SPATIAL PERIODICITIES

IN

SURFACE-NEGATIVE RESPONSE

TRANSMISSION

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ABSTRACT

The relationship between peak latency (time interval from the beginning of the stimulus artifact to the peak of the negative-going wave) of the surface-negative response and the recording distance from the site of stimulus was determined in nine experiments on cats' cerebral cortex. Seven of these experiments were done on neuronally isolated slabs and two on the intact cortex. The responses were recorded at very small distance intervals and peak latency measurements were made from averaged responses. Each averaged response was obtained from 60 to 80 responses recorded at a single point on the cortex and summed by an average response computer. Three general types of curve describing the relationship between peak latency and recording distance were obtained:

(I) Curves made up of successive S-shaped components.

(II) Curves which have a rather long segment which is relatively flat.

(III) Curves which are almost completely linear throughout.

Each type of curve contained periodic inflections which suggest the existence of spatially periodic structures in cats' cerebral cortex. The spatial periodicity of these structures has a value of about 2-3 mm. Some of the Type I and Type II curves had regions where peak latency actually decreased with an increase in recording distance.

A passive resistance-capacitance network was constructed to mimic, in a physical model, the results obtained in the biological preparation. The network finally arrived at produced results that fit the biological data somewhat better than did the straight line of best-fit for that data. A new theory, drawing on the biological data and on

mechanisms implied by the model, is proposed to explain the results obtained from this study. It postulates the existence of two major pathways for the surface-negative response. One of these is a surface pathway while the other is a deeper and faster conducting pathway. The lower pathway sends up branches which meet with the surface pathway at regular spatial intervals. Both pathways are hypothesized to be dendritic in nature and to contain electrotonic junctions which extend the two pathways to distances of 15 mm and greater. The results obtained from the biological preparation and from the model suggest that the membrane time constant of cortical dendrites in the cat is in the order of 5 msec and that the faster conducting pathway contains dendritic fibres whose mean diameter is four times the mean diameter of such fibres in the slower pathway.

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I. INTRODUCTION

The surface-negative response has been extensively studied and reported on ever since it was first delineated by Adrian in 1936. Notwithstanding, the rather large volume of research devoted to this response has not yet dispelled completely our ignorance of the elements involved in its production and transmission. A number of theories (which will be discussed in the following section) have been advanced, but none of these is supported by sufficient experimental evidence to establish it conclusively as the uniquely correct one.

The purpose of the study undertaken in this thesis was to seek a better understanding of how the surface-negative response is produced and transmitted laterally along the cerebral cortex. Since presently-available techniques do not permit the tracing out of its pathway from fibre to fibre or from cell to cell, resort was had in trying to extract information carried in the actual waveform of the surface-negative response. It was decided to concentrate on one feature of this information, namely the peak latency of the response. This parameter was defined, for the purposes of measurement, as the time interval from the beginning of the stimulus artifact to the peak of the negative-going wave.

It had been noted in this laboratory (Pinsky, 1967) that the shape of the surface-negative response recorded at different distances from the site of stimulation bore a marked resemblance to the shape of transient waveforms which may be recorded at different sections of a resistance-capacitance (RC) model of a dendritic fibre. The resemblance of the two sets of responses, one biological, the other derived from a physical model, led to the suggestion (Pinsky, 1967) that the surface-

negative response may be produced regeneratively in apical dendrites at the site of stimulation and then conducted passively and decrementally along these fibres through the molecular layer of the cerebral cortex. Details of both the model and its biological counterpart are provided in the body of this thesis.

An interesting property of the fibre model was noted when it was found that the peak latency of the transient waveform plotted against the number of RC-sections between the point of recording and the input terminals of the model yielded an S-shaped curve (see Fig. 19). This observation permitted the theory put forward by Pinsky to be tested by examining the spread of surface-negative responses over the long axis of a neuronally-isolated slab of cerebral cortex. If the theory were correct, then a plot of surface-negative response peak latency vs. distance from the stimulated site should be seen to yield an S-shaped curve, with the top of the "S" occurring at the terminating point of the apical dendrites which were transmitting the response. A preliminary experiment on an isolated cortical slab did in fact show an S-shaped relationship between peak latency and stimulus-recording distance, with the top of the "S" occurring in the region between 8 mm and 10 mm from the stimulated site (Pinsky, 1967). However, too few data points were available from these first observations to permit a precise evaluation of the true nature of the curve relating the two variables.

The work presented in this thesis was originally intended to see just what type of curve does relate the peak latency of the surface-negative response to recording distance. One of the first experiments in this study happened to be done on intact visual cortex, and this gave a curve of peak latency vs. distance which appeared to be composed

of two successive S-shaped curves instead of the single S-shaped curve observed by Pinsky. It was then decided to see whether this result could be duplicated. Techniques were developed (see METHODS) to enable peak latency measurements to be made very accurately and to be obtained at very small distance intervals. It was felt that if peak latency measurements could be made with sufficient accuracy, and if a high enough resolution in distance intervals could be achieved, any deviations (such as that seen in the experiment just mentioned) from the results expected for a simple conduction system should show up in the graph of peak latency vs. distance.

The evidence which accrued from the present studies of peak latency vs. recording distance suggested a new theory to account for the production and transmission of surface-negative responses. Also, as a means of testing some consequences of this new theory, a resistance-capacitance model of certain postulated cortical structures was built, using as structural elements the electrical analogues of dendritic fibres. Both the biological theory and the principles underlying the choice of elements in the model are treated in the DISCUSSION section of this thesis.

II. HISTORICAL REVIEW

A. PREAMBLE

Direct electrical stimulation of the cerebral cortex has been used by a number of investigators (e.g. Adrian, 1936; Burns, 1950; Purpura and Grundfest, 1956; Brooks and Enger, 1959; Frank and Pinsky, 1964; Ochs and Suzuki, 1965) over the past 45 years as a method of studying mechanisms of brain function. The first attempt to record an electrical response produced by this kind of stimulation appears to be that of Bartley and Bishop (1933), who worked on rabbit cerebral cortex. They were for the most part unsuccessful in this endeavor. However, they reported that in one instance they observed a response with a duration slightly shorter than that of spontaneous positive waves which were occurring at a frequency of about three per second. They gave no record or clear description of this response so it is virtually impossible to state what they had observed. An interesting aspect of their study, though, is that they did their work on partially isolated areas of cortex, formed by making an incision around three sides of an area of cortex and then lifting this area upon a small metal platform which served as an earthed lead. The pial blood supply was left intact. This preparation is remarkable in that similar methods for isolating portions of cerebral cortex from neuronal connections with other parts of the brain were not developed until more than fifteen years later when Burns (1949) and Kristiansen and Courtois (1949) independently, and almost simultaneously, worked out techniques for cortical isolation.

The first clear report of changes in electrical potential recorded at the surface of the cerebral cortex in response to direct stimulation (applied at the pial surface) was presented by Adrian (1936) who carried out his study on the intact cerebral cortex of rabbits, cats,

and monkeys. He found two types of response, which he referred to as the superficial response and the deep response. The superficial response was a negative-going wave, while the deep response was a positive-going wave that required a shock two to three times the threshold strength needed to produce the former.

Adrian described the superficial response as a monophasic potential change lasting about 10 msec and having a maximum value of 100 μV. He could elicit it from any cortical area in cats, rabbits, and monkeys. The response had a definite threshold and was not altered "in any way" (p. 133, Adrian, 1936) as stimulation proceeded at rates as high as 8 per second. The amplitude of this response became larger with increasing stimulus strengths but its time relations (i.e., latency, width) altered very little.

Adrian noted the great resistance of the superficial response to anaesthetics and to anoxia. Increasing the depth of anaesthesia tended to raise the threshold but the response could still be elicited. He was able to get a response for as long as 5 minutes after complete circulatory failure in the cat preparation.

B. THE SURFACE-NEGATIVE RESPONSE FROM ADRIAN'S EARLY WORK TO PRESENT-DAY INVESTIGATIONS

The superficial response has been renamed several times since Adrian's early work. It is referred to as the "first component" by Chang, the "negative wave direct cortical response" (N-wave DCR) by Ochs, and as the "surface-negative response" by Burns. While the names are different, it may be assumed, for the sake of convenience, that the response originated in the same cortical elements for each of these

investigators. However, differences in techniques and animal species no doubt would create some dissimilarities in the responses produced. For the sake of convenience, the superficial response will be henceforth referred to in this text as the surface-negative response.

Burns (1950) found that the surface-negative response had a definite threshold and also that the response increased in magnitude with an increase in stimulus strength up to 5 times the threshold value, after which there was no further increase in response size. Brooks and Enger (1959) gave a mean value of 6 times threshold stimulus strength to produce a maximal response. They also found that upon supramaximal stimulation the response would be somewhat depressed within about 2-3 mm of the stimulated point, and that this depression was not noticeable at greater recording distances.

There is some disagreement among various authors in their measurement of the response duration. Adrian gave a value of 10 msec, Burns (1950) a value of 50 msec which he later reduced to 20 to 30 msec (1951), and Ochs (1956) gave a value of 10-20 msec.

Even more controversial are estimates of the farthest distance from the stimulating electrodes at which the response can be recorded. Adrian (1936) reported 4 mm, Chang (1951) 5 mm and Burns (1950) 10 mm. The graphs of Brooks and Enger (1959) indicate that they recorded the response as far as 14 mm from the stimulating electrodes.

Conduction velocity also has been reported differently by the various authors. For the cat, Chang (1951) gave a value of 1 m/sec while Burns (1950) said 2 m/sec. For the monkey, Chang found only 0.6 to 0.7 m/sec while Rosenblueth and Cannon (1942) reported 3 m/sec. Suzuki and Ochs (1964) gave a value of 0.5 to 1.0 m/sec for the rabbit.

Many of the discrepancies mentioned in the foregoing are most likely the result of differences in the experimental techniques used by the investigators. For instance, Chang's stimulating electrodes were positioned a mere 0.5 mm apart while those of Rosenblueth and Cannon were 3 to 8 mm apart. Also, later authors recorded potential differences between an electrode on the area of interest and an electrode placed far enough away to make it "indifferent" with respect to that area. Earlier authors, such as Adrian or Rosenblueth and Cannon, had recorded the potential differences between electrodes placed only a few millimeters apart. Methods of anaesthesia differed too. Chang, Ochs, and Adrian, for the most part, used barbiturates. Rosenblueth and Cannon used chloralose anaesthesia and, in some of his studies, so did Burns. In addition, the latter did his work on isolated cortical slabs. When one takes into account all these differences, it is surprising that there was any agreement at all among the different authors.

There is agreement, however, on the high degree of resistance shown by the surface-negative response to various general anaesthetics and to anoxia. Adrian's observations on this point have already been mentioned in the previous subsection. Chang (1951) reported that it took 1.5 minutes of nitrogen administration to effect complete failure of the response. The effects would start to be reversed about 11 minutes later if oxygen was restored shortly after complete stoppage of cortical activity. Burns (1951) states that ethyl ether, chloroform, chloralose, pentothal and nembutal, given in quantities estimated to produce surgical anaesthesia in a normal cat of the same weight, had no effect on the surface-negative response. The same held true for anoxia produced either by nitrogen administration or by restricting the main arterial supplies with clamps.

Of all the aspects of studies on the surface-negative response, perhaps the one most beset with conflicting and contradictory reports is that which has to do with cuts. Chang (1951) stated that he was unable to abolish the surface-negative response by a 1 mm incision between the stimulating and recording electrodes (4 mm apart), but that a 3 mm cut did prevent its transmission. However, Burns and Grafstein (1952) found that a cut only 0.13 mm deep was enough to abolish the response. Ochs (1956),on the other hand, found that the response could be obtained with little change even after a cut which severed all of the cortical layers. He found that it required a cut through both the cortex and underlying subcortical fibres to eliminate the response. Although this study was done on rabbits, Ochs and Booker (1961) reported that the same results obtained in both cats and rabbits. Then, in 1965, Ochs and Suzuki found that in preparations in which the only intact layer was the molecular layer (i.e., all other cortical layers and some underlying white matter were cut), the surface-negative response had the same latency as in the intact cortex, and travelled the same distance with stimulus strengths similar to those used in the intact preparation. Ochs and Clark (1968a) concluded from this that axons in the molecular layer are the laterally transmitting elements and that with respect to the study by Ochs and Booker in 1961, where a deeper lateral spread was found with complete cortical cuts, "it appears that transmission was effected by a relatively few superficial fibres in the molecular layer escaping the cutting procedure" (p. 101, Ochs and Clark, 1968a).

C. THEORIES OF SURFACE-NEGATIVE RESPONSE ELECTROGENESIS AND TRANSMISSION

Theories as to what might be the elements involved in the production and transmission of the surface-negative response go back as far as 1936 with Adrian. He believed that the potential gradients which he observed with his particular recording technique might well be produced by elements extending parallel to the surface and activated in the region of the stimulating electrodes. These elements, he thought, were more likely to be dendrites than nerve fibres, "for the potential changes are too slow to be the result of nerve action potentials of the usual kind" (p.136, Adrian, 1936). Adrian considered as likely candidates either the horizontal cells of Cajal with their laterally spreading dendrites, or else the superficial branches from the apical dendrites of pyramidal cells.

(1) Burns and Grafstein

Burns (1950) suggested that the stimulus used to produce the surface-negative response excites a random arrangement of cell processes which lie close to the cortical surface just under the stimulating electrodes. The response then spreads radially outward along the conductors which are beneath the stimulating electrodes and which extend to a maximum distance of 10 mm. This theory holds that synapses are probably not involved because of the rapid attenuation of the response with increasing distance from the stimulating electrodes. Burns plotted the amplitude of the surface-negative response against the reciprocal of the recording distance from the stimulated point. His results from experiments on three cats gave a straight-line relationship

and Burns felt that this relationship was consistent with the view that the conductors involved could be 1 cm long and be randomly distributed in a superficial cortical plane.

Burns and Grafstein (1952) added to this theory from their study of the distribution of surface-negative response potential with respect to the depth of a recording microelectrode beneath the pial surface. They found that the surface-negative response was recorded as a positive-going wave from about 0.6 to 3.0 mm beneath the pial surface and had a maximum positive value at about 0.75 mm beneath the pial surface. Such a distribution of potential suggested to these investigators that the elements responsible for the surface-negative response have limbs which run radially downward through the grey matter and even below it. These "limbs" were visualized by the authors as being axons which stretch from the bottom of the cortical slab to the pial surface where they divide to give rise to long branching filaments responsible for the tangential spread of the response. Thus, during the surface-negative response, the upper part of these neurons is depolarized and becomes a "sink" of current flow whose "source" is from the resting radial extensions.

Using a monopolar stimulating microelectrode, Burns and Grafstein found two peaks of excitability for the surface-negative response, one occurring at a depth of 0.4 mm and the other at a depth of 2.0 mm below the pial surface. They suggested that this result indicates the existence of two families of branches on the main limb, one near the surface and the other at a depth of 2.0 mm. The authors postulated that branches would make the stimulating current more effective since they should increase the number of neurons which could be affected by the stimulating current. The upper branches are

consistent with the surface conductors previously mentioned. The lower peak of excitability was taken to be the result of stimulating the cell bodies of the responsible neurones, or alternatively, the result of a possible second family of branches occurring at 2.0 mm depth.

Further support for the surface conductor theory of Burns and Grafstein came from their finding that a cut which extended from the pial surface to a depth of only 0.13 mm was enough to abolish lateral transmission of the response.

(2) Chang

Chang (1951) is of the opinion that the horizontally-running branches of apical dendrites belonging to pyramidal cells are directly stimulated by a weak stimulus current and produce the surface-negative response as seen by the recording electrodes. With stronger stimulation, the "impulses" which arrive at the recording electrode arise not only from the point of stimulation but also from deeper layers of the cortex, "presumably from the bifurcating point of the apical dendrites and from the cell bodies of the pyramids" (p. 7, Chang, 1951). The pyramidal cell bodies are presumed by Chang to have been indirectly excited via smaller cells and fibres which lie in the upper layers and are excited directly by the stimulus current. The reason for his postulating the arrival of impulses from deeper layers was that upon stronger stimulation a positive-going wave is observed to occur before the surface-negative response, and, on the basis of volume conductor theory, this positivity is indicative of a negative sink in the deeper layers.

Chang found that an incision 1 mm deep into the cortex between the stimulating and recording electrodes failed to abolish the response. This he interpreted as ruling out the involvement, to any great degree, of the horizontally running Cajal cells. However, the cut did cause the surface-negative response to arrive later, to be reduced in size and to have a more pronounced prepositive wave. Chang, therefore, suggested that not only does lateral transmission take place along the horizontally coursing branches of apical dendrites but also (as in the case of the cut) through a deeper route for which he proposes two likely candidates:

(1) the bifurcating point of the apical dendrites,

(2) pyramidal cell bodies in the second and third layers which could be indirectly excited as mentioned above.

Thus, Chang was not too concerned over the knowledge that "the horizontal course of the apical dendrites is not more than 2 mm in one direction" (p. 9, Chang, 1951) because this length is doubled when it is considered that two such sets of branches are connected to the same shaft. This postulate would have been adequate to suit Chang's observations, since he found that he could not record the surface-negative response much farther than 5 mm away from the stimulated point.

(3) Eccles

Eccles (1951) postulated the stimulated and transmitting elements involved in the surface-negative response to be nerve fibres (axons of horizontal cells or afferent fibres from the thalamus) of the

same type and distribution as those described in Burns' 1950 paper. However, he did not believe that these fibres could give rise to the surface-negative response as seen by the recording electrodes. Rather, he postulated this response to be the result of synaptic potentials initiated in the apical dendrites of pyramidal cells by presynaptic activity in the horizontal fibres. Eccles suggested that each of these fibres would contribute synapses to any apical dendrites it met as it travelled along in the molecular layer. Hence, the surface-negative response would decrement as it travels away from the stimulated point because, while near the stimulated point there are both long and short fibres, farther away only the longer ones remain.

Purpura and Grundfest (1956) support Eccles' postsynaptic potential theory on the basis of their observations of the effects of d-tubocurarine on the surface-negative response. They found that i.v. injection of 3 mg/kg d-tubocurarine diminished after 50 sec, and eliminated after 70 sec, the surface-negative response in the cat's suprasylvian gyrus. These effects were reversible. They postulated that d-tubocurarine was exerting its effects by blocking synaptic transmission at the apical dendrites. Their work has been questioned by Ochs (1959) on the basis of his finding that the effects of low blood pressure on the surface-negative response were similar to those produced by d-tubocurarine. Doubtless, the histamine-releasing ability of d-tubocurarine could cause a profound fall of blood pressure in the experimental animal.

(4) Brooks and Enger

Brooks and Enger (1959) distinguished between slowly-conducted surface-negative potentials and rapidly-conducted ones on the basis of the "reinforced" responses which they observed (see next subsection). They suggested that the slowly-conducted surface-negative potentials are due either to direct or to synaptic excitation of pyramidal cells. The responses with the faster conduction velocity were proposed to be initiated "synaptically on other pyramidal cells after fast conduction at about 10 m/sec in tangential fibres" (p. 761, Brooks and Enger, 1959). Brooks and Enger suggest that these "tangential fibres" could be corticocortical axons, recurrent collaterals of pyramidal cells, axons of stellate cells, or a mixture of all of these.

(5) Ochs, Suzuki and Clark

The theory presented by Ochs and Suzuki (1965) is somewhat similar to that of Eccles (1951). They proposed the laterally transmitting elements to be axons which travel in the molecular layer and which have "a divergent type of synapse distribution on a large number of apical dendrites in the responding region." (p. 105, Ochs and Clark, 1968a). Two possible candidates suggested by Ochs and Suzuki (1965) for the laterally-travelling axons are the recurrent collaterals of pyramidal cells and axons of stellate cells. They exclude afferent axons on the basis of a study which they did on chronic cortical islands where they found that transmission was still present even after degeneration of afferent terminations (Suzuki and Ochs, 1964). It should be noted, however, that in the chronic isolated island study,

the dimensions of the isolated area were only 3 x 5 mm, and the investigators did not attempt to record the response any further than 3 mm from the stimulated site.

Ochs and Suzuki (1965) proposed that the surface-negative response as recorded by surface electrodes is the response of apical dendrites to synaptic excitation by the laterally travelling axons. The resulting responses in the apical dendrites are considered to be of an active type (Ochs and Clark, 1968b) on the basis of temporal-spatial interaction studies where there was noted a period of occlusive interaction between responses initiated at different sites. This period of occlusion was found to last from 20-40 msec (Ochs and Booker, 1961). A similar occlusive interaction has been reported by Frank and Pinsky (1964). Ochs and Clark (1968b) speculated that such occlusive interaction is indicative of "refractoriness in the common set of responding dendrites" (p. 114, Ochs and Clark, 1968b) and that, hence, the responses themselves must be of the active type in order for refractoriness to be involved.

Further evidence for their views is taken from their observations on the effect of topically-applied gamma-amino butyric acid (GABA). Using a preparation in which only the molecular layer remained intact between the stimulating and recording electrodes they found that 1% GABA placed on the stimulated and conducting sites failed to block the surface-negative response. However, when placed on the responding site (i.e., the recording location) the surface-negative response was abolished. Assuming the GABA depresses apical dendrites (Bindman, Lippold and Redfearn, 1962), but not axons, the results suggest that the surface-negative response is a postsynaptic response, generated

in apical dendrites by axons which travel from the stimulated site via the molecular layer.

In addition to the axons travelling in the molecular layer, Ochs and Suzuki (1965) suggested the existence of either an intracortical or a corticocortical pathway to account for their observation that transmission of the surface-negative response occurred in preparations where the superficial cortical layers were cut and also, to a lesser extent, in preparations with complete cortical cuts. A corticocortical pathway was considered by them to be involved in transmitting the response to distances beyond 14 mm as seen in the graphs of Brooks and Enger (1959). However, Ochs and Clark (1968a), on the basis of their studies with tetrodotoxin, are of the opinion that these deeper pathways are nonexistent. They found that even in intact cortex, a drop of tetrodotoxin (10^{-5} g/ml) placed between stimulated and recording sites completely blocked conduction of the surface-negative response within a few minutes of application. This concentration of tetrodotoxin was 20 times that which Frank and Pinsky (1966) used to block the surface-positive response.

(6) Pinsky

Pinsky (1967) was struck by the similarities between surface-negative response waveforms at various distances from the site of stimulation on the brain and those recorded at various points along a resistance-capacitance model of a dendritic fibre (see DISCUSSION). As a result he suggested that stimulating the surface of the cerebral cortex to produce the surface-negative response causes regenerative activity to occur in apical dendrites at the site of stimulation. This activity then spreads electrotonically along these apical dendrites which course horizontally through the molecular layer. Like Chang

(1951), Pinsky considered the response to travel down one set of dendrite branches to the apical shaft of a pyramidal cell, and then up to the surface layer again through the other set of branches linked to the apical shaft at its bifurcating point. However, since this would likely not provide a pathway long enough to conduct the response 10 mm or farther, Pinsky proposed that electrotonic coupling between apical dendrites was involved. Impedance-matched electrotonic synapses would permit passive conduction of the response from fibre to fibre without distorting the shape of the response from that which would be expected were a single long dendritic fibre involved. Neurohumoral synapses, on the other hand, would not be consistent with the progressive flattening out of the surface-negative response at farther and farther recording distances.

D. HISTORICAL PRECEDENT FOR THE SUBJECT MATTER OF THIS THESIS

Chang (1951) was the first to study the relationship between latency and recording distance for the surface-negative response. He found that latency varied linearly with conduction distance for the surface-negative response in both cat and monkey. However, as Eccles (1951) points out, Chang measured his conduction times to the point of reversal from the positive deflection of a prepositive wave, which occurred just before his negative response, to the initial negative deflection of the surface-negative response. This parameter is difficult to measure accurately, since it is hard to detect exactly when the reversal in potential has occurred. Also, the parameter is greatly affected by the presence of the prepositive wave which may or

may not be associated with surface-negative response conduction times. Peak latency is a more precisely defined parameter. Hence, it was used by subsequent investigators (e.g., Brooks and Enger, 1959; Pinsky, 1967) to study latency vs. distance relationship in surface-negative response transmission, and the parameter which Chang used has been largely discarded.

Brooks and Enger (1959) found in cats that with weak stimulation the surface-negative response amplitude decayed in height linearly with an increase in stimulus-recording distance, and travelled up to 3 to 6 mm from the stimulating electrodes. With stronger stimulation, the response again declined in height up to about 5 or 6 mm away from the stimulating electrodes but then, from 6 to 10 mm, underwent an increase in height and then entered a new region of decline. Brooks and Enger called this phenomenon "reinitiation" if the response had declined to zero before reaching the area of renewed strength. If it had not declined completely to zero the phenomenon was termed "reinforcement". Supramaximal stimulation produced reinforcement at both 5 mm and at 10 mm.

The feature of these "reinforced" or "reinitiated" responses which is most pertinent to this thesis is that Brooks and Enger report them as "occurring 1 to 3 msec earlier than would be expected for simple conduction" (p. 761, Brooks and Enger, 1959).

Pinsky (1967) did a preliminary experiment to determine the relationship between peak latency of the surface-negative response and the distance from the site of stimulus. As mentioned in the INTRODUCTION he obtained an S-shaped curve.

III. METHODS

A. PREPARATION OF ANIMAL

Cats, weighing 2-5 kg, of both sexes were used. Ether anaesthesia was induced by placing the animal in a closed wooden box, slightly larger than 1 cubic foot in volume and having a glass window for observation. The box also had a small upper chamber separated from its main chamber by a wire gauze. A cotton pad soaked with ether (diethyl ether, Squibb) was introduced into this upper chamber immediately after the animal had been put in the main chamber. When surgical anaesthesia had been attained the cat was transferred from the box to the operating table and, until the trachea could be cannulated, anaesthesia was maintained by placing a wire-gauge cone, containing an ether-soaked cotton wad, over the animal's face. The trachea was then cannulated and connected by a short rubber tube to a variable-bypass ether bottle. The right or left femoral vein was cannulated to permit the injection of drugs and fluids when such were deemed necessary. A Czermak holder (Palmer) was used to position and steady the animal's head for surgery. The fur on top of the cat's head was wetted down with saline before a midline incision was made through the scalp. The scalp was separated from the right and left temporal muscles, and both temporal muscles were reflected from the skull. They were then clamped with hemostats as far laterally as possible and the clamped-off portions of muscle were removed and discarded. Decerebration took place next. To accomplish this, a high-speed dental burr was used to cut away a small rectangle of bone (about 10 x 4 mm) just caudal to the postero-superior margin of the tentorium cerebelli. The length of the rectangle

ran parallel to this margin. Bone wax (beeswax with 1% phenol) was employed to reduce the bleeding which invariably occurred from the skull during the drilling procedure, and the debris produced by the drill was flushed away with warm saline (37°C). After the dura had been exposed it was slit along the length of the rectangle witha #11 scalpel blade. A wire-loop electrocautery knife, constructed out of 0.025-inch diameter stainless steel wire, was used to make the decerebration cut. The loop of the knife was about 5 mm in diameter and was continuous with a wire stem extending 2.5 cm out of an acrylic handle. Decerebration was accomplished by inserting the loop of the knife through the slit in the dura and guiding the flat surface of the loop along the posterior surface of the tentorium cerebelli while pushing the knife through the brain stem. As soon as brain stem section was completed, the tracheal cannula was immediately transferred from the ether bottle to a rubber bellows respiratory pump (Palmer) which maintained the cat's respiration for the remainder of the experiment.

The dental burr was next used to remove a small circle of skull about 1/2 inch in diameter from the left or right parietal bone. This circle was enlarged with bone rongeurs to expose as much as possible of the cerebral hemisphere. Bleeding from the skull was checked by sealing off the offending areas with bone wax. Bone chips and blood were flushed away with warm saline (37°C) which also kept the brain surface moist. After exposure of one hemisphere was complete, a saline-soaked pad of cotton was placed on the unprotected surface and the other cerebral hemisphere was exposed in like manner. On occasion the skull over the midline between the two hemispheres was

partially removed; this procedure sometimes caused venous bleeding, necessitating the typing off of the vessels involved. The reason for removing such a large portion of the skull was to allow the brain as large an area as possible to undergo expansion should swelling occur. Use of the burr was kept to a minimum as it appeared to be a factor responsible for inducing brain swelling.

After the bone had been removed from both sides, the dura mater was cut away with a pair of very fine iris scissors to expose the pial surface. Neuronally isolated slabs of cortex were cut on the right and left suprasylvian gyri in a manner somewhat similar to the method of Burns (1950). First, a small area at the posterior end of the gyrus to be isolated was electrocauterized. The brain tissue beneath this area was removed to the depth of a few millimeters by sucking it away with a tapered glass tube attached to a water tap aspirator. Also, a small hole was aspirated to the lateral ventricle to provide an outlet should cerebrospinal fluid pressure increase. A slab of about 4 mm thickness was then cut anterior to the sink hole using the same procedure as Burns (1950). One slight modification was to cut a distinct posterior border for the slab about 2 mm anterior to the sink hole. In this way the slab produced had a well-defined rectangular boundary measuring approximately 5 mm wide and 15-20 mm long. Slabs were cut on both hemispheres to allow a choice of the healthier-looking slab for experimentation.

With the operation completed the animal was moved to the recording table and its head mounted in a stereotaxic instrument (David Kopf, #1504). The edges of the scalp were stitched around a metal ring

so that a reservoir was formed into which mineral oil at 35°C could be poured to cover the exposed brain to a depth of a few millimeters. Body temperature was maintained at about 37°C by an electric heating pad which was controlled by a rectal thermistor probe. Control of the brain's temperature was achieved by immersing into the mineral oil either an electric coil or, in later experiments, two small indicator lamps. The brain was maintained at a stable temperature in the range of 34 to 36 degrees Centigrade.

To ensure good muscle relaxation in the experimental animal, 40-80 mg/kg of Gallamine (Flaxedil, Poulenc) was injected through the cannula in the femoral vein about once every hour. The same route was used to inject an overdose of sodium-pentobarbital into the cat at the termination of the experiment.

As each experiment required up to 8 hours of uninterrupted viability, those animals which survived to the recording table but gave out before the experiment had been completed are included in the mortality figure. This turned out to be 60%.

B. CONSTRUCTION OF RECORDING ELECTRODE ASSEMBLIES

Special recording assemblies were constructed to provide sufficient resolution and accuracy in measurement of distance. These assemblies consisted of individual electrodes arranged 0.3-0.5 mm apart in a straight line. An intermediate stage of their construction is shown in Fig. 1. Lengths (approx. 5 cm) of 0.005-inch diameter silver wire, both ends of which were soldered to separate lead wires, were carefully stuck side by side on a piece of masking tape so that their

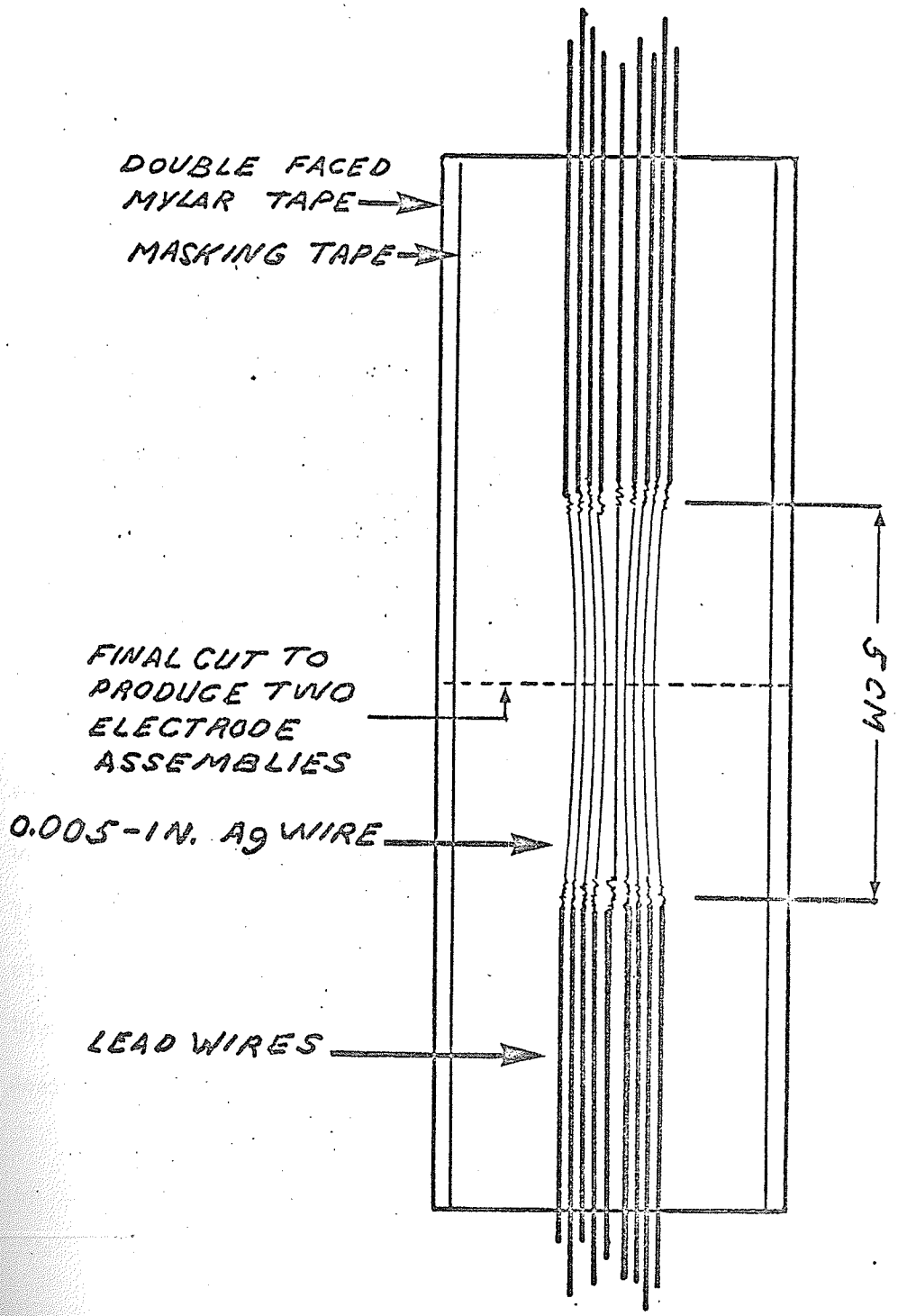

Fig. 1 INTERMEDIATE STAGE IN THE CONSTRUCTION OF A RECORDING ELECTRODE ASSEMBLY

middle portions lay within 0.3 to 0.5 mm of each other. The masking tape was held flat against the table surface by a piece of double-faced mylar tape (Nationwide Adhesive Products, Inc.). Great care was taken to ensure that the wires did not make contact with each other. A very thick coat of epoxy paint was then brushed on the surface of the silver wires and on a short portion of the lead wires at either end. A drying time of two days was allowed. The masking tape was then carefully peeled away from the mylar tape and a razor blade used to cut the silver wires in half, thus yielding two recording assemblies; these were carefully freed from the masking tape. To make the electrodes more visible a small section of epoxy paint was cut away from the electrode tips with a scalpel blade, thus leaving them to protrude from the assembly by about 0.7 mm. The electrode tips were then chlorided by immersing them in isotonic saline and passing an anodal current of about 25 microamperes per electrode through them for 15-20 minutes.

The chlorided electrode assembly was glued with Glyptal Cement (General Electric) to a 3/16-inch diameter brass rod. The leads were soldered to 24-gauge stranded vinyl-coated wires about 3 feet in length. These were in turn soldered in proper order onto a terminal strip mounted on a small wooden block. The recording amplifiers could then be coupled with clip leads to the terminal strip lugs of the desired recording electrodes.

C. STIMULATION AND RECORDING

Bipolar electrodes, constructed out of 0.010-inch platinum-10% iridium wire, were used for surface stimulation. The beaded electrode tips were arranged to lie approximately 1 mm apart on the pial surface.

Fig. 2 shows the waveforms of two Tektronix 162 waveform generators and one Tektronix 161 pulse generator which were connected together so as to give a stimulus pulse every 10 seconds. The pulse output of the driving waveform generator was attenuated 50:1 and fed through an operational amplifier (Philbrick, P35AU) into a separate channel on the tape recorder used to store the biological responses. This pulse, called the "prepulse", occurred 15 msec before the stimulus pulse and was needed in data analysis to trigger the sweep of the average response computer. In a later experiment, the prepulse was fed into all the recording channels through a "mixed" input to each operational amplifier. This was done both to reduce tape "jitter" (see below) and to provide an extra channel for data.

The stimulus pulse obtained from the Tektronix pulse generator was passed through a 1:1 transformer (Hammond 835) so as to isolate the stimulus current from ground. To minimize the duration of the stimulus artifact, the stimulus pulse used was of very short duration (50 μsec). The stimulus current was adjusted to be slightly more than that which just produces a maximal response; this enabled the response to be recorded consistently at distances of up to 14 mm from the stimulating electrodes.

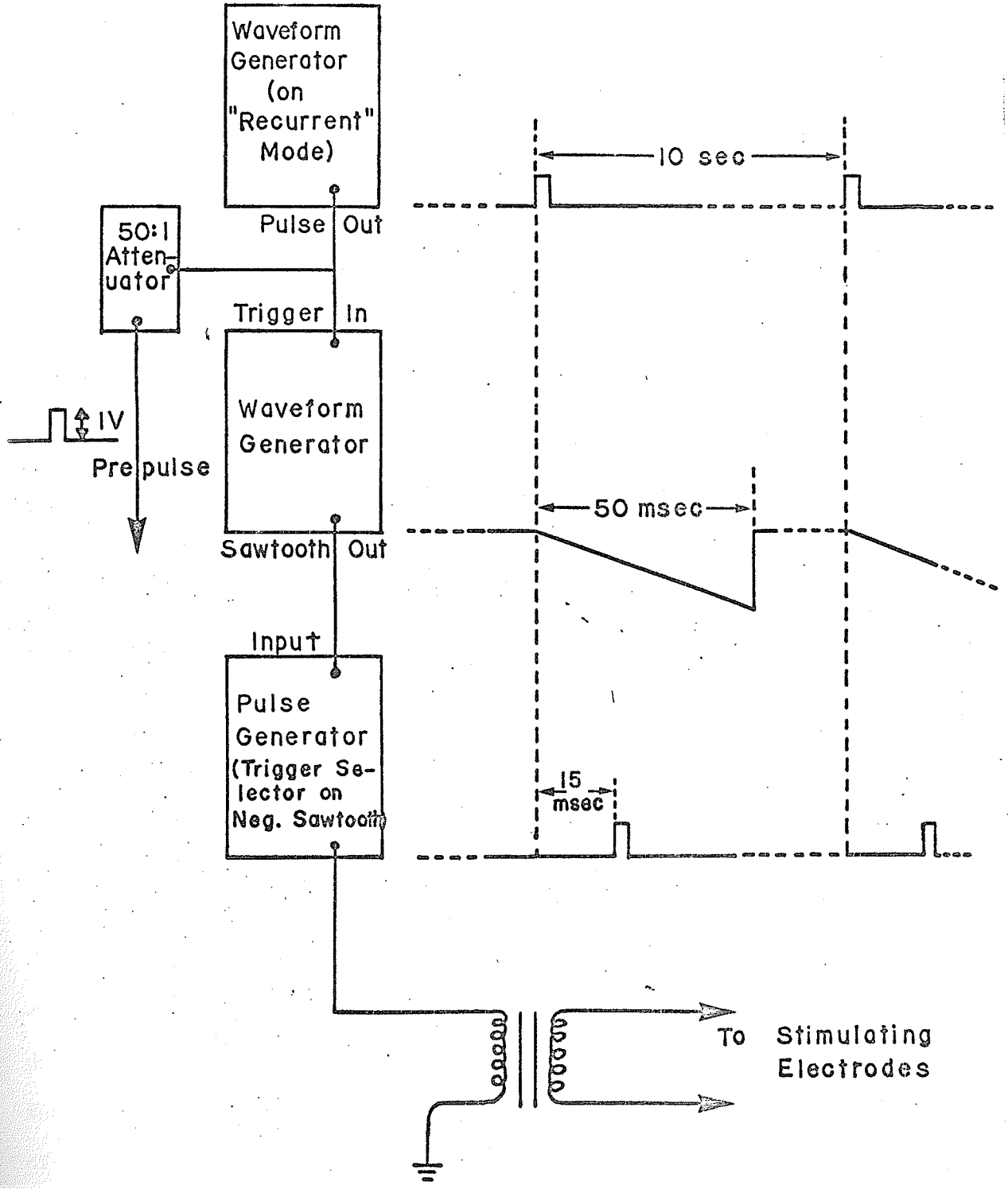

Fig. 2 ELECTRICAL ARRANGEMENT FOR STIMULATION

The stimulating and recording arrangement is illustrated in Fig. 3. The recording electrode assembly was arranged by eye to lie as close as possible to the stimulating electrodes, on the perpendicular bisector of an imaginary line joining the two beaded tips of the stimulating electrodes. This effectively minimized the shock artifact. None of the recording assemblies spanned a distance greater than a few millimeters; for this reason the assembly had to be moved to different positions on the perpendicular bisector to enable a distance of about 14 mm ultimately to be covered. The distance spanned by each position of a recording assembly is represented by horizontal black lines at the bottom of the graphs showing the relationships between peak latency and recording distance (see Figs. 9, 10 and 11). The numbers associated with these black lines on the graphs shows the order in which the various positions were assumed. Sometimes two different electrode assemblies were used at the same time, one of which was kept stationary and the other of which was moved to different positions. Such was the case in the experiments whose results are shown in Figs. 10 and 11. The black line with no number in these figures represents the stationary electrode assembly.

The electrode assemblies which assumed different positions over the course of an experiment were moved by means of a micrometer-driven hydraulic drive mechanism similar to the one described by Burns (1961) for microelectrode work. Both cylinders, however, were of approximately equal diameter thus giving a 1:1 ratio of micrometer-to-electrode movement. The purpose behind using such a mechanism was to permit easy manoeuvring of the assembly precisely into a desi location.

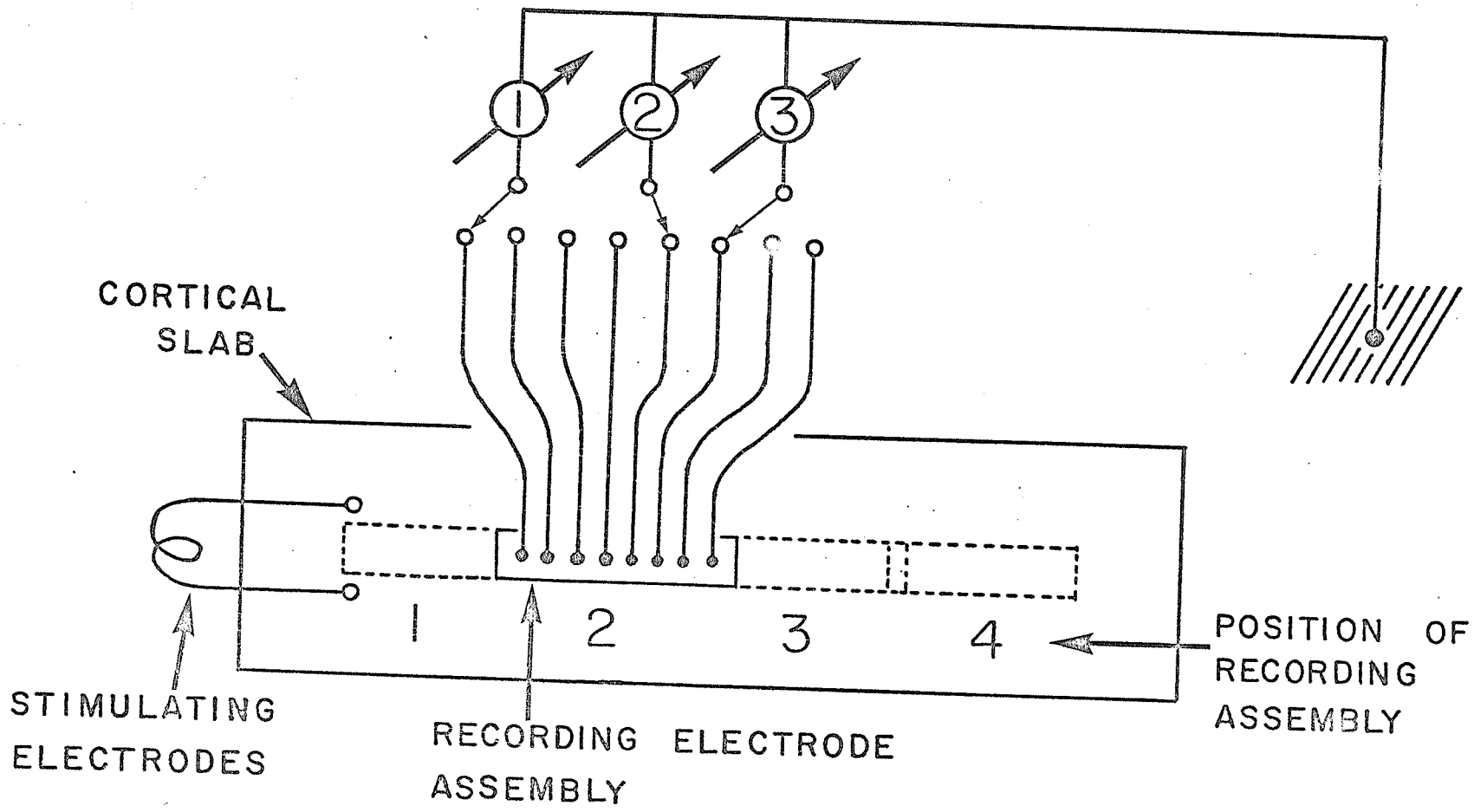

Fig. 3 Stimulus–Recording Setup

The recording electrode assembly had often to be rotated through different angles for placement on the pial surface at various recording distances in order to have the electrodes lying flat on the surface in each position. This was provided for by an angulation movement on the electrode holder to which the hydraulic drive was attached. The distance of the electrode assembly from the stimulating electrodes, for a given position, was determined by first lining up the front end of the assembly with the tips of the stimulating electrodes and then moving it to the desired recording position. The distance travelled from the stimulating electrodes to the recording position was read off the micrometer screw of the drive mechanism. The true recording distance for any one electrode in the assembly was then calculated simply by adding this distance to the distance of the individual electrode from the front end of the assembly. This latter distance was obtained outside the experiment under an optical microscope fitted with a calibrated graticule.

While interrecording electrode distance could be very accurately determined, to $\pm$ 0.08 mm, the stimulus-assembly distance was not taken to be more accurate than $\pm$ 0.5 mm due to the curvature of the pial surface and to the difficulty in lining up accurately the front end of the recording assembly with the stimulating electrodes. These errors, coupled with the error involved in trying to position the electrode assembly parallel to the perpendicular bisector previously mentioned, are probably responsible for the discontinuities seen in the curves of Figs. 9 and 10.

A silk wick electrode (in 1% agar-saline gel) was placed on the frontal bone and led off via a chlorided silver wire to serve as the common indifferent electrode for all surface recording leads.

D. SIGNAL AMPLIFICATION

All the signals were amplified by differential amplifiers (Grass, P5 and DP9B) with cathode follower inputs, and recorded on a magnetic tape recorder (Precision Instrument, PI-6200). A diagram of the recording equipment setup is provided in Fig. 4. The preamplifier time constants were set to be from 200 to 500 msec. A stage of gain was provided between the preamplifier output and the tape recorder input. This was achieved through the use of operational amplifiers (Philbrick, P35AU and P65AU) which served two other very important functions:

(1) to convert differential input into single-ended output

(2) to ensure that the output signal did not rest on any DC level other than zero with respect to ground.

These two features were necessary to meet the input requirements of the tape recorder. The output of the tape recorder was monitored on a four-trace oscilloscope system (Tektronix 502 oscilloscope coupled to two Tektronix Type CA dual-trace beam splitters). This permitted a continual check on recording system gain and linearity and, as well, on the responsiveness of the brain.

Sixty to eighty responses were obtained from any electrode before switching the preamplifier to input to another electrode. In some experiments only three preamplifiers were available; in such circumstance one electrode (henceforth, to be called the "point of reference") was left always coupled to the same amplifier while inputs of the remaining

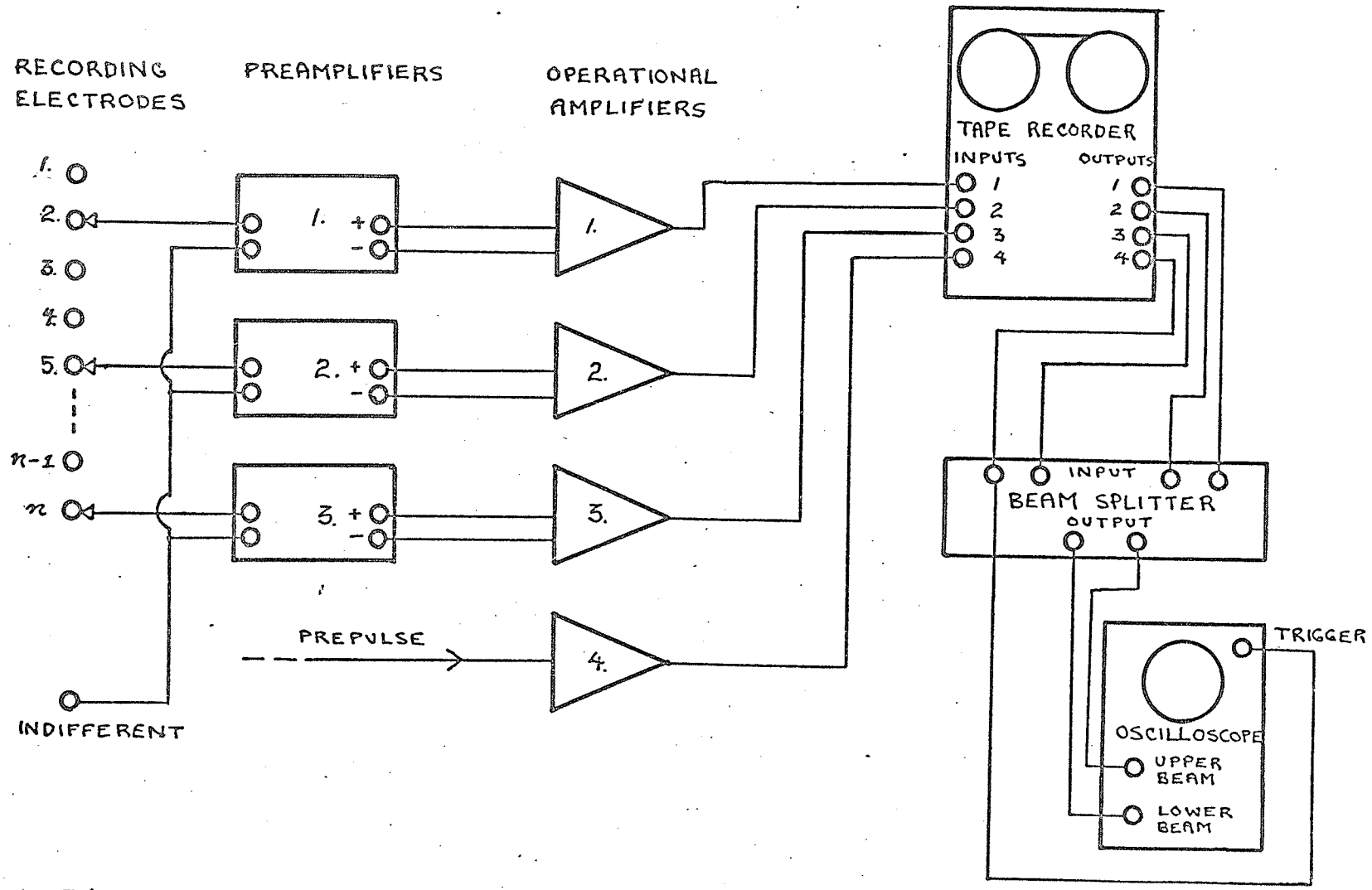

Fig. 4 ELECTRICAL ARRANGEMENT FOR RECORDING

two preamplifiers were switched around in haphazard sequence to the remaining electrodes of the recording assembly. This was done to provide continuity from one run to the next and to minimize the influence of systematic errors on the results. The need for a "point of reference" was eliminated in experiments where six preamplifiers were used. This was the case for the experiments shown in Figs. 10 and 11. In these experiments six contiguous electrodes were recorded from simultaneously for each run.

Stimuli were delivered to the preparation at the rate of one in every ten seconds. The total time required to record a complete experiment was about 8 hours.

E. ANALYSIS OF DATA

Fig. 5 gives a diagrammatic representation of the setup used to average the responses. The tape recorder channel which contained the prepulse was amplified through an operational amplifier and then fed into a Schmitt-trigger level detector circuit. For those experiments in which the prepulse was recorded on all tape recorder channels a high-pass filter circuit with a variable attenuated output was constructed for each channel and connected in series with the summing operational amplifier. A diagram of this circuit is shown in Fig. 6. The attenuator of each circuit was adjusted so that the prepulses from each channel all came out at the same amplitude. The high-pass filter attenuated most of the biological signal, allowing only the prepulse and high frequency bursts of cortical activity to get through. These prepulse signals were then fed to the operational amplifier input which served as the summing point. Thus if random high frequency activity due to spontaneous cortical bursts were to occur on any given channel

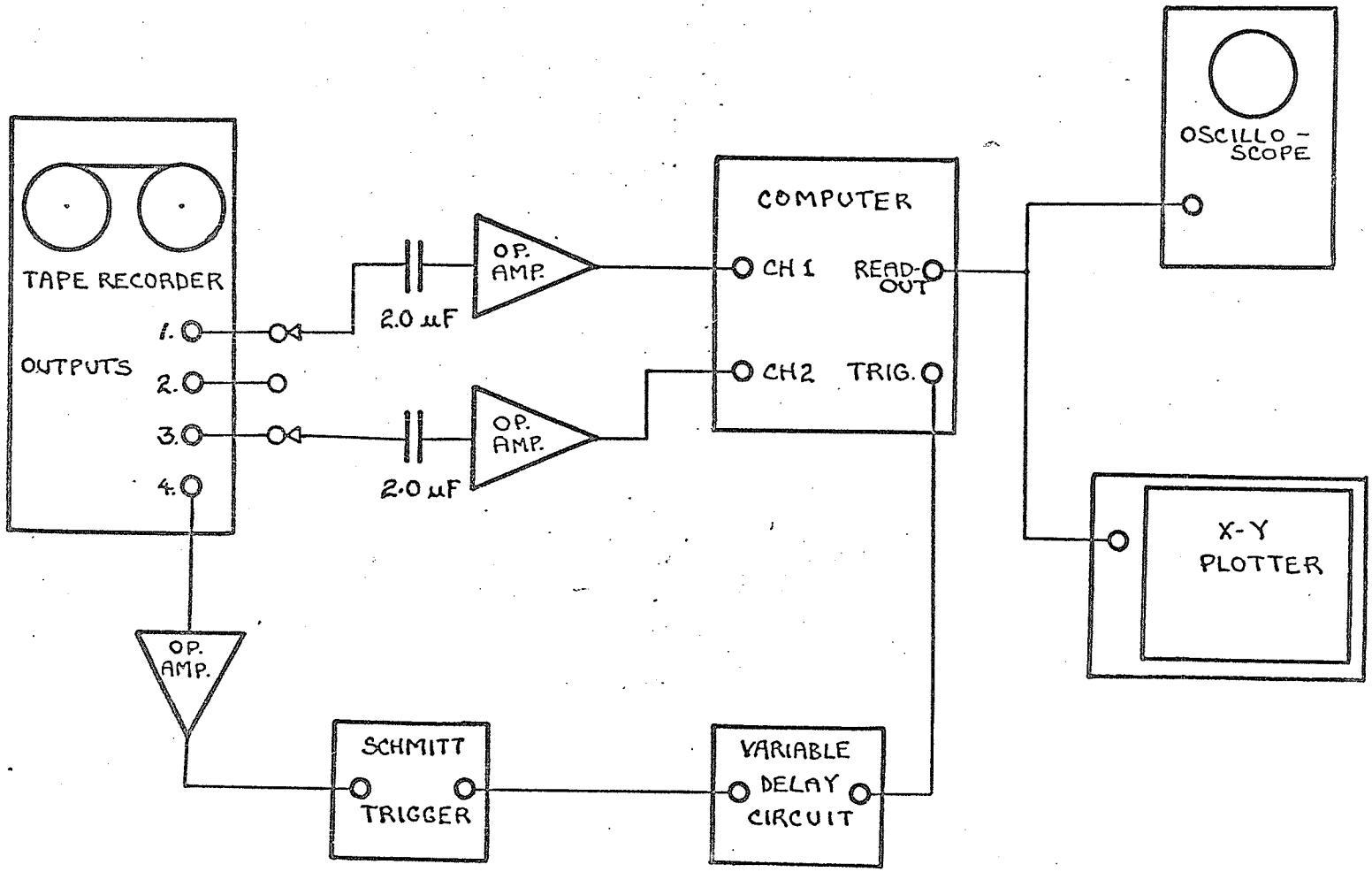

Fig. 5 CIRCUIT FOR RESPONSE AVERAGING

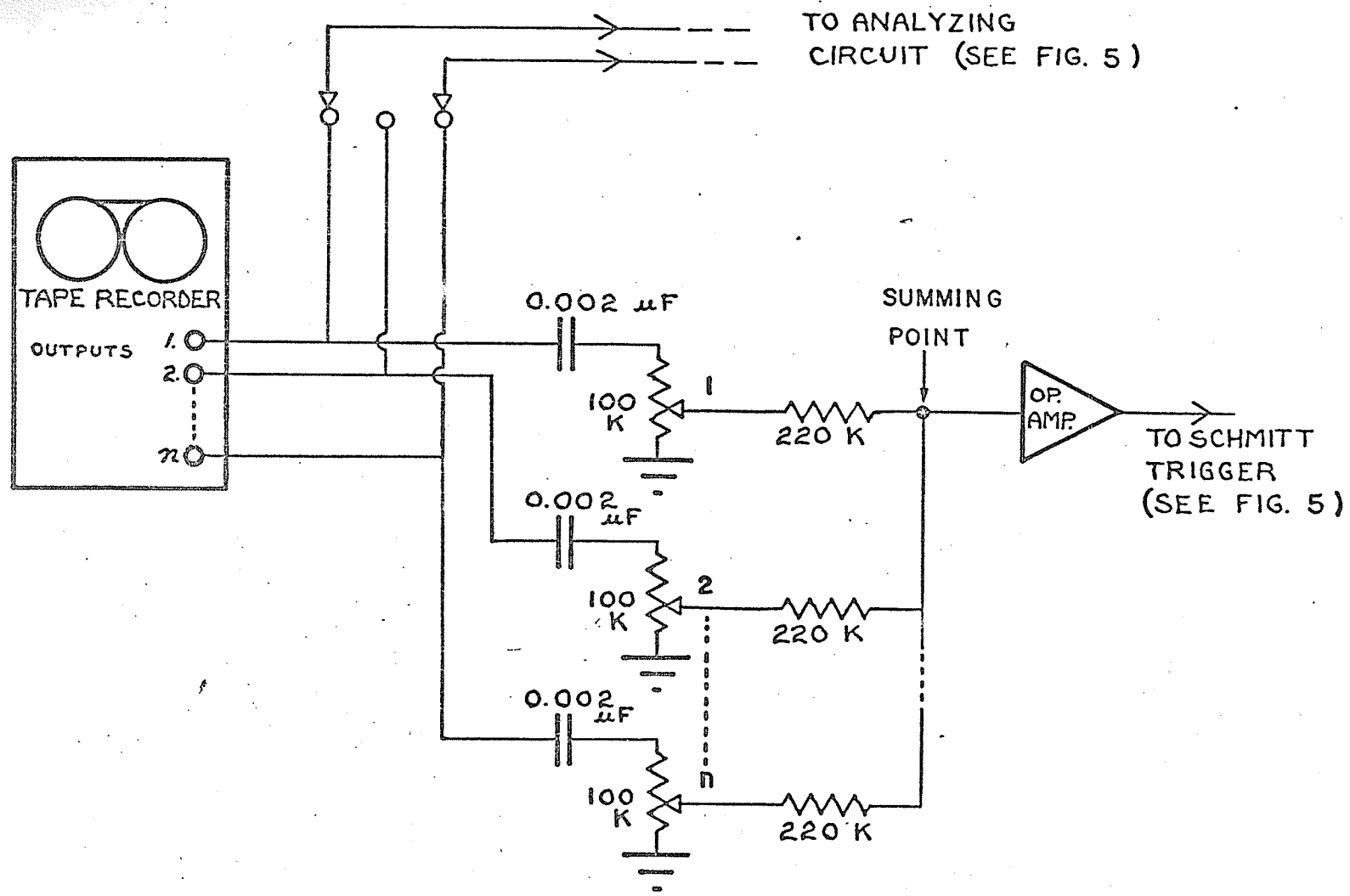

Fig. 6 Adding Circuit

or channels, it would not cause the Schmitt-trigger circuit to fire because such biological activity did not occur on all the channels simultaneously and hence could not add to a level sufficiently high to reach the threshold of the Schmitt-trigger circuit. This prevented the biological activity from providing the analyzer with a spurious triggering signal and thereby increased the accuracy of the averaged result. The adding circuit proved also to be effective in reducing the apparent "jitter" in the timing of the leading edge of the prepulse caused by the 5 kHz carrier frequency of the tape recorder FM system. This jitter was reduced, by virtue of a six-channel mixing circuit, from a previous value of ± 25 μsec to a very acceptable ± 10 μsec. It may be recognized that this improvement is due to the virtual increase in sampling rate which occurs with an increase in the number of channels employed in a fequency-modulated carrier system. This subject has been fully treated by Schwartz (1959).

The output from the Schmitt trigger was used to initiate a variable-delay circuit which consisted of a Tektronix 162 waveform generator coupled to a Tektronix 161 pulse generator. Finally, the pulse produced from the pulse generator triggered the sweep of an average response computer (Enhancetron, 1024). The delay circuit permitted the response to be placed at a convenient time location on the computer sweep; a delay value was chosen so as to include the stimulus artifact on the sweep. Once chosen, the delay value was kept constant for the analysis of all the responses from a given experiment.

The computer sweep used had a total length of 32 msec. 512 words were allotted to each of the two channels thus providing a

resolution of one word per 62.5 μsec. The tape recorder channel, containing recorded data to be analyzed, was fed into the computer via an operational amplifier; this latter served to adjust the gain to the desired amount and also to bring the DC level of the signal to that suitable to the input requirements of the computer. For recording from points far away from the stimulating electrodes, where the signal to noise ratio is quite low, a 2.0 μF capacitor was put in series with the operational amplifier input, giving an effective time constant of about 50 msec. This filtered out much of the baseline shifting due to spontaneous electrical activity in the cortex. To ensure that the surface-negative signal was not being distorted, comparison of the same response, recorded first with direct coupling, and then with the capacitor in the circuit, was made on a storage oscilloscope (Tektronix, RM564). This procedure was carried out with responses recorded from points most distant from the stimulating electrodes as these responses were of the longest duration and would have been most affected by the capacitive coupling. The two different traces were seen to be completely superimposable on the storage screen, and it was taken that the capacitive coupling caused no change in the response parameter (peak latency) being studied at any recording distance.

Since the computer built up an accurate average only after receiving a very large number of responses, it was necessary to send in the same 60-80 responses up to eight times to ensure a proper averaging. Such a procedure was very time-consuming and it took from 100-200 man-hours to complete the analysis of a single experiment. This placed a limitation on the number of experiments which could be done over a given time.

After a response had been averaged, it was read out on an inkwriting X-Y recorder (Moseley 7035A). Fig. 7 is a sample of such a response read out at two different speeds. Peak latency measurement is made off this form of readout in the following manner:

The time interval from the beginning of the readout to the negative peak of the averaged response is measured; this gives the value of the interval marked "a". The interval marked "b" is the time interval from the beginning of the readout to the beginning of the stimulus artifact. Peak latency, then, is simply the value "a-b".

The value "b" was determined by the setting of the delay circuit (see Fig. 5). Provided that this setting was not moved, once a suitable value had been chosen, "b" would remain constant for all the responses averaged. Hence, "b" was measured only on the response closest to the stimulating electrodes (where the stimulus artifact was, conveniently, largest and best defined) and this value was used for all the other responses which were averaged. Any error involved in this measurement would then be constant throughout and thus would not distort the results as it might were it determined separately for each averaged response.

A set of draftman's french curves were used to smooth out that part of the X-Y trace where the peak of the averaged response occurred; this greatly aided the accurate determination of the peak. As this procedure always involved some error of judgment, a response was read out at three different stages in the averaging process (e.g., at 4 x 60 responses, 6 x 60 responses, 8 x 60 responses) and the peak latency determined separately for each. The three values thus

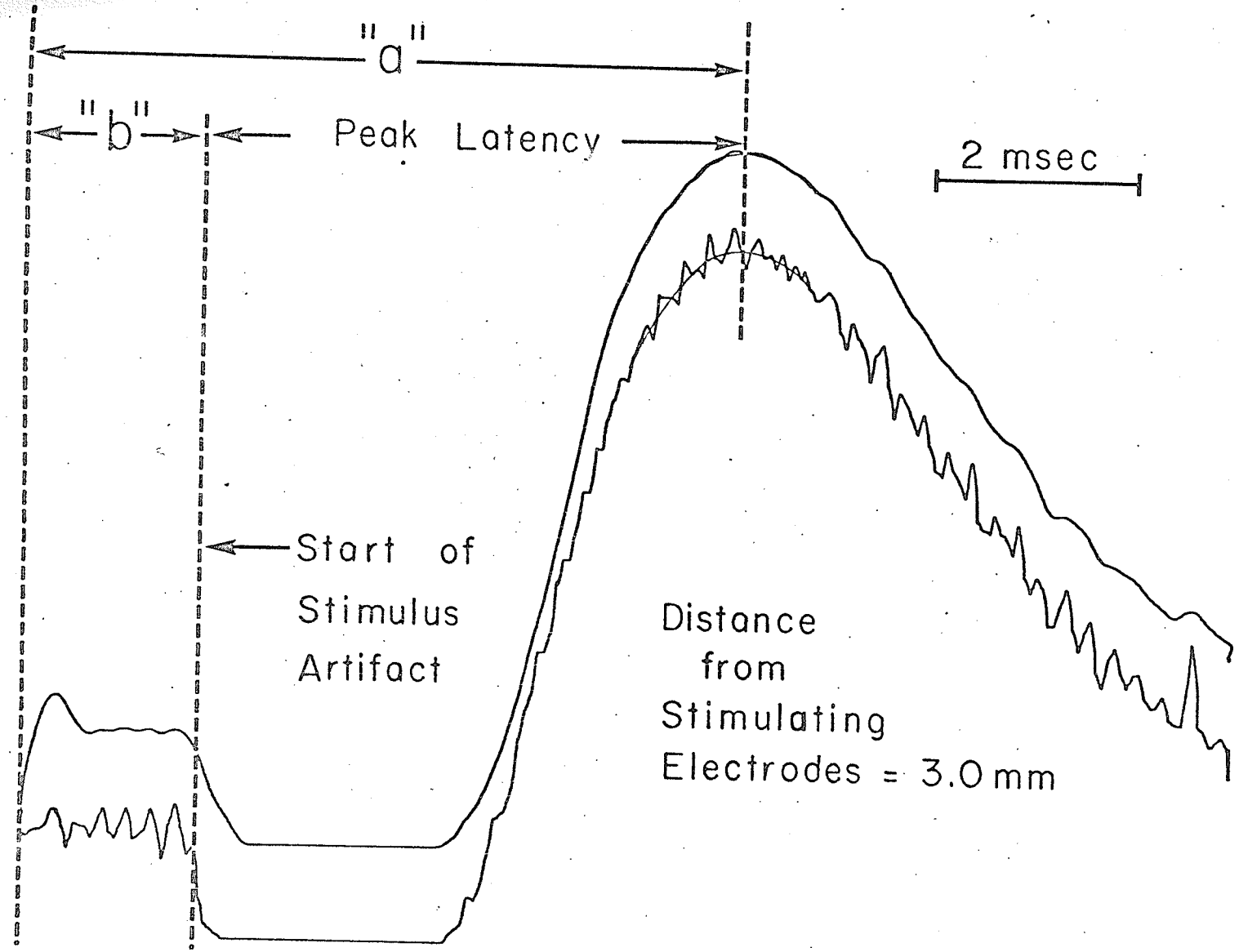

Fig. 7 Determination of Peak Latency From X-Y Recorder Readout of Averaged Response

obtained were averaged and their mean taken as the peak latency measurement for that response. The deviation from this mean was generally within ± 50 μsec for responses recorded within 7 or 8 mm of the stimulating electrodes. For responses more distantly recorded, the deviation could go from ± 100 μsec to, seldomly, as high as ± 200 μsec. Several times, the averaging process was done in duplicate to check on the ability of these procedures to eliminate subjective error and yield reproducible results. This involved erasing the computer memory and repeating the entire analysis of the responses to be averaged. In no instance did the difference in values so determined for peak latency lie outside the just-stated deviations from the mean obtained before erasure.

IV. RESULTS

A. RELATIONSHIP BETWEEN PEAK LATENCY AND DISTANCE

The relationships between peak latency of the surface-negative response and the distance between stimulating and recording electrodes were studied in seven neuronally isolated slabs of cerebral cortex and in one preparation each of the intact suprasylvian and marginal gyri. The results showed that, in general, peak latency tends to increase with increasing stimulus-recording distance. However, the relationship is neither strictly linear nor is it even a simple one. Furthermore, the curves were not all alike in form. The curves relating peak latency to distance could be divided into the following three general types:

(1) Curves made up of successive S-shaped components.

(2) Curves which have a rather long segment which is relatively flat.

(3) Curves which are almost completely linear throughout.

These various types are described fully in the following.

(1) Type I: Curves made up of successive S-shaped components

This type of curve was the most common result, with five out of the nine curves falling into this group. Fig. 8, an example of this type of curve, is the result of an earlier experiment done on intact cortex in the right marginal gyrus of a cat. Silk wick recording electrodes were used and the responses were stored on film. An electrode placed at 3.1 mm was used as a "point of reference" (see METHODS). Peak latency measurements were made with the aid of a

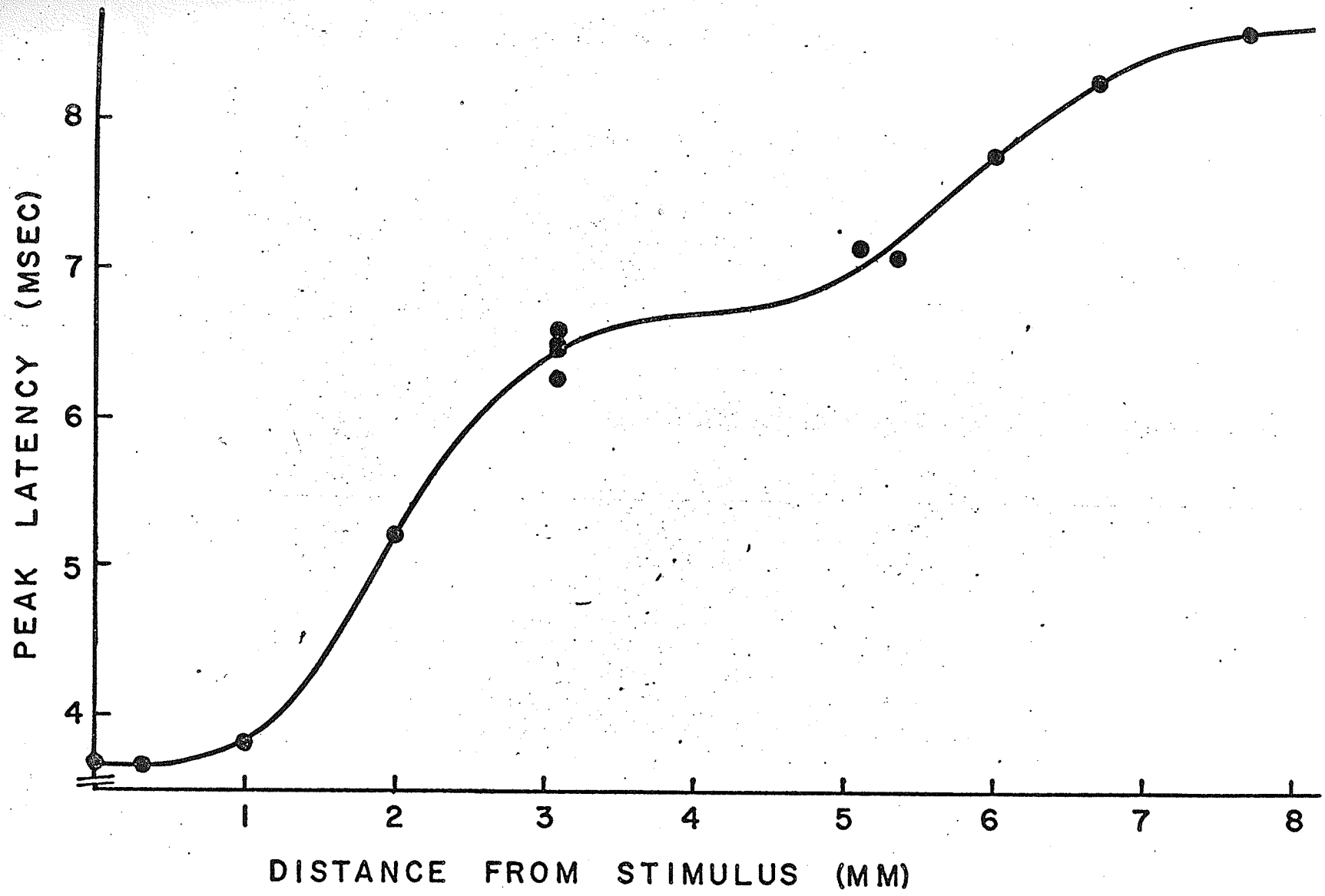

Fig. 8 Experiment No. 1

Dagmar viewer. Each point of the graph represents the mean peak latency of 8-10 responses.

The curve of peak latency vs. distance obtained in this instance may be seen to consist of two successive S-shaped components. Fig. 8 shows the slope of the rising phase of the second S-shaped component to be less steep than that of the first component. If each S-shaped component is regarded as signalling the involvement of a discrete group of dendritic fibres, then the difference in slopes of the rising phases would appear to indicate that the second S-shaped component represents transmission over a group of fibres whose conduction velocity is faster than that of fibres which carry the response over the region described by the first S-shaped component curve.

Another example of this type of curve is seen in Fig. 9. In this experiment an 8-electrode recording assembly was used. One electrode, different for each position of the recording assembly, was maintained as a "point of reference" (see METHODS) since only three recording channels were available. The need for such a "point of reference" can be seen by the spread of values at each point so used (e.g., at 3.8 mm, 5.7 mm, and 8.5 mm). The cause of this spread of values is unknown, although it may have been due to variation in the physiological state of the preparation or to very slight movement of either the stimulating or recording electrodes. However, despite this spread, the values of peak latency obtained from any three simultaneously-recorded points follow the general shape of the plotted curve. By way of illustration, the three points symbolized by open squares in Fig. 9 represent points from which responses were recorded simultaneously.

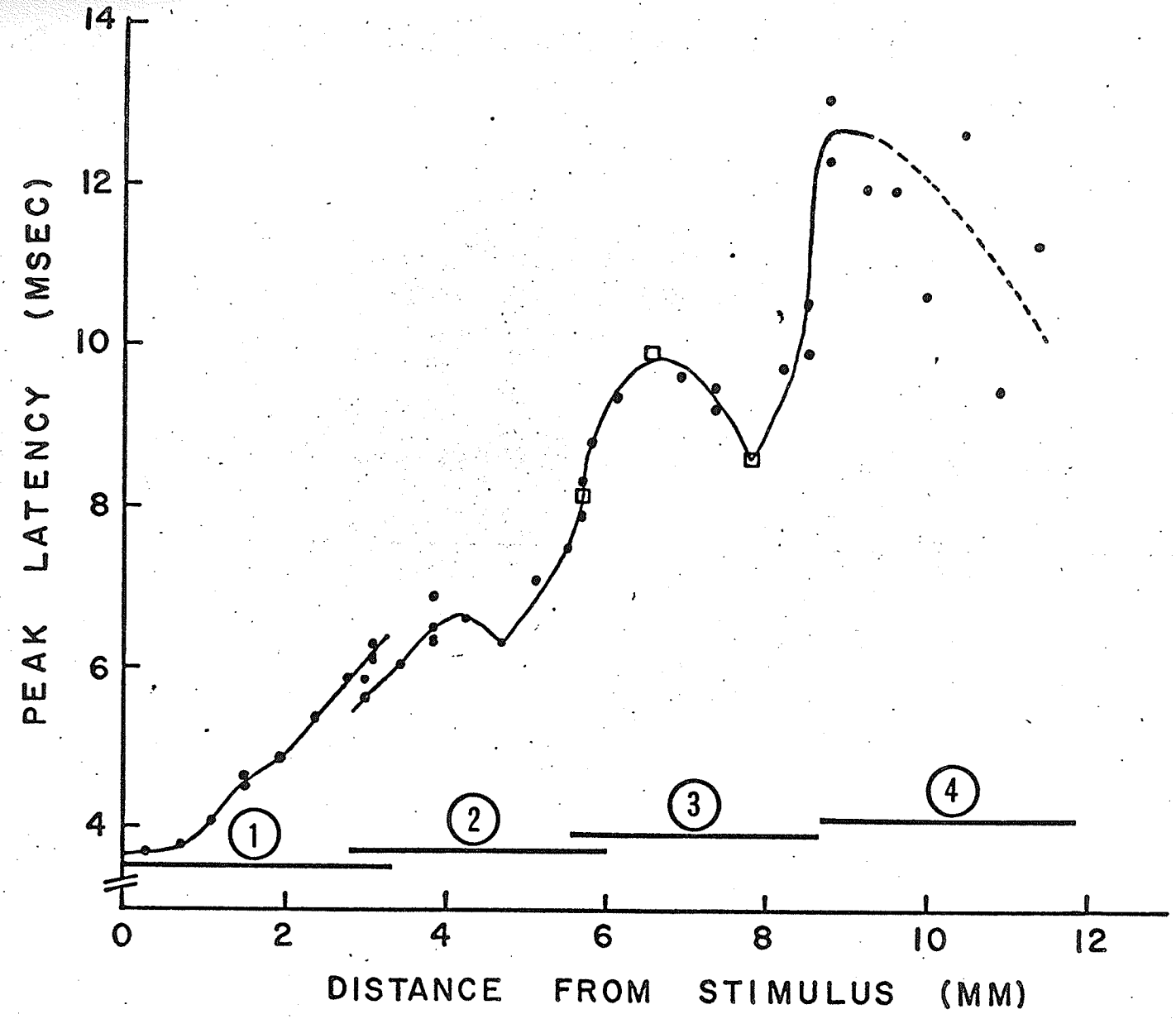

Fig.9 Experiment No.7

It can be seen in Fig. 9 that the rising phase of each succeeding S-shaped component curve is steeper than that of its predecessor. This would seem to indicate, in this instance, the involvement of successive fibre groups each with a slower velocity than the group which preceded it. The situation is in direct contrast to that of Fig. 8, discussed in the foregoing. Table I shows that of the five Type I curves the slope value of the steepest portion of each S-shaped component curve:

(a) increases with distance from the stimulated site for two out of five Type I curves,

(b) decreases with distance from stimulus site for one Type I curve,

(c) varies irregularly with distance from the stimulus site for the remaining Type I curves.

The pattern of slopes of the S-shaped component curves, then, is not consistent for all the examples of this type of curve. It will take more experiments to establish which pattern is the predominant one.

It may be noted that the slope of any portion of the curve of peak latency vs. distance is the inverse of the mean velocity of the peak of the surface-negative response for that portion. Any region of the curve where the slope decreases in value with an increase in distance must represent a region of increasing velocity, and the first derivative of velocity with respect to time is acceleration. Hence, a region where the slope of the curve changes to a less positive or a more negative value may be regarded as a region of "acceleration". Conversely, a region where the slope of the curve changes to a more positive or a

EXP. NO.	PREPARATION	PEAK LATENCY (MSEC) AT 0.0MM	STEEPEST SLOPE (MSEC/MM) FOR COMPONENT				END POINT (MM) OF FIRST COMPONENT	LENGTH (MM) OF INTERVAL		WIDTH (MM) OF REGION OF "ACCELERATION"			PEAK LATENCY (MSEC) AT END OF COMPONENT			MINIMUM SLOPE (MSEC/MM) OF REGION OF "ACCELERATION"			LARGEST PEAK LATENCY VALUE (MSEC)
			1	2	3	4		1	2	1	2	3	1	2	3	1	2	3	
1	INTACT Right Marginal Gyrus	3.7	1.4	0.8			4.1			0.9			6.7			0.3			8.6
2	SLAB Right Suprasylvian Gyrus	3.9	0.9	0.9	0.8	1.5	3.0	1.5	3.5	0.5	0.7	2.3	5.3	5.8	6.5	0.3	-0.3	-0.2	8.0
3	INTACT Right Suprasylvian Gyrus	5.8	1.0	1.5	1.8		2.8	3.9	2.9	0.6	1.7	1.6	6.9	9.3	10.8	0.0	0.1	-0.1	11.9
4	SLAB Right Suprasylvian Gyrus	5.7	1.2	2.8	1.1		4.6	3.6		1.9	1.4		7.1	9.9		0.5	-0.3		11.8
7	SLAB Left Suprasylvian Gyrus	3.7	1.1	2.4	4.3		4.7	3.1	3.1	0.8	1.3		6.3	8.6	9.5	-0.7	-1.4		13.1

Table I: Type I Curves

less negative value will be defined as a region of "deceleration". These terms will be used in the remainder of this thesis to describe these portions of the curves.

An interesting physiological result is revealed by regions of "acceleration" in Type I curves (Fig. 9). It can be seen that these regions occur at somewhat regular spatial intervals. In Fig. 9 the value of this interval is approximately 3.0 mm. This kind of spatial periodicity is a feature of all types of curve obtained, and for the successive S-shaped component type of curve it has a mean interval value of 3.1 mm (average of interval values in Table I).

A number of instances were observed in Type I curves where the slope of the curve had negative values for short distances. In Fig. 9, there are three of these regions of negative slope. In this instance these regions exhibit a tendency to become more pronounced the farther away they occur from the stimulating electrodes. However, such a pattern is not a consistent result for all the curves in which such regions are found.

(2) Type II: Curves with a long region of relative flatness

Three out of the nine curves fall into this category. Each of these curves contains a relatively flat portion which spans a distance of some 3 to 5 mm. Fig. 10 shows one such curve having a flat region beginning at about the 4 mm point and extending to about the 8 mm point. In the remaining two curves of this type, the region of flatness begins at about 3.5 mm for one and at about 5.0 mm for the other.

These curves, besides having this region of relative flatness, exhibit most of the properties of the successive S-shaped component type of curve. They all contain two or more S-shaped components and

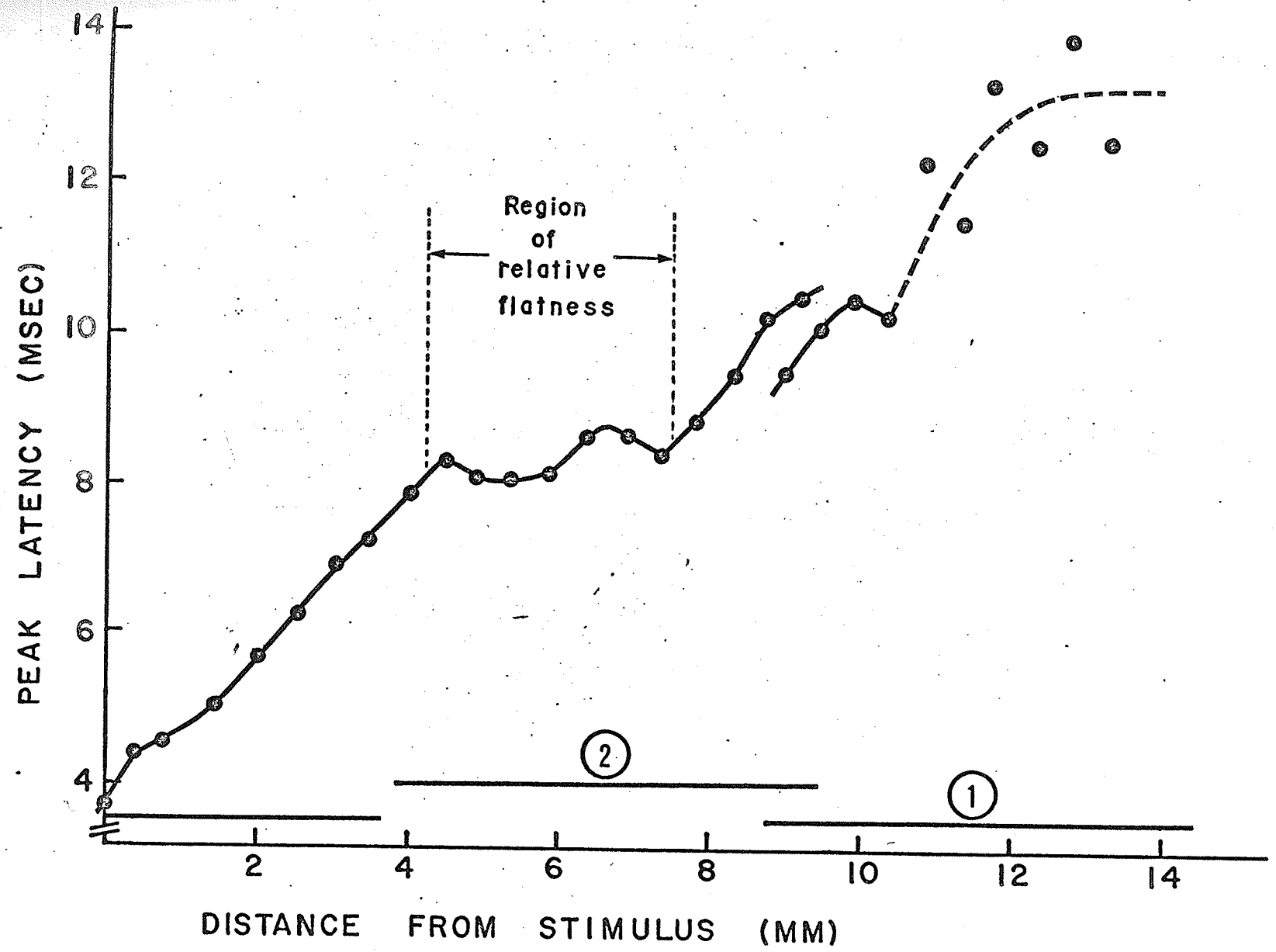

Fig.10 Experiment No. 8a

some have regions of negative slope as well. Fig. 10 shows three S-shaped components and three very short regions of slightly negative slope, two of which occur in the relatively flat region.

Also present in the Type II curve is a spatial periodicity similar to, but less pronounced than, that observed in Type I. Short regions, where the slope of the main curve deviates towards zero or even towards a negative value (i.e., regions of "acceleration"), appear to occur at regular intervals. Fig. 10 has a mean interval value of 2.4 mm. The mean interval length for all the Type II curves is 2.5 mm. A summary of the experiments in which Type II curves were obtained is given in Table II.

(3) Type III: Relatively linear curves

Only one example of this type of curve was observed and it is shown in Fig. 11. This curve is strikingly linear by comparison with curves of Types I and II. Its general slope is also much steeper than that of the other curve types. This can be seen from the fact that it reaches a peak latency value of 12 msec at a stimulus-recording distance of only 7 mm whereas the other curve types generally do not reach this value in peak latency until 10 mm or more from the point of stimulation. Hence this curve probably belongs in a category by itself even though it is composed of minor S-shaped component curves. It too has short regions where the slope deviates from the general trend of the curve and takes on a smaller value; these regions of "acceleration" appear to occur at regular intervals of about 2 mm. Absent from the curve are regions of negative slope.

EXP. NO.	PREPARATION	PEAK LATENCY (MSEC) AT 0.0MM	STEEPEST SLOPE (MSEC/MM) FOR COMPONENT				END POINT (MM) OF FIRST COMPONENT	LENGTH (MM) OF INTERVAL		WIDTH (MM) OF REGION OF "ACCELERATION"			PEAK LATENCY (MSEC) AT END OF COMPONENT			MINIMUM SLOPE (MSEC/MM) OF REGION OF "ACCELERATION"			LARGEST PEAK LATENCY VALUE (MSEC)
			1	2	3	4		1	2	1	2	3	1	2	3	1	2	3	
5	SLAB Right Suprasylvian Gyrus	4.1	0.8	1.0			4.2			0.6			7.1			0.0			13.1
6	SLAB Right Suprasylvian Gyrus	3.9	2.4	0.7	0.7		3.7	2.5		1.4	1.0		6.9	7.4		0.0	-1.1		8.0
8a	SLAB Right Suprasylvian Gyrus	3.7	1.2	1.0	1.7	2.6	5.3	2.0	2.9	0.7	0.6	0.6	8.0	8.4	10.3	-0.7	-0.7	-0.4	14.0

Table II: Type II Curves

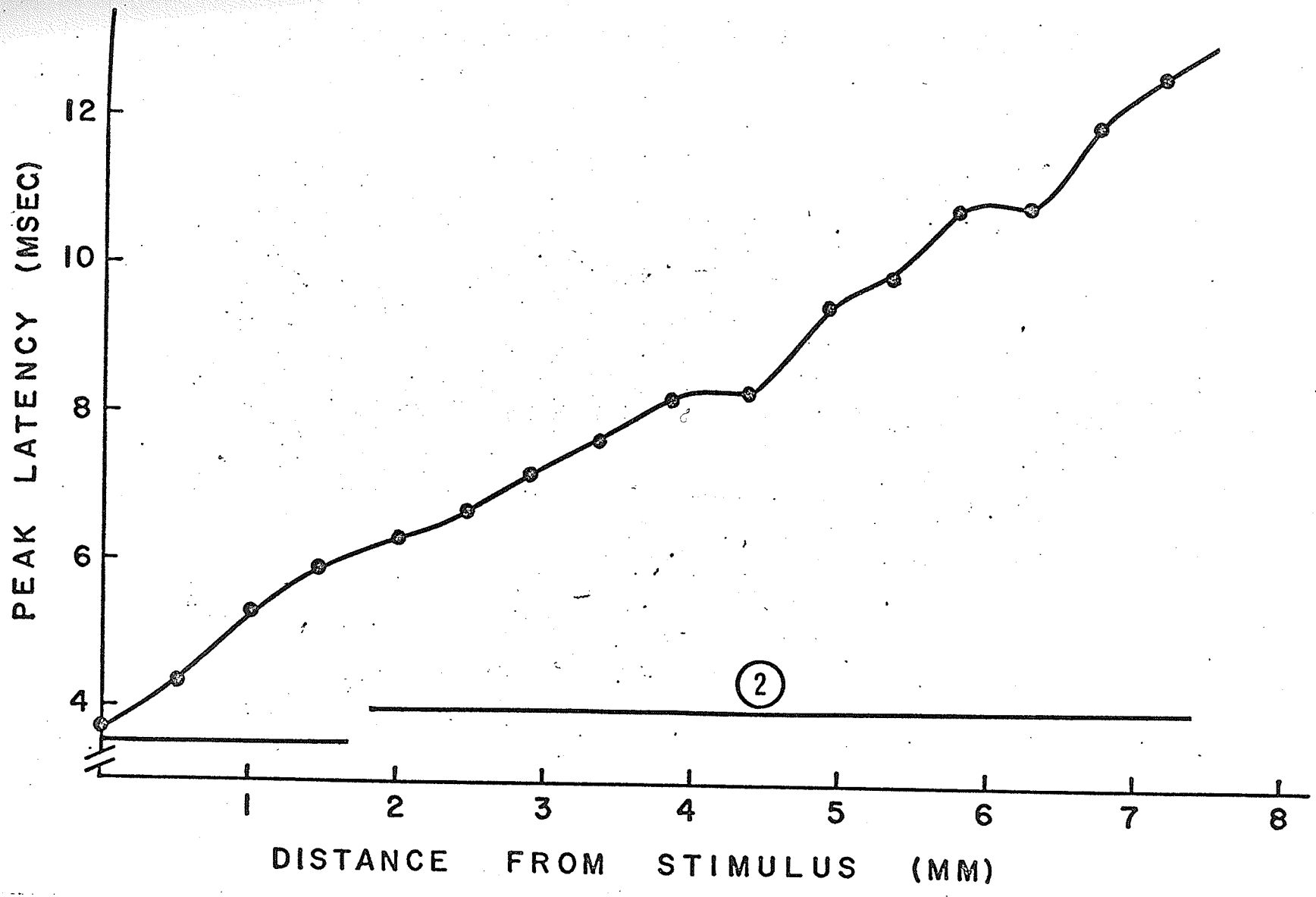

Fig.11 Experiment No. 8b

EXP. NO.	PREPARATION	PEAK LATENCY (MSEC) AT 0.0MM	STEEPEST SLOPE (MSEC/MM) FOR COMPONENT				END POINT (MM) OF FIRST COMPONENT	LENGTH (MM) OF INTERVAL		WIDTH (MM) OF REGION OF "ACCELERATION"			PEAK LATENCY (MSEC) AT END OF COMPONENT			MINIMUM SLOPE (MSEC/MM) OF REGION OF "ACCELERATION"			LARGEST PEAK LATENCY VALUE (MSEC)
			1	2	3	4		1	2	1	2	3	1	2	3	1	2	3	
8b	SLAB Right Suprasylvian Gyrus	3.6	1.8	1.1	1.3	1.6	2.5	1.9	1.9	1.2	0.5	0.5	6.6	8.2	10.8	0.2	0.0	0.1	14.3

Table III: Type III Curve

B. TABULATION OF RESULTS OBTAINED FROM THE STUDY OF PEAK LATENCY vs. DISTANCE

The data from each curve of peak latency vs. distance has been summarized in Tables I-III to show certain characteristic and measurable features of these curves. The features so chosen are illustrated in Fig. 12 and are listed in the following:

(1) The value of peak latency at zero distance.

(2) The slope of each S-shaped component at its steepest point. This was taken to be the slope of the straight line drawn through those two points of the S-shaped component which gave the steepest slope.

(3) The distance from the stimulus site to the end of the first region of "acceleration" (i.e., to the end of the first S-shaped component).

(4) The values of the intervals between successive regions of "acceleration", measured from the end of one region of "acceleration" to the end of the next.

(5) The "width" of each region of "acceleration". This parameter was measured from the point of maximum "acceleration" instead of from the actual beginning of a region of "acceleration" since the latter is very difficult to determine. Such a region was considered to extend up to the point where the curve started to show "deceleration".

(6) The value of peak latency at the end of each S-shaped component.

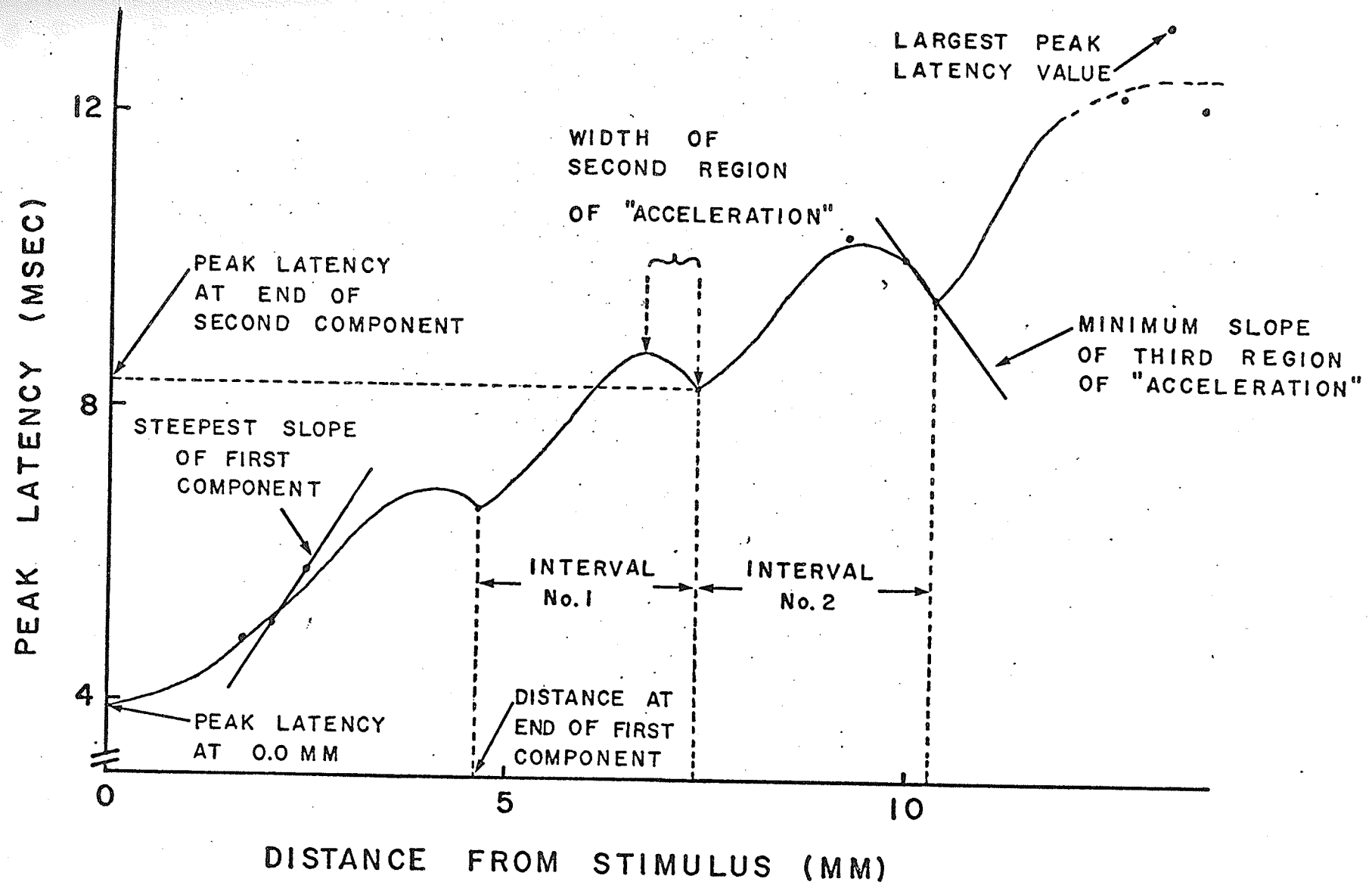

Fig. 12 Illustration of measurement of curve features. (Curve shown is contrived)

(7) The slope of a straight line drawn through those two points of a region of "acceleration" which gave the least positive or the most negative slope value.

(8) The maximum value of peak latency.

Fig. 12 illustrates how these measurements were made. Measurements obtained at points of reference (see METHODS) were averaged before estimating the parameters just listed. Tables I-III contain, for the three types of curve observed, the measurements obtained from all the experimental data.

The data on isolated slabs in each of the columns in these three tables was averaged and the mean of each column is shown in Table IV. This averaged data shows that the slope of each successive S-shaped component is larger than that of the preceding one. These differences, however, are not significant and, hence, more data is required to establish whether such a pattern is really present. Similarily, neither the average lengths of successive intervals nor the average "widths" of successive regions of "acceleration" differ significantly from one another. The same may be said for the averaged data on minimum slopes for successive regions of "acceleration". It is interesting to note, however, that the lengths of the two successive intervals from the averaged data have a mean value of 2.7 mm; the distance to the end of the first region of "acceleration" for the averaged data (i.e., 4.0 mm) is almost exactly equal to one and one-half times this mean interval value.

A "composite" curve was drawn from the information contained in Table IV, and it is shown in Fig. 13. This curve was obtained in the following manner:

EXP. NO.	PREPARATION	PEAK LATENCY (MSEC) AT 0.0MM	STEEPEST SLOPE (MSEC/MM) FOR COMPONENT				END POINT (MM) OF FIRST COMPONENT	LENGTH (MM) OF INTERVAL		WIDTH (MM) OF REGION OF "ACCELERATION"			PEAK LATENCY (MSEC) AT END OF COMPONENT			MINIMUM SLOPE (MSEC/MM) OF REGION OF "ACCELERATION"			LARGEST PEAK LATENCY VALUE (MSEC)
			1	2	3	4		1	2	1	2	3	1	2	3	1	2	3	
2, 4-7, 8a, 8b	Isolated Slabs	4.1 ±0.3	1.3 ±0.2	1.4 ±0.3	1.7 ±0.6	1.9 ±0.4	4.0 ±0.4	2.4 ±0.3	2.9 ±0.3	1.01 ±0.2	0.9 ±0.2	1.1 ±0.6	6.8 ±0.3	8.1 ±0.6	9.3 ±1.0	-0.1 ±0.2	-0.6 ±0.2	-0.2 ±0.1	11.8 ±1.0

Table IV: Composite curve data, giving the mean and standard error of the isolated slab data contained in the columns of Tables I–III

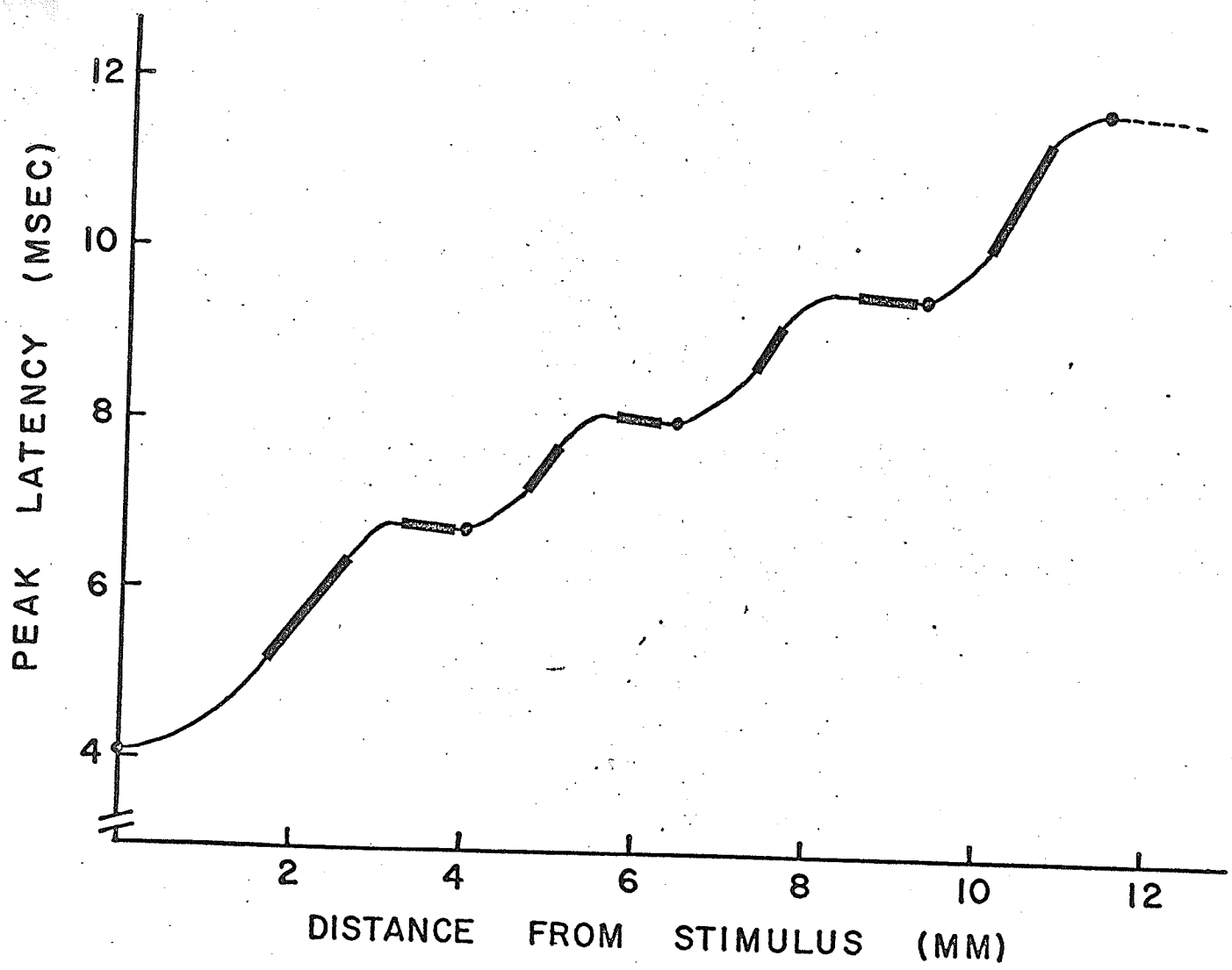

Fig. 13 Composite curve drawn from information in Table IV

(1) The peak latency values at 0.0 mm and at the end of each S-shaped component were plotted

(2) From the endpoint of each component plotted in (1), a straight line, whose slope was the minimum slope value (Table IV) for the respective region of "acceleration", was extended to the left and then curved downwards when it had been extended for a distance equal to the value of the "width" of the respective region of "acceleration".

(3) The line in (2) was curved downwards smoothly to the left until it attained the steepest value of slope for the respective S-shaped component. It was then curved gently to meet the end point of the preceding S-shaped component (or to meet the 0.0 mm point for the line drawn from the first region of "acceleration").

(4) The last S-shaped component was drawn simply by constructing an elongated S-shaped curve, whose maximum slope concurred with that for component #4 in Table IV, and whose highest point was that of the largest peak latency value in Table IV.

The slope values, obtained from Table IV, for the composite curve are accentuated in that curve by thickened portions.

This curve was drawn to give an approximation of the "average" peak latency vs. distance curve to be found in cerebral cortex isolated in the cat suprasylvian gyrus, and represents a summary of the data obtained in this present study.

C. COMPARISON OF THE RELATIONSHIPS BETWEEN PEAK LATENCY AND RECORDING DISTANCE TAKEN FROM STIMULATED SITES ONLY 2 mm APART

The curves which appear in Figs. 10 and 11 were obtained from two different sites of stimulation in the same isolated slab. In Fig. 14 both curves have been replotted on one graph to permit a comparison of their relationships. Fig. 15 shows a diagram of the stimulating-recording setup for this experiment. The stimulated regions were 2 mm apart, and all the responses were recorded from S_2 before recording them from S_1. This experiment was facilitated by the use of six recording channels. This enabled many more points to be recorded from in a given period of time than was possible with the three recording channels used previously. Also, since six points could be recorded from simultaneously, the need for a "point of reference" was eliminated.

The position of S_1 is used as the zero point on the X-axis for both curves in Fig. 14. As noted previously, the two curves are quite dissimilar, one belonging to Type II and the other to Type III. This would seem to indicate that not all points on the cortex are physiologically identical.

Another interesting feature is that the few points plotted in the reverse direction for the curve obtained from S_2 show a much different slope (i.e., in terms of magnitude) from those first few plotted in the forward direction. This indicates that, at least in this instance, the "field" about the stimulated point which carries the surface-negative response is not bisymmetrical.

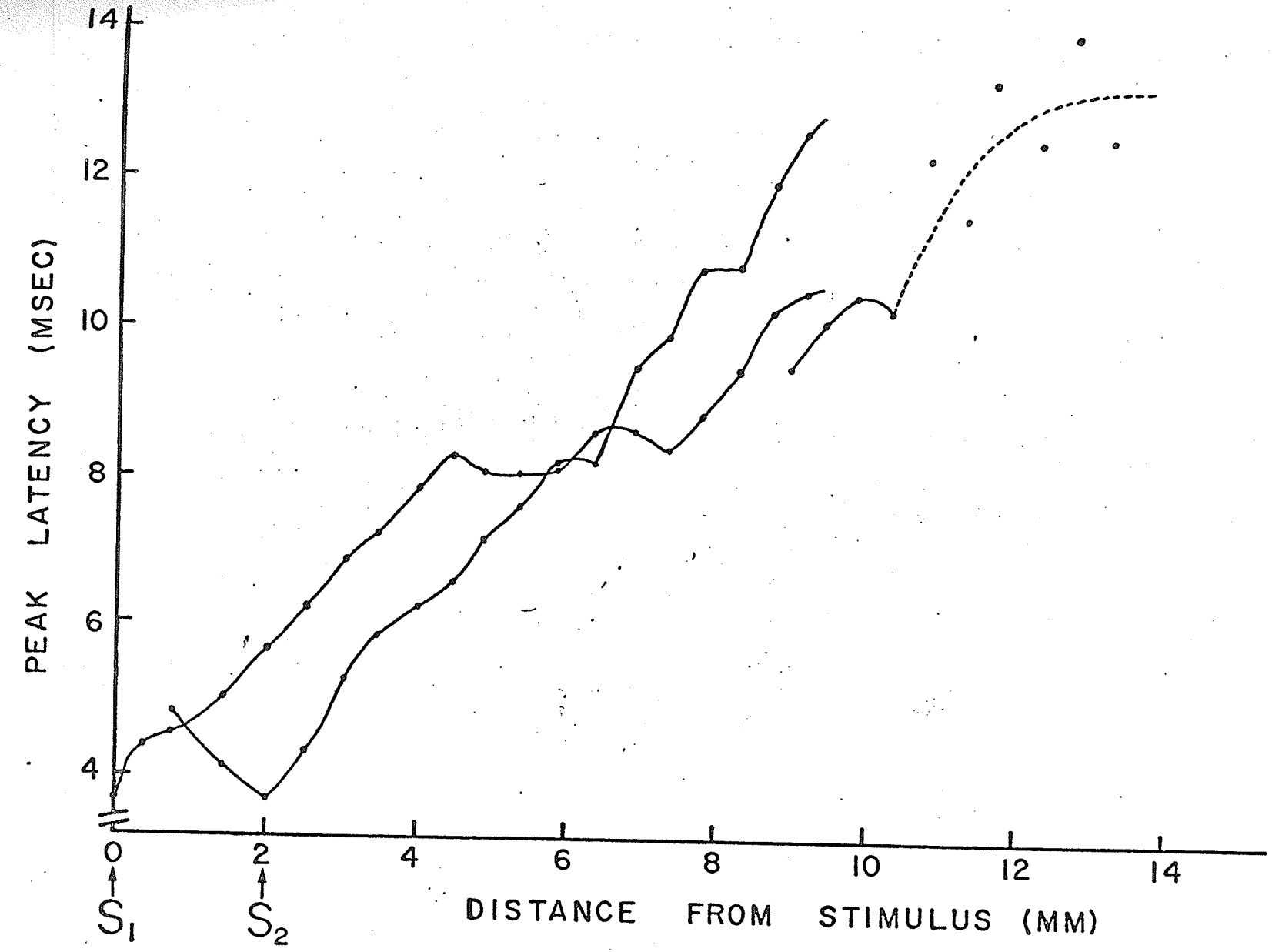

Fig.14 Experiment No. 8

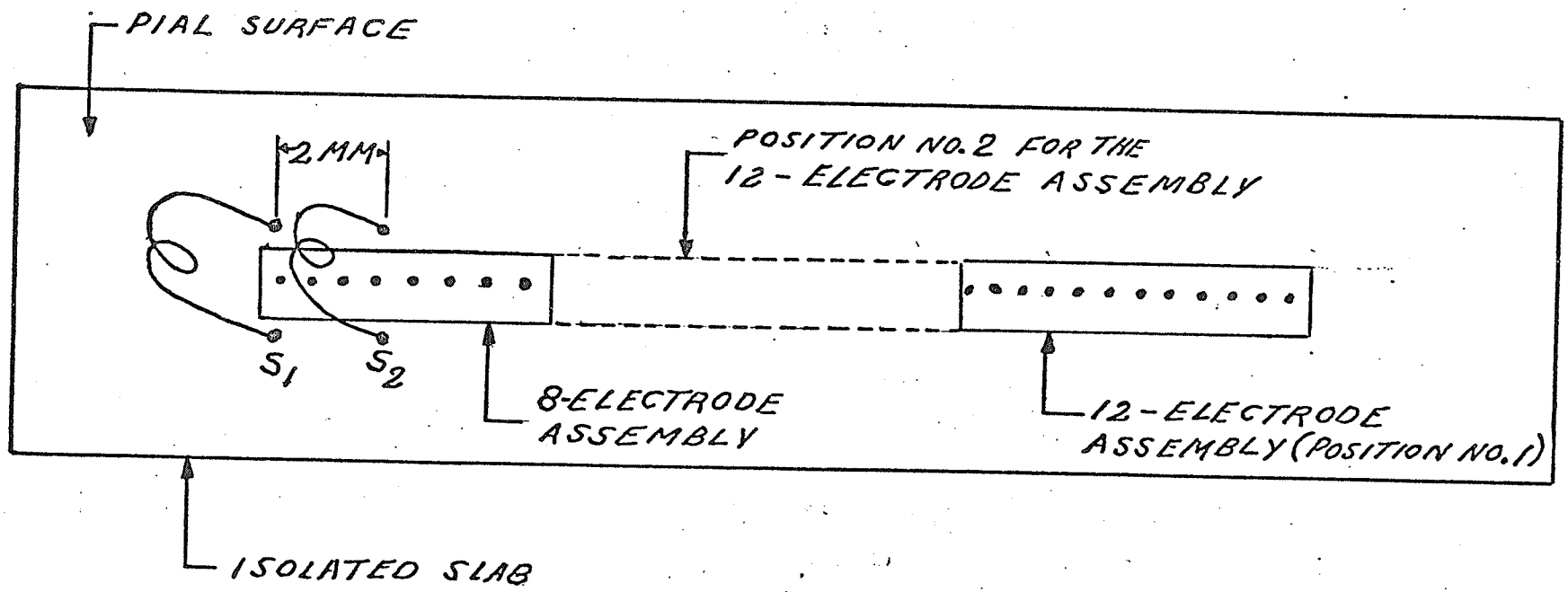

FIG. 15 STIMULUS-RECORDING SET UP FOR EXP. NO. 8

V. DISCUSSION

A. SOME IMPLICATIONS OF THE RESULTS

The results indicate that peak latency is not a simple function of distance from the stimulating electrodes. On the contrary, it would appear that the relationship is actually quite complex and that multiple pathways may be involved in the lateral transmission of the surface-negative response. While it is tempting, on the basis of Fig. 19, to view each S-shaped component curve as signalling the involvement of a discrete group of fibres some 2 to 5 mm in length, the regions of negative slope observed in some of the curves make such a hypothesis less plausible. These regions of negative slope point to the existence of a fast conduction pathway (or pathways). Such a pathway would be "hidden" from the recording electrodes except at small regions where it would manifest itself by reducing the peak latency from the value which would be expected were a simple type of conduction to be the case. The fact that the regions of "acceleration" seem to occur at regular intervals would indicate that the cortex has some regular structural pattern (whose functional value ought to be a good source of speculation). It is very interesting to note that the distance to the end of the first region of "acceleration" of the composite curve of Fig. 13 is approximately one and one-half times as long as the other two intervals. Since the last two intervals are about equal in length, it would appear that they represent a basic interval of brain structure and that the distance to the end of the first region of "acceleration" is merely a three-halves multiple of this basic interval. If this be true, then for some unknown reason, the stimulation initiates the surface-negative

response at the middle rather than at the beginning of one of these basic intervals.

B. OTHER THEORIES IN THE LIGHT OF THE OBSERVATIONS PRESENTED HERE

It is very difficult, on the basis of the evidence obtained from this study, either to advance as correct or to discard once and for all any of the older theories on surface-negative response production and lateral transmission. However, the new evidence presented here certainly requires that the details of these theories undergo a certain measure of refinement to retain their plausibility. For a number of the older theories this requirement will make them appear less appealing than they might have been formerly.

Burns' theory (Burns, 1950) of randomly arranged conductors of equal length (1 cm) and similar properties (e.g., conduction velocities) appears to be definitely excluded in the light of the present observations since it would be very difficult to see how the observed regions of "acceleration" could be accounted for by his theory. Even if there were proposed a periodic interspersion of high-velocity surface fibres, the regions of "acceleration" would never occur to the point of creating a negative slope in the curve relating peak latency to distance. This phenomena can occur only if the higher-velocity pathway is "hidden" from the recording electrode for the greater part of its course of travel, and makes its "appearance" solely at restricted regions. Chang's apical dendrite theory (Chang, 1951) similarly lacks a higher-velocity route. He did suggest the possibility that, with strong stimulation, impulse initiation could occur not only from the apical dendrites

directly under the stimulating electrodes but also from the bodies of the pyramids or from the bifurcating apical shafts of the pyramids. However, Chang considered that the arrival at the recording electrode of the deeper layer impulses would be much later in time than those which travelled horizontally from the stimulating electrodes and therefore, this deep route would be even slower than the surface route, making it incapable of producing the regions of "acceleration".

The theory of Eccles (1951) is amenable to inclusion of higher-velocity pathways. He proposes that lateral conduction of activity (arising from cells near the stimulating electrodes) is carried by axons coursing through the molecular layer and that the recording electrode for some reason (unexplained by Eccles) does not see the axonal impulses, but rather only the synaptic potential generated in the apical dendrites by the axonal impulses. Since the axonal activity remains "hidden" to the recording electrode, one could postulate some periodic arrangement of slow and fast conducting axons travelling laterally in the molecular layer in order to account for the periodic regions of "acceleration" observed in curves of peak latency vs. distance.

The theories of Ochs and Suzuki (1965) and Ochs and Clark (1968a) are similar to that which Eccles (1951) proposed and, hence, the same considerations would apply for the most part to their theories as well. Another possibility exists, however, in that Ochs and Suzuki (1965), in order to account for the longer transmission (up to 14 mm) shown in the graphs of Brooks and Enger (1959), did not dismiss the likelihood of some activity travelling either in intracortical or corticocortical pathways. Such pathways, however, would have to display

some type of periodicity and also would have to be of higher conduction velocity than the surface axons in order to account for the periodicity observed in the curve relating peak latency to recording distance. Similar remarks are applicable to the theory of Brooks and Enger (1959).

C. PREVIOUS STUDIES ON PEAK LATENCY vs. DISTANCE STUDIES CONSIDERED IN THE LIGHT OF THE RESULTS PRESENTED HERE

Brooks and Enger (1959) found unexpectedly low values of peak latency (their "reinforcement" phenomenon, see HISTORICAL REVIEW) at only two distances from the stimulating electrodes, 5 mm and 10 mm. This present study has only one experiment where the preparation is similar to that of Brooks and Enger, and that is the experiment on the intact suprasylvian gyrus (see Experiment No. 3 in Table I). In this experiment, the endpoints of the regions where peak latency deviated (i.e., decreased) from the general trend of the curve occurred at three distinct distances from the stimulating electrodes, 2.8, 6.7, and 9.6 mm. The experiments done here on the isolated slab preparations show somewhat similar results in that there are always more regions where peak latency deviates from the simple linear relationship than were observed by Brooks and Enger. Moreover, the present results show these regions to occur at somewhat regular intervals of 2 to 3 mm.

Brooks and Enger believed all sites on the gyrus to be equivalent, stating that "it is unlikely that the points of re-establishment described above depend upon a special distribution of the responsible cells" (p.774, Brooks and Enger, 1959). That this is not so with regard to peak latency is evident from the graphs shown in Fig. 14. These

were obtained from the experiment done with two different sites of stimulation only 2 mm away from each other on the same suprasylvian gyrus (see RESULTS). In that particular experiment, two entirely different curves of peak latency vs. distance were generated from the two stimulation sites.

The curve obtained by Pinsky (1967) was S-shaped in form and extended over a distance of 10 mm. It is quite conceivable that the top of the "S" represents a region of "acceleration". The absence of evidence for other regions of "acceleration" in this curve was most likely due to the lack of adequate resolution in measurement of distance and peak latency.

The theory which Pinsky presented for the production and transmission of surface-negative responses becomes compatible with the data from the present study when, in addition to the electrotonically-coupled dendritic pathway at the pial surface, one postulates a deeper dendritic pathway whose conduction velocity is greater than that at the surface. Such a theory is developed more fully in the following.

D. A NEW THEORY FOR SURFACE-NEGATIVE RESPONSE PRODUCTION AND TRANSMISSION

A new theory for surface negative production and transmission has been proposed (Beaubien and Pinsky, 1968) to take into account the data presented in this thesis. The theory hypothesizes the existence of two major cortical pathways for the lateral transmission of the surface-negative response; a surface pathway which runs along the molecular layer, and a lower layer pathway of faster conduction velocity which intersects the surface pathway at regular intervals. A pictorial representation of the postulated elements in such a system is provided in Fig. 16.

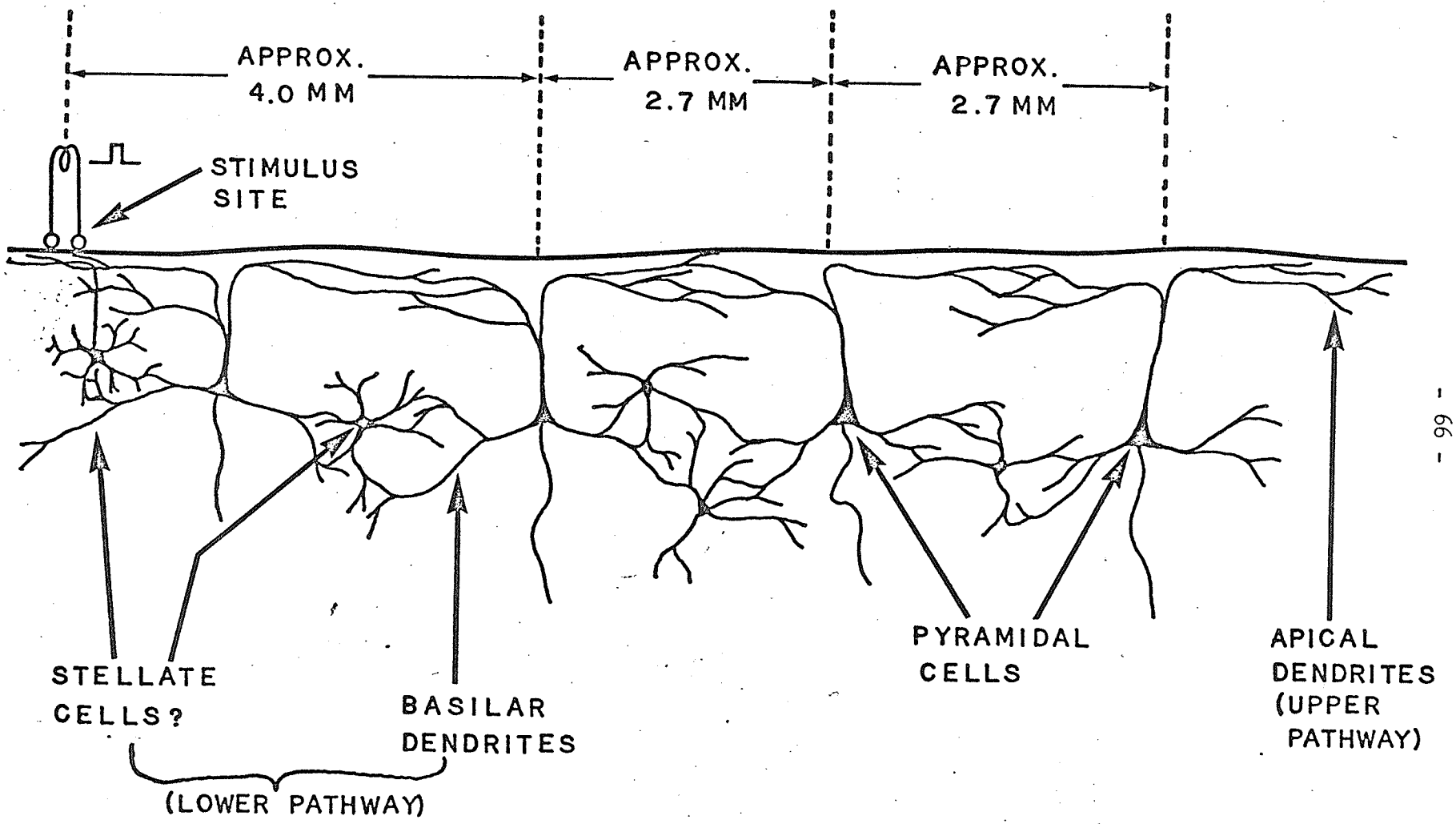

Fig. 16 Theoretical Transmission Pathways For The Surface-Negative Response

The theory suggests that both of the two pathways are dendritic in nature and that surface-negative response activity travels passively and decrementally along them from an initial point of regenerative excitation. The upper pathway is postulated to consist of apical dendrites extending laterally through the molecular layer. The biological source of excitation is taken to consist of locally occurring regenerative activity initiated by the stimulus current in apical dendrites situated immediately below the stimulating electrodes. The lower pathway would consist of the basilar dendrites of pyramidal cells in conjunction with the dendrites of intermediate cells which do not send dendritic processes up to the molecular layer. At regular intervals of 2 or 3 mm, the lower pathway diverts some of its activity upwards to the molecular layer via the apical shafts of pyramidal cells. Since the end of the first region of "acceleration" in the composite curve (Fig. 13) occurs at a distance of 4.0 mm, the point of initial excitation for the lower pathway must somehow be initiated in the middle of one of the fundamental intervals (which have a mean value of 2.7 mm for the composite curve of Fig. 13) occurring between regions of "acceleration". Therefore the theory postulates that the intermediate cells of the lower pathway which do not send dendritic processes to the molecular layer are being directly stimulated at the region immediately below the stimulating electrodes (possibly through direct stimulation of axons of Scholl's S_2 type of stellate cell). These interlinking cells might well be a mixture of Scholl's S_1 and S_2 types of stellate cell. Scholl found the S_1 type to occur in

very high numbers at Zone III (550-850 μ below the pial surface) of the visual cortex of the cat (Scholl, 1955). These are represented diagrammatically in Fig. 16. It should be noted that the first interval in this system is 4.0 mm since it is composed of one and a half of the major intervals which are 2.7 mm long. This situation represents that of the composite curve drawn in Fig. 13.

The major assumption in this theory is that conduction from cell to cell along the lower pathway must take place through electrotonic junctions occurring at points of contact between dendritic fibres. This assumption is required from the original hypothesis that spread of activity be passive and decremental. Junctions of an electrotonic nature have been found in the nervous systems of certain vertebrate as well as invertebrate species (Pappas and Bennett, 1966; Bennett, Aljure, Nakajima and Pappas, 1963; Bennett, Pappas, Gimemez and Nakajima, 1967). Direct histological evidence is lacking as to the existence or non-existence of similar electrotonic junctions in the suprasylvian gyrus of the cat. Nevertheless, the high degree of success of the model described in the following section begins to make quite plausible the suggestion that electrotonic transmission is responsible for the lateral spread of the surface-negative response.

E. A RESISTANCE-CAPACITANCE MODEL TO TEST THE NEW THEORY

As mentioned in the INTRODUCTION section of this thesis, Pinsky (1967) noted that the shape of the surface-negative response recorded at different distances from the site of stimulation bore a marked resemblance to the shape of transient waveforms which may be recorded at different sections of a resistance-capacitance model of a dendritic fibre. Fig. 17 shows a surface-negative response recorded from the pial surface of a cat's isolated suprasylvian gyrus at three different distances from the stimulating electrodes. These waveforms should be compared to those of Fig. 18 which were recorded from different sections (whose number is shown to the left of each waveform) of a resistance-capacitance transmission line model of a dendritic fibre. The model fibre is depicted in the lower half of the diagram. The parallel resistance and capacitance for each section of the transmission line represent the membrane resistance and capacitance to be found per unit length of an unmyelinated nerve fibre. The series resistance linking the sections together represents the axoplasmic resistance. A brief pulse (shown in the uppermost trace) is fed into the input of the fibre model to produce the transients shown in the lower three traces.

An S-shaped curve is obtained when the peak latency of the transient waveform is plotted against the number of RC-sections between the input of the transmission line and the point of recording. Fig. 19 shows a general curve of this type obtained from a model which consisted of 46 RC-sections and represented a fibre of arbitrary diameter.

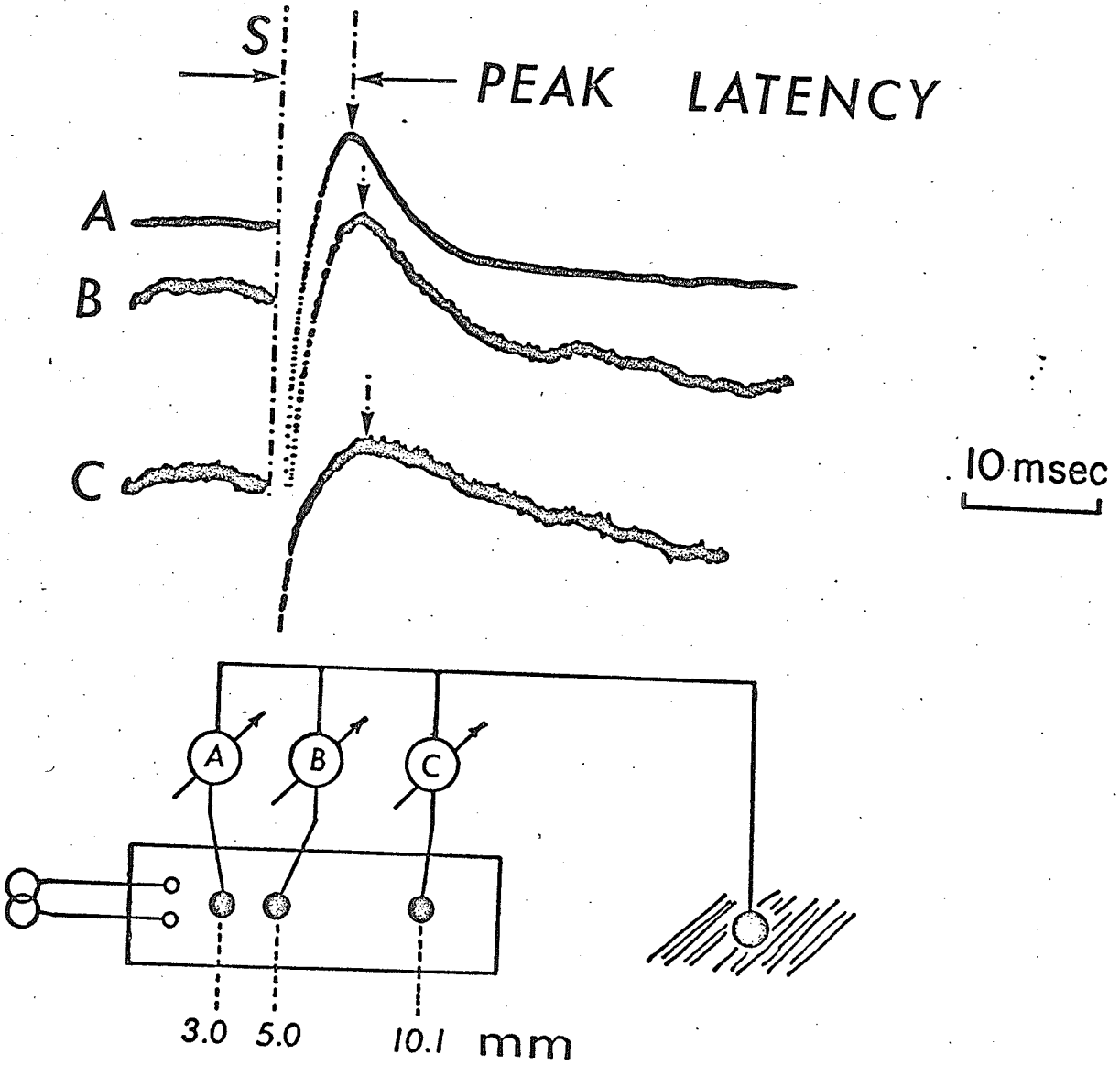

FIG. 17 A SURFACE-NEGATIVE RESPONSE RECORDED SIMULTANEOUSLY AT THREE DIFFERENT DISTANCES FROM THE SITE OF STIMULUS IN AN ISOLATED CORTICAL SLAB. LOWER HALF OF DIAGRAM SHOWS STIMULUS-RECORDING SETUP. VOLTAGE GAINS ARE DIFFERENT FOR EACH TRACE.

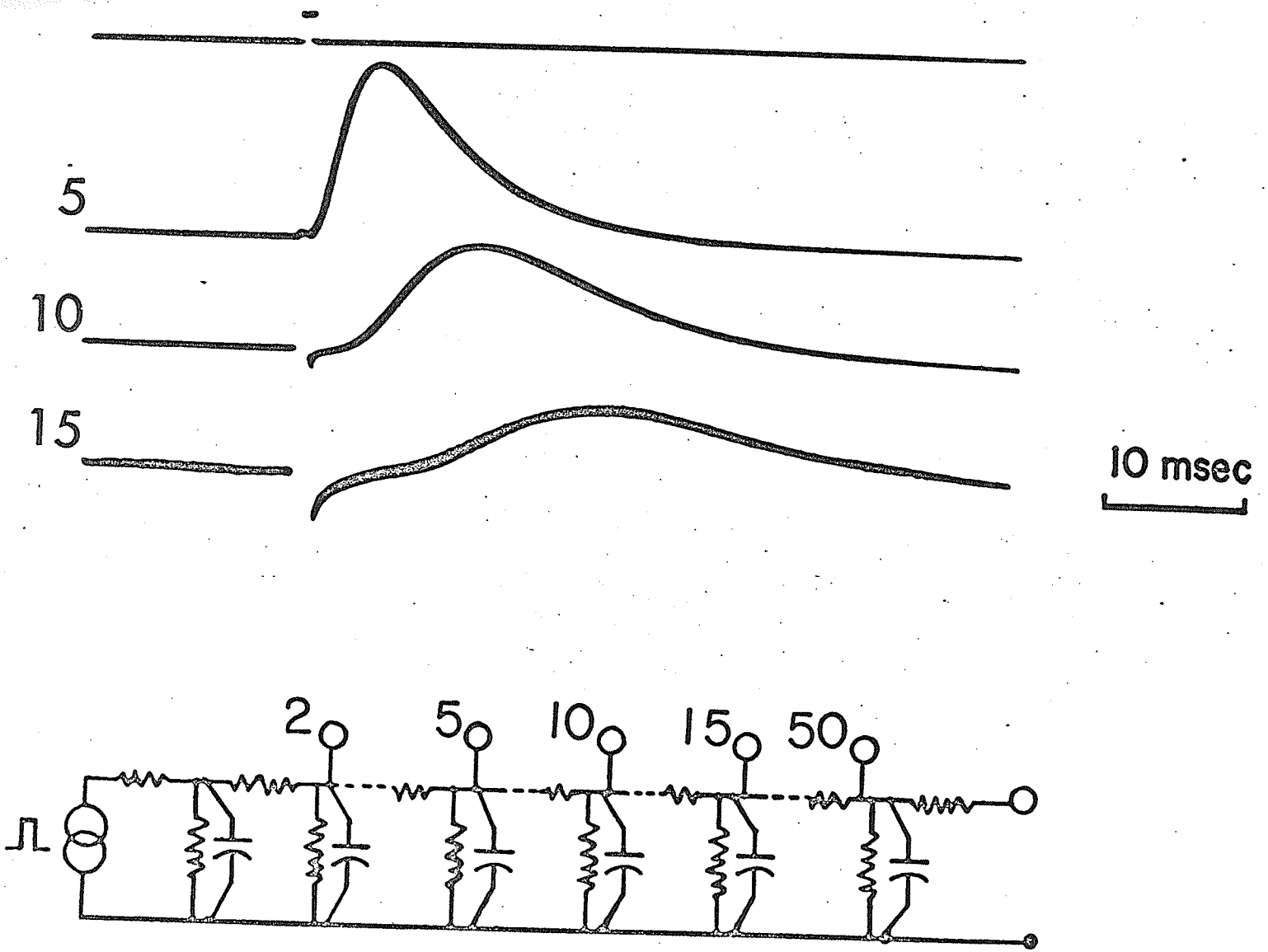

FIG. 18 RESPONSE OF AN RC FIBRE MODEL TO A BRIEF PULSE. WHEN A BRIEF VOLTAGE PULSE (UPPER TRACE) IS APPLIED TO THE INPUT OF THE RESISTANCE-CAPACITANCE FIBRE MODEL (LOWER DIAGRAM), THE TRANSIENTS SHOWN IN THE LOWER THREE TRACES CAN BE RECORDED AT THE SECTION WHOSE NUMBER APPEARS TO THE LEFT OF THE TRACE. DIFFERENT VOLTAGE GAINS WERE USED FOR EACH TRACE.

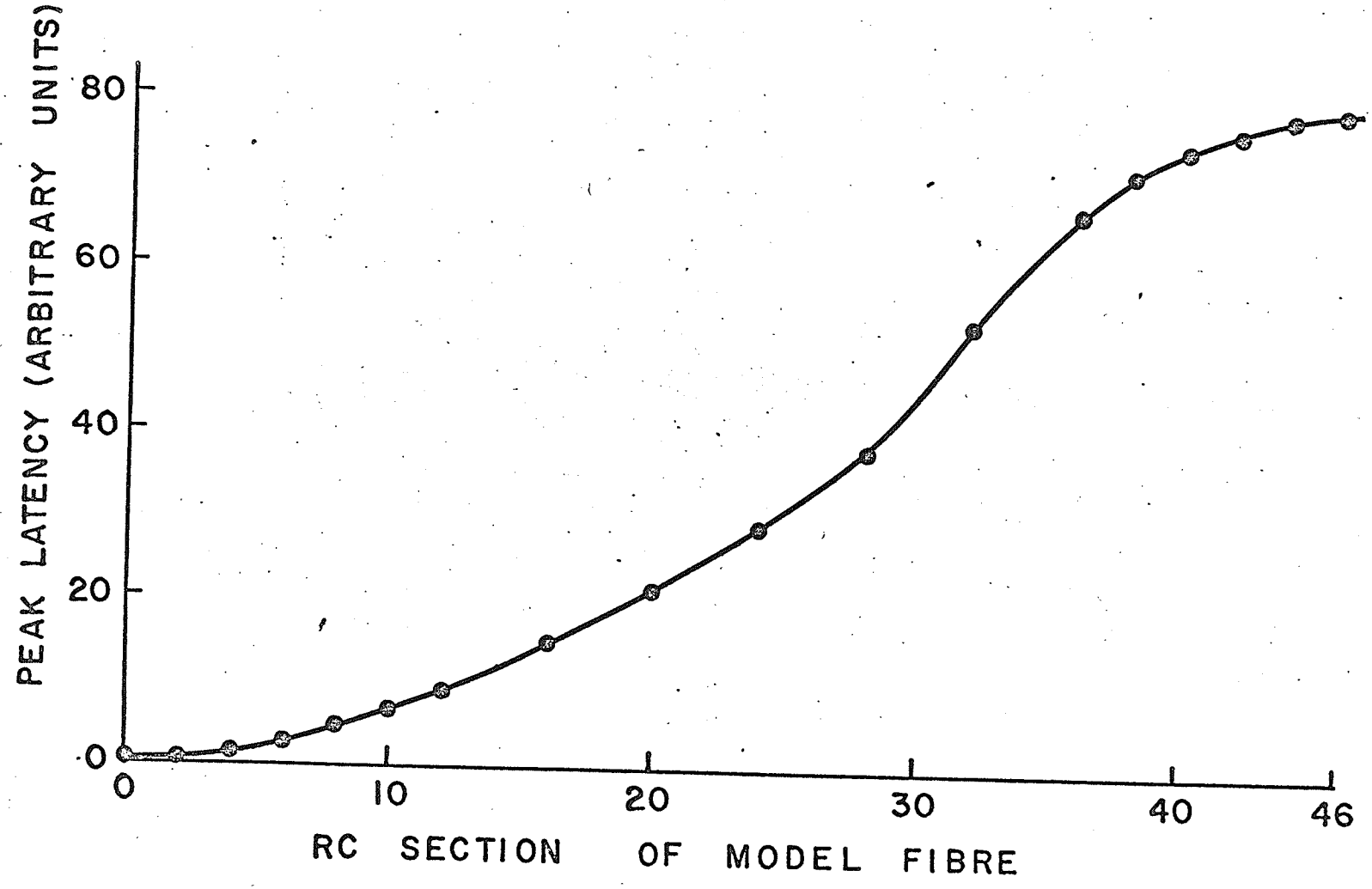

Fig. 19 Graph of Peak Latency vs. Distance for a 46—Unit Fibre Model of Arbitrary Diameter

The theory put forward in the preceding subsection was tested by constructing two such RC transmission lines to model dendritic fibres of two different diameters. These were coupled at regular intervals as shown in the lower portion of Fig. 20. The diameters of the modelled fibres were chosen on the basis of the data presented by Scholl (1953). It can be calculated that, in the visual cortex of the cat, the average diameter of the seven basal dendrites which Scholl reports is about 3.0 μ at a distance of 20 μ from their perikarya. On the other hand, the average diameter of five apical dendrite fibres (from the visual cortex) at a distance of 140 μ from their apical ramification (i.e., at a point in the molecular layer) can be calculated to be about 1.4 μ. This latter measurement, however, is very likely to have been based on a biased sample since the resolution of the optical microscope does not go much beyond 1 μ and this would prejudice against the observation of many small fibres. It is highly probable then, that the average diameter of apical fibres in the molecular layer may well be less than a micron. For this reason, in the construction of the RC model, a ratio of 4:1 was chosen to represent the diameters of the lower and upper dendritic pathways respectively. Also, for the sake of convenience, a further approximation was made in that the model fibre representing the upper pathway was constructed to mimic a dendritic fibre of 1 μ diameter, and that representing the lower pathway was constructed to mimic a dendritic fibre 4 μ in diameter. Details of the calculations used to arrive at the actual values of resistance and capacitance to represent fibres of the chosen diameters have been provided by Fatt and Katz (1950).

It so happened that each RC section of both the models representing fibres of the two chosen diameters corresponded to a dendritic fibre length of 0.6 mm. Since 3 is an integral multiple of 0.6, it was easier to construct a model system on the basis of an interval value of 3 mm such as existed in the single experimental curve of Fig. 9, rather than on the interval value of the composite curve of Fig. 13 whose mean value was about 2.7 mm. Hence, the model was constructed to simulate the situation in Fig. 9 instead of that in the composite curve.

The upper portion of Fig. 20 illustrates the rationale behind the choice of coupling points in the model. Three RC-sections were chosen to represent the initial one-half interval and five RC-sections to represent each of the full intervals (3 mm apiece). One RC-section of 4 μ line (equivalent to an ascending fibre distance of about 0.6 mm) was thought adequate to represent the linkage distance between the two pathways. An approximation to this situation was achieved simply by adding an extra RC-section of 4 μ line to that part of the 4 μ pathway which joins the point of stimulus to the first point of coupling. The two RC lines were connected at each coupling point by a resistance whose value was made equal to the square root of the product of the series resistances used in the two lines. This choice of coupling resistance was arrived at by analogy with the situation where two transmission lines of unequal impedance are coupled to each other by a transmission line whose characteristic impedance is the geometric mean of the two (Slater, 1942).

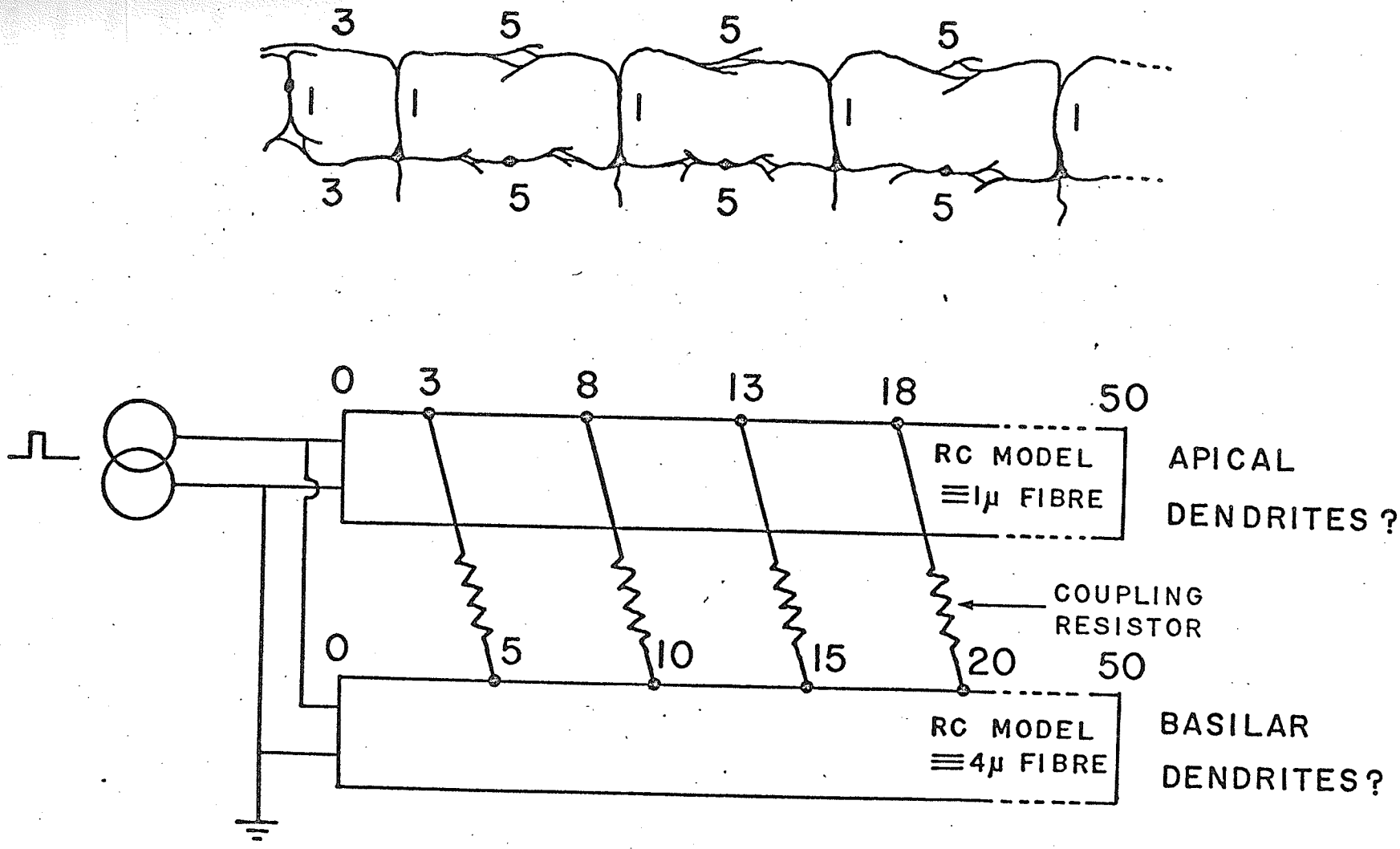

Fig.20 Upper diagram shows the number of RC sections chosen to represent various portions of the theoretical pathways. Lower diagram shows final RC model.

Each of the lines was composed of 50 RC-sections. It may be seen from Fig. 19 that, in such a transmission line, the curve relating peak latency to the number of sections distant from the input is described by an essentially straight line between sections 5 and 20. Hence it may be taken that any marked deviations from this degree of linearity over the same portion of the 1 μ pathway represented in the model are due solely to interactions between the two pathways.

The final version of the two-pathway model is shown in the lower diagram of Fig. 20. Brief (1.0 msec) voltage pulses were applied to the input of the model and measurements were made of the peak latencies of the transient wave patterns recorded at each section along the 1 μ line up to section No. 18. The curve of peak latency vs. distance obtained from the model is plotted in Fig. 21. It may be seen that this curve is remarkably similar in form to the biological curve of Fig. 9.

An obvious difference between the two curves, however, is seen when the overall slope of the model curve is compared with that of the biological one. A best-fit straight line for the biological data shown in Fig. 9 gives a slope of 0.808 msec/mm. The best-fit straight line for the model data, based on a value of 0.6 mm equivalent fibre distance per RC-section, has a slope of 1.57 msec/mm. These differences in slope may largely be due to the choice of too large a membrane time constant in the model. A value of 10 msec was chosen for this since such a value is reasonably close to that of 7.5 msec which Rall (1960) estimates as the membrane time constant for cat motoneurons, and also since 10 is a more convenient number than 7.5 to work with mathematically. The true value of the membrane constant of dendritic

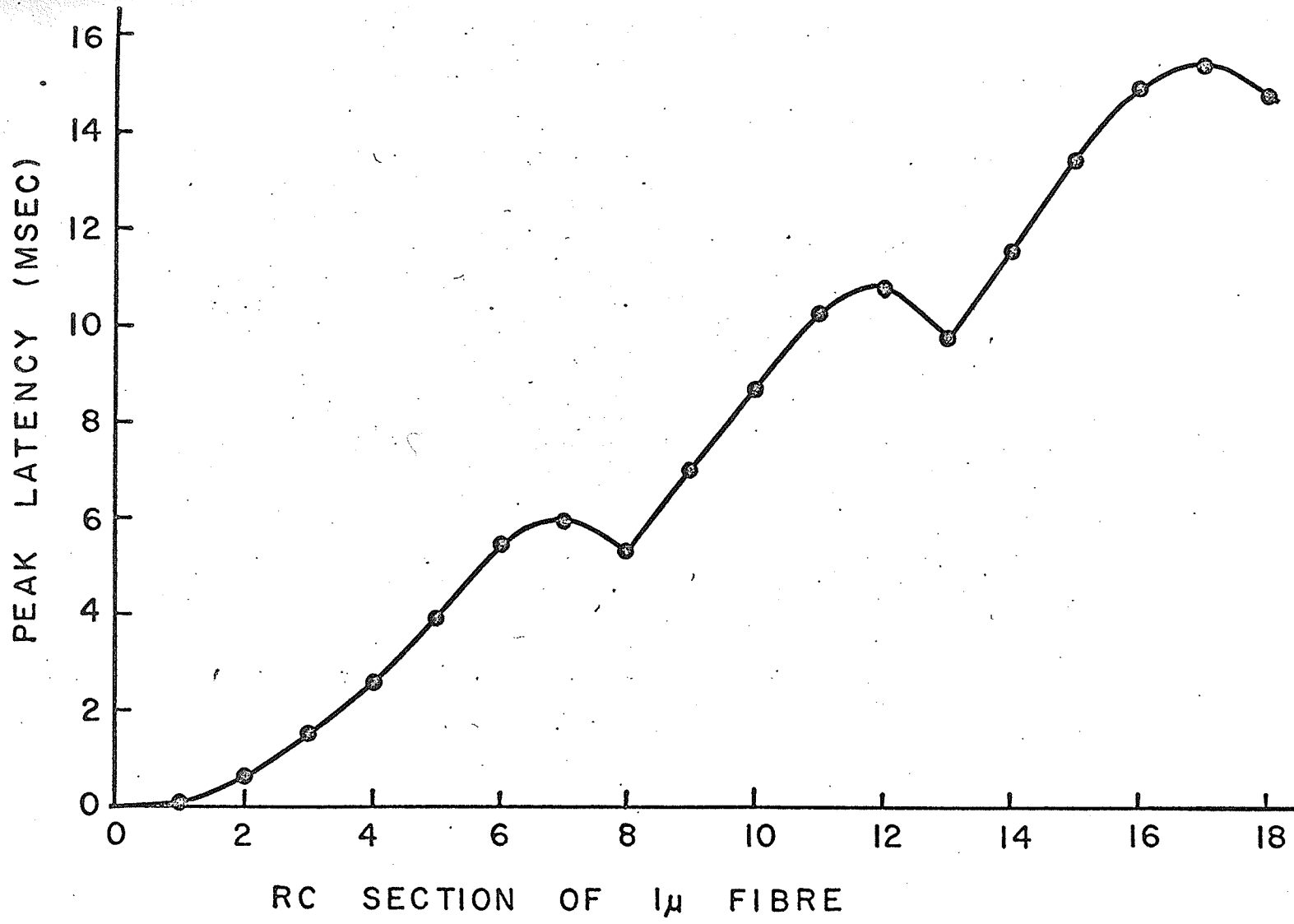

Fig.21 RC Model

fibres in the cerebral cortex is unknown. Nevertheless, if lateral transmission of the surface-negative response does actually take place via dendrites then the curve of peak latency vs. distance obtained from Experiment No. 7 (see Fig. 9) suggests that the membrane time constant of the dendrites carrying the response is smaller than 10 msec but that it is also much larger than the membrane time constant of about 1 msec observed for invertebrate axons (Hodgkin, Huxley and Katz, 1952). Such membranes are mentioned here for comparison since they have no myelin sheath as is the case for dendrites in the cerebral cortex of mammals. It is likely, then, that the membrane time constant of dendritic fibres in the cerebral cortex of the cat has a value which lies between 1 and 10 msecs and it may be hazarded that a value of 5 msecs is not an unreasonable suggestion for this parameter.

Another difference between the curves obtained from the model and from the biological data is seen in the observation that the curve plotted from the model starts out with a value of peak latency which is very close to zero whereas the curve in Fig. 9 starts out with a peak latency of 3.7 msecs. An initial value of peak latency comparable to that in Fig. 9 was present in all the peak latency vs. distance curves obtained in this study. This value represents the time required for the regenerative mechanism (which was initiated by the stimulus current) to reach its peak of activity.

In order to make the model curve more suitable for comparison with the biological curve shown in Fig. 9, a value of 3.7 msec was subtracted from the highest point (12.7 msec) of the latter curve (as fitted to the data points in Fig. 9). The ratio of the value so obtained (9.0 msec) to the highest point of the model curve (15.5 msec) was taken

to be the conversion factor necessary to adjust the difference in slope which could be accounted for by the use of an incorrect membrane time constant. Each point of the model curve then was multiplied by this conversion factor (0.58) and to this product was added 3.7 msec to compensate for the time presumably required for the biological generator to reach its peak activity. These modified values of peak latency for the model curve are shown plotted in Fig. 22 along with the curve from Fig. 9; it can be seen that the two curves are very similar.

The "widths" of the regions of "acceleration" in the model curve are approximately equal, ranging from about 0.7 to 0.8 mm. This is comparable to the mean "width" of 1.0 mm for the regions of "acceleration" of the composite curve (Fig. 13). The steepest slopes for each of the S-shaped components of the model curve are 1.46, 1.62 and 1.75 msec/mm, listed in order of occurrence from the input of the model. This pattern of slopes increasing with each successive S-shaped component agrees well with the tendency shown by the data for the composite curve in Table IV.

To test statistically the degree of similarity between the two curves plotted in Fig. 22 their correlation coefficient was determined. Peak latencies for the points of the biological curve were compared with the values of peak latency predicted by the model curve at the same "distance" measurements. The coefficient of correlation was found to have a value of 0.961. While this is a very high degree of correlation, it should be noted that the correlation coefficient for the biological curve and a best-fit straight line determined by least squares analysis was found to be 0.947. This value,

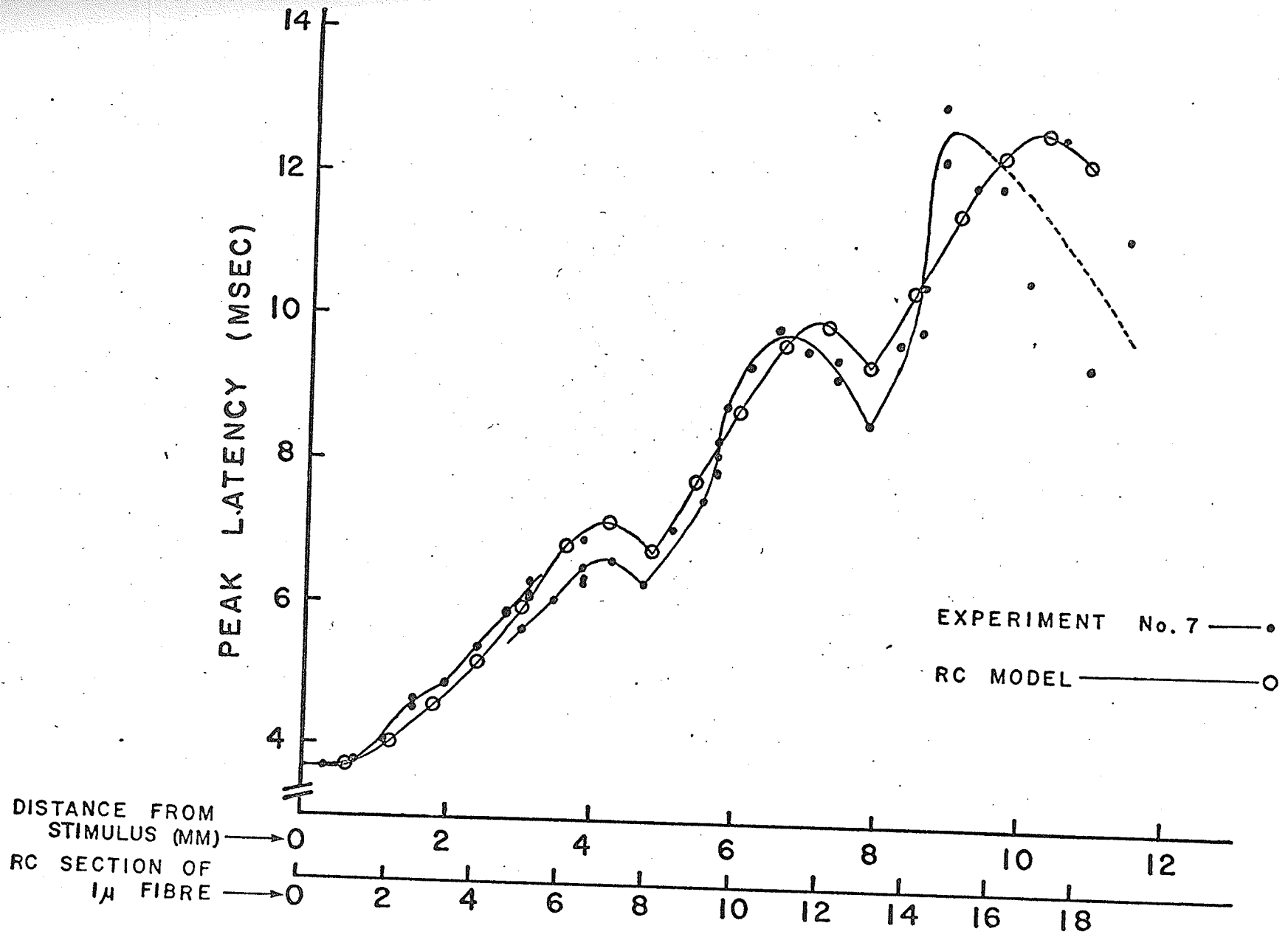

Fig.22 Comparison of Exp. No.7 with RC Model

while slightly lower than that for the model curve, does not differ significantly from it. It cannot, therefore, yet be said that this model, as it stands, is significantly better than a model which would generate the best-fit straight line relationship between peak latency and distance from input.

The failure of the model to mimic the biological curve significantly better than the best-fit straight line does not mean that the theory behind the model is incorrect or no better than a theory which would generate a straight line relationship between peak latency and distance from the stimulus site. It simply means

(1) that the model has to be modified slightly to fit better the biological picture which Fig. 9 represents. For instance, the fact that the regions of "acceleration" in the curve of Fig. 9 are more pronounced than those of the model curve may indicate that a diameter ratio greater than 4:1 should have been used in the fibre models representing the two pathways.

(2) that the spread of values at the points of "reference" in Fig. 9 has to be reduced or eliminated. This has been accomplished in the experimental curves of Fig. 10 and 11 where six recording channels, instead of only three, were used simultaneously. Unfortunately, a Type I curve, which the model was constructed to mimic, has not yet been obtained with this improved recording technique.

Models have not yet been constructed to mimic the biological situations represented by Type II and Type III curves. If the theory presented in the previous subsection is correct, the regions of relative flatness observed in the Type II curves may indicate the presence of a very high number of coupling points, occurring very close together over a spread of about 3 mm, between the two pathways. Alternatively, the Type II curve may result from multiple lower pathways of varying velocities which couple to the surface pathway over the region of relative flatness. The higher velocity pathways would couple to the surface pathway at the more distant points in the region of relative flatness.

The Type III curve (almost linear) might be explained on the basis of very "loose" coupling between the two pathways (i.e., the lower pathway sends far fewer fibres to the surface at the regions of "acceleration" than it would in the case of the Type I curves). Another explanation for the Type III curve could be that the ratio of fibre diameters in the two pathways is less than 4:1.

F. A MEANS OF CONVERTING TIME INTO SPACE AS SUGGESTED BY THE EXPERIMENT SHOWN IN FIG. 14

The curves plotted in Fig. 14 suggest a mechanism whereby the brain might distinguish the time interval between the arrival of activity at two points separated by a distance of only a few millimeters in the cerebral cortex. With the curves plotted as they appear in Fig. 14, they intersect each other at 0.9, 5.7, 6.0 and 6.6 mm from S_1.

This indicates that maximum interaction (e.g.,summation) of the responses to the two stimuli would have occurred at these points of intersection if S_1 and S_2 had been applied simultaneously. However, if the two stimuli had not occurred simultaneously, e.g., had S_1 occurred 100 μsec after S_2, then different points of intersection (and interaction) would have resulted. The new points of intersection would be found simply by raising the entire S_1 curve by 100 μsec in peak latency. Since the points of interaction have changed, the brain now has information which differs from the situation where S_1 and S_2 occurred simultaneously. The brain can now recognize this new pattern of interaction as an indication that S_2 occurred 100 μsec later than S_1.

Similarily, the brain would receive a different pattern for any other time intervals (within about $\pm$ 2 msec) between S_1 and S_2. The points of interaction for one dimension in the brain (i.e., a straight line along the surface of the cortex may be found simply by shifting the S_1 curve up by an amount equal to the interval value for cases where S_1 occurs after S_2, and down by this amount where S_1 occurs before S_2).

The degree to which the brain could distinguish one interval from another (i.e., its time resolving ability) should depend upon the total number of possible points of interaction between the responses in different pathways. Conceivably, this can be very high in the three-dimensional system which the cerebral cortex provides. Not only is there a high density of cells (60 cells per 10^6 μ^3; Scholl, 1953) in the cortex but, also, each of these cells has multiple inputs; each of these inputs in turn, would have its own unique effect on the cell depending upon the distance of the synapse from the soma and, as well, on

the sequence of impulse arrival at individual synapses (Rall, 1961, 1964; Pinsky, 1967). An idea of the enormity of possibilities involved may be conjectured from Scholl's estimate (Scholl, 1953) that the region infiltrated by the dendrites of a single cell contains between 2000 and 4000 perikarya, and from Eccles' estimate that the number of synapses on the dendrites of a single large cortical cell may be in excess of 10,000 (Eccles, 1966).

Taking such estimates into consideration it is not inconceivable that the time resolution of the cortex may be an order smaller than a microsecond---perhaps even as small as one-tenth of a microsecond---and this would be accomplished not with well-defined pulses, having sharp leading and falling edges such as those used in modern computers, but with waveforms similar in shape to those seen in the surface-negative response!

It is not difficult to conceive that a system of many interacting pathways functions in the brain to analyze various important aspects of sensory information arising from the external or internal environment. An informational feature of importance to such a system will be contained in the time interval between impulses arriving in the cortex at unique points which are sufficiently close together to permit interaction between the responses generated at those points. For example, the locale of a point source of sound in the external environment could be recognized by the detection, in the postulated interacting system, of the difference in phase between the sound pressure variations in the listener's two ears. The resolution of this detection has been shown to be as small as 6 μsec (Klumpp, 1953), a value already discussed as well within the capability of an interval-detecting system that can be deduced from the results illustrated in Fig. 14.

The existence of another system for the recognition of detailed sensory information might be extrapolated from the suggested ability of the brain to convert a temporal pattern into a spatial pattern. The system of interaction pathways could equally well convert spatial patterns on the retina into spatial patterns of interaction in cortical dendritic pathways. It is worth noting that a sufficiently extended version of the two-pathway model shown in Fig. 20 of this thesis is potentially useful as a real-time computer for recognition of temporal and spatial patterns.

Finally, it might be speculated that the process of sensory experience or of learning might in some way be a determinant of those neuronal features important to the temporal-spatial and spatial-spatial systems described above. These features might be very simple factors such as fibre diameter or synaptic density. If there is such experience-related modification of pathways in the interacting system then recognition by the brain of both temporal and spatial patterns might be expected to be related to discernible ordered arrangement of neurones and their associated processes in the cerebral cortex.

VI. CONCLUSIONS

The following conclusions may be drawn from the results obtained in this study:

(1) The relationship in the cat's cerebral cortex between the peak latency of the surface-negative response and the recording distance from the site of stimulus is not adequately described by a straight line. This relationship, while it contains a significant linear component, is actually quite complex. There are periodically-spaced regions of "acceleration" present in all the curves plotted to describe the relationship. Another obvious deviation from linearity is seen in regions of relative flatness which occur in some of these curves.

(2) A passive resistance-capacitance network was constructed to reproduce, in a physical model, the essential features of the peak latency-distance relationship observed in the biological preparation. Certain tentative conclusions may be drawn from that network which was finally arrived at to best reproduce the biological result:

(a) The surface-negative response travels along two different pathways in the cerebral cortex. One of these pathways runs near the surface of the cortex (presumably in the molecular layer) and the other pathway runs in deeper (submolecular) layers. The latter pathway intersects with the surface pathway at regular spatial intervals.

(b) Each of these regularly-spaced pathway intersections coincides with the end of a region of "acceleration" in the curve relating peak latency

to stimulus-recording distance. The distance between these regions is about 2-3 mm.

(c) The velocity of response transmission differs in the two pathways. Lower response velocity occurs in the molecular layer pathway. The difference in velocity may be accounted for by the difference in mean diameter of the fibres which constitute the respective pathways. Fibres belonging to the faster conducting pathway in the submolecular layers have the larger mean diameter; this is about four times the mean diameter of fibres in the molecular layer pathway.

(d) Many features of the biological response and their correspondence with the behavior of the electrical model are, at present, most economically explained by assuming that electrotonic junctions exist between neurons in the pathways which carry the response.

(e) Dendritic fibres in the cerebral cortex of the cat have a membrane time constant of about 5 msec.

(3) The resistance-capacitance model produced a result which fits the biological data better than does a best-fit straight line. However, both the electrical model and the acquisition of biological data will have to undergo certain refinements before a statistical significance can be shown for the difference in fit.

(4) All points on the cerebral cortex, even those only 2 mm apart on the same gyrus, cannot be considered to be physiologically identical.

VII. RECOMMENDATIONS FOR FUTURE WORK

Considerable amounts of information can be obtained from the techniques used in this study for the analysis of waveforms generated in the cerebral cortex. It is strongly recommended that these techniques be extended and improved upon. This should take place along two major lines:

(1) Electrode assemblies should be designed to record surface potentials from points 200 to 300 microns apart from one another on the cerebral cortex. These assemblies should be constructed so as to permit surface recordings in 2 dimensions instead of the single dimension (i.e., a straight line along the length of the gyrus) used in this study. Also electrode systems should be designed to permit simultaneous recording from points at different depths (100 to 200 microns apart) within the cerebral cortex. The ultimate, of course, would be to have a recording assembly which permits simultaneous recording from a three-dimensional matrix of points which are within 100 to 300 microns of each other. No doubt this would give us a very close approximation of the manner in which the cortex itself "sees" the information which it receives, processes, stores and produces.

(2) Data recording and analogue-to-digital (A-D) conversion should be attempted simultaneously on as many channels as possible in order to avoid errors due to slight movement of stimulating or recording electrodes or to alteration in the condition of the animal. Such errors inevitably result from having to record individual points at different times. High-speed A-D converters should be used to achieve

a data sampling rate of about one sample per 20 μsec in each channel. With this facility the vast amounts of digitalized information which would ensue from the simultaneous handling of many recording channels could immediately be stored in a memory buffer of large capacity and with multiple parallel access. It could then be fed more slowly, between stimuli, into a high-speed digital computer for averaging and analysis. The experimenter would then have results quickly enough to decide how to continue with the experiment, e.g., to produce a lesion at a certain location. With regard to the surface-negative response, other parameters, such as response amplitude and waveform area, should be measured to determine the relationship they have with respect to recording distance from the site of stimulus.

Precise surgical techniques should be developed to produce strategically located lesions in the cortex. This would permit a comparison to be made between the curves of peak latency vs. distance obtained just before and immediately after placing lesions selectively in the molecular or submolecular layers of the cortex.

Correlative histological studies should also be carried out to determine the exact location of lesions and placement of electrodes. Furthermore, relationships between cytoanatomic structures and physiological results (e.g., the presence of electrotonic junctions) might be found with the use of such techniques as phase-contrast and electron microscopy.

Experiments should be done to determine the resolution of the structural "fields" which carry the surface-negative response. This could be accomplished by finding out how far a monopolar stimulting electrode would have to be displaced from a given point on the

cortex before a new curve of peak-latency vs. recording distance is produced.

Sensory-evoked responses could also be very profitably studied with the suggested techniques. It is quite conceivable that these will be powerful enough to enable the experimenter to tell, solely from an examination of cortical responses, what sort of stimulus is being presented to the animal. For example, an experimenter studying responses in the visual area of the cortex might be able to deduce, from an analysis of the responses, the nature of an image being flashed on the animal's retina. The image of a triangle might be expected to produce a unique pattern of cortical responses which is distinguishable from the response pattern produced by a square or a circle.

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