimulus represents the afferent volley and ascending activation of the cortex has undergone alteration since recent evidence (63, 46) has tended to corroborate Eccle's (34) interpretation that the initial surface positivity represents deep post-synaptic potentials. This modification is reflected in the different interpretations of the initial surface positivity of the recruiting response advanced by Arduini and Terzuolo (10), who visualized a very large afferent volley which waxed and waned and by Verzeano, Lindsley and Magoun (74), who assigned almost all of the surface potential change to intracortical events. In the latter paper, this emphasis on intracortical mechanisms was carried even further when the 8-12/sec. rhythmicity was explained in terms of reverberating circuits which were depicted as being predominantly intrinsic to the cortex and thalamus and largely independent in each of these two regions.

Identification of the histologic structures producing these electrocortical waves. Because of the differences in the surface configuration between recruiting responses and the primary response, Dempsey and Morison (28) suggested that the recruiting potentials might be mediated by the unspecific cortical afferents described by Lorente de No (53). The unspecific afferents were originally described as having terminations in all cortical layers with the greatest number of collaterals distributing to the sixth layer. These structures, therefore, differ markedly from the specific afferents which end in a brush formation in the fourth and lower third layers (55).

Chang's revival (22) of Cajal's original classification of cortical synapses (66) gave impetus to more refined attempts to correlate intracortical potentials with known cortical histologic structures (see below).

Chang reviewed the description of Cajal's axo-somatic and axo-dendritic synapses, changed their names to peri-corpuscular and para-dendritic respectively and imputed to them entirely separate and distinct functional characteristics. The peri-corpuscular connections appeared to be designed for the reliable transfer of sensory information in an almost one-to-one relationship. On the other hand, the paradendritic endings seemed more appropriate for modulation of the excitability of the cell body so as to facilitate or inhibit transmission over pericorpuscular synapses.

Recent work in Jasper's laboratory with microelectrodes has led to a synthesis of Dempsey and Morison's hypotheses about the nature of the cortical afferents mediating the responses of the two thalamic systems and Chang's ideas about the two kinds of cortical synapses (40, 46, 47). On the basis of the changes in potential configuration with respect to cortical depth, the primary response appeared to involve the specific cortical afferents which presumably activate Golgi type II cells which in turn probably have pericorpuscular synapses with the pyramidal cells. On the other hand, the responses to repetitive stimulation of the non-specific system seemed to be mediated by the unspecific cortical afferents which were assigned terminations on the apical dendrites of cortical cells in paradendritic synapses. On the basis of a similar laminar-potential distribution, it appeared as if the spontaneous spindle bursts were mediated by the same pathways as the recruiting response.

There have been a number of studies concerning the interaction of specific and unspecific cortical responses which suggest that these two systems may actually involve some of the same cortical elements.

Dempsey and Morison (29) showed that superimposition of specific and unspecific responses in the sensori-motor cortex was possible without blockade. Jasper and Ajmone-Marsan (41) found that the surface negative components of the primary visual response and the recruiting potentials do interact and therefore the conclusion was drawn that they involve common neuronal elements, probably the apical dendrites of pyramidal cells (47). The interaction between these two responses has recently been studied at the unitary level by Li (44). He has shown that unspecific cortical responses are capable of facilitating the unitary activity evoked by stimulation of the specific system.

The role of apical dendrites. As a result of extensive studies of the primary visual response, Bishop (13) became convinced that the apical dendrites of pyramidal cells were capable of supporting antidromic but not orthodromic conduction. Further exploration of cortical dendritic potentials (25) led him to the belief that the apical dendritic membrane was capable of graded responses only and hence representative or a more primitive type of irritable tissue. Earlier work by Chang on the functional characteristics of apical dendrites (21) had emphasized the slow conduction velocities which seemed to be characteristic of these structures rather than any propensity which they might have for graded responses. Nevertheless, both Bishop and Chang have imputed to the apical dendrites and to their synaptic contacts the primary function of regulation of cell body excitability.

With these ideas about the nature of cortical apical dendrites as a background, Bishop has recently undertaken a study of these 8-12/sec. waves (26). He has equated the recruiting and augmenting responses and illustrated their similarity to spontaneous spindle waves. All three of these potential phenomena are, he believes, essentially dendritic potentials. He has assigned the basic frequency of these waves to recovery characteristics of certain synaptic regions on the apical dendrites of the cortical pyramidal cells.

In summary, the overall trend in the literature has been to identify the cortical response to sensory volleys with specific cortical afferents and with pericorpuscular synapses. The recruiting response, however, seems to be mediated by the unspecific cortical afferents which are presumed to have primarily paradendritic terminations on apical dendrites of cortical pyramidal cells. The latter system could serve to regulate the receptivity of pyramidal cells to incoming sensory signals and also to control the cortical elaboration of the sensory signals. Most investigators in this field have felt that the unspecific cortical system and apical dendrites are the main anatomical structures involved in the spontaneous spindle waves.

In spite of the fact that these ideas have been supported by a wealth of experimental observations, there are certain gaps and inconsistencies which demand that the scheme presented above be revised or amplified. 1) There has been a growing awareness that much of the work on recruitment may be misleading in that special precautions were not taken to prevent contamination of the recruiting response by the commonly overlooked augmenting responses. This point has been emphasized by Hanberry and Jasper (38). 2) A study by Lindsley, Bowdan and Magoun (49) showed that most of the specific as well as the unspecific thalamic nuclei were essential for normal cortical spindling in cerveau isolé preparations. 3) Although n. ventralis anterior and n. reticularis thalami have generally been regarded as occupying a key position in the diffuse thalamic projection system (37, 38), very little effort has been made to determine the cortical mechanisms underlying the short latency recruitment obtained by repetitive stimulation of these nuclei. (These waves have many of the features of augmenting responses.) 4) Li and Jasper (48) noted that spontaneous spindle waves as recorded with a cortical microelectrode were often seen to reverse at a depth which was the same as the termination of <u>specific</u> cortical afferents.

Because of such uncertainties Brookhart and Zanchetti (19) recently reevaluated the problem using relayed and evoked corticospinal responses (62, 76) to relate changes in the excitability of this cortifugal system and its related neurons to the cortical surface potentials of augmenting, recruiting and spindle waves. Several special precautions were taken in this study. Based on the anatomical findings of Nauta and Whitlock (60), strictly midline thalamic nuclei were employed in the study of the recruiting response in an effort to avoid stimulation of fibers of passage from specific thalamic nuclei. In order to avoid superimposed effects of tripped spindles highly aroused immobilized preparations were used. Spindling was produced by thermocoagulation of the mesencephalic tegmentum with sparing of the pyramidal tract on one side so that spindling could be studied in unanesthetized animals. Gross pyramidal electrodes were used in order to assay the changes in responsiveness of a <u>population</u> of cortico-spinal neurons, rather than the behavior of isolated units. The results of this study were these: both augmenting and spindling waves were accompanied by conspicuous relayed pyramidal volleys and by marked alterations in cortico-spinal responsiveness as tested by cortical stimulation during these waves. On the other hand the recruiting waves were accompanied by a small relayed volley or no relayed volley and by no detectable alterations in cortico-spinal responsiveness. These results suggested that similar mechanisms underlie both augmentation and spindling and that recruitment is produced in an entirely different manner. Two hypotheses were suggested to account for these differences; 1) The two classes of response might involve entirely different patterns of intracortical current distribution with different potentialities for ephaptic excitation of cortical neurons (4), or alternatively, 2) the differences in responsiveness might be due to differences in transynaptic activation. One possibility suggested was that augmentation and spindling involve cortical activation primarily at the somata and basal dendrites of the pyramidal cells and that cortical recruitment involves activation of similar cells at their apical dendrites.

The present series of experiments represents an attempt to test these hypotheses by recording these three cortical wave forms at different measured depths within the sensorimotor cortex.

METHODS

Theoretical Considerations

The technique employed in the present study, that of recording at different measured depths within a rather restricted portion of the central nervous system, is one which has been widely used. For this reason, there has grown up a generally accepted group of assumptions regarding current flow around neurons in a volume conductor which has proven to be of great usefulness in the interpretation of potentials obtained with extracellular microelectrodes. The most thorough treatment of this problem is to be found in Lorente de No's monograph (54). More qualitative treatments of the subject are available, however (25, 50, 56).

1) Slow waves. The first assumption which is generally made is that brain tissue is a homogeneous conductor having only ohmic resistance. It follows, therefore, that a microelectrode which is situated within this brain tissue extracellularly records the IR drop of potential established across the resistance of the brain tissue by the flow of current outside the active elements. Changes in potential are recorded when the electrode is in an area where the predominant stream of current is flowing out of cell membranes (sources). Conversely, negative going potentials are recorded when the electrode is in an area where the predominant stream of current is flowing inward at the sites of cell membrane depolarization (sinks). It must be remembered, however, that zero potential cannot be equated with zero current flow. For example, if the tip of a monopolar recording electrode is situated between a source and a sink at a point which is at the same potential

as the indifferent electrode, it will not register any potential change. Nevertheless, this point may be in very dense current flow. Therefore it is best to estimate the pattern of current flow by comparing monopolar recordings which were made at many different recording loci.

Having thus estimated the direction of current flow, it is possible to describe potential recordings made at different depths within a volume of nervous tissue in terms of the distribution of current sinks and sources in a way which will be meaningful. A sink is usually indicative of activation of neural elements at excitatory synapses. Sources which are present in association with an adjacent sink usually signify that other portions of the <u>same</u> cells as those being activated are furnishing current for the depolarized zone. In some cases, however, sources and sinks may indicate the existence of after-potentials rather than synaptic activation.

The responses studied in this experiment consist of such huge potential fluctuations that it may be assumed that they can arise only from a multitude of cells so oriented that sources and sinks arising in different parts of the same neuron will summate with sources and sinks arising from comparable parts of other neurons. This summation is most likely to occur if 1) the duration of the potential changes are long and 2) if the activity is well synchronized— a relative thing depending upon the duration of the potential changes and 3) if the neurons are uniformly oriented and stretched out in such a way that the parts of neurons acting as sinks are undiluted by parts of other neurons acting as sources and vice versa. The brief spike-like potentials recordable from axons and from cell bodies are probably too brief to contribute appreciably to the large slow waves, i.e. most of the slow waves probably do not represent envelopes of unitary spikes (48). Their origin has usually been assigned to pre- and post-synaptic potentials and/or so-called dendritic potentials. The cortical pyramidal cells are generally regarded as the neurons which produce most of the large cortical slow waves by virtue of their numerical superiority, their long apical dendrites and their uniform vertical orientation. Similar arguments may also be made for the various types of corticipetal axons since these structures also are long and uniformly oriented. The specific cortical afferents would seem to be especially likely to contribute large potentials because of the invariable location of the massive bushy terminals in the fourth and lower third layers.

Spikes. It is generally assumed that the great majority of spike-like potentials which are recorded with wire microelectrodes from the cerebral or cerebellar cortices represent extracellular recordings of the activity of single cortical cells in the region of their cell bodies, probably within 50 to 100 microns of these structures (18, 20). In most of the present experiments 12.5 and 25 micron diameter wires were employed. However, in two experiments, micropipettes of less than one micron diameter were used. With both wire and glass electrodes, spikes were most abundant in the cortical layers which contain the largest cell bodies (Layers II-V). When wire electrodes were used, no spikes above and below these levels could be distinguished with certainty, although the micropipettes sometimes did record spikes beyond these limits. It should be mentioned, however, that no special attempts were made to lower the penetrating electrode by small increments in an effort to find unitary spikes since the primary objective in this investigation was that of studying the slow waves.

In any experiment in which unitary activity is examined, the effects due to injury must be clearly distinguished from those due to physiologic activity. At every recording site recordings of the spike activity which was present was made only after the obvious signs of injury had subsided (usually after several minutes). The unitary activity which remained was often sensitive to mechanical peripheral stimuli to the skin or fur of the animal and was usually decisively affected by the repetitive thalamus stimuli. The fact that these units responded to physiologic stimuli such as rubbing fur etc. minimizes the possibility that they were only capable of responding ephaptically by virtue of injury. In the fifth layer it was frequently possible to follow a single unit for 20 minutes or so without any noticeable change in its behavior. While it is impossible to say that such unitary activity is entirely normal, the response of these units to peripheral and thalamic stimuli favors the belief that the patterns of spike discharges recorded in these experiments represent patterns of "normal" activity in cortical neurons under the conditions of the experiments.

It must be emphasized that in contrast to the interpretation of slow waves outlined above, there is no obvious reason why spikes from pyramidal cells should be recorded preferentially to those from other cells. However, it has been suggested that the size of unitary spikes recorded extracellularly is related in a general way to the size of the cell body of the responding neuron (48). The experience in this investigation tended to corroborate these findings, especially when wire electrodes were used. The largest spikes were almost invariably recorded at the level of the fifth layer as measured by histologic control. Since the pyramidal cells as a group have rather large cell bodies, it is reasonable to assume that many of the extracellular spikes did originate in these cells.

The general approach taken in the examination of the unitary activity accompanying these responses was not focused upon the behavior of isolated cells but was directed toward defining in a general way the parameters of the massive regulation of whole populations of units which characterized some of these giant slow potentials.

Technique

The experiments to be reported have been carried out on well over 40 cats. Because of the many difficulties in this type of experiment the data from only 21 cats was thoroughly analysed. However, the observations which were made on the other animals were consistent with those reported. The surgical preparation of the animal was carried out under ether anesthesia. The trachea was routinely cannulated and both carotids were isolated with loose ligatures prior to mounting the head in a stereotaxic frame. The cranial vault was exposed and small trephine holes were made to permit the introduction of thalamic stimulating electrodes or mesencephalic coagulating electrodes. The sensorimotor cortex was exposed through the frontal sinus and the cisterna magna was opened by carefully cutting a hole in the dura underlying the atlanto-occipital membrane. It was found that doing this procedure early in the experiment often greatly reduced the respiratory and cardiac pulsations of the brain. Following the surgical procedures, the scalp, neck muscles, auricular and infraorbital areas were infiltrated with 1 percent procaine or 0.1 percent pontocaine. The animal was placed on artificial respiration after the administration of decamethonium bromide and was maintained immobile at a dose level of 1 mg. repeated every 45 to 60 minutes after the discontinuation of ether. The time necessary for setting up the remainder of the experiment was sufficiently long for the dissipation of ether effects to be virtually complete. In the experiments requiring spontaneous spindle bursts, the animals were subjected to a lesion of the mesencephalic tegmentum by the use of thermocoagulation produced by radio-frequency currents. Following this procedure the animal was usually no longer maintained on decamethonium bromide in order that artificial respiration could be discontinued and thereby one source of brain movement partially elemented. Immediately after the surgical procedures a well of Jeltrate was constructed around the opening through the frontal sinus and for the duration of the experiment the exposed cortex was kept covered with warm mineral oil. Opening of the dura overlying the frontal cortex was postponed as long as possible in order to preserve "physiologic" conditions.

Thalamic stimulating electrodes were concentrically bipolar with a tip separation of approximately 0.5 mm. and were placed stereotaxically. Stimulating pulses were rectangular pulses which were slightly distorted by an isolating transformer. Pulses of 0.08 to 1 msec. duration and two to five volts intensity were employed. The stimulus parameters were adjusted so that reliable and reproducible cortical responses were obtained. It was generally felt that the amplitude of the evoked responses utilized should be roughly comparable to those of the spindle bursts in the cerveau isolé preparations (500 to 1000 microvolts) and therefore suprathreshold stimulus intensities were usually used. Optimum frequencies for the responses varied considerably from experiment to experiment but were in the range of 5-12/sec. The recruiting response generally required lower stimulus frequencies than the augmenting waves.

In order to verify the thalamic electrode placement, histologic controls were used. At the termination of each experiment, the head of the animal was perfused through the left carotid artery with 10 percent formalin in physiologic saline. The thalamic stimulating electrode was left in situ for several hours while the brain hardened. Before removing the brain, the vertical stereotaxic planes were marked by inserting electrodes at appropriate levels while they were wet with India ink. The brain was removed, blocked, frozen and sectioned at 100 microns. The sections through areas of diencephalic electrode tracks were stained with carbol-thionin.

During the experiments, the optimum position for thalamic stimulation was determined by monitoring the evoked responses on a multichanneled electroencephalograph (Grass Model III). In spindling experiments, the completeness of the mesencephalic lesion was estimated in this same way. Having established the adequacy of the mesencephalic lesion or the thalamic stimulating electrode placement, the responses as they appeared over the entire exposed frontal cortex were visually mapped with a spring-mounted ball-tipped silver wire in order to choose the recording site which best suited the purposes of the experiment.

Once a suitable spindling, augmenting or recruiting response had been obtained in the preparation and an optimum recording site chosen in the manner indicated, all subsequent cortical recording was done with either very fine wires or micropipettes. In the majority of experiments, either 12.5 or 25 micron diameter nichrome wires were employed. These were insulated with enamel except at their tips. The 12.5 micron wires were more satisfactory for the recording of slow waves since they dimpled the cortex much less during initial penetration. However, in general, the unitary activity was more easily visualized with the 25 micron wires. This may be due to greater injury produced by the large wires or it may be that the larger electrode tips are able to record unitary activity from a much larger volume of cortex. In order to rule out the possibility that the use of wires of this size was giving unreliable results because of excessive damage, very fine micropipettes were employed as the penetrating electrode in two experiments. These presumably had a tip diameter of less than one micron. (Resistance was 20 meg. when filled with 3 M KCl and measured in normal saline.) The results obtained with the micropipettes were comparable to those which were obtained with the wires. The surface dimpling produced during the entry of the micropipettes into the cortex was comparable to that caused by the 12.5 micron wires, at least to visual observation through a dissection microscope. Because the amplitude of the spikes was larger and isolation of individual units was more common, the unitary activity recorded with the micropipettes was easier to evaluate than that seen with the wires. However, the general features of the unitary activity as recorded with the micropipettes was comparable to that obtained with the wires. The wire microelectrodes were used in the majority of experiments because 1) adequate facilities for using micropipettes were not available during the period of time in which most of the experiments were carried out, 2) identification of the recording site was easier with the wire electrodes because of the opportunities for depositing stainable metallic ions in the tissue,

3) the parallel walls of the wire electrode shafts caused no further dimpling with penetration after the tip entered and 4) even at recording sites which were 2 to 3 mm. from the cortical surface, the diameter of the part of the wire electrode in the superficial layers was still relatively small and therefore produced less damage to the superficial parts of the cortex than did the expanding shaft of the tappered micropipettes. In all experiments, the surface monitoring electrode was a 25 micron wire. This kind of electrode was employed in an effort to minimize distortion of the cortex and to obtain surface recordings very close to the penetrating electrode in order to sample as nearly as possible the surface responses of the column of cortex from which the penetrating electrode was recording.

The positioning of the penetrating electrode was accomplished with a very high degree of precision by the use of a Leitz micromanipulator. The surface monitoring electrode was placed by means of a micrometer driven manipulator fashioned from a discarded Ranson stereotaxic instrument.

Both surface and deep recordings were displayed on oscilloscopes driven by matched, differentiating preamplifiers. When micropipettes were used, a cathode follower preceded the input stage of the preamplifier. Visualization of unitary activity was facilitated by inserting a 0.005 to 0.0005 microfarad condenser at the input of the preamplifier in order to attenuate the slow potentials. All recordings were monopolar, the reference electrode being placed on the neck muscles, scalp margins or the stereotaxic frame.

In order for any reliable correlation to be established between the potentials recorded during the experiment and histologic features of the cortex, it was absolutely essential that accurate depth measurements of the recording electrode be made. There are a number of sources of error in depth measurement. One of the most serious is the dimpling of the cortex which occurs with the entry of the penetrating electrode. This is greatly minimized if the piarachnoid is removed. This was accomplished either by digestion of the membrane by crystals of trypsin or else by careful dissection of the pia using sharpened jeweler's forceps. Once adequate skill had been acquired, the latter method was used almost exclusively. It was found to be somewhat easier to visualize the pia if the cortex were kept covered with warm mineral oil during the dissection. The surface responses were always compared before and after dissection of the pia in order to detect gross signs of cortical damage which might have resulted from the trauma of the dissection.

Many difficulties of a mechanical nature vitiated the depth measurements. Many of the animals with mesencephalic lesions developed cerebral edema during the course of an experiment. In some instances this was relieved by ventriculostomy, but in others this maneuver failed to arrest the swelling. Restriction of the mesencephalic lesion and the exercise of extreme care when surgical manipulations were performed around the superior sagittal sinus were measures employed in an attempt to reduce the incidence of this complication. Because of the nature of the experiments, even the slightest amount of edema which displaced the cortex only a fraction of a millimeter was incompatible with the completion of an experiment. Another difficulty encountered was that cardiac and respiratory pulsations of the brain were sometimes uncontrolled by cisternal drainage. However, cortical restraint in the form of a plastic plate with a hole in it was used in only one experiment. In general, if pulsations persisted, the experiment was terminated in view of the fact that it was very difficult to evaluate the degree to which any form of restraint would interfere with the blood supply to the cortex.

In an experiment in which responses at different depths are compared, it is essential that the responses remain as nearly as possible absolutely identical during the recording procedure. For this reason, once a penetration had been started, an attempt was made to complete the series within a reasonably short time (1-2 hrs.). It is partly for this reason, that unitary activity was sampled at regular depth intervals rather than handled as a study of the behavior of single units.

At the termination of each penetration, the bottom of the electrode track and several additional points at measured depths from the surface were marked by depositing nickel ions (20). Current was passed for 20 sec. at 5 microamperes. Following the intra-arterial perfusion of formalin and removal of the brain at the conclusion of the experiment, the brain was allowed to fix in formalin for several days. After this, frozen cortical sections were cut at 75 microns (57). These sections were later treated by the Terman-Schmeltzer technique (20) to precipitate nickel ions and were then stained with Pyronin Y. In the completed slide, the nickel ferricyanide precipitate was seen as a green bulls eye against the red Nissl stain. The central deposit was taken as the tip of the electrode.

In most experiments, the difference between the depth of the recording electrode as measured by the micromanipulator and that measured from the histologic sections was within 50 microns. In those few experiments in which the discrepancy between these two forms of depth measurement was around 100-200 microns, there was usually evidence of shriking or swelling in that the distances between the different cortical marks were all greater or less than that indicated by the micromanipulator when the marks were made. From the measurement of these distances between marks it was possible to compute a shrinkage or a swelling ratio. The confidence with which this method of depth measurement was used was supported by the frequent striking correlations between the depth of appearance of the largest unitary potentials and the histologic boundary of the fifth layer. The major limitation of any technique of this sort is that the identification of the cortical layers is such a subjective matter.

Permanent records of the oscilloscopically displayed responses were made by photographing the excursions of the oscilloscope beam, which was stationary along its time axis, on continuously running film. The 35 mm. film recordings were projected for examination with the aid of a photographic enlarger. Measurements of time and amplitude were made directly from the projected image in some instances or from pencil tracings of the image. In order to facilitate comparisons of time and amplitude relations, superimposed tracings of many waves have been made.

RESULTS

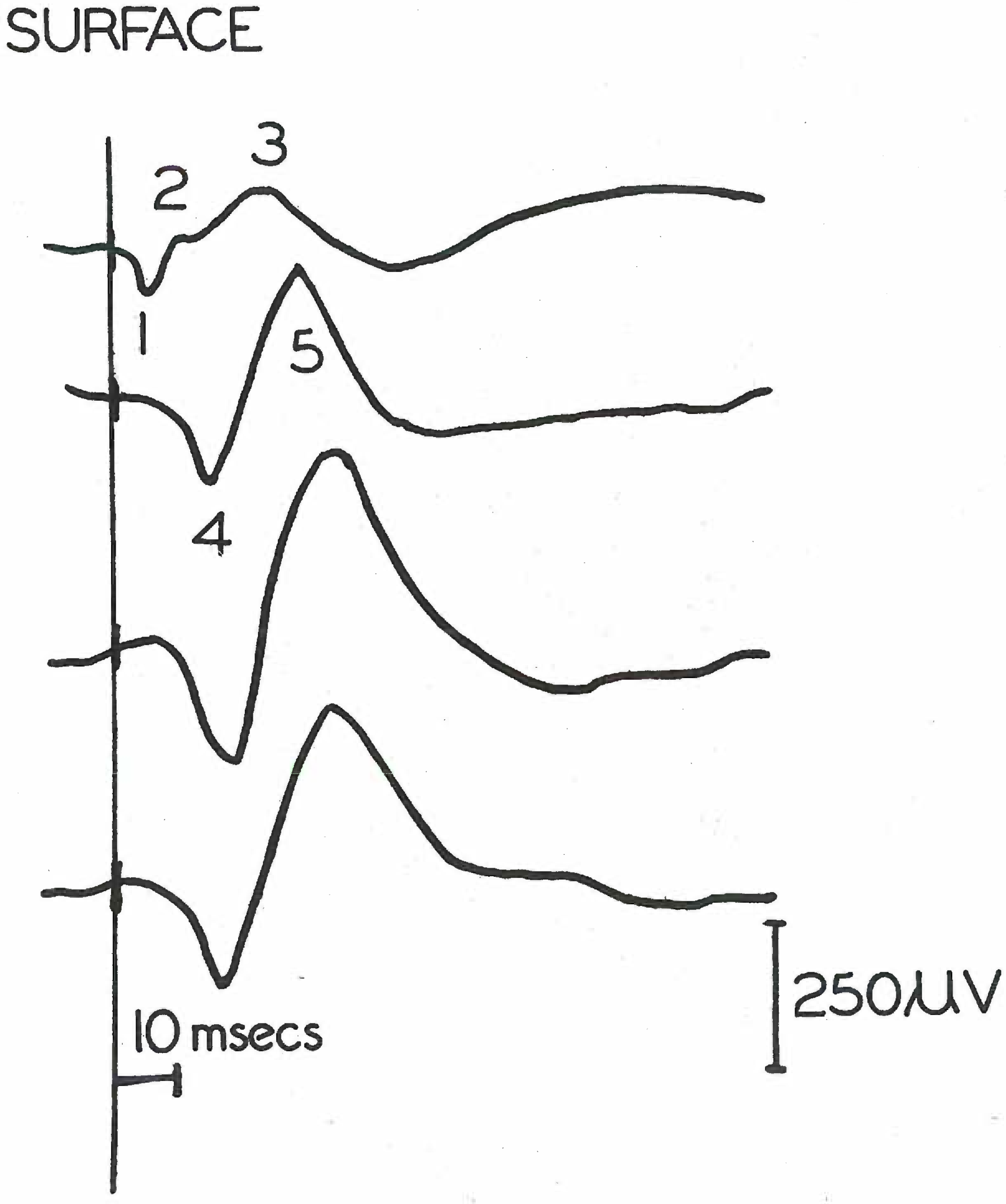
Slow Waves

Augmenting response

In their original description of the augmenting response (30, 31) Dempsey and Morison distinguished sharply between this response and the response to single shock stimulation of the specific thalamic nuclei, the primary response. The differences between these two responses are illustrated in figure 1. These are tracings of the responses to successive shocks to a specific thalamic nucleus. The first response is the primary response and consists of three components: a spike-like surface positive deflection(1) which is almost continuous with the stimulus artifact, a second positive or negative deflection(2) which has a latency of 0.5-0.8 msec., and a prolonged negative going deflection (3). The important point is that component 1 of the primary response remains the same or becomes reduced in amplitude with 8-12/sec. repetition of the thalamic shock. In the response illustrated, it has virtually disappeared with the second shock. With stimulation at this frequency, a later positive-negative sequence develops (4-5) and reaches enormous proportions after only two or three shocks. With a very long train of shocks it tends to wane only slightly. The positive deflection has a latency approximately equal to that of the second and third component of the primary response. The so-called augmenting response may be obtained by stimulation of the thalamus, the internal capsule, the medial lemniscus and suggestions of it may be seen when a peripheral nerve is repetitively stimulated (31). The primary response is localized to a smaller cortical area than the augmenting

FIGURE 1

Comparison of the surface configuration of a primary response with that of augmenting responses. Tracings of oscillograph records derived from a monopolar electrode on the posterior sigmoid gyrus. From above downward, the first four responses to 8/sec. threshold stimulation of n. ventralis lateralis. The first response is the primary response and the next three responses are augmenting responses. Note the disappearance of component 1 of the primary response in the subsequent responses. See description in text. In this and all subsequent figures, upward deflection indicates negativity of the active electrode in comparison with the reference electrode. (4-19-57)


SURFACE
1
2
3
4
5
10 msecs
250µV

response and for any given thalamic stimulus, cortical areas can be found from which each response is recordable without the other (30). The response illustrated is representative of the type of response sought in the selection of recording sites in these experiments. The advantage of this is to be found in the fact that the large amplitude augmenting responses are virtually uncontaminated by the primary response. Thus most of the experiments have involved recording from a cortical zone outside of the primary receiving area related to the point stimulated in the thalamus.

Most of the thalamic stimulating sites were either in VPL or in the adjacent portion of the internal capsule. For these placements, the largest and purest augmenting waves in the paracruciate area were usually obtained around the post-cruciate dimple. This particular spot is ideal for studies of this kind because of the slight concavity of the cortical surface and the presence of a large artery in the dimple which greatly facilitates dissection of the pia. Most penetrations at this particular site seemed to be perpendicular to the cortical layers and hence probably parallel to the axes of the pyramidal cells. In order to isolate the effects of superimposed triggered cyclic waves (17) relatively long trains of augmenting responses were used. In almost all experiments the responses maintained a large amplitude even with very long trains of stimuli and showed little fatigue when repeated trains of stimuli were delivered in close succession. In some preparations and particularly when threshold stimuli were utilized, the early responses (roughly the third through the twelfth in the train) showed a much larger amplitude than the later waves. In other words, it appeared as if a burst of triggered cyclic waves were reinforcing the evoked waves. Nevertheless, the potential distribution with respect to depth was comparable in both the early and late responses so that they will be handled as a unit in the following description.

A typical response to repetitive stimulation of VPL as seen at different depths within the cortex is illustrated in figure 2. This was recorded from a zone in which the primary response was not very well developed. The striking features of the response taken as a whole are these: the response at the surface and through layer I is a positive negative sequence. In layer II, the peak time of these phases has shifted slightly earlier and a late positivity has become apparent. By the third layer, the response has become initially negative with an after-positivity. As the lower third and fourth layers are entered the negative going deflection rises earlier and the crest of the negativity is thereby broadened. The same general pattern is maintained down into the fifth and upper sixth layers with a gradual decrease in the amplitude of the initial negativity. Within the sixth layer the initial negativity again becomes more peaked as it becomes progressively smaller and smaller in amplitude. Associated with this decline in amplitude of the initial negativity, the after-positivity becomes more and more prominent. The changes are indicative of the development of a large sink which reaches its maximum at about 10 msec. and extends roughly from the third through the fifth cortical layers.

Another way in which these changes may be visualized is by graphing potential against depth for a series of points in time. This type of graph is illustrated in figure 3. The ordinates are potential and the abscissas represent depth expressed both in terms of cortical layers

FIGURE 2

Augmenting responses recorded at different cortical depths. Tracings of oscillographic recordings made with a 12.5 micron nichrome wire during a single penetration in the posterior sigmoid area. Each tracing was taken from the largest response occurring during a single train of responses initiated by stimulation of n. ventralis posterolateralis with suprathreshold shocks at 10/sec., 0.08 msec. The depth of the electrode tip at the time of recording is indicated to the left of each tracing. The responses are arranged in two columns in order of progressive depth. On the right, the depths of successive recordings are indicated in relation to the position of the cortical layers as they were identified on the histologic control. On this scale, solid horizontal lines represent easily identified boundaries between cortical layers and dotted horizontal lines indicate indistinct boundaries. The changes in configuration of these waves with depth are described in the text. Components a and b are indicated in this figure by small letters. Time and voltage calibrations are indicated at the bottom of the figure.

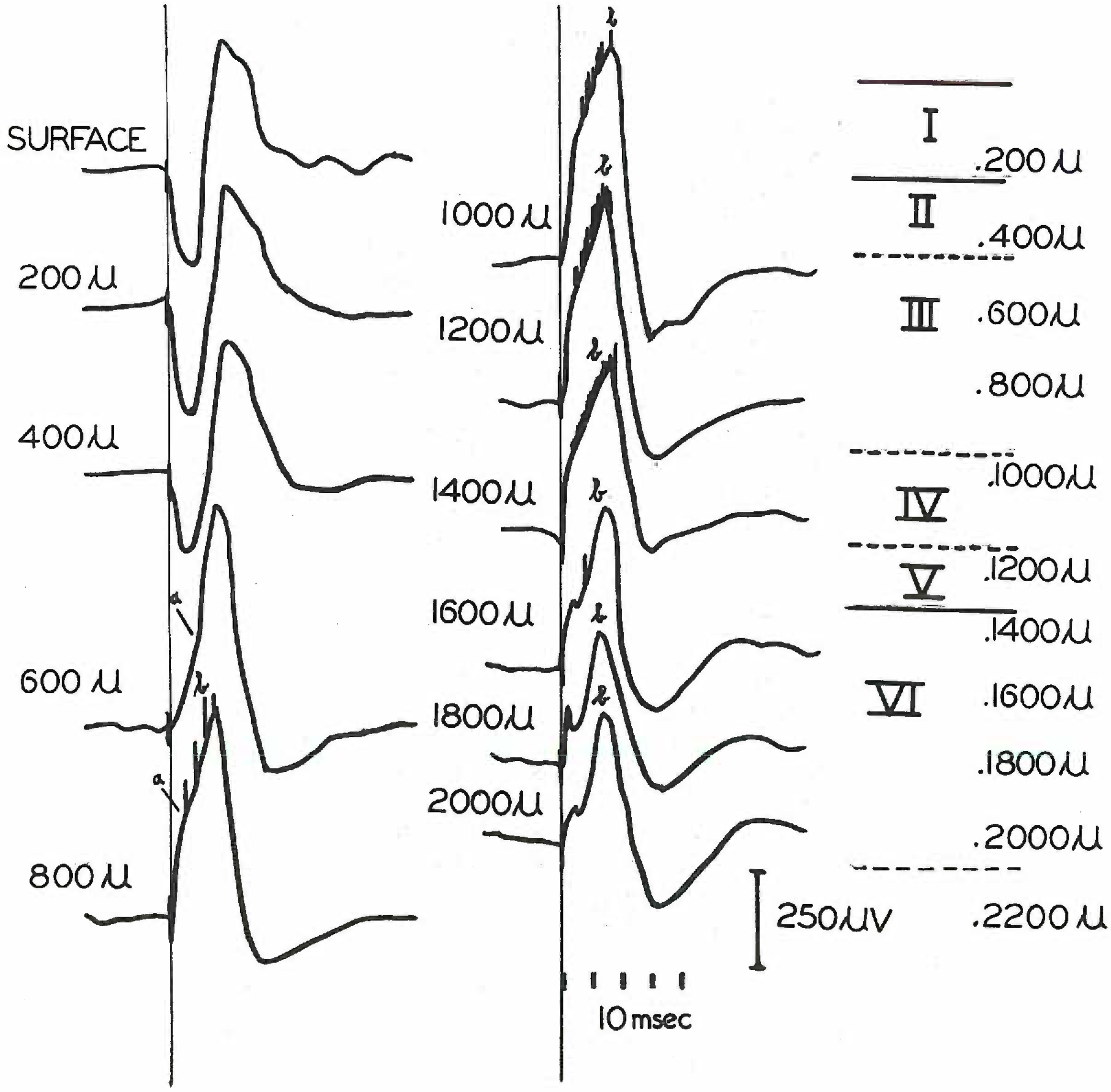
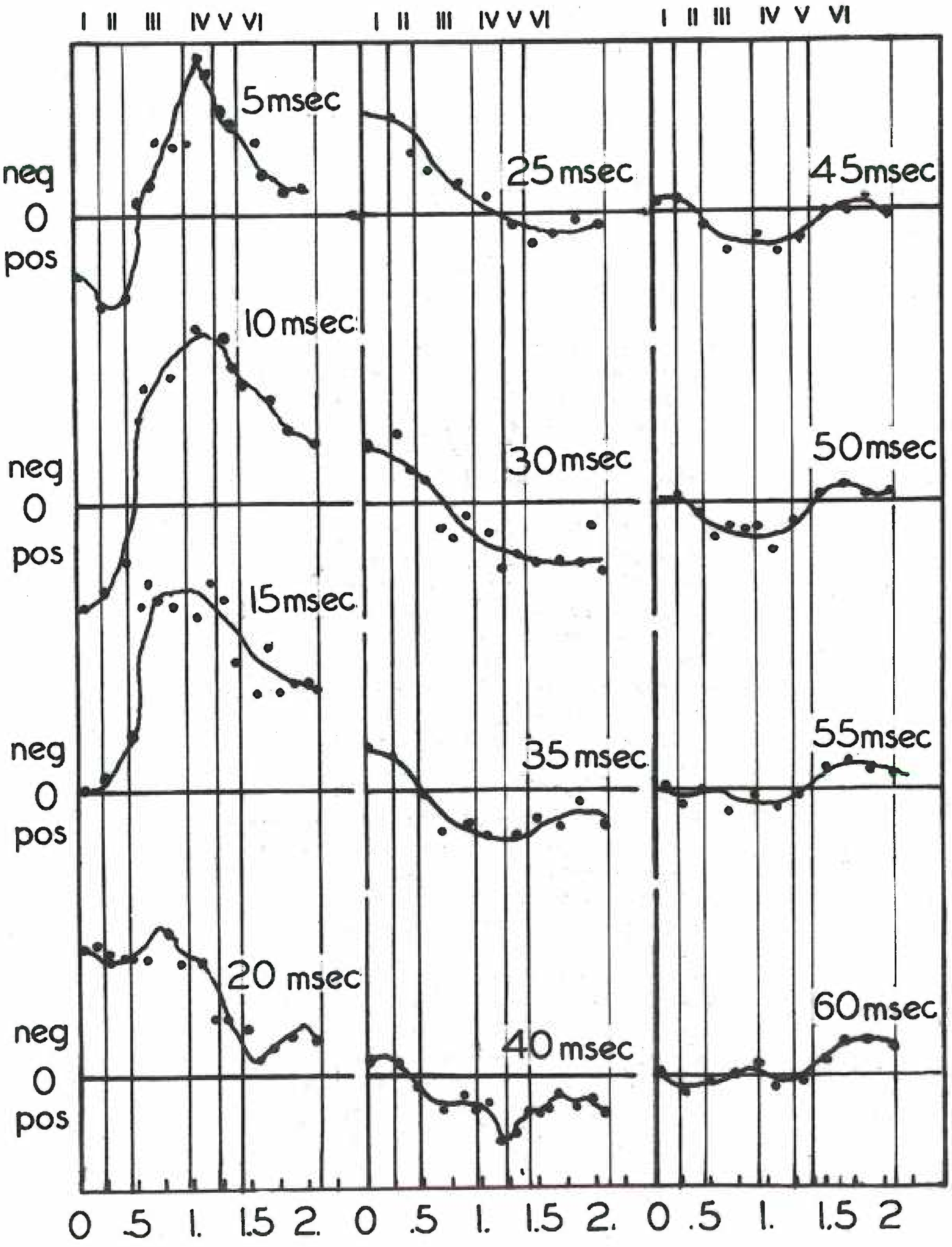

SURFACE
200 μ
400 μ
600 μ
800 μ
a
b
1000 μ
1200 μ
1400 μ
1600 μ
1800 μ
2000 μ
I
II
III
IV
V
VI
.200 μ
.400 μ
.600 μ
.800 μ
.1000 μ
.1200 μ
.1400 μ
.1600 μ
.1800 μ
.2000 μ
.2200 μ
250 μV
10 msec

FIGURE 3

Depth-potential distribution of the responses illustrated in figure 2 at a succession of points in time. The ordinates are voltage. Each individual graph represents the potential difference between the active and indifferent electrodes at the indicated time after the stimulus and at a series of different depths. In each graph, potential difference is plotted vertically, negativity of the recording electrode above and positivity below the zero line. Depth of the recording electrode below the surface is indicated in millimeters on the lower horizontal ordinate and in terms of cortical layers on the upper horizontal ordinate. The light vertical lines indicate the boundaries between cortical layers. The entire figure thus describes the changes in depth-potential relations at 5 msec. intervals following the stimulation. The graph for 5 msec. shows the development of sink peaking at the level of the fourth cortical layer. At this time layers I and II are serving as current sources. Succeeding graphs show the accent of this sink toward the cortical surface and finally its progressive decay. (8-19-56)



I II III IV V VI
I II III IV V VI
I II III IV V VI
5msec
10 msec
15msec
20 msec
25 msec
30 msec
35 msec
40 msec
45msec
50msec
55msec
60msec
neg
0
pos
neg
0
pos
neg
0
pos
neg
0
pos
0 .5 1. 1.5 2.
0 .5 1. 1.5 2.
0 .5 1. 1.5 2

(top of figure) and as depth in microns (bottom of figure). The points in time selected for these depth-potential graphs are indicated for each individual graph. The graph at five msec. shows the distribution of the initial sink with its peak at the level of the fourth layer. At ten msec. the sink has broadened to encompass the third layer also. The next series of graphs up to about forty msec. shows the slow ascent of this sink toward the cortical surface and then its decay in the molecular layer. In all graphs, this sink is bounded by sources. In this particular set of graphs, the later potential fluctuations are small by comparison with the striking early changes. From graphs such as this and from observations made at very small depth increments, it appears that the surface negativity represents the arrival at the surface of the sink which was initiated in the deeper layers.

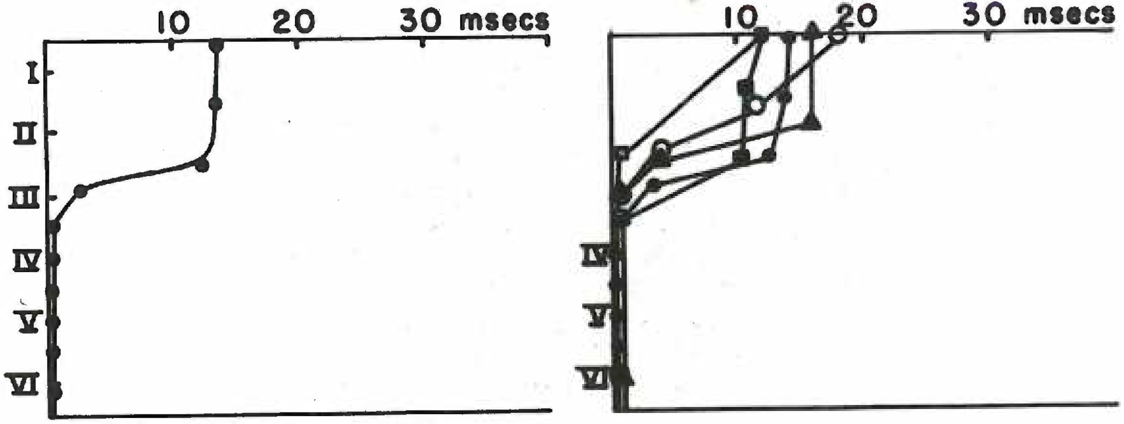
The progressive ascent of this sink can be summarized in a different fashion (see figure 4). The onset time of this sink (arbitrarily taken as that time at which the tracings cross the 0 potential line before becoming negative to the indifferent electrode) can be graphed as a function of depth in layers. Graphs of this sort are shown in the upper half of figure 4. The same kind of graph can also be made for the peak-latency of this sink (lower half of figure). The graphs for the experiment which has been illustrated in figures 2 and 3 is shown on the left in figure 4 and composite graphs for this and five other experiments are shown on the right. The curves in the two composite graphs exhibit considerable uniformity. The depth-onset curves indicate that all of the augmenting responses are characterized by an initial deep negativity which has a very early onset. Other portions of these curves show more variation. The inflection in both types of curves occurs somewhere

FIGURE 4

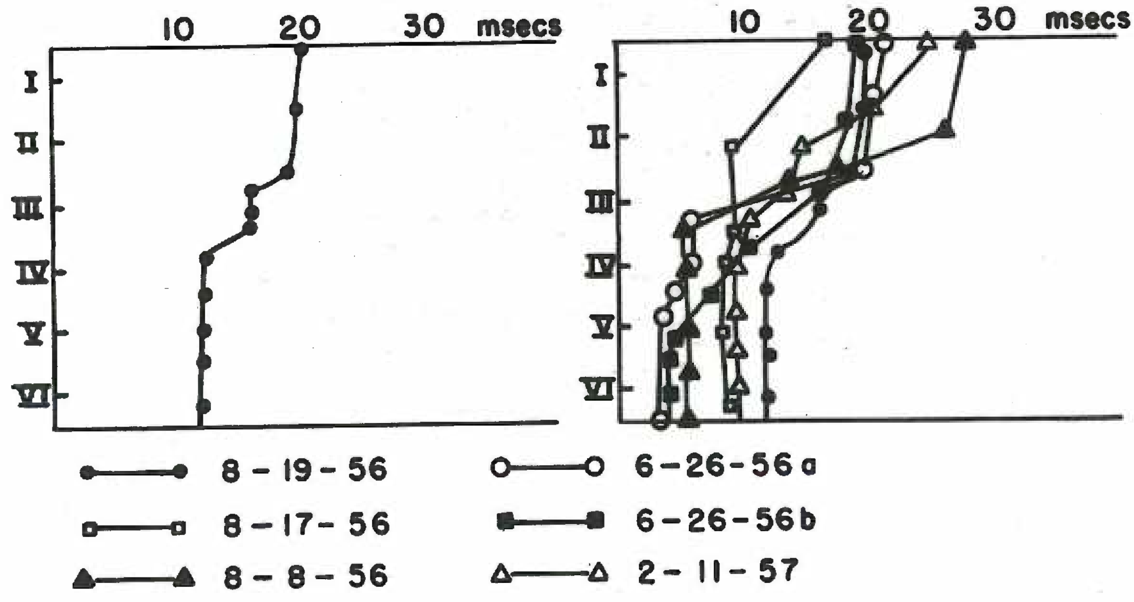
Time to onset and time to peak of the intracortical sink as related to depth during augmenting responses. The graphs on the left side of the figure are taken from the experiment which was illustrated in figures 2 and 3. The graphs on the right side of the figure are composite graphs of 6 similar experiments. The individual tracings are coded in terms of the date of the experiments according to the key at the bottom of the figure. The ordinates represent depth and the abscissae represent time. The onset time of the sink was arbitrarily taken as the time at which the recordings crossed the zero potential line in the direction of increasing negativity. The depth-onset curves indicate that the sink develops immediately after the stimulus in the third and in deeper layers, and progressively later in the more superficial layers, suggesting that the activity underlying the sink is conducted upward from its origin. The composite depth-peak latency graphs of this ascending sink divide into two classes in the fifth and sixth cortical layers.

AUGMENTING RESPONSE

Depth : Onset



Depth:Peak Latency



between layer II and the upper border of layer V.

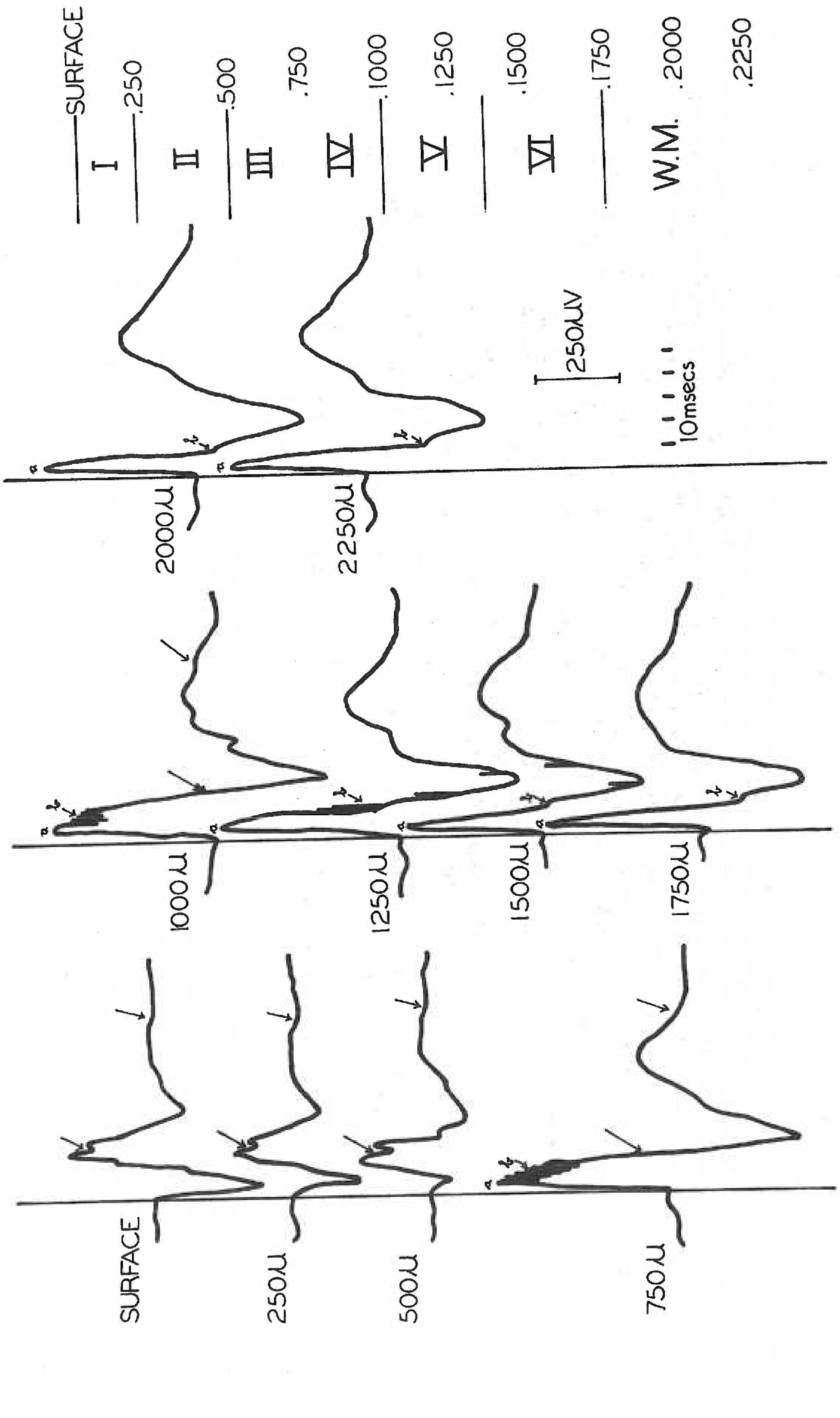
It should be pointed out quite emphatically that the boundaries of many of these cortical layers are quite indistinct and that although layers I and V are usually well demarcated, the intervening layers are actually of questionable identity even in the best of histologic preparations (69). The important thing about these graphs is that the initial inflection of these curves usually occurs somewhere roughly half way between the upper border of the fifth layer and the lower border of the first layer. It has been pointed out (8) that the so-called "reversal point" for the primary response may vary with the size of the recording electrode, generally being higher when very fine micropipettes are used. In the present experiment, only slight differences in the depth of the inflections of these curves were noted even though electrodes with tips as large as 25 mu and as small as 1 mu or less were employed in studying the augmenting response. Although the boundaries of layers II through IV are very difficult if not impossible to make out in this particular cortical area, composite depth latency graphs based on the rather subjective estimation of layers showed much more congruity than those based on absolute depth in microns. Explanations for this are the obvious variations in depth of layers in different animals and at different sites in the same animal, and also the fact that many electrode penetrations were not perpendicular to the cortical layers. For these reasons it was felt that these relations were best summarized in terms of depth by layers.

One item in figure 4 is of special interest. The curves in the composite depth: peak latency graph divide into two distinct classes in the deeper cortical layers. This divergence suggests that the deep sink may actually be formed by two elements each of which should be identifiable in some responses. Such a double deep negativity appeared in the responses illustrated in figure 5. In the recordings from the third and fourth layers, the initial negativity did indeed have two humps which are labeled a and b. Peak a corresponds to the earlier class in the composite graph and peak b corresponds to the later class. In some responses a predominated and in others b predominated. When peak b predominated as it did in the records shown in figure 2, it could be seen to decrease in amplitude in the fifth and sixth layers. However, when peak a predominated as illustrated in figure 5, it suffered very little attenuation in the deeper cortical layers and white matter. On the other hand, if deflection b in figure 5 is followed down through the fifth and sixth layers, it is seen to decrease markedly with depth. In the deep layers and white matter, this deflection is only evident as a discontinuity on the later phases of the response.

So far, little mention has been made of the later phases of the augmenting response. These were of rather small amplitude in the responses illustrated in figure 2 but have assumed rather large proportions in the responses illustrated in figure 5. In this latter figure the arrows demarcate a sequence of potential changes which is most conspicuous in the deep cortical layers and white matter in the form of a late positive-negative component. This complex was usually correlated with the appearance of a negative-positive wave in the surface records (also demarcated by arrows) which seemed to ride on the crest of the surface negativity of the augmenting response. In figure 5 it is very difficult to trace out the changes which it shows in the upper cortical

FIGURE 5

An augmenting response of more complex waveform recorded at different cortical depths. These are tracings of oscillographic recordings made during a single penetration in the posterior sigmoid area. The recording electrode was a 25 micron wire. Responses were chosen from the largest amplitude waves in each train but were specifically selected for the demonstration of discontinuities in these waves. The stimulating electrode was in n. ventralis posterolateralis. The same presentation as that employed in figure 2 has been adopted in this illustration. The tracings at different depths are arranged in columns with the depth designated beside each tracing. The depths of the cortical layers are indicated with respect to the recording depths on the right of the figure. No horizontal line has been drawn between layers III and IV because this boundary was very indistinct in the slides from this experiment. Small letters a and b again signify components of the initial deep negativity. The arrows demarcate the portions of each wave which presumably contains the "recruiting like" component. These arrows were left out of the deep tracings (below 1250 mu) in order to avoid interfering with the indication of component b. The late negative-positive wave in these deep waves nevertheless still represents this added component which is similar to the recruiting response. Time and voltage calibrations are indicated in the lower right corner. Suprathreshold stimulus intensities were used. Pulse duration 0.3 msec. (6-26-56)


SURFACE
250μ
500μ
750μ
1000μ
1250μ
1500μ
1750μ
2000μ
2250μ
a
b
250μV
10msecs
SURFACE
.250
.500
.750
.1000
.1250
.1500
.1750
.2000
.2250
I
II
III
IV
V
VI
W.M.

layers because it still rides on the negativity of the earlier components. However, by the third layer it appears as if the surface negative-positive complex had reversed and been added algebraically to the basic pattern of the augmenting response. It is noteworthy that this component maintains about the same amplitude in the white matter recordings.

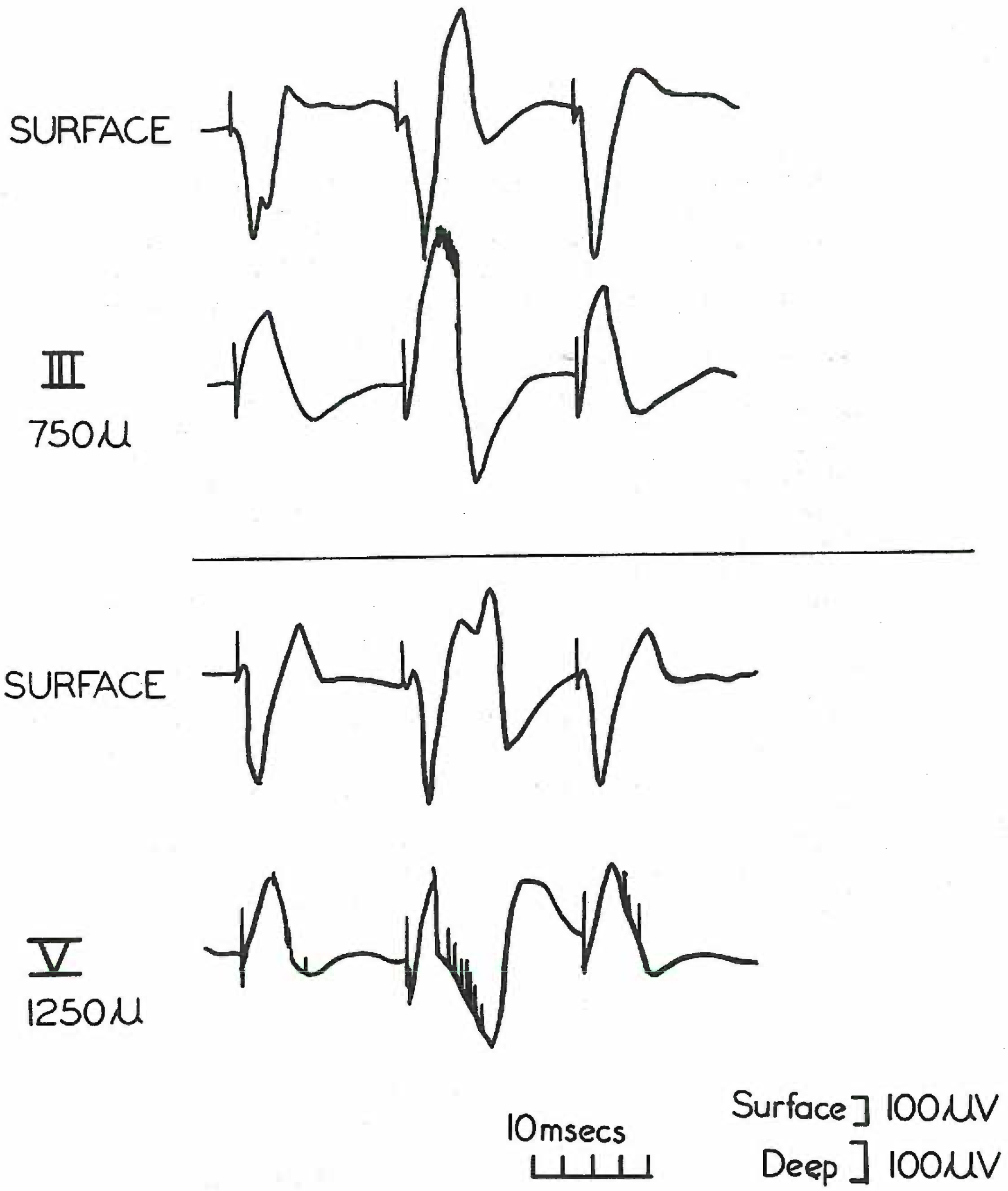
Responses of the type illustrated in figure 5 suggested the possibility that the late phases of the augmenting response may not always represent a simple continuation of the neuronal events responsible for the earlier and more constant electrical changes. Rather, in many instances it seemed as if the late phases might be produced in part by an event which was entirely different from that producing the earlier waves. The records of figure 6 offer support for this possibility. The responses in this experiment were unique in that at a single stimulus site and with constant stimulus parameters, the slow waves showed a great deal of variation both in amplitude and in configuration, even within a single train. In each of the pairs of tracings from this experiment, deep and surface responses are compared. The variations shown were not confined either to the third or fifth layers but simply happened to be most clearly illustrated in the recordings from these layers. In the upper pair of tracings the center response is of larger amplitude than those on either side and is smooth and diphasic in its contour both at the surface and at the level of the third layer. It would appear that in this case, the increased amplitude of the surface after-negativity and the corresponding deep after-positivity were the result of the increased intensity of the activity represented by the preceding component. However, in the lower pair of tracings which

FIGURE 6 (Above)

Comparison of surface and deep augmenting responses from an experiment in which the wave configurations showed marked variability. Upper tracing of each pair (taken from oscillographic recordings) shows surface responses; lower tracing of each pair shows deep responses recorded simultaneously with a 25 micron wire. Recording locus, posterior sigmoid; stimulating site, n. ventralis posterolateralis. The selection of these variations does not imply that they are characteristic of the layers represented. The records chosen illustrate clearly the <u>dual</u> <u>nature</u> of the deep after-positivity. In the upper pair of tracings, the center augmenting wave is of considerably larger amplitude than those preceding or following it. Note the enhanced deep initial negativity (with the appearance of unitary activity on its crest) and the correspondingly increased deep after-positivity. In this case, the phases are continuous. In the lower pair of tracings, however, the center response shows the addition of a separate surface negative-positive sequence and a simultaneous deep positive-negative sequence. In this case, the early deep negativity is not enhanced. Stimulus intensity suprathreshold, 1 msec. pulse duration, 8/sec. (8-8-56)

FIGURE 7 (Below)

The first four waves in a train of augmenting responses as recorded from the white matter during 8/sec. supramaximal stimulation of n. ventralis posterolateralis. The photograph illustrates the progressive development of the sharp initial deep negativity which was labelled <u>component</u> <u>a</u> in figure 5. This first component is clearly seen to grow progressively in amplitude with the repeated thalamic shocks. (6-26-56)


SURFACE
III
750μ
SURFACE
V
1250μ
10msecs
Surface] 100μV
Deep] 100μV


W.M.
500μV
10msec

shows surface responses compared to responses recorded in the fifth layer, an additional element has been added onto the basic pattern in the center response. It appears as a late negative-positive sequence at the surface and as a concomitant deep positive-negative wave in the fifth layer recordings. Therefore, there are two kinds of deep after-positivities shown in these records: 1) that which directly follows the deep negativity and varies in amplitude in a direct way with the earlier phase and 2) another deep positivity which does not vary directly with the earlier component. In most experiments, this second component was very difficult to identify because of smooth summation with the earlier wave. Because of the similarity of this additional component to the predominant wave form in the recruiting response (see below), it may be described as a "recruiting like" component.

Interpretation. Component a. The most reasonable interpretation of component a is that it represents some manifestation of the afferent volley. Unfortunately, the presence of the primary response in most records which show component a has prevented the detailed analysis of the early phases of this component and the presence of component b obliterates its later phases. If component a represents the thalamocortical volley in the afferent axons themselves, one would expect that it would be preceded by a prodromal positivity and followed by a metadromal positivity except in the regions of its terminations. The fact that component a decrements very little as the white matter is entered favors this interpretation of component a as the afferent volley. Another possibility is that it represents electrotonic spread of pre-synaptic potentials along the afferent axons in a manner analogous to the dorsal root potential in the spinal cord (51). The fact that component a is not detectable above the third layer is consistent with the probability that the type of afferent fibers involved are predominantly "specific cortical afferents" of a type similar to those mediating the primary response.

If component a does represent the afferent volley, then it is of interest to examine the development of this component during the early part of a train of augmenting responses. Figure 7 illustrates the beginning of a train of augmenting responses as recorded from the white matter. Component a is the initial, sharp negativity. This component clearly waxes during these early responses. This suggests that the cortex is the recipient of progressively larger and larger afferent volleys during the waxing phase of the burst. Therefore, it would seem that the "augmentation" is not strictly a cortical phenomenon but may be in part thalamic. Actually, this possibility has been supported by much more direct evidence. Dempsey and Morison (31) observed that augmentation occurred at the thalamic level in decorticate preparations, but stimulation of the internal capsule in thalamectomized animals failed to produce cortical augmenting responses.

Component b. The peak designated as component b is much more likely to represent post-synaptic events. It has its greatest amplitude in the very cellular middle cortical layers in which almost all of the unitary activity was visualized (see below). Furthermore, it is temporally coincident with this unitary activity. This fact can be appreciated in figure 2 and 5 since signs of unitary activity are detectable in the third and fourth layers as a thickened baseline or fuzz on the crest of this negative wave. The crest of component b is also timed with the relayed pyramidal volley which accompanies these waves since both events are coincident with the initial positivity of the surface recordings (19). The fact that component b is accompanied by a surface positive deflection suggests that the superficial extensions of these cells are serving as potential sources for the deep sink in the region of the cell bodies. All these temporal correlations point to the involvement of the pyramidal cells in the production of component b.

The late "recruiting-like" component. Because this component is rarely seen in any degree of isolation from earlier elements, it is extremely difficult to interpret. As will be apparent later, however, it bears many similarities to the recruiting response. Perhaps it represents contamination by recruitment. This is particularly likely in responses to stimulation of the internal capsule. (In some experiments in which good augmenting responses were obtained with very low intensity stimulation of VPL or VPM, this "recruiting-like" component was very poorly developed.) Other explanations for the presence of this element are 1) that it is due to indirect activation of the recruiting nuclei via the connections from specific to unspecific nuclei or 2) that it represents activation of unspecific afferents which originate in these specific nuclei. Both of these last two possibilities are consistent with the anatomical data of Nauta and Whitlock (60).

The ascent of the sink. The ascent of the sink, which first develops in the third and fourth layers, toward the cortical surface is similar although slower in its time course to that which has been described by other investigators for the primary response (24, 46) and for the antidromic response to stimulation of the pyramidal tract (23). Its origin in these waveforms has been ascribed to antidromic invasion of the apical dendrites (24, 23, 46) or to dendritic post-synaptic potentials produced by activity in recurrent collaterals of pyramidal cells (65). Allowing for greater temporal dispersion, these same explanations might also be applied to the ascending sink encountered in the augmenting response. An alternative to these explanations is that it represents activation of superficial structures via an ascending multineuronal chain of neurons (9).

Comparison of the augmenting response with the primary response. The records which have been presented bear remarkable similarities, except for a slower time course, to those which have been obtained by similar techniques in studies of the primary response (63, 46). As with the primary response, the potential distribution with respect to depth strongly suggests that the cortical augmenting responses are initiated by activity arriving over the specific cortical afferents. If both primary and augmenting responses are in fact mediated by this kind of corticipetal fiber, then what accounts for the differences in the primary and augmenting responses?

One explanation to be considered is that the primary response involves the direct activation of this type of afferent and the augmenting response involves the more indirect activation of the same kind of afferent. The identical population of afferents are probably not involved since the cortical distribution of primary and augmenting responses at a given thalamic stimulating site is different even though there is some overlap (30). The indirect pathway which is activated in the augmenting response would presumably include thalamic interneurons and cortico-thalamic feedback. Dempsey and Morison have presented conclusive evidence supporting the essential participation of thalamic mechanisms in augmentation (31) (see above). The primary response, however, can be produced by direct stimulation of the internal capsule when the thalamus has been destroyed (31). This line of reasoning leads to the supposition that the differences in amplitude, time course and cortical distribution between the primary and augmenting responses are dependent upon these additional thalamic mechanisms which are necessary for the appearance of the augmenting response. These additional thalamic pathways, however, appear to activate a slightly different and considerably larger population of the same kind of afferent neuron as those directly excited by the stimulating current which gives rise to the primary response. The fact that Brookhart and Zanchetti (19) found that some primary responses were associated with alterations in cortico-spinal responsiveness similar to but less pronounced than those associated with augmentation suggests again that these are primarily quantitative differences as far as intracortical mechanisms are concerned.

There is, of course, the alternative possibility that there may be definite differences in intracortical mechanisms underlying the primary and augmenting responses which are not easily detected by the techniques employed in the present study. For example, all of the specific cortical afferents may not terminate in the same way. Some may converge on one type of cell and others on another. Some may converge on cell bodies of cortical cells and others on basal dendrites. The possibilities for the existence of differences which are beyond the resolution of present techniques are nearly limitless.

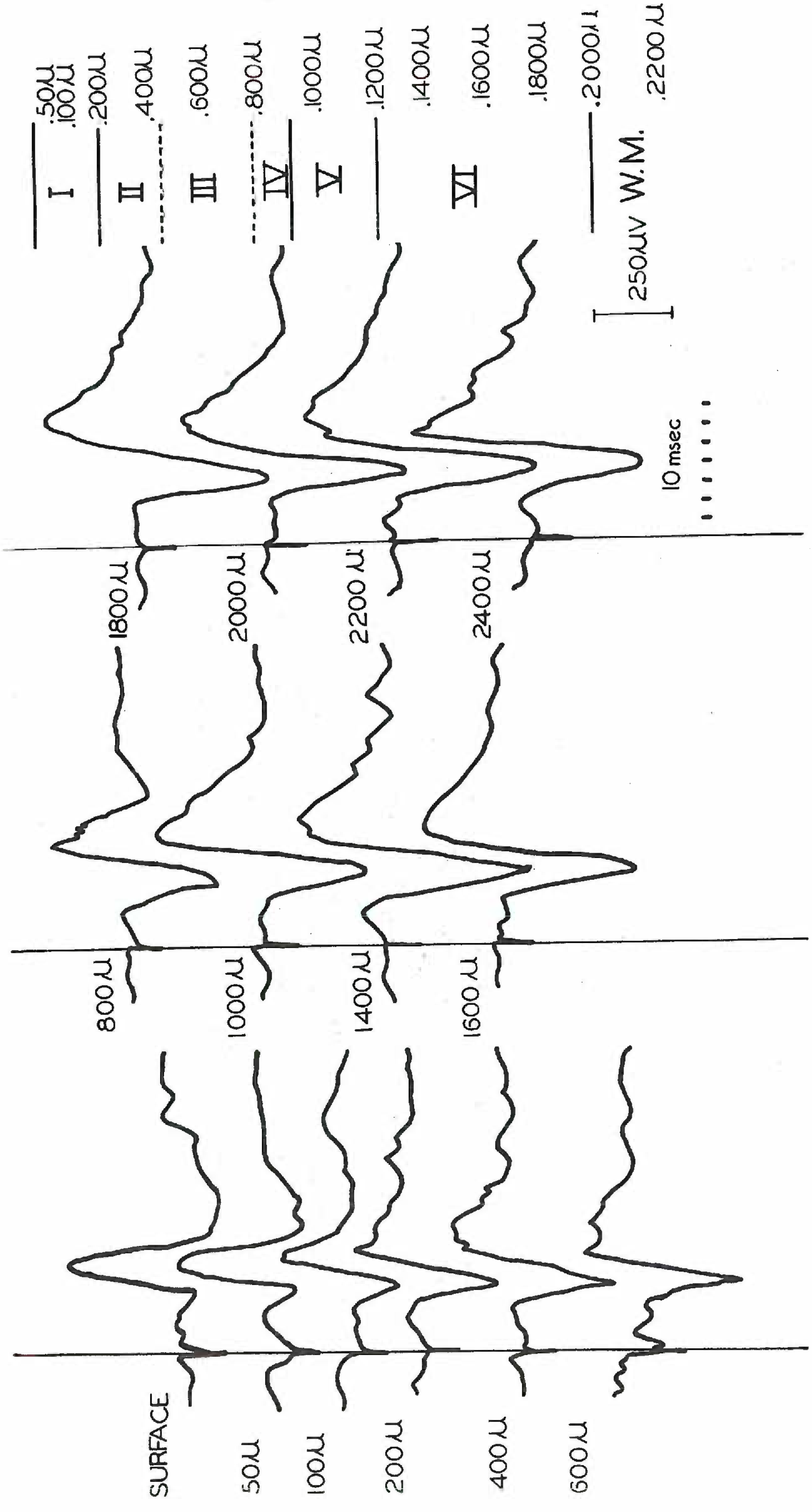
Recruiting response

The present observations were confined to those recruiting responses evoked by repetitive stimulation of the midline thalamic nuclei. They were recorded on the anterior sigmoid area where these responses are particularly well developed (37). The adherence to strictly midline stimulation is based upon the probability that these responses are least likely to be contaminated by augmenting responses as the result of stimulation of fibers of passage from the specific system (60). As with the augmenting response, long trains of stimuli were employed in an attempt to differentiate the effects of superimposed "triggered cyclic waves". In contrast with the augmenting waves, there often appeared to be a marked difference in configuration between the early and late responses (see figure 10).

A typical recruiting response is illustrated in figure 8. It is obvious that the changes in potential with respect to depth are strikingly different from those encountered in the augmenting response. The differences between augmenting and recruiting responses are most striking in the deep layers of the cortex where the phase sequence of the two responses is exactly opposite. In augmentation, the deep layers of the cortex showed a negative-positive diphasic potential change and in these records of the recruiting response, the configuration of the deep responses is primarily a positive-negative sequence. In the recruiting responses shown in figure 8, changes from the surface configuration are apparent even after the electrode had been lowered only one hundred microns into the cortex. At this level the initial positivity had already grown in amplitude. As the recording electrode penetrated the different cortical layers, the changes of potential were continuous

FIGURE 8

A typical recruiting response as recorded at different cortical depths. The form of presentation is the same as that adopted in figures 2 and 5. These are tracings of recruiting responses produced by stimulation of n. reuniens (supramaximal, 6/sec., 1 msec.) and recorded oscillographically from the anterior sigmoid gyrus using a 12.5 micron wire. In this experiment, there was very little waning of the response with prolongation of the stimulus train, suggesting that these waves are relatively uncontaminated by the effects of superimposed triggered cyclic waves. The responses recorded at different depths may be compared as if they were recorded simultaneously. A detailed description of these changes in potential configuration with increasing depth is presented in the text. (8-20-56)


SURFACE
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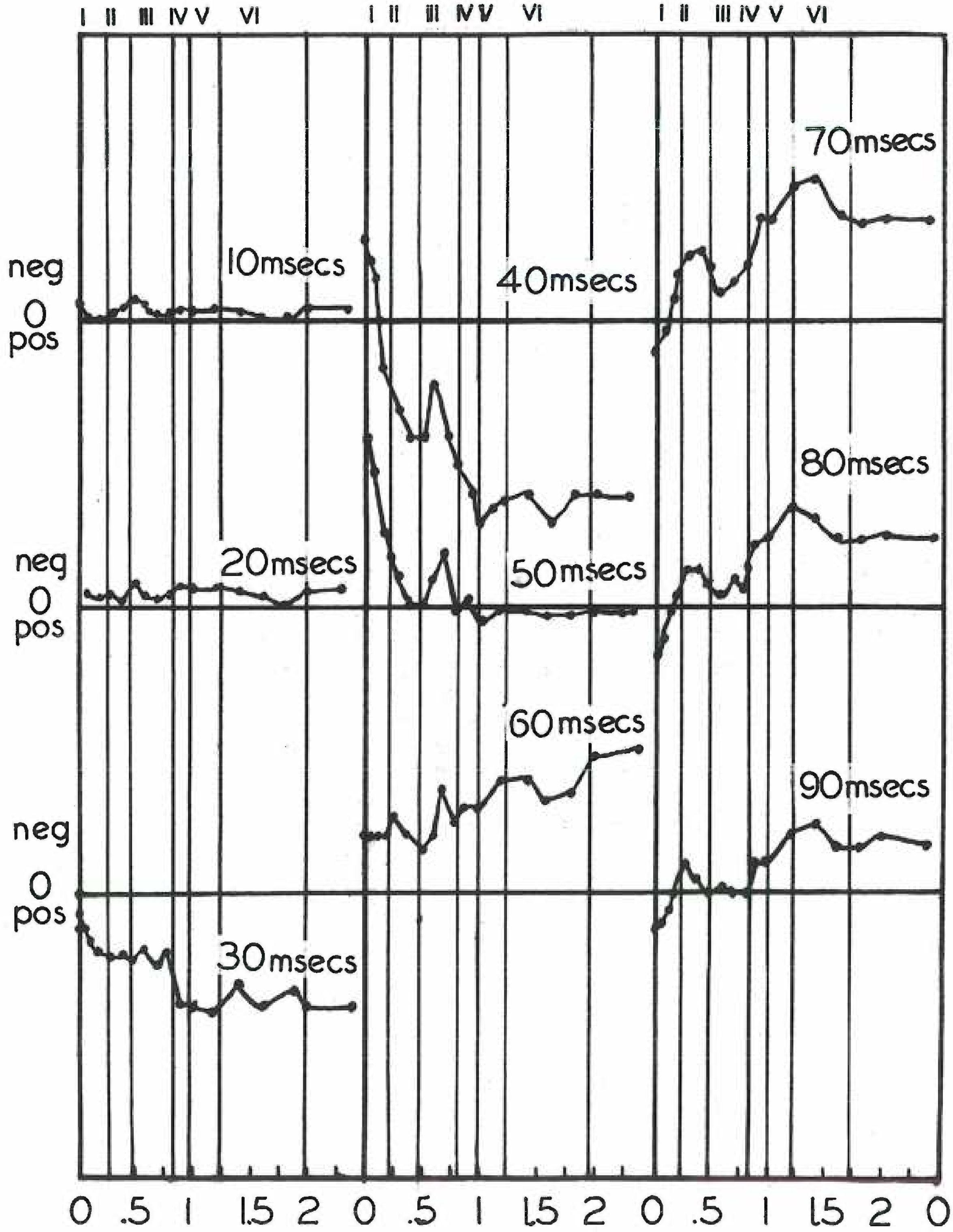
2200μ
2400μ
.50μ
.100μ
.200μ
.400μ
.600μ
.800μ
.1000μ
.1200μ
.1400μ
.1600μ
.1800μ
.2000μ
.2200μ
I
II
III
IV
V
VI
W.M.
250μV
10 msec

rather than abrupt. The initial positivity became progressively more and more prominent with deeper penetration until the response was predominantly positive in sign. The deep responses were characteristically larger in amplitude than the surface responses. The deep after-negativity varied in its amplitude from experiment to experiment. In some penetrations, a constant discontinuity between the deep positive and negative phases could be discerned. In other experiments, the deep after-negativity was almost absent.

The same technique of graphic presentation of potential-depth-time relations which was utilized in the analysis of augmenting responses may also be utilized with respect to recruiting responses. Such graphs are presented in figure 9. This data is taken from the same experiment as that in figure 8. Figure 9 is comparable in every way to the graphic presentation in figure 3 on the augmenting response except that time intervals of 10 msec. rather than 5 msec. were chosen. During the first 20 msec. the cortex is almost isoelectric i.e. these are fairly long latency responses at all cortical depths. Then, at about 30 msec. the cortex as a whole becomes positive with the greatest positivity appearing in the deepest layers and in the white matter. Superimposed on this general cortical positivity there develops a very superficial negativity at 40 through 50 msec. Between 50 and 60 msec. there is a very abrupt change in the graph and at 60 msec. the whole cortex has become negative with the greatest negativity appearing in the deep layers and in the white matter. This deep negativity gradually subsides over the subsequent 30 msec. (The small humps and troughs seen in these graphs were not constant from experiment to experiment.) Most of these graphs show rather constant transcortical gradients which do not exhibit a

FIGURE 9

Depth-potential distribution of the responses illustrated in figure 8 at a succession of points in time. The form of presentation employed in this figure is identical to that which was used in figure 3, with which this figure should be compared. Note that 10 msec. intervals rather than 5 msec. intervals are graphed. The changes in cortical potential gradients with time are described at length in the text. The small deviations in these curves were not present in similar graphs made from other experiments.


I II III IV V VI
I II III IV V VI
I II III IV V VI
neg
0
pos
10msecs
20msecs
30msecs
40msecs
50msecs
60msecs
70msecs
80msecs
90msecs
0 .5 1 1.5 2 0 .5 1 1.5 2 0 .5 1 1.5 2 0

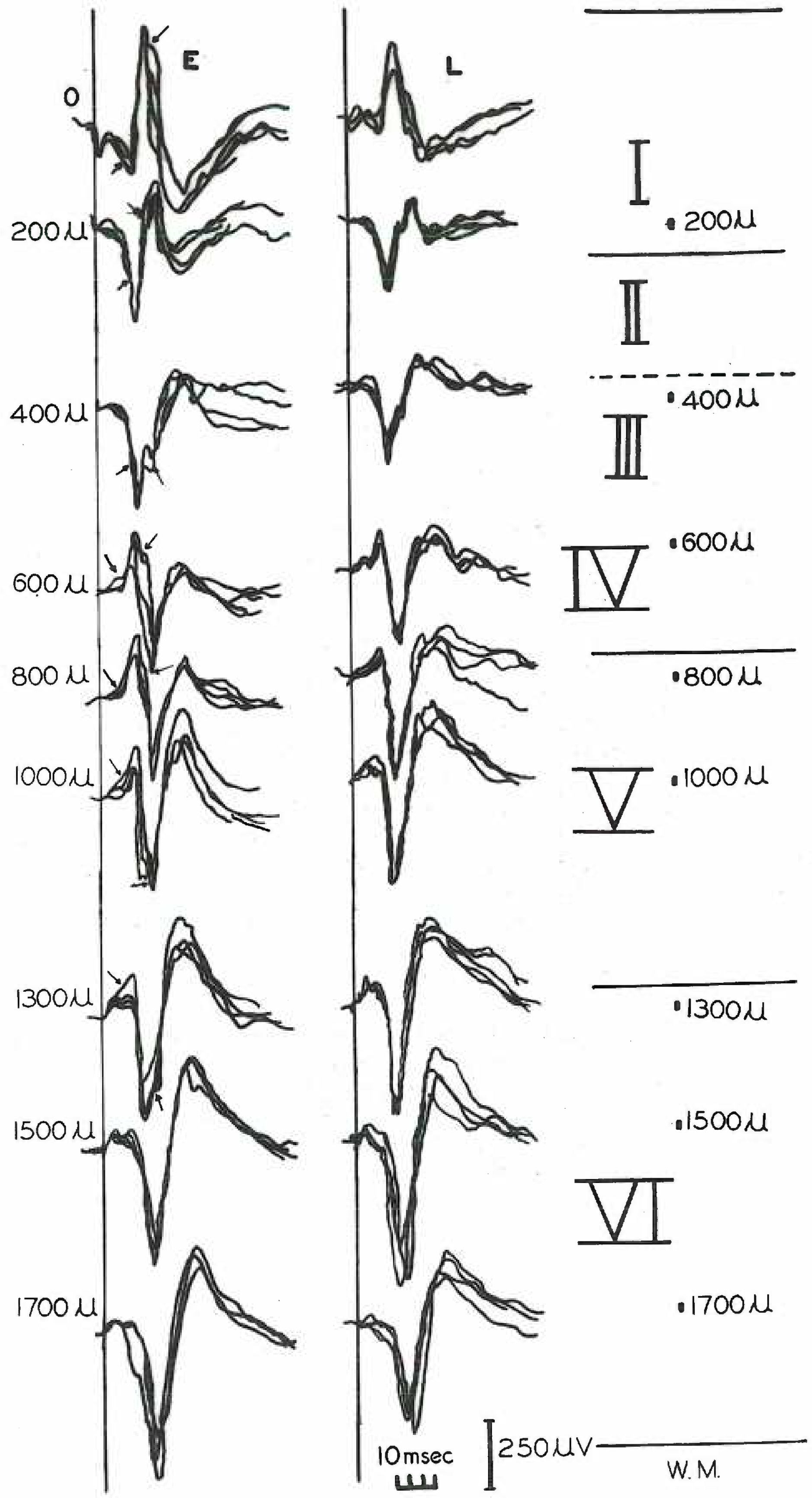
decrease of potential at the cortico-white matter boundary. In fact, they often continue to increase down into the white matter. Superimposed on the early cortical and white matter positivity there appears a more sharply localized sink in the most superficial cortical regions which is most clearly seen in the graph at 50 msec. This superficial sink is the one element in these graphs which most clearly seems to be localized to the cortex.

In some of these responses there was an initially negative deflection in the middle cortical layers which preceded the predominant deep positive-negative sequence. When present, this early deep negativity was usually much more prominent in the early (5-15 in the train) responses than the later, smaller responses. Figure 10 shows superimposed tracings of the early (E) and late (L) recruiting responses in one series. The initial deep negativity in the early responses is marked by arrows directed at the discontinuities between this added complex and the underlying potential sequence. In the tracings of the early waves it can be seen that this initial deep negative phase is largest in the third, fourth and upper fifth layers. By comparing these potentials with the superimposed tracings of the smaller amplitude later responses, it is clear that the predominantly deep negative component has been added algebraically to the basic underlying deep positive negative sequence. Because of this, the initial positivity has been reduced in the responses from the early part of the train.

The surface recording of the early recruiting responses reveals that this initial deep negativity is accompanied by an inconspicuous but nevertheless discernible surface positive-negative sequence which rides on the negative going deflection of the underlying recruiting response.

FIGURE 10

Variations in recruiting waves recorded during early and late portions of a stimulus train. Each column of superimposed tracings represents potential changes recorded at various depths in the anterior sigmoid gyrus as indicated to the left. Column E represents responses recorded early (5th to 15th), Column L responses recorded late (20th to 30th) in trains of stimuli delivered to n. interventralis and n. ventralis medialis (0.5 msec., 6/sec.) Note that the fundamental recruiting pattern (see figure 8) appears during the late waves only. In column E, the small arrows are directed at discontinuities which delimit temporally components which are present in early responses only. These added components distort the fundamental recruiting pattern through the addition of potential sequences which resemble those seen during augmenting waves. Note that the initial deep negativity of the added component is most prominent in the fourth and upper fifth layers of the cortex. (1-26-56)


E
L
0
200μ
400μ
600μ
800μ
1000μ
1300μ
1500μ
1700μ
I
II
III
IV
V
VI
200μ
400μ
600μ
800μ
1000μ
1300μ
1500μ
1700μ
10 msec
250μV
W. M.

Thus it would seem that this added component is similar to the basic pattern of the augmenting response in two respects: 1) at the surface they both appear as a diphasic positive-negative wave, 2) in the depths of the cortex, they are predominantly negative in sign and have their greatest amplitude in the third and fourth layers. This added component in the augmenting response may therefore be described as an "augmenting-like component".

Interpretation. Basic pattern. Considering the basic pattern of the recruiting response as described in the discussion of figures 8 and 9, the events underlying the characteristic potential changes may be divided into those which are probably intracortical in origin and those which more likely reflect subcortical activity. The superficial sink which was most prominent at about 50 msec. seemed to be well-demarcated by the source below and therefore probably does represent activity originating within the superficial cortical regions. Other investigations in which cortical responses to stimulation of other portions of the diffuse thalamic projection system were examined (74, 47) have revealed a sink which extends into deeper cortical layers than is the case with these responses to strictly midline thalamic stimulation. It may be that the cortical terminations of the axons mediating the responses to midline thalamic stimulation are more superficial than those from the rest of the system.

The other more continuous potential gradients which were described may be primarily reflections of activity in subcortical structures. This is more likely in the case of the early (30-50 msec.) deep positivity than for the late (60-90 msec.) deep negativity since the latter sometimes decreased in amplitude as the white matter was penetrated by the recording electrode. There is the possibility, therefore, that the deep after-negativity represents activity in the deep part of the cortex. This may originate by downward conduction of activity represented by the earlier superficial sink.

Altogether, the cortical potential changes associated with recruitment are much more difficult to interpret than those in augmentation. The fact that most of the cortical gradients in recruitment fail to show the sharply defined sinks bounded by sources which were so easily detectable in augmentation, favors the hypothesis advanced by Ajmone-Marsan (7) that the potential configurations associated with recruitment actually represent the overlapping of two potential fields. Probably both cortical and subcortical activity contribute to these gradients. With the exception of the paper of Verzeano, Lindsley and Magoun (74 see introduction), most investigators have found that rather large recruiting potentials may be recorded after ablation or functional depression of the cortex (10, 17). The waves which remained have usually been reversed from the normal configuration when recorded monopolarly indicating that some of the original recruiting potential did arise from the cortex itself. Hanberry and Jasper (38), using bipolar recording electrodes, demonstrated in a striking way that cortical ablation abolished augmenting responses but not recruiting responses. This agrees closely with the results of the present experiments which show that it is very likely that most of the augmenting response results from intracortical events but that much of the recruiting response cannot be adequately explained until the contribution of subcortical elements is more precisely known. It is somewhat a paradox that although the recruiting potentials have been studied far more extensively than the augmenting response, the former are still far more difficult to interpret.

The augmenting-like component. In the description of the augmenting response it was suggested that a "recruiting-like" sequence may contribute to the later phases of many augmenting responses. It was suggested that this might be the result of activation of fibers of passage from unspecific nuclei or current spread to these nuclei. In the present description of the recruiting waves it has been noted that, in the early responses of a train particularly, there are often suggestions of the superimposition of an "augmenting-like" element on the early parts of the recruiting waves. However, this added element occurs after a latency of 20 msec. (figure 10). This precludes the possibility of contamination by stimulus spread to the specific thalamic nuclei or by stimulation of fibers of passage from these nuclei. Anatomical connections have been demonstrated between the two systems of thalamic nuclei (60) and Magoun's group, on the basis of physiologic data, has emphasized the participation of the association nuclei in the recruiting process (70, 71). These considerations favor the interpretation that this added complex represents the activation of neuronal connections to the specific nuclei. It may be that a strict dichotomy does not exist in a functional sense between recruitment and augmentation and that the distinction is only useful in indicating the predominance of one system or the other. In view of the fact that this "augmenting-like" component was more prominent in the early responses in a train, it may be suggested that the triggered cyclic waves which presumably underlie the waxing and waning in a train of recruiting responses often preferentially reinforce this added component.

Spindling

The electrocorticographic pattern of the spindling isolated brain is complex and variegated. Different parts of the cortex often seem to spindle quite independently although occasionally the whole structure behaves as a unit and all leads of the encephalograph will show a burst pattern simultaneously. If the waves which comprise the bursts are examined in detail it will be noted that the polarity and contour of the individual waves vary remarkably from area to area. Two monopolar leads have to be placed within a millimeter or so of each other if synchronous waves are to be seen in the two channels. In short, it would seem that spindling is an enormously complex phenomenon and that any approach toward an understanding of the intracortical mechanisms underlying these large spontaneous potentials had better begin with humble objectives. For this reason, the present experiments were limited in the following ways: 1) Recording sites were confined to the anterior and posterior sigmoid gyri since it was in these regions that the evoked waves had been most closely examined. Furthermore, the pyramidal tract arises from these areas and its behavior during these waves has been extensively studied (6, 19). 2) The early experiments in this part of the project were limited to those waves which had prominent initial positive deflections. These will be referred to as "Type I" spindles. In later studies, waves of different configuration were examined and those waves with prominent initial negativities were recorded. These will be referred to as "Type II" spindles. 3) In the study of both types of waves, only the largest amplitude responses were studied in detail. It was quite remarkable how stable one particular wave form was at any given recording site. If it were not for this fact, these experiments could not have been carried out.

Type I spindles. These are spindle waves which begin with a prominent surface positivity. Their time course was somewhat briefer than the type II spindles, and they were usually found to be largest around the post-cruciate dimple. In order to compare the responses at different depths it was absolutely essential that the surface responses be monitored at a point as close as possible to the penetrating electrode. It was usually possible to obtain a placement within a fraction of a millimeter of the penetration site. The typical responses which were obtained with the surface criteria mentioned above are illustrated in figure 11. In this figure it is apparent that these waves (at least the largest waves in a burst) seem to start with a sharp surface positive going deflection. Using this as a relatively constant and easily identified point in time on the surface record, the responses at different depths could be put on the same time scale and thereby compared.

The usual way in which this comparison was carried out was by superimposing tracings from the same depth in which the surface monitor responses matched and then arranging these tracings on the same time base using the surface monitor records as a common point of reference. This kind of presentation is illustrated in figure 12. These tracings present a picture which is strikingly similar to the augmenting waves, although the wave form as a whole is more spread out. The diphasic positive-negative waves at the surface and in the first cortical layer became triphasic positive-negative-positive waves in the second layer and finally very large negative-positive waves in the third and fourth layers. This complex became somewhat smaller in the fifth layer and then practically disappeared as the sixth layer and finally the white

FIGURE 11

Type I spindles recorded at the surface and at different depths within the cortex. The tracings are presented in simultaneously recorded pairs, the upper of each pair representing potential changes recorded from a surface monitor (S. M.), the lower representing changes occurring at the depth indicated to the left of each depth tracing. In the right, the depths of the successive recording positions are indicated in relation to the cortical layers. Note the phase reversal between surface and depth recordings first occurring at the middle of the third layer (750 mu). (5-3-56)

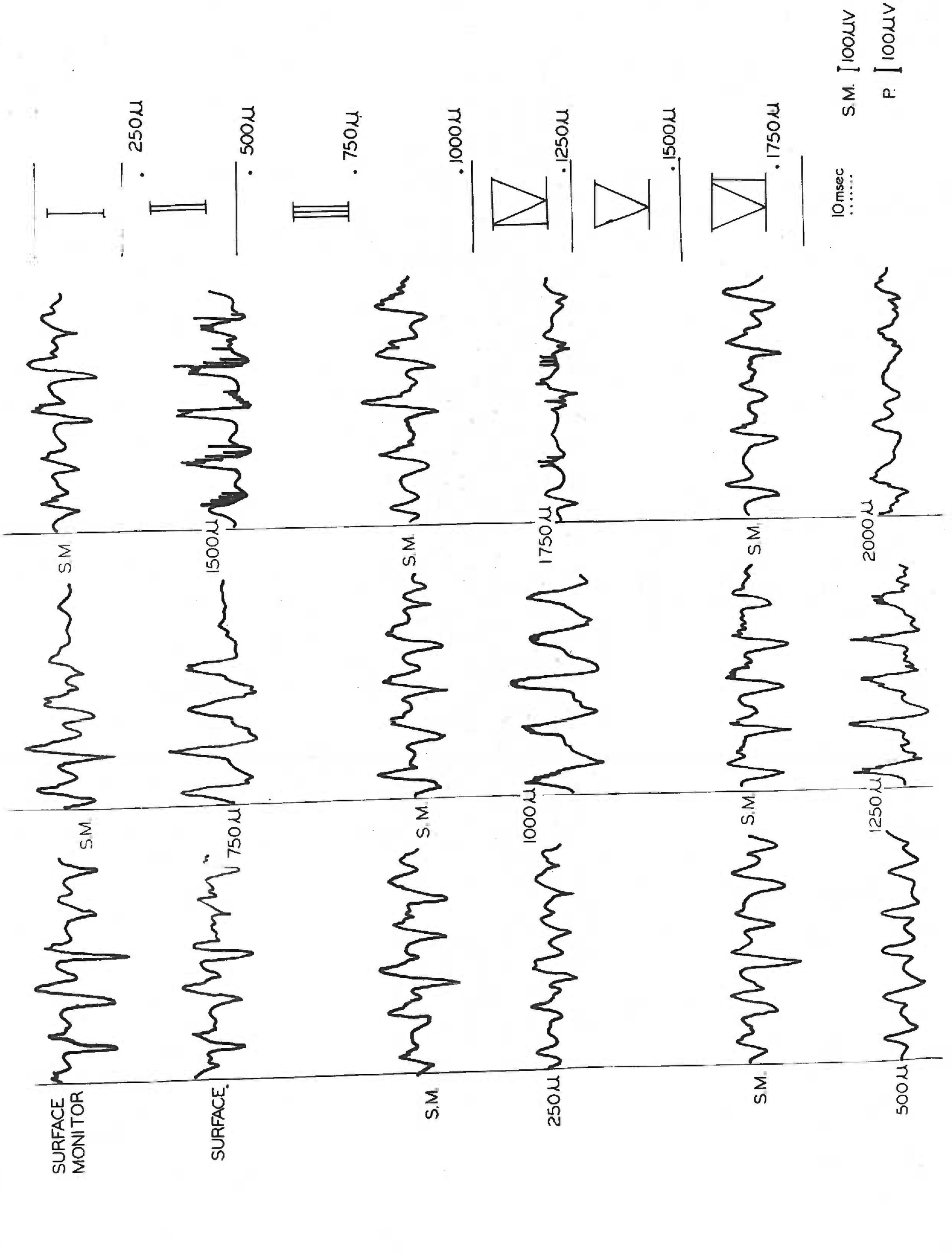
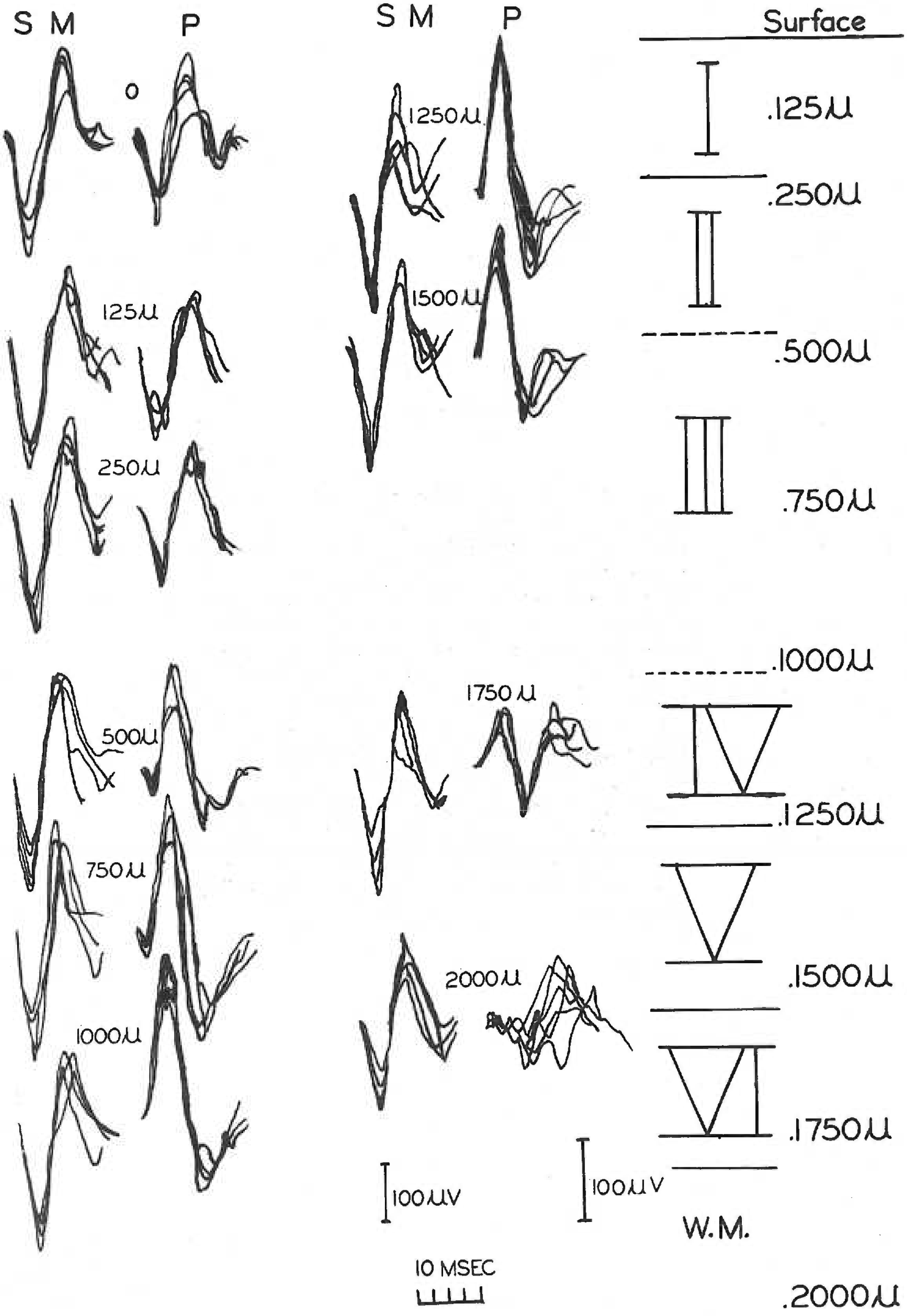

SURFACE MONITOR
S.M.
S.M.
SURFACE
750µ
1500µ
S.M.
S.M.
S.M.
250µ
1000µ
1750µ
S.M.
S.M.
S.M.
500µ
1250µ
2000µ
250µ
500µ
750µ
1000µ
1250µ
1500µ
1750µ
10 msec
S.M. 100µV
P. 100µV

FIGURE 12

Superimposed tracings of type I spindles as recorded at the surface and at different depths in the posterior sigmoid gyrus. In this figure, taken from the same experiment as figure 11, superimposed tracings of oscillographic records from the surface monitor electrode (S. M.) and from the penetrating electrode (P) have been arranged in pairs side by side. The depths of the penetrating electrode are indicated to the left of each depth tracing. Note the similarities in these records to those which were shown for augmenting responses (see figures 2 and 5). Note scatter of white matter recordings. (5-3-56)


S M
P
0
125μ
250μ
500μ
750μ
1000μ
S M
P
1250μ
1500μ
1750μ
2000μ
100μV
100μV
10 MSEC
Surface
I
.125μ
.250μ
II
.500μ
III
.750μ
.1000μ
IV
.1250μ
V
.1500μ
VI
.1750μ
W.M.
.2000μ

matter were entered by the recording electrode. All that remained in the white matter was the suggestion of a positive-negative sequence.

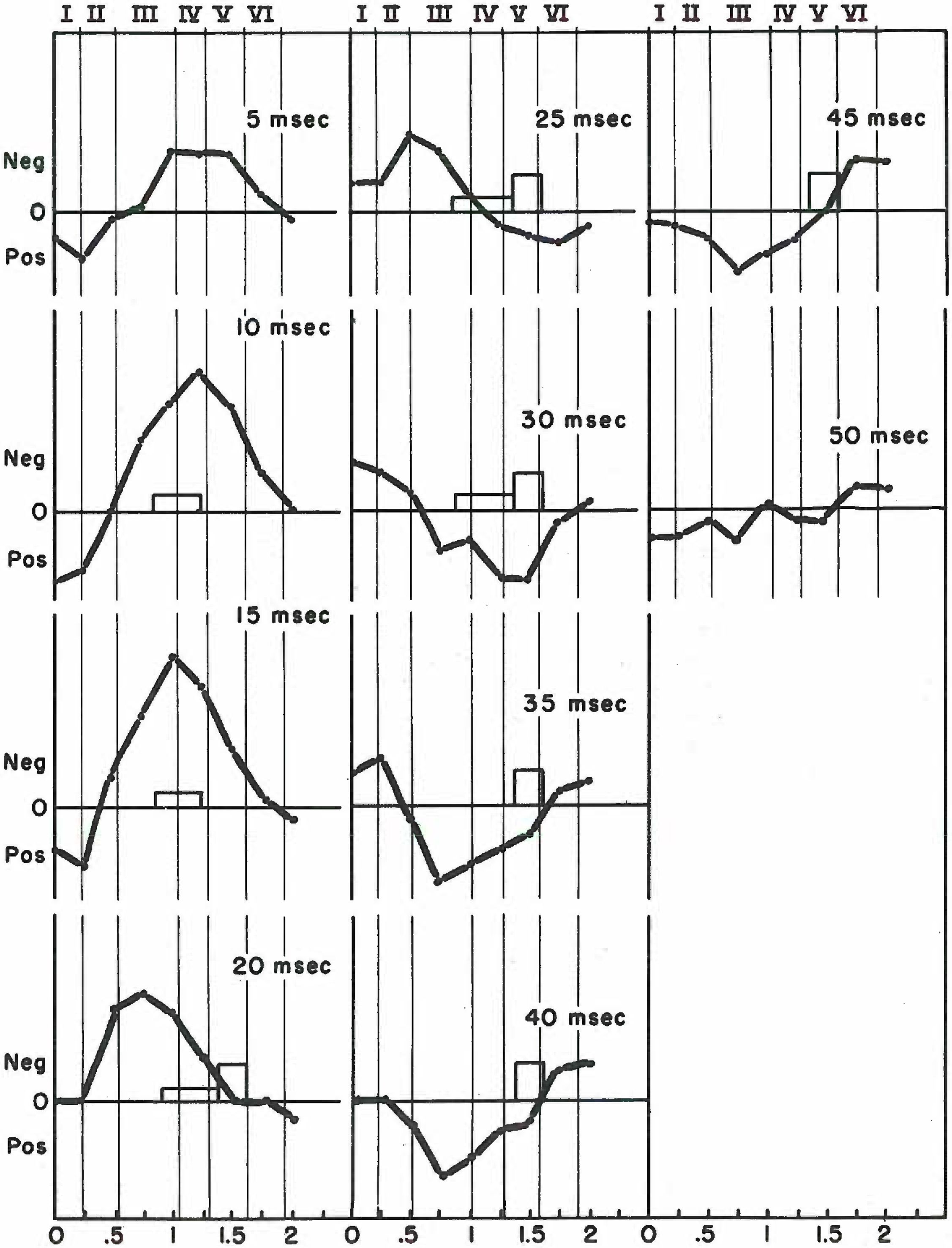
Returning to figure 11, the same features may now be more clearly discerned in the single tracings. It was often possible to make out the suggestion of unitary activity present as "fuzz" or a thickened baseline on the crest of the remarkable initial sink in the third and fourth layers. If one were to compare these waves with those seen in augmenting responses, then this deep initial negativity would be analogous to component b rather than component a of the augmenting response. The larger fifth layer units can be seen in figure 11 in the trough of the deep after-positivity.

As with augmentation, these potentials may be more readily related to depth if a depth-potential graph is constructed (figure 13). This series of graphs also points up the origin of the early sink in the third and fourth layers and illustrates its upward ascent with prodromal and metadromal sources above and below it. Composite depth, onset and depth, peak-latency curves can also be used to summarize the data from several experiments on type I spindles (figure 14). Here again the similarity to those for the augmenting responses is very striking indeed.

A few special comments are necessary concerning the obvious similarities between these illustrations and graphs of spontaneous type I spindles and those for the evoked augmenting waves. The difference in time course is perhaps accountable in terms of the difference in synchrony which would be expected between spontaneously occurring events and those which are produced by very brief thalamic shocks. A less easily explained difference is to be found in the very small amplitude of the potentials in the sixth layer and white matter during spindling

FIGURE 13

Depth-potential distribution of the responses illustrated in figures 11 and 12 at a succession of points in time. The presentation employed in this figure is identical to that which was used in figure 3. Note the marked similarity to the changes shown in figure 3. (5-3-56)



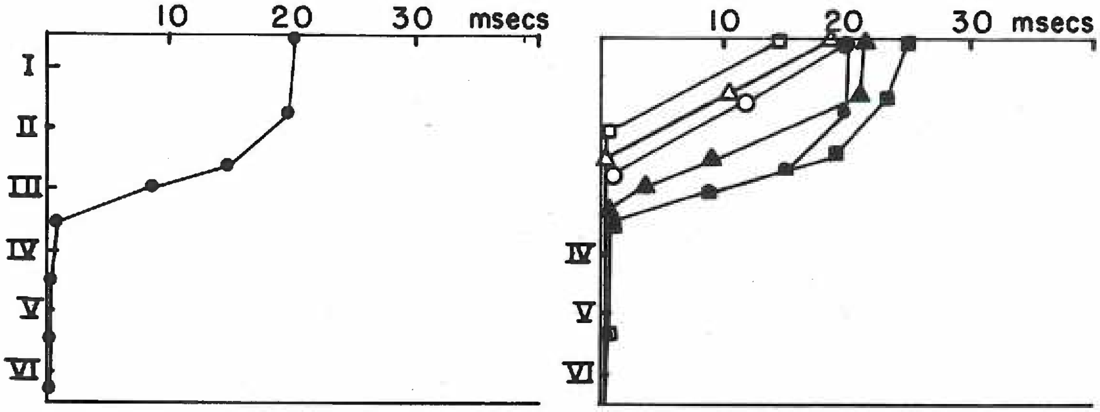
DEPTH DISTRIBUTION OF POTENTIALS
(SPINDLE WAVES)

FIGURE 14

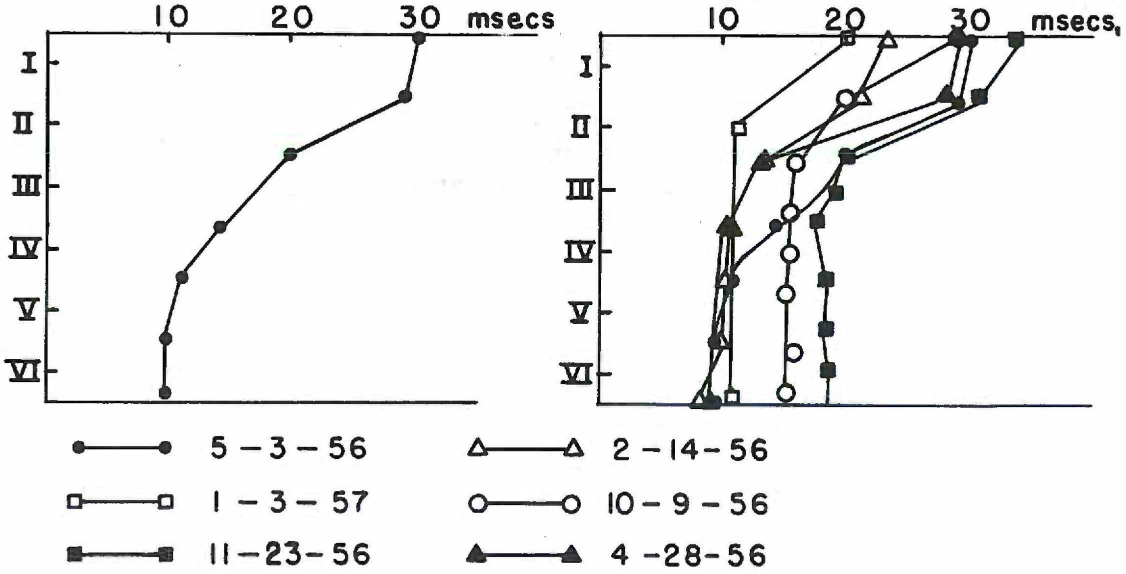
Time to onset and time to peak of the intracortical sink as related to depth during type I spindles. This presentation is identical in every way to that which was employed in figure 4. The graphs on the left side of the figure are taken from the same experiment illustrated in figures 11, 12 and 13 (5-3-56). The graphs to the right summarize the observations made during six comparable experiments. Note the marked similarity of these graphs to those which were presented in figure 4 on the augmenting response.

TYPE I SPINDLES

Depth : Onset



Depth : Peak Latency



as compared with the amplitude of the deflections recorded at the same levels during augmentation. Taking all available facts into consideration, the most probable explanation for this particular difference is that in augmentation, adjacent areas of cortex were undergoing potential fluctuations which were highly synchronous with those sampled by the penetrating electrode in its course through the cortical layers. On the other hand, during spindling, the adjacent cortical areas may have been decidedly out of phase. As the penetrating electrode went deeper and deeper, it eventually entered areas where axons from adjacent areas of cortex were coursing. During augmentation these were all in step and tended to summate, while during spindling the potentials were highly desynchronized. The scatter of the superimposed tracings in figure 12, which were taken from the white matter responses, testify to the probable mingling of effects in white matter recordings.

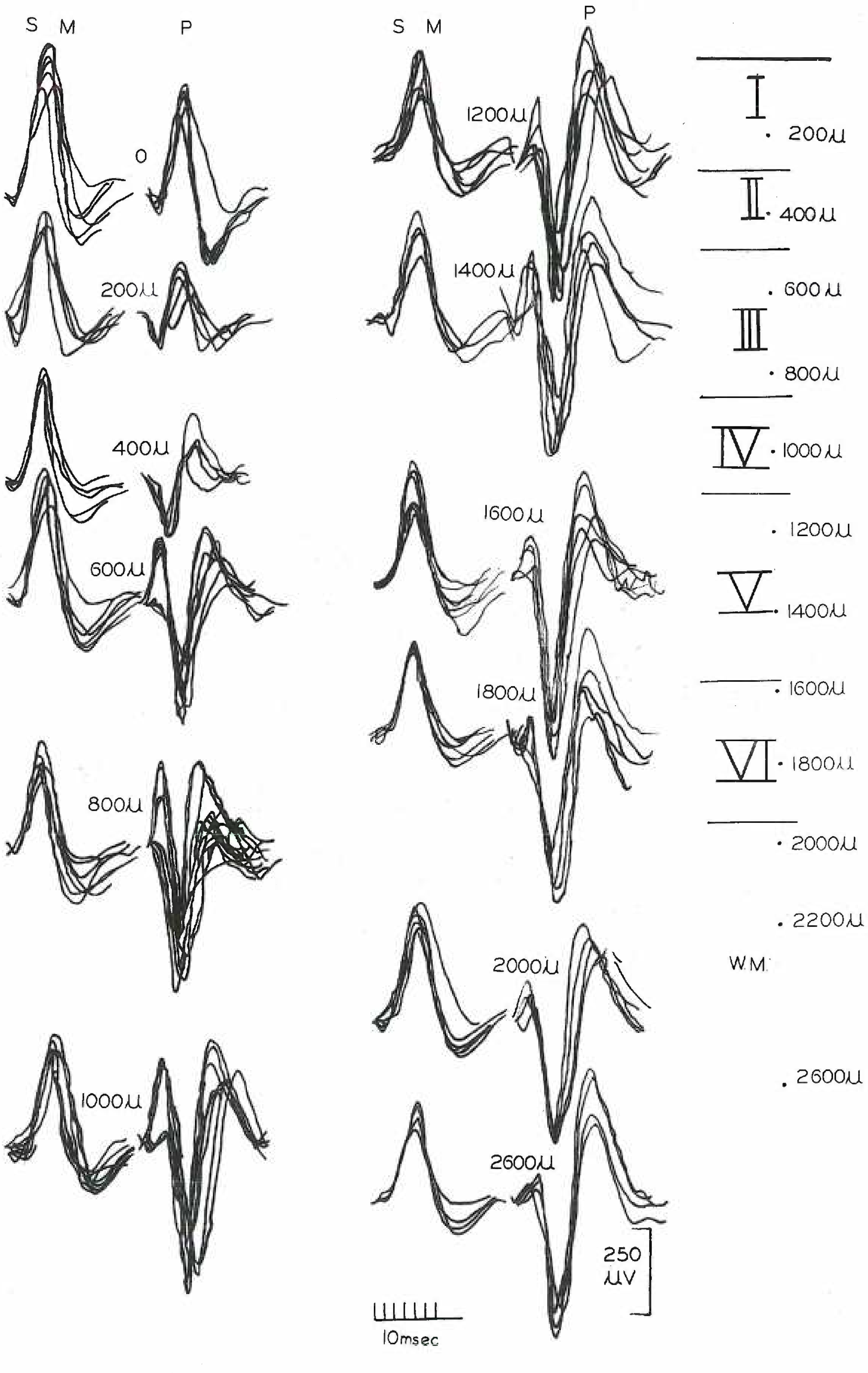
Interpretation. The interpretative possibilities for these waves are very much the same as those which were made for augmentation. No deflection corresponding to component a was identifiable, perhaps because of a less synchronized afferent volley or because of the greater role of intrinsic cortical mechanisms in spindling. The initial deep negativity is assignable to depolarization in the vicinity of the cell bodies. The concomitant surface positivity again may represent the source provided by superficial extension of the cells whose parakarya are acting as sinks. The slowly ascending sink is another common feature of these two waves and the same possibilities apply to it as were suggested in the discussion of the augmenting response. It has been suggested (73) that the after-positivity encountered in deep cortical and thalamic recordings during spindling may represent summated positive after-potentials.

This is a reasonable possibility. However, the data on the type II spindles to be presented below suggest that few of the waves in cortical spindles are due to the operation of a single intracortical mechanism. Indeed, the records suggest that most of these waves are the manifestation of more than one intracortical event. Until it becomes possible to isolate the components completely, certain identification of the late positivity is impossible.

Type II spindles. These are the spindles which have an initial negativity. They were usually most well developed on the anterior sigmoid gyrus. In attempting to select recording sites for the study of type II spindles, it was found that most waves actually had some initial positivity in the surface records. Figure 15 presents tracings derived from one experiment in which type II spindles were studied. A superficial examination of these waves discloses a general resemblance to recruitment as presented earlier. As was the case with recruitment, the deep responses were predominantly positive in sign. As indicated in figure 15, the surface waves from different bursts were remarkably constant in time course and phase. However, despite this constancy, the recordings from the third and fourth layers fell into two distinct classes. These were differentiated on the basis of the presence or absence of initial negativity. This observation leads to the hypothesis that many of these spontaneous waves are actually "mixed". In figure 15 it can be seen that the presence of this initial negativity in some of the deep responses occurred in greatest amplitude in the third and fourth layers. This is strongly suggestive that type I components may appear in some of these type II waves.

FIGURE 15

Superimposed tracings of type II spindles as recorded at the surface and at different cortical depths within the anterior sigmoid gyrus. The same method of presentation has been utilized in this figure as was used in figure 12. If these waves are compared with the responses illustrated in figures 8 and 10, the general similarities of type II spindles to recruitment are quite striking. Note also the manner in which the early portions of the waves in the third and fourth layers (600 - 1,000 microns) divide into two distinct classes. However, the surface recordings (S. M.), made simultaneously with these deep recordings, are all congruous. (1-10-57)


S
M
P
0
200µ
400µ
600µ
800µ
1000µ
1200µ
1400µ
1600µ
1800µ
2000µ
2600µ
250 µV
10msec
I
II
III
IV
V
VI
W.M.
· 200µ
· 400µ
· 600µ
· 800µ
· 1000µ
· 1200µ
· 1400µ
· 1600µ
· 1800µ
· 2000µ
· 2200µ
· 2600µ

One test of this possibility was to examine more of these so-called type II waves for evidence of these mixed effects. It soon became obvious that these mixed types of waveforms were by no means rare. Figure 16 shows a collection of surface responses taken from an experiment which clearly shows that a diphasic positive-negative sequence may precede what is predominantly a surface negative wave. These then are clearly mixed responses which appear to contain both type I and type II spindle components in that order.

Figure 17 shows tracings from the fourth layer in a spindling experiment in which type I, type II and distinctly mixed responses were all seen at the same placement. In the mixed responses, the discontinuity between the two components is evident even in the superimposed tracings. The photograph in the lower part of the figure shows that many of the responses without prominent discontinuities are probably mixed but very smoothly summated. Typically, the burst may start out with mixed responses and end with what appear to be almost pure type II responses. In this illustration there is only the slightest suggestion that the surface waves contain the early diphasic positive-negative sequence which has been linked with the initial deep sink. Although the mixed responses usually seemed to make up the first part of the burst as in this figure, a wide sampling of bursts disclosed that the mixed and type II responses may appear in almost any order. When clearly evident mixed waves appeared, they always appeared in the sequence illustrated, i.e. type I precedes type II.

Interpretation. As with the recruiting responses, the interpretation of these type II waves is enormously difficult. At the present time,

FIGURE 16

Surface recordings of individual spindle waves showing evidence of mixture. These individual surface waves were selected from a number of spindle bursts. They have been placed in vertical rows to facilitate comparison. The arrows indicate the most constantly observed discontinuity in the surface spindle waves. This type of discontinuity indicates the separation of a positive-negative sequence from an underlying negative-positive sequence. Such waves are regarded as representative of mixed (I - II) spindles. (10-9-56)

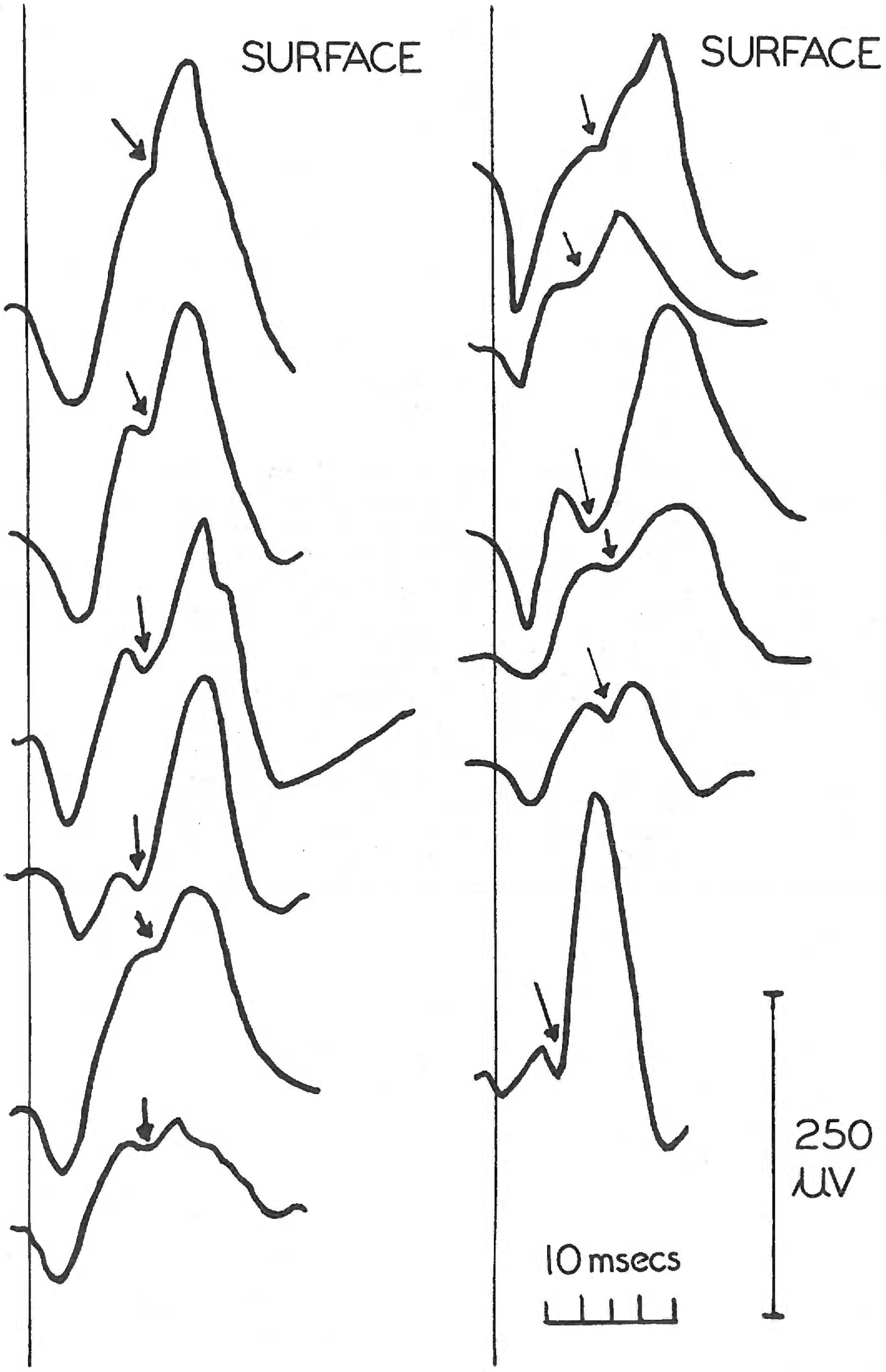
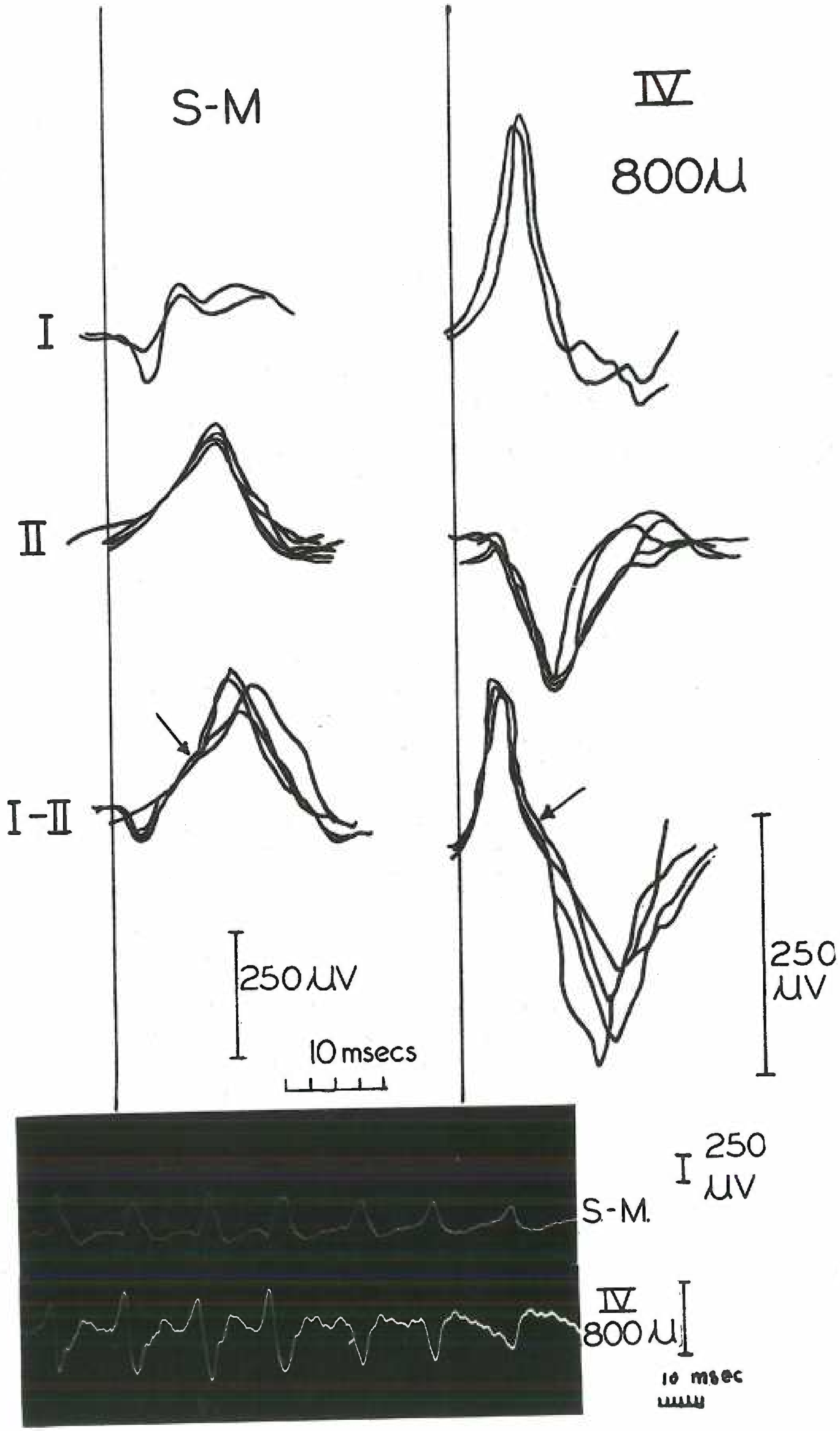

SURFACE
SURFACE
250
µV
10 msecs

FIGURE 17

Superimposed tracings of type I, II and mixed (I - II) spindle waves at the surface and in the fourth layer of the anterior sigmoid gyrus. The type of spindle wave is indicated on the left. The tracings in the first column are from the surface monitor, (S. M.), those in the second column from the penetrating electrode. The arrows indicate the discontinuity between the two components in the tracings of the mixed responses. The photograph in the lower part of the figure shows smoothly summated mixed waves and type II waves as they appear in a burst. Upper line, surface monitor; lower line, waves as recorded by penetrating electrode with tip in fourth layer. Note that the first four waves seem to be mixed (large initial deep negativity) even though the initial surface positivity is small. The last three waves seem to be pure type II waves. This is a common sequence, i.e., the burst starts out with mixed waves and ends with pure type II waves. (9-26-56)


S-M
IV
800 µ
I
II
I-II
250 µV
10 msecs
250 µV
I 250 µV
S-M.
IV
800 µ
10 msec

the similarity of these potentials to the recruiting response can simply be pointed out and the possible equivalence of these two waveforms reaffirmed.

Unitary Activity

As was mentioned in the introduction, the study of unitary activity was strictly a subsidiary aim of this project, the primary effort having been directed toward an understanding of the slow potential fluctuations. However, it soon became apparent that some of these waveforms were closely related temporally to all of the units recordable with the types of electrodes employed in this study. For this reason, at every recording site, an effort was made to record the activity of the population of units in the vicinity of the electrode tip.

Figure 18 illustrates in a striking manner some of the similarities and differences in population unitary response during augmentation and recruitment. These records were taken from an experiment in which both augmenting and recruiting responses were recorded from the same locus.* In both of these responses it is evident that the apparently random unitary activity which prevails after the injury effects have subsided (bottom tracing) is converted into grouped discharges by both types of repetitive thalamic stimuli. The pattern of unitary response in both cases is characterized by the appearance of a group of spike discharges both preceded and followed by periods of unitary silence. However, there appears to be a considerable difference in the temporal dispersion of the grouped discharges associated with the two different waveforms. The groups of unitary discharges appear to be much more compact in the

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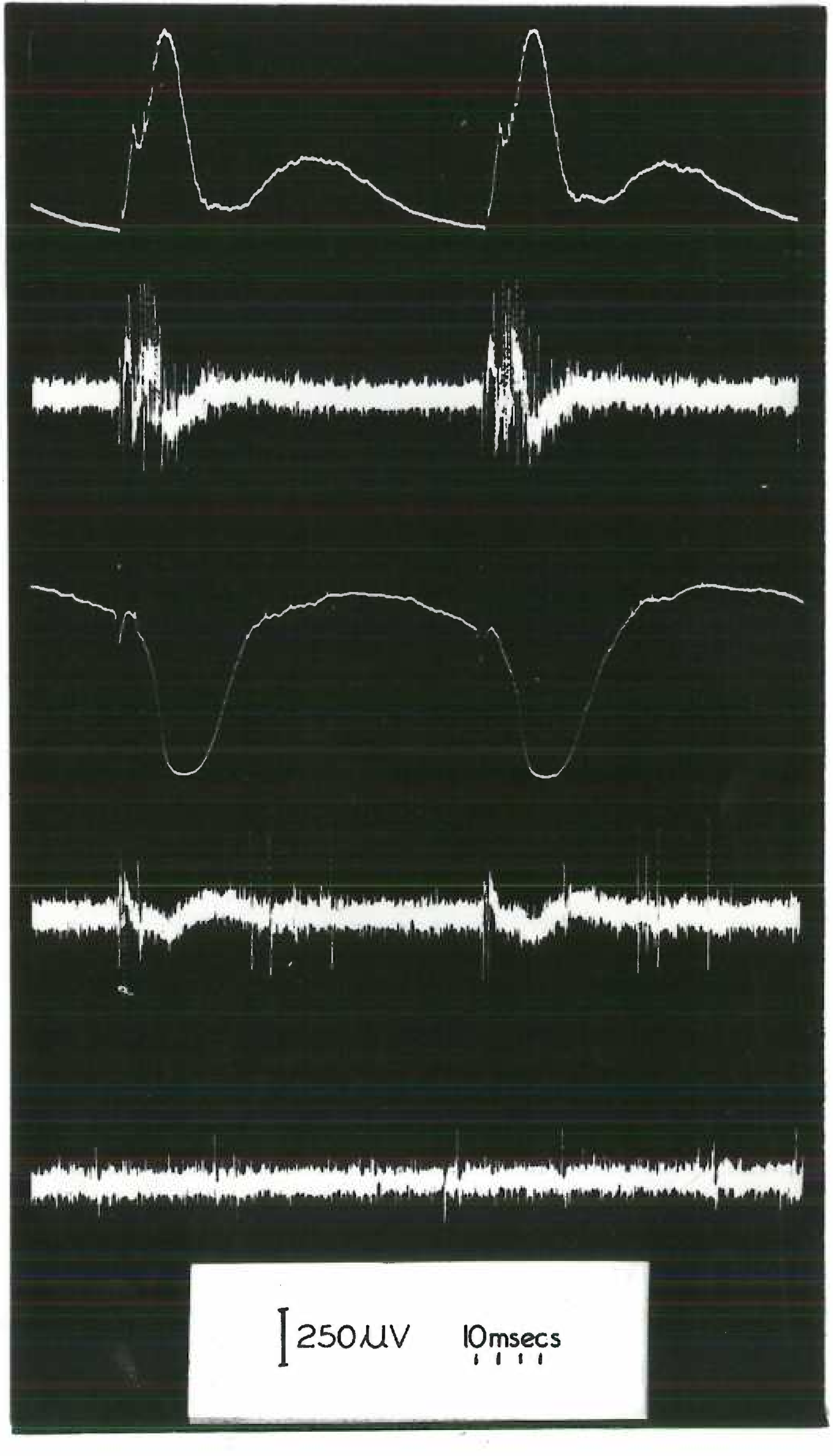
*A micropipette was used in this experiment and was situated in the sixth layer. The illustration shows unitary activity which is typical of that which was routinely encountered in the third, fourth, and fifth layers. Therefore, many of these spikes may arise from axons.

FIGURE 18

Comparison of patterns of unit activity during recruiting and augmenting responses. All records derived from a single micropipette in the sixth layer of the anterior sigmoid gyrus. Records one and two (from above) recorded simultaneously during stimulation of n. ventralis lateralis (1 msec., 6/sec.). In record two slow waves were attenuated by virtue of the short time-constant of the amplifier. Note the number, placement and grouping of the unitary activity during these augmenting waves. Records three and four recorded simultaneously during stimulation of n. ventralis medialis (1.0 msec., 6/sec.). Amplifier conditions unchanged. Note infrequent, late, poorly grouped unitary activity during these recruiting waves. Record five illustrates the background unitary activity in the absences of thalamic stimulation. (4-19-57)


250 µV
10msecs

augmenting response than in recruitment, yet the slow waves are of comparable amplitude, (although, of course, of different polarity and shape).

The same kind of unitary grouping has often been described in association with spindle waves. (73, 48) Figure 20, on the right, shows the fifth layer unitary activity as seen in a spindle burst and in individual spindle waves. On the basis of their surface configuration, the individual waves have been labelled as type I, mixed and type II waves. Those waves which contain a type I component are associated with the repetitive discharge of a large fifth layer unit. The pure type II wave is accompanied by smaller more scattered unitary spikes.

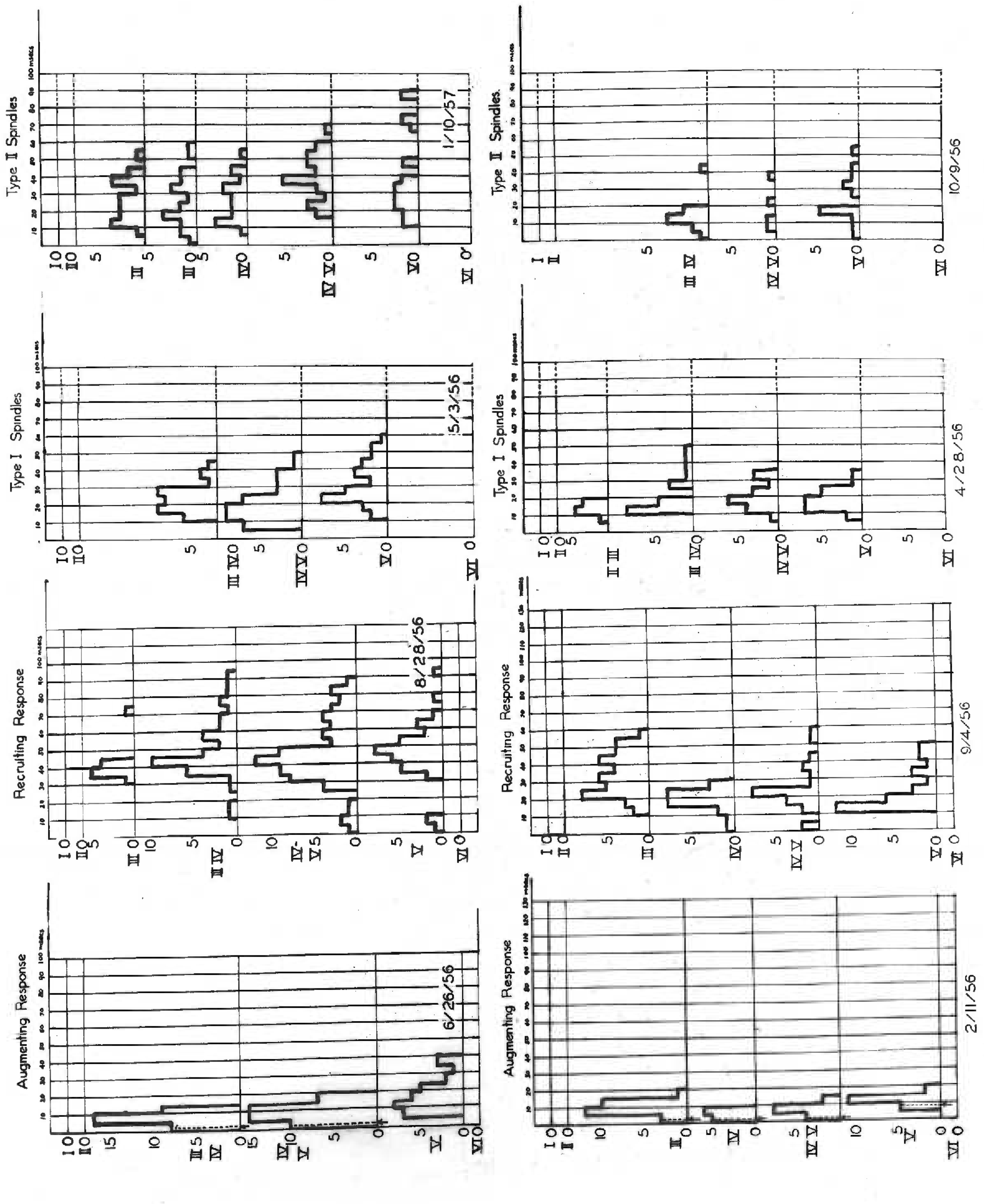
In order to estimate how accurately recordings such as these represent the cortical unitary activity as it was seen in a number of experiments and at different cortical depths, an attempt was made to summarize quantitatively the unitary data obtained during these experiments. In those experiments with the most distinct unitary spikes, an attempt was made to count the total number of spikes present in individual responses during given time intervals at the depths selected for the study of slow waves. This means that the discharges of a population of units was handled as a group. No attempt was made to analyze the pattern of activity of individual units in a statistical manner. It was often very difficult to say with certainty whether a given spike represented a single unitary response or the nearly simultaneous discharge of several units. As a result, many spikes which were counted as single unitary discharges were probably multiple discharges. However, the error produced by this kind of misinterpretation is such that estimates of central tendency for grouping will tend to be low since the more compact the grouping of units is, the greater will be the likelihood of this type of error. This method of analysis is to be considered semiquantitative rather than quantitative.

The data from eight experiments are graphically summarized in figure 19. Each of the four columns of graphs illustrates the results from two experiments. The experiments represented in the first column were concerned with augmentation, those in the second column with recruitment, those in the third with type I spindles and those in the fourth with type II spindles. The ordinates designate number of spikes, the abscissas designate time. Each individual histogram represents the frequency distribution of all spikes associated with five of the largest amplitude waves in a burst of responses. The histograms provide a means of comparing the central tendencies of unitary activity in different responses. However, the amplitudes of the different histograms are not comparable because there was considerable variation in the amount of unitary activity recorded in different experiments and also because of the errors in counting which were described above.

Comparing the two kinds of evoked waves, it is clear that the unitary activity associated with augmenting responses occurs over a much shorter time interval and exhibits a greater central tendency than the unitary activity which accompanies recruiting responses. In the augmenting response, the time of onset and cessation of unitary activity was sharply demarcated at different depths. The fifth layer activity is both later in onset and peaks at a later time than the activity in the third and fourth layers. Although the amplitudes of the histograms are not strictly comparable for the reasons cited above, it would seem that the augmenting response is accompanied by more dense unitary

FIGURE 19

Frequency distribution of unitary activity with respect to time and depth in augmenting, recruiting, type I and type II spindle waves. The data from two studies of each of these waveforms are presented in each column. The type of waveform is indicated at the top of each block of graphs, the experiment number at or near bottom. The ordinates designate number of spikes; the abscissae time, indicated in msec. across top of each block of graphs. The vertical lines are placed at 10 msec. intervals. The position of the recording electrode for each individual histogram is indicated by roman numerals to the left of each graph. In some cases the recording site was at a boundary between layers (e.g. IV - V). Each individual histogram represents the frequency distribution of all spikes associated with five of the largest amplitude waves in a train of responses. The dotted vertical lines in the histograms for the augmenting responses indicate the time at which the shortest latency unitary spikes were seen. Note indication of no spiking in layers I, II and VI in all experiments. Note periods of unitary silence in graphs. See text for further details.


Type II Spindles
1/10/57
Type I Spindles
5/3/56
Recruiting Response
8/28/56
Augmenting Response
6/26/56
Type II Spindles
10/9/56
Type I Spindles
4/28/56
Recruiting Response
9/4/56
Augmenting Response
2/11/56
100 msecs

activity than recruitment. The same impression was borne out in the records from two experiments in which both augmenting and recruiting responses were recorded in the same penetrations. In many recordings of these evoked responses in which there was considerable spontaneous activity in the background, the periods of unitary silence which were associated with the thalamic stimuli were as striking as the grouped unitary discharges. This suggests the participation of inhibitory phenomena in these responses. (19, 45)

The differences between the unitary activity associated with the two kinds of spindle waves were not as striking as those between augmenting and recruiting responses. Nevertheless, the unitary activity associated with type I spindles does exhibit a greater central tendency and does seem to occur over a much more restricted period of time than is the case with unitary activity accompanying the type II spindles. Only in the experiment of 5-3-56 is there an indication that the fifth layer units may discharge at a later time than those in the third and fourth layers.

If it were possible to say with assurance that these histograms exhibited a <u>normal</u> distribution, then it would be possible to express these differences in central tendency in statistical terms. However, such an assumption cannot be made.

Several special points are worthy of mention. 1) Although the recruiting responses which appear in the largest part of the train were associated with unitary "grouping", the smaller amplitude late waves in the train were usually accompanied by apparently random unitary activity. This was rarely the case with the late augmenting waves which consistently showed tight unitary grouping unless <u>just threshold</u> stimulus intensities were employed, in which case only the largest responses were associated with tightly grouped discharges. 2) In recruitment, sometimes the unitary bursts seemed to be out of step with the slow waves and the clumps of spikes would often start before the stimulus artifact. This almost never occurred during augmentation. 3) In a train of evoked waves, the number of spikes associated with each slow wave often showed a good correlation with the amplitude of the slow potentials. However, there were cases in which increasing the stimulus intensity at an augmenting site seemed to decrease the number of spikes in each group, even though the slow waves were of large amplitude. 4) In contrast with the evoked waves, the smallest amplitude spindle waves were often associated with the largest number of unitary spikes. Although all of these observations are of some interest, they can not readily be fitted in with the data presented above.

In the description of the slow waves, it was pointed out that augmenting and type I spindles showed many similarities and that recruiting and type II spindles showed many similarities. The graphs of the spike activity also reveal a similarity between these two types of response. Here also, the effects of the spontaneous waves tend to be more dispersed temporally. The graphs of the augmenting unitary activity in the fifth layer show a shift in latency and mean when compared to the graphs for the third and fourth layers. No such shift is demonstrable in most of the type I spindles. (However, as mentioned above, the graphs for 5-3-56 show a suggestion of a shift in mean.) This may be due to an actual difference in the mechanisms underlying augmentation and the type I spindles or it may be a function of temporal dispersion and the uncertainty of the arbitrary zero time point which was adopted in the case of the spontaneous waves.

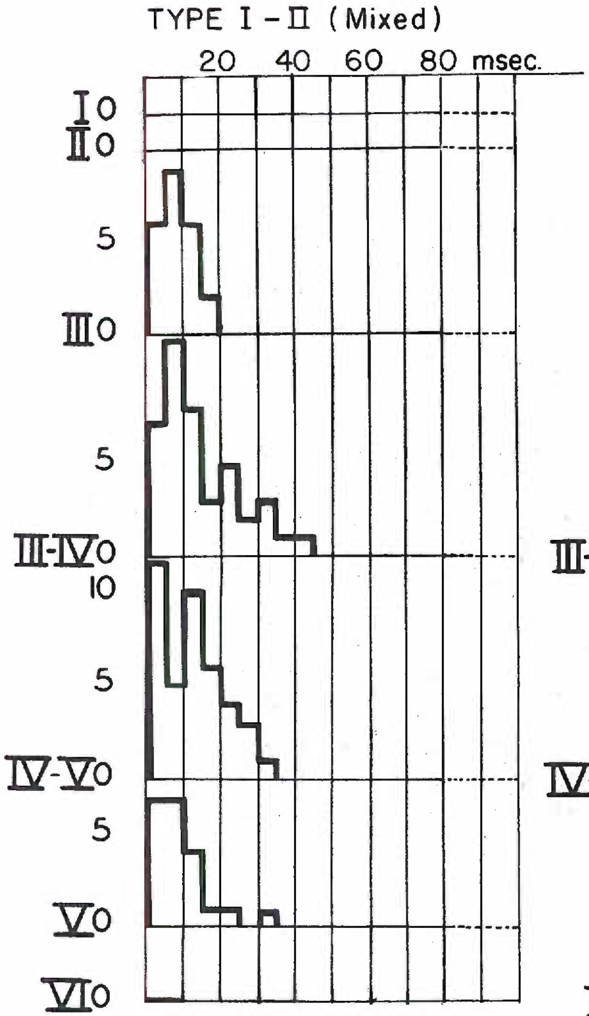
Figure 20 contains a series of similar graphs comparing mixed spindles (which contained type I slow waves) with type II spindles. (Samples of the individual waves are illustrated to the right of the graph and have already been described.) These waves were recorded in the same preparation, at the same recording site and in many cases within the same burst. The graphs disclose not only the greater central tendency in those waves which contain type I elements, but also suggest that the actual number of unitary spikes associated with each wave may be greater.

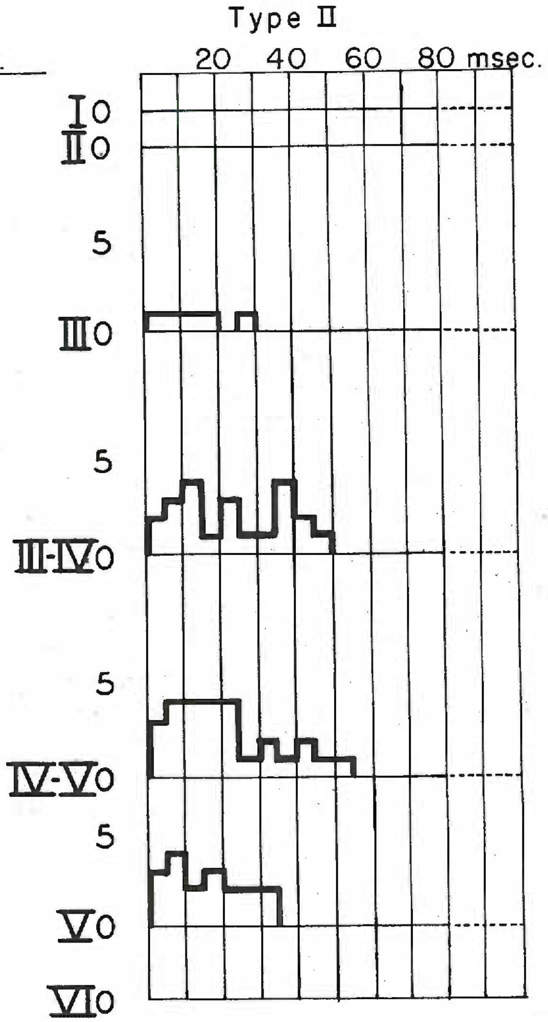
If the time course and depth distribution of the unitary activity which has been illustrated in these figures 19 and 20 is compared with the corresponding slow waves of each type of response, (figures 2, 8, 12, 15) it is clear that the unitary activity in augmenting and type I spindles is fairly well correlated with the time course of the large initial deep sink which appears in both of these responses. This correlation was most striking in the third and fourth layers where the unitary bursts would usually ride on the crest of the deep negativity. In the fifth layer, the spikes would often occur on the descending limb or in the trough of the after-positivity. These relations may be seen in figures 2, 5, and 11.

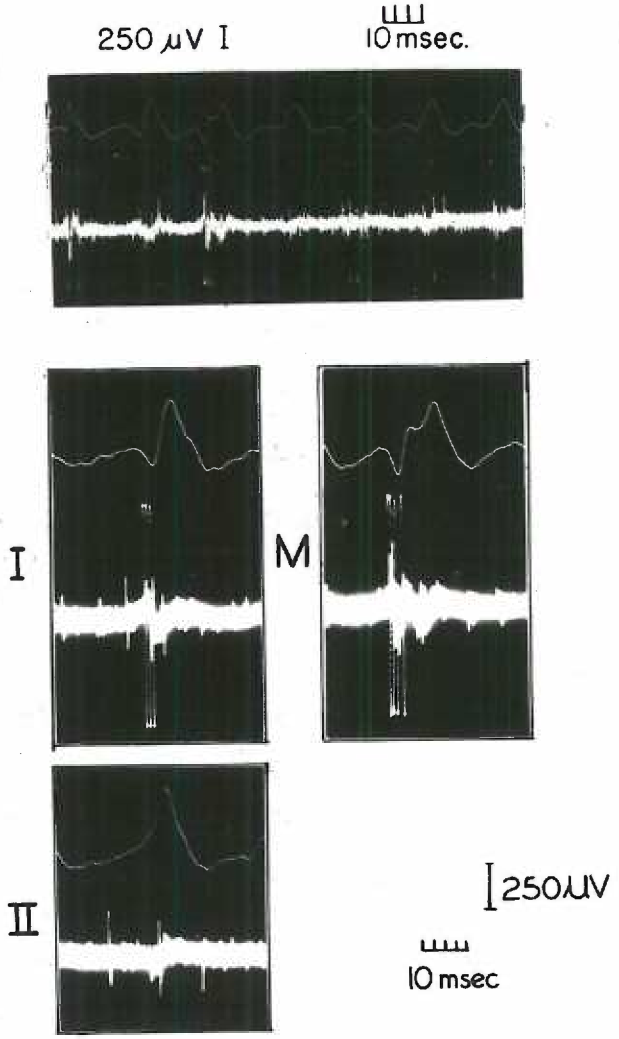
It would seem, therefore, that the sink in the third and fourth layers which develops in augmenting and recruiting waves represents synaptic activation of the neurons in these layers at the level of their cell bodies and basal dendrites. Some of the cells may be spindle cells but many are probably pyramidal cells. The timing of the unitary responses in augmenting and type I spindles, particularly in third and

FIGURE 20

Comparison of the frequency distribution of unitary activity with respect to time and depth during type I, type II and mixed spindle waves all recorded from the same recording sites. The photographs on the right illustrate unitary activity from the fifth layer as seen during these different varieties of spindle waves. (Recording system similar to that used for records of figure 18.) The top photograph shows fifth layer spikes (discernable in the second tracing as very faint lines) as they appear in a spindle burst. The top line represents the simultaneously recorded slow waves at the surface. The bottom three photographs show the fifth layer unitary activity (lower line) associated with each type of individual spindle wave as identified by surface configuration (upper line). The roman numerals to the left of each photograph indicate the type of spindle wave. Note the repetitive discharge of a large fifth layer unit in association with those waves containing type I components. The graphs in the left part of the figure are identical to those shown in figure 19. Type I spindle waves occurred in pure form so infrequently that this form of presentation could not be applied to them. Note skewedness of unitary activity associated with mixed waves. The peak of the histograms in this graph would be temporally coincident with the type I components. Note also greater absolute number of spikes in the mixed waves. (9-26-56)


TYPE I - II (Mixed)
20
40
60
80 msec.
I 0
II 0
5
III 0
5
III-IV 0
10
5
IV-V 0
5
V 0
VI 0


Type II
20
40
60
80 msec.
I 0
II 0
5
III 0
5
III-IV 0
5
IV-V 0
5
V 0
VI 0


250 μV I
10 msec.
I
M
II
250 μV
10 msec

fourth layers, is the same as that of the relayed pyramidal volley, i.e. during the period of initial surface positivity (19). Studies of the cortical distribution of unitary response to antidromic pyramidal stimulation has indicated that the so called "Betz cells", using Phillip's definition (64), may be found at levels from about 500 to 1800 microns from the surface (72). This would include the layers which were found to have grouped discharges coincident with the pyramidal volley.

During recruitment and type II spindles, the unitary activity was not consistently correlated with any phase of the deep slow potentials. Often individual units would be correlated with the deep positivity or with the superimposed initial deep negativity which appeared in some of the mixed forms. However, populations of cortical units seemed to be unrelated to any particular portion of the slow waves.

There are two reasons for suspecting that much of the unitary activity which is seen during recruitment is controlled by underlying triggered cyclic waves. 1) Sometimes the unitary activity appeared in grouped discharges which preceded the thalamic stimuli and 2) the late waves in the trains of recruiting responses, which would presumably have little of triggered waves, usually showed almost random unitary discharges.

In general, then, recordings of the unitary activity associated with recruiting and type II spindles suggest that these waveforms involve a less powerful, less synchronized and probably more indirect activation of the neurons whose cell bodies lie within the third, fourth and fifth layers.

DISCUSSION

The experiments reported lead to the construction of the hypothetical scheme diagramed in figure 21, namely that these three kinds of 8-12/sec. waves represent the algebraic summations of two basic potential-time-depth patterns. The word "patterns" is emphasized because the present investigation does not provide the kind of evidence which makes it possible to say with any assurance that the identical neurons are involved whenever a given pattern appears. Nevertheless, it is perfectly justifiable to describe these two patterns in terms of the common electrical characteristics which they exhibit in these different waveforms.* The most remarkable feature of Pattern A is the development of a large initial sink in the third and fourth layers. This sink then slowly ascends toward the surface. The unitary activity associated with Pattern A occurs in very dense bursts at strictly defined time intervals. In some responses exhibiting Pattern A, the unitary activity in the fifth layer started later and continued for a longer time than that which was present in the third and fourth layers. The purest examples of Pattern A are to be found in the augmenting response and in type I spindles. The sequence of potential changes with respect to depth seen in Pattern B are not completely describable in terms of intracortical sinks. The first electrical event is the development of a source in the deep cortical layers which becomes even larger in the

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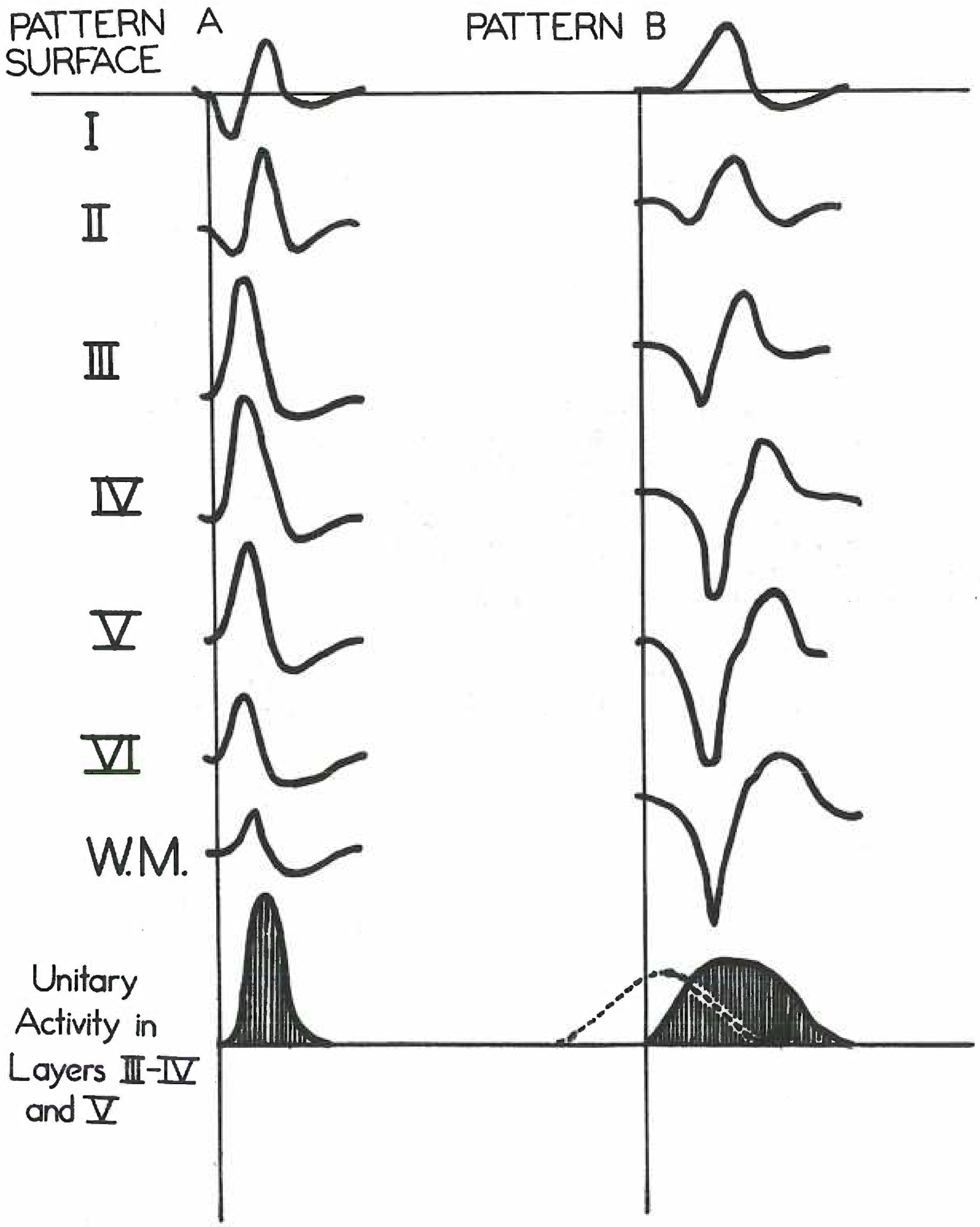
*On the basis of numerous similarities it must be said that the possibility that comparable patterns in different waves may, in fact, represent activity in the same neural structures is strongly suspected.

FIGURE 21

Schematic representation of the two fundamental kinds of 8 - 12/sec. waveforms. No absolute time scale has been included because the duration of these patterns varies depending upon whether they are evoked or spontaneous in their appearance. These represent typical monopolar recordings which may be obtained at different cortical levels (indicated by roman numerals on left.) Pattern A is shown in left column, Pattern B in the right. The frequency distribution of unitary activity from the middle cortical layers is graphed in a schematic fashion at the bottom of each column.


PATTERN A
SURFACE
PATTERN B
I
II
III
IV
V
VI
W.M.
Unitary Activity in Layers III-IV and V

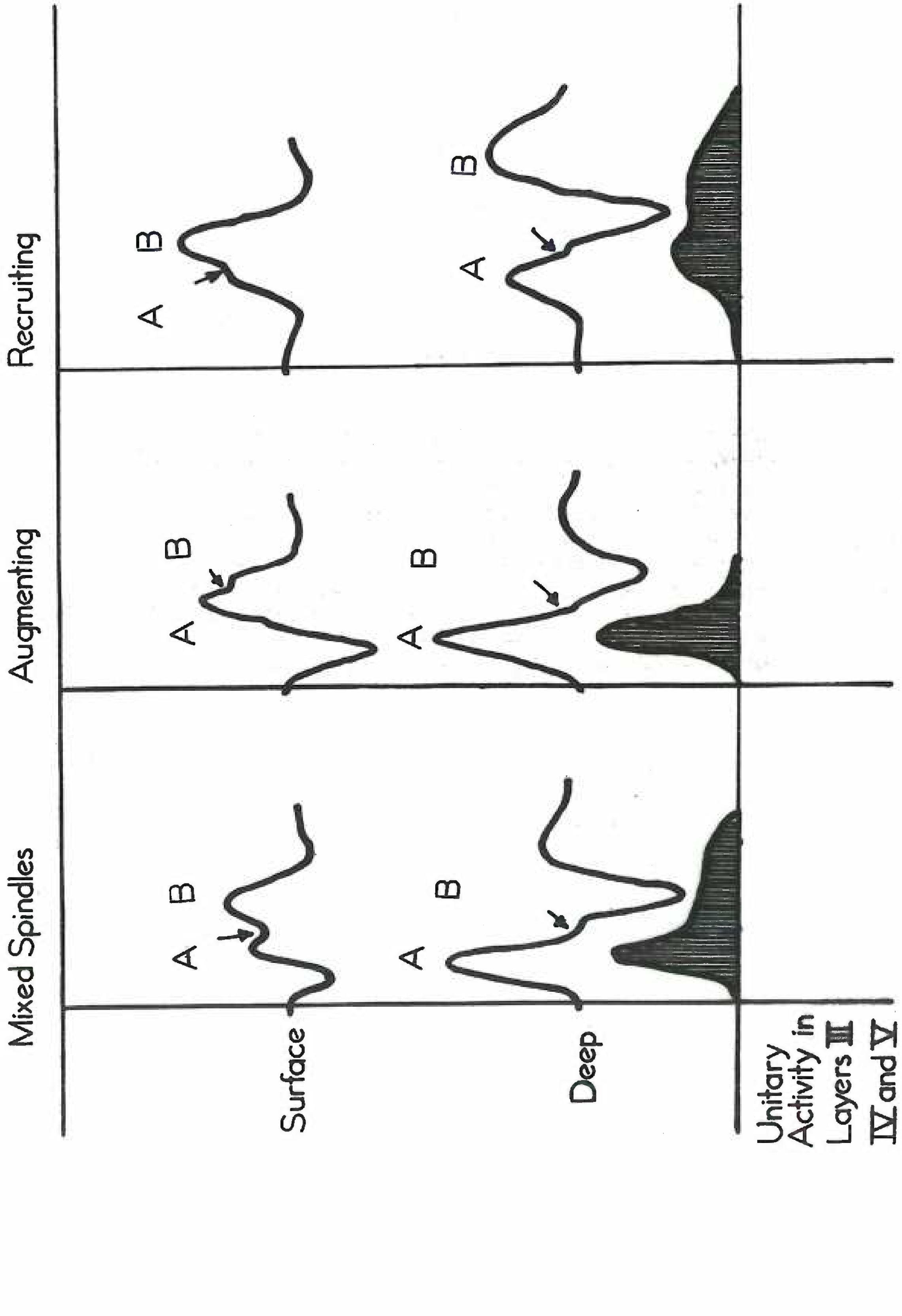
white matter. This presumably is a source providing current for some subcortical sink. Superimposed on this source after a delay of about 10 msec. there develops a very superficial cortical sink thus creating a negative-positive transcortical gradient. After about 20 msec. this gradient suddenly becomes reversed in direction. Although this might represent the development of a deep cortical sink, it is not always bounded inferiorly by a source in the white matter. The definitive interpretation of this pattern awaits further knowledge of the simultaneous electrical changes occuring in deeper subcortical structures. The unitary activity associated with Pattern B tends to be scattered, dispersed over a relatively long time interval and inconsistent in its time distribution from one response to another even within the same train. During evoked waves, unitary activity was always clustered during the surface positivity and early negativity of the Pattern A responses. However, the clustering during Pattern B responses was not invariably associated with the surface negativity in all preparations in that it sometimes preceded the thalamic stimulation. This is indicated by the dotted line in figure 21.

A comparison of type A and type B responses reveals the striking differences between the contours of these two types of activity as they are manifested by recordings from the third to fifth layers. At these levels of the cortex, the phase sequences of the two patterns are almost exactly opposite to each other.

The observations made in these experiments lead to the conclusion that many of the waveforms studied are the results of an algebraic summation of these two patterns. The waveforms illustrated in figure 22 are diagrammatic representations of the results of this summation as they

FIGURE 22

Schematic representation of the way in which Patterns A and B are believed to occur in the more usual mixed forms. Kinds of mixed responses indicated at top of figure. Upper row of diagrams, surface monitor; lower row, deep electrode recordings. Again the frequency distribution of the unitary activity in the middle cortical layers is diagramed. Arrows indicate the usual position of the discontinuities which can often be seen in recordings of mixed responses.


Mixed Spindles
Augmenting
Recruiting
Surface
Deep
Unitary Activity in Layers III IV and V
A
B
A
B
A
B
A
B
A
B
A
B

have been seen in all three forms of electrocortical activity. In mixed spindles the relative dominance of Pattern A over B and of B over A varied through a wide range. In all mixed augmenting responses Pattern A predominated clearly over Pattern B. In all mixed recruiting responses Pattern B clearly predominated over Pattern A. The presence of these mixtures of Patterns A and B was often suggested by the discontinuities which are indicated by the arrows in figure 22. In all cases, the time-course of the surface potential change was not a completely reliable index of the purity of the basic pattern. In many instances, the depth records were essential for the clear differentiation of pure and mixed responses. This was particularly true of spontaneous spindles, perhaps because of the greater degree of temporal dispersion in thalamocortical volleys which initiated this form of activity. The distribution of the unitary activity was also of assistance in detecting the existence of an obscure Pattern A.

Whenever the two patterns appeared together, the elements of Pattern A immediately preceded the elements of Pattern B. This raises the question of whether or not the events associated with Pattern A caused those responsible for Pattern B by activation of intracortical or interareal connections. It might seem possible that whenever Pattern B appeared in isolation (as it often did in midline recruitment), it was actually the result of cortico-cortical activation from an area of cortex where Pattern A predominated. This possibility was not ruled out by the present experiments since the studies were limited to the paracruciate area and the recruiting response to midline thalamic stimulation may be present in many other cortical areas, e.g. prorean, cingulate and subcallosal cortices. However, this same question has been attacked before by cortical ablation studies (37, 29) and the findings have been such that cortico-cortical spread cannot be regarded as essential for the production of cortical recruitment. This then favors the possibility that the presence of Pattern B alone is not dependent upon the presence of the events associated with Pattern A in adjacent cortical areas and that it is an independent pattern set up directly by thalamo-cortical afferents. The invariable temporal precedence of Pattern A over Pattern B at a single cortical focus cannot be accounted for by the data presented here. There are two basically different possible explanations. It may be that the thalamo-cortical volleys responsible for the two patterns are conducted at different velocities such that the volley producing the events underlying Pattern A always arrive at the cortex before the volley that results in Pattern B. Alternatively, the A-B sequence may be dependent upon transfer of activity from one thalamic source to the other over intrathalamic nuclear connections (60).

Given two distinct and apparently independent patterns, what factors account for the striking differences? The amplitudes of both the surface and deep potentials are comparable and therefore it seems unlikely that the differences between these two patterns are strictly quantitative. A very good possibility is that these two patterns involve two different types of thalamocortical afferents. Although it is not possible to say whether the initial deep sink in Pattern A represents either 1) activity in thalamo-cortical afferents themselves or 2) the post-synaptic depolarizations caused by these afferents, its position with respect to depth corresponds to that of the afferent terminals in both cases. By almost unanimous agreement among anatomists, the specific cortical afferents and in the fourth and lower third layers (55, 59, 60). There are a number of ancillary arguments which also support the contention that Pattern A is initiated by specific cortical afferents. It is in the third and fourth layers that short latency, tightly packed unitary spikes appear. The design of the bushy endings of the specific afferents is such that they might be expected to command an enormously large population of third and fourth layer neurons. Such appears to be the case from the dense clustering of the grouped unitary discharges. Pattern A uniformly predominates in cortical augmentation which is produced by repetitive stimulation of VPL and VPM, and these nuclei are known to send specific afferents to the somesthetic cortex (55, 59, 60). The fact that Pattern A can be seen in a rudimentary form after a fairly long latency in some recruiting responses is not inconsistent with these ideas in view of the known anatomical connections of the midline nuclei to the specific nuclei (60). Finally, the remarkable similarity of Pattern A to that which is seen in the primary response is consistent with the general interpretation that the primary response is mediated by specific afferents (40, 63, 46).

Regarding Pattern B, there are a number of factors which make it difficult to correlate the pattern of slow wave changes with what is known about the anatomy of cortical afferents. In the first place, there has been wide variation in the descriptions of cortical afferents other than the "specific" ones. Lorente de No's original descriptions (53) emphasized that the unspecific afferents send collaterals to all cortical layers with the greatest number of terminals going to the sixth layer. Nauta (59) has described fibers which end in all cortical layers except the first. Sholl (69) points out that some Golgi preparations show a number of rather fine axons running straight through the lower part of the cortex to end in the more superficial parts of the cortex with the exception of the outermost portions. The origin of all the horizontally running fibers in the outermost cortical layer is not definitely known, although some may come from the deep stellate cells (69). Furthermore, Nauta and Whitlock (60) have shown that some afferents from the midline and intralaminar cell groups which go to the marginal strips of neocortex adjoining the rhinal and cingulate sulci enter the cortex as deep tangential fibers and end only in the deep cortical layers. Nauta and Whitlock state quite emphatically that the cortical afferents terminating in all cell layers and ramifying in layer I cannot be interpreted categorically as representing cortical projections from nonspecific thalamic nuclei. Because of this uncertainty about unspecific afferents, the only thing which can be said with conviction is that Pattern B probably does <u>not</u> involve activity initiated by the specific cortical afferents.

It cannot be denied that both Pattern A and Pattern B are associated with activity in postsynaptic intracortical neurons. It remains to be determined whether both forms of response involve the same population of intracortical neurons or whether the activated post-synaptic elements are different in the two cases. Some information bearing on this subject has been obtained from studies of the responses of cells of origin of the cortico-spinal system. Brockhart and Zanchetti (19) demonstrated clear differences in the changes of electrical excitability of these neurons during augmenting (Pattern A) and recruiting (Pattern B) waves, and offered explanations for contradictory results obtained by previous workers (11). More recently, however, Parma and

Zanchetti (61) have noted that the relayed pyramidal volley associated with augmenting waves may be altered by properly timed recruiting waves. This observation suggests that both types of electrocortical activity induce changes in the same cortico-spinal neurons.

These observations on the role of cortico-spinal neurons, plus the theoretical considerations regarding slow waves (see introduction), plus the sheer numerical predominance of pyramidal cells in the cortex all suggest that both Patterns A and B involve the activation of pyramidal cells. However, the undeniable difference in the two patterns favors the possibility that they represent activation of these cells at different loci. The idea that pyramidal cells may be activated at different loci has been the very backbone of theory about cortical function which has grown out of Adrian's masterful discussion appearing in his fifth chapter of The Mechanism of Nervous Action (2). Practically all subsequent theorizing has been an extension of these ideas. By far the greatest emphasis has been placed upon the differences in synaptic function ascribable to terminations 1) on the apical dendrites and 2) on the cell bodies of the pyramidal cells.

As described in the introduction, the predominant emphasis in the literature on the intracortical mechanism of these 8-12/sec. waves has been focused on the role of apical dendrites. Pattern B has features which could be interpreted as indicating the presence of a very superficial cortical sink consistent with the depolarization of apical dendrites. As was pointed out earlier, however, some of the cortical potentials in this pattern may reflect primarily subcortical events.

It is very unlikely that Pattern A represents activity initiated at the apical dendrites of pyramidal cells. However, the depth distribution of potential in Pattern A is compatible with two possible modes of activation of pyramidal cells. Since the initial sink in this pattern develops in the third and fourth layers, it may represent activity either 1) at the basal dendrites and cell bodies of the third and fourth layer pyramidal cells or 2) on the lower part of the apical dendritic shafts of the fifth layer pyramids. If it is accepted that most cortical spikes recorded with wire electrodes represent the all-or-none discharges of the cell body or axon hillock, the data on unitary activity offers greater support for the first possibility. It was the unitary activity in the third and fourth layers which was most precisely correlated temporally with the relayed pyramidal volley and with the time course of the slow potential sink. The fifth layer unitary spikes often occurred at time periods somewhat later than these two events.

Within the immediate region of the cell bodies of pyramidal cells there are two possible sites of synaptic activation: the cell body itself or the basal dendrites.* The similarity of Pattern A to that of the primary response favors the possibility that Pattern A may also involve pericorpuscular activation of pyramidal cells through the agency of Golgi type II cells. In this case, the more prolonged time course of Pattern A must be explained on the basis of more dispersed presynaptic events, i.e. either the afferent volley or the star-shaped interneurons.

In consideration of synapses on basal dendrites, there is no *a priori* reason for discounting the possibility that many functional

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*It deserves to be mentioned that there is till doubt in the minds of some anatomists about whether there are actually any cortical dendritic synapses (69).

parallels exist between apical and basal dendrites. In a recent statistical study by Sholl (68), these two classes of cortical dendrites were treated as separate systems and were compared on the basis of branching, length and opportunities for synaptic contact. Both systems of dendrites converge around a focal point; the bifurcation of the shaft of the main apical dendrite in the case of the apical system and the cell body in the case of the basal system. Eccles (35) has recently suggested that dendritic post-synaptic potentials might be capable of initiating all-or-none propagated responses at these two foci. The existence of propagated spike responses in the main apical dendritic shaft of hippocampal pyramidal cells has recently been demonstrated (27, 36).

In view of the current speculation about dendritic function, it is appropriate to suggest not only that the early phase of Pattern A is a manifestation of basal dendritic potentials but that the bursts of unitary spikes associated with this pattern represent the discharges of some central trigger zone in the region of the cell body which is being driven electrotonically by basal dendritic sinks. This is different from the role traditionally assigned to apical dendritic potentials as regulators of cell body excitability (22, 40). The difference in the function of apical and basal dendrites may be primarily dependent upon the relative spike thresholds of the foci of these two dendritic systems. Perhaps, by virtue of a lower spike threshold, the trigger zone at the center of the basal dendritic system is more apt to respond with compact trains of spikes to prolonged dendritic catelectrotonus than is the focus at the main apical bifurcation.

Apart from the synaptic activation of basal dendrites, ephaptic influences might also control these structures to some degree. Adrian (2, 4) has stressed the possible role of ephaptic influences in synchronizing the activity in many neurons which individually have the propensity for spontaneous rhythmic firing. Overlapping dendritic fields might play a role in this process, and it is not inconceivable that the interdigitations of basal dendrites might play a part in synchronizing the spontaneous type I spindles which appear to be related to activity in basal cellular structures.

SIGNIFICANCE OF THE EXPERIMENTS

The results of the present study suggest that many of these 8-12/sec. waves represent algebraic summations of at least two basic patterns. This supposition offers a possible explanation for many of the disparities, often at the observational level, which have appeared in the literature. First, the question of whether the spindle waves are more closely related to recruiting or augmenting responses may now be re-evaluated in the light of the observation that some spindles seem to fit Pattern A more closely and others Pattern B. The former then are "augmenting-like" spindles and the latter, "recruiting-like" spindles. The fact that changes in cortico-spinal responsiveness associated with spindling are almost identical with those occurring during augmentation (19) is consistent with the presence of Pattern A in both of these processes. (It will be remembered that, in general, Pattern A is accompanied by more highly synchronized firing of cortical units.) However, the fact that at *some* recording sites, spindle waves are predominantly representative of Pattern B is consistent with the repeated observations by a number of workers which have led to the equation of recruitment with spindling. The failure of Brookhart and Zanchetti (19) to detect the presence of "recruiting-like" spindles may have been due to a sampling error. In their experiments, the cortical testing shocks were triggered by the first large wave in a burst. Therefore, the large early waves in the burst were sampled in preference to the smaller later waves in the waning phase of the train. The present experiments showed that the early waves in the burst more often contained Pattern A (type I spindles) then the later waves. Although one must be cautious in transposing results in the cerveau isolé to those which are found in anesthetized preparations, it may be that interaction studies in which surface or transcortical leads have been used (29, 56) tend to emphasize the common elements in recruiting and spindling because the "augmenting-like" elements in the latter are often only apparent in the middle cortical layers.

The generally accepted notion that the waves which comprise the EEG are predominantly changes taking place in apical dendrites (25, 26) demands modification in view of the results presented here. The presence of large sinks in the third and fourth layers strongly argues for the equal participation of more basal structures although the waves may still be primarily dendritic in origin. It is suggested that the specific as well as the unspecific system may participate in the spindling mechanism to the degree that one is justified in saying that the spindling process is a very general affair and in fact that probably most of the thalamus spindles. Such a seemingly extravagant statement is not out of keeping with the results presented by Lindsley, Bowdan and Magoun (49).

And finally, it would appear mandatory that future students of electrocortical phenomena take cognizance of the fact that at least two basically different forms of cortical response may be involved in the production of what appear to be similar surface potential changes.

SUMMARY

1. Electrocortical augmenting, recruiting and spindle waves have been recorded at measured depths within the sensori-motor cortex of cats using fine wire and glass microelectrodes.

2. Each of these three waveforms has been described in terms of the slow potential changes which were recorded at different cortical depths and in terms of the temporal distribution of the associated unitary activity in the middle cortical layers.

3. Two basic depth-time-potential <u>patterns</u> have been identified in these three waveforms. These two patterns have been designated as Pattern A and Pattern B, and both have been described in terms of the common electrical characteristics which they exhibited whenever they have appeared in the three different waveforms. The interpretation of the neural mechanisms underlying the production of these two patterns has been discussed at length.

4. Pattern A clearly predominates in augmenting responses and Pattern B clearly predominates in recruiting responses. In spindling preparations, waves may be detected in which either Pattern A or Pattern B predominates. However, most spindle waves appear to represent a mixture of these two patterns.

5. It is concluded that future investigators of cortical augmenting, recruiting or spindle waves must take cognizance of the fact that what appear to be similar surface potential changes may be produced by at least two basically different forms of cortical response, as revealed by recordings made within the cortex.

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