RECENT ADVANCES IN INVERTEBRATE PHYSIOLOGY

Recent Advances in Invertebrate Physiology

A Symposium

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FOREWORD

The idea of a meeting on the Pacific Coast of physiologists interested in the invertebrates was first conceived by Professor A. W. Martin of the University of Washington. In December 1954, he asked the members of the editorial committee for this volume to work with him in organizing a symposium on recent advances in the physiology of the invertebrates. When plans were well along, in the early spring of 1955, certain actions of the administration of the University of Washington were interpreted by many of the invited speakers and members of the committee as prejudicial to accepted principles of academic freedom. As a result, the present writer was asked to accept responsibility for completing the organization so well begun by Professor Martin, and the meeting was held on the campus of the University of Oregon in Eugene in September 1955. We are especially indebted to the National Science Foundation, which provided the bulk of the funds for travel expenses, board, and lodging for the participants in the meeting, and underwrote the publication of this volume. The Tektronix Foundation of Portland, Oregon also contributed generously to the support of the meeting, and the University of Oregon provided facilities and secretarial and administrative assistance.

The primary aim of the symposium was to afford an opportunity for physiologists interested in the invertebrates to become better acquainted personally, and to exchange information and ideas. In this aim, the meeting was eminently successful. Limitations of time and funds made it impossible to bring together more than a small group; the present volume is designed to bring to a wider audience some of the material presented at the symposium.

The committee wished to place as few restrictions as possible on the free interchange of views. Consequently, no attempt was made to obtain verbatim accounts of the formal presentations or of the subsequent discussion. The papers in this volume were prepared by the authors to cover the same material as their oral presentations, but are not necessarily identical with the papers as they were read. It will be obvious to the reader that the papers are of various types. Some are reviews of a large amount of material from an entire field; others are accounts of personal research in a more limited field. Two papers presented at the meeting, by C. L. Prosser and T. H. Waterman, are not included here. B. J. Krijgsman, whose paper is included, was unable to attend the meeting. It was impossible, within our limitations of space, time, and funds, to cover the whole vast subject of invertebrate physiology; the selection of subjects included

here, though to some extent arbitrary, may be said to give a fair representation of the most active areas of research at the present time.

I should like to take this opportunity to express my personal gratitude to the other members of the committee for their helpful cooperation in planning the meeting, and in the preparation of this volume; to Miss Marjorie Foxworthy (now Mrs. Charles Turbyfill) for her many services before, during, and after the meeting; to Mr. Robert P. Bronson for his help with travel arrangements; and to my students, A. S. Hu, R. M. Myers, J. H. McAlear, and R. V. Crisera, for their help during the meeting. Mr. George N. Belknap, University editor, and Mr. Donald Shepardson, superintendent of the University Press, have been very helpful in seeing the book through the press.

BRADLEY T. SCHEER
Eugene, Oregon

CONTENTS

NEURONAL INTEGRATIVE MECHANISMS*

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Integration is to put parts together into a whole. Such a process occurs in organisms at many levels, from the subcellular to that of the community. The levels of interest for the present purpose begin with a whole neuron, therefore do not embrace an analysis of the mechanisms in the cell or its membrane, and extend only one or two steps up the hierarchy, through closely knit groups of neurons to relations between such groups, but not so far as the level of the whole nervous system of any animal. This limitation is not one of appropriateness but is imposed by our methods and present understanding, as physiologists.

Indeed our understanding of the actual mechanism of nervous integration, our insight into the unit behavior which might account for this subtle and complex result, is so meager that it may be asked, what can we say? This paper makes no pretense of accounting for very much normal behavior, and will conclude by emphatically invoking as yet unknown levels of interaction; but it makes an effort to say what can be said today about the properties of neurons which must be involved in, and in certain cases appear even to account for, the observed integration. It goes little beyond a list of the properties—each of which provides a degree of freedom or an available mechanism for altering the input-output function. These properties generally are additive, so that with only a few it is possible to obtain rather complex permutations. Still our knowledge permits a very limited foray into the vast field of higher nervous integration, and I am emboldened for it only because so few have undertaken to bring together the several mechanisms that are now known (see Fessard, 1954, 1956), while one often still hears instances of thinking on these problems in which the neurons are treated as purely digital or are otherwise oversimplified.

One further disclaimer is necessary. We must deal with observed properties of neural units even though they cannot be explained by current theories of cellular mechanism. So we are not accounting for the properties; rather in enunciating the phenomena which may explain higher levels, we are formulating the problems awaiting attack at molecular levels.

Let us return to the definition of our problem. Integration, I said, paraphrasing the dictionary, is to put parts together into a whole.

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Now, what is the whole which is referred to? At the levels below behavior, neurophysiologists today regard it as a pattern in time and space of quantal events, each event brief compared to the events of behavior; these are the impulses in the efferent nerve fibers. At the level of the single neuron we may perhaps best express the whole as the probability of firing within the next given interval of time, or we may revise "firing" to read "change of state influencing another neuron," since it seems to me important to recognize the possibility of subthreshold events as adequate stimuli even though clear cases are not yet known. We can formulate our definition in simple terms like these if we but recognize, and then put aside for the present, those variables which the neuron integrates into its probability of firing which are not immediately determined by other neurons, e.g., general chemical milieu, physical deformation, and temperature. Expressed in terms of impulses or changes of state effective upon other neurons, integration at the unit level then becomes in the general case a relation between input and output which is either more or less than one. Usually this means the algebraic summing of separate neuronal channels one or more of which produces more or less than one output pulse for each input pulse; so long as this is true, the channels may have equal or different weights in their effect upon output and the same or opposite sign, i.e., excitation or inhibition. But we have to admit also the case where only one input channel reaches the neuron under consideration, for in our type of system a qualitative difference between inputs is not an essential condition; the integrating cell does not know whether the signals come in the same or different channels. The essential feature is that the neuron place some value, other than one, upon at least some of its incoming signals, according to their intensity, time course, time of arrival, and the locus upon the neuron where they impinge. This definition of integration at the neuron level will then include all junctions except those that are purely 1:1 relays. It will certainly include many neuroeffector junctions in which therefore the nonnervous cell is the integrating cell. Sensory neurons certainly integrate in the broad meaning given first, putting together different quantities in the milieu into a probability of firing. And they may do this in part by means or with properties which will help us to illuminate junctions. But if any should object to the notion that receptors already integrate, they may wish to exclude receptors on the ground that there is no input from other neurons —it is not nervous integration. But sometimes there is! The same cell, the same terminal ramifications may be transducers of mechanical simuli and postsynaptic elements under nervous control (e.g., Kuffler and Eyzaguirre, 1955; Lowenstein, 1956).

You have patiently listened to my definition of integration. We are supposed to talk about recent advances in invertebrates, and I must accord-

ingly confide in you my definition of this category. For present purposes invertebrates shall mean any animals which an invertebrate zoologist finds interesting.

Some Properties of Units Permitting or Influencing Integration

At the level of the single neuron we may first list a number of the properties or conditions which classical or recent experimental facts indicate as the probable bases of the ability of the neuron to integrate incoming signals. Obviously all the static and dynamic characteristics of the cell more or less directly permit or determine the activity, but we shall enumerate only some of them, at the same time expressing the hope that extension of intracellular analysis like those of Hodgkin, Huxley, Katz, Cole, Grundfest, Eccles, and others will isolate further factors and show their degree of lability and variation in junctional membranes.

The *resting potential* is often thought of as a fixed character which has only one value which is "normal," its maximum value. The evidence, however, can be construed to suggest that some synaptic regions normally have a membrane potential which is less than its maximum, and can be pushed either way and maintained at new levels. The level of this potential affects not only the spike height but the excitability and the magnitude and sign of after-potentials and of subthreshold responses.

Spike threshold and its time course after activity, the excitability cycle, require no development here beyond the reminder that we have little information on these crucial properties in synaptic regions of various preparations and animals. *Accommodation*, in particular, has not been examined comparatively or in junctional regions; and examination is the more necessary since the recent discovery that the classical rise in threshold with slowly rising stimuli does not in fact obtain in the frog axon free of connective tissue. (Tasaki and Sakaguchi, 1950; Diecke, 1954). There are, however, other effects of maintained or slowly changing subthreshold depolarization, as on the form and size of the spike. This is important for us because of the possibility that the action of terminals, dendrites, and somata may be similarly influenced (see below under subthreshold lability). There may be great differences in the minimal slopes, below which threshold is never reached, in different types of neurons.

Based on the distribution of thresholds or of synaptic endings in a group of neurons, there can be curves of various shapes relating input (number of synchronized fibers) to output (number of postunits firing). The variable relation of input to output becomes of greater potential value as an integrative mechanism when the output of one group of neurons is in

turn the input for another order of neurons and both have nonlinear curves. Addition of output-input curves can in the extreme case readily produce a step function, representing a kind of labile multiunit threshold providing stability and discrimination (Fessard, 1954).

Besides the spike threshold we must recognize a separately variable *subthreshold excitability*. This is manifested as a nonlinear increase in the membrane potential with increase in stimulating current below spike threshold (Fig. 1). The active, graded response which does not propagate does not have a threshold, but it has a very labile excitability.

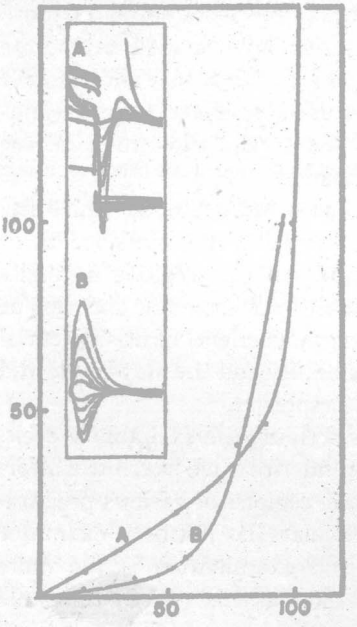

Fig. 1. Stimulus-response relation of the subthreshold local potential in the third-order giant fiber of the squid. Stimulus applied to the stellate ganglion directly; recording from the same ganglion. Two experiments are shown: A. Cathodal stimuli, whose voltages are shown by the upward deflected square tops, elicit local responses, whose amplitudes are shown by the downwards deflected triangular waves, plus one spike which goes off scale and is seen as a descending phase above the base line. Plotted as per cent of threshold on abscissa, per cent of maximum recorded local potential on ordinate (spike off scale). B. Cathodal stimuli (not shown) give responses above base line, anodal stimuli of same intensity below. Plotted as above but ordinates are cathodal response minus anodal to show the development of nonlinear, nonelectrotonic, "active" local response. (From Bullock, 1948; reprinted with permission of the *Journal of Neurophysiology*.)

Subthreshold activity exhibits lability also in other ways (Bullock, 1948; Bullock and Hagiwara, 1955). Its rate of rise and especially its rate of fall vary even from moment to moment under repeated low-frequency stimulation. It may hesitate for many milliseconds before growing up into a spike or starting its fall. Its spatial decrement may vary, possibly as a consequence of change in time course or possibly as a consequence of a labile decremental propagation. In some conditions, there is a heightened excitability after a subthreshold response, beginning without any refractory period (e.g., fresh axon of squid). But in other conditions there occurs a depression after such a response, with a recovery which requires many milliseconds (e.g., fatigued axon or synapse of giant fibers of squid). This depression may be followed by a supernormal period. These considerations

gain in significance if we believe that integrative neurons are typically under tonic subthreshold influence.

The excitability we have spoken of so far is excitability to artificial stimulation of limited kinds. But the outstanding characteristic of synapses is their sensitivity to some consequence of activity in other neurons, and we need not be concerned here whether that is one or more specific chemicals or nonspecific ions. We do need to note: (1) that the response may be *excitation or inhibition;* (2) that one and the *same input channel* (presynaptic fiber) can cause one or the other, depending on the level of the membrane potential of the postsynaptic neuron; (3) that different presynaptic fibers can cause response of the same sign but *different rates of rise, facilitation, maximum height, etc.*, as in crustacean muscle; (4) that these differences may be *discontinuous and unequal* in the proportional rôle of the several characters measured; (5) that summation of the different kinds of input in the same postjunctional cell may be complex (crustacean muscle, crayfish central giant-to-motoneuron synapse); and (6) that inhibition is not just the reciprocal of excitation as measured by its effect on various aspects of activity.

A highly variable property of the utmost importance for integration is the *response of the postsynaptic unit to repeated presynaptic impulses.* In some cases (e.g., *inhibitory escape* in the cardiac ganglion of lobsters) the initial effect of a sustained barrage gradually diminishes as measured by the output of the postunit, reaching a plateau at a new level (Fig. 2). In the example referred to this happens in some seconds at a frequency of presynaptic activity of 20-40 per sec. In other cases (e.g., the synapse of pacemaker upon follower cell in the same ganglion) there is actually what may be called *defacilitation*—the postsynaptic potential to the second presynaptic impulse is less than to the first, the difference being proportional to the frequency. This may be regarded as a consequence of relative refractoriness. Its importance lies in the fact that it happens in a frequency range within the normal firing range of these ganglion cells. The more familiar cases are those of *facilitation*—which should be distinguished from temporal summation by the criterion that each response or increment is greater than the last. The magnitude of facilitation and its rate of growth and decay vary widely. As an example, their consequences can be clearly seen in Wiersma's comparison (1952b) of the responses to the same average frequency delivered with alternately long and short intervals and delivered with uniform intervals. Some junctions give the same response (small, slowly decaying facilitation), others respond enormously more to the paired train (large, rapidly decaying facilitation).

Another group of properties with profound influence upon output, especially in the formation of patterned bursts, is in the domain of *after-*

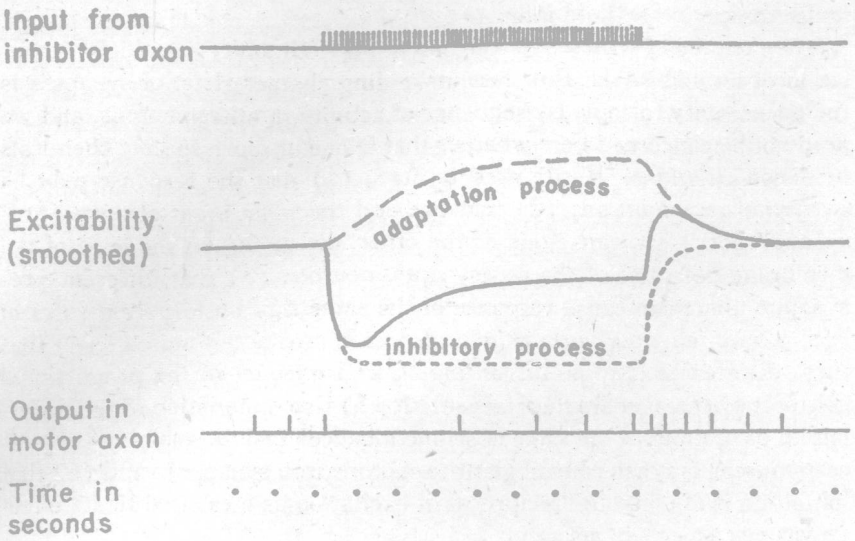

Fig. 2. Diagram of the response of a single unit of the cardiac ganglion of a lobster to stimulation of the inhibitory axon. Each vertical line represents an impulse. Maintained activity in the inhibitor produces, first, deep depression, followed by partial escape or adaptation. Termination of inhibitor activity produces a postinhibitory excitation after a brief latency or inhibitory after-effect. The observed input and output are related by an algebraically summing series of processes, including many of those listed in the text. Just two of these, which are moreover not directly measured but inferred, are shown here. (After Maynard.)

effects. These may be positive or negative or both in sequence, of various relative durations and magnitudes. To say the same thing in more familiar terms, there may be an after-discharge following cessation of presynaptic excitatory bombardment or an after-inhibition following the end of inhibitory influx, and there may be, with or without this positive after-effect, a rebound effect—postexcitatory depression or postinhibitory excitation. When phases of opposite sign succeed each other, they may be affected independently by various factors, as though manifesting separate underlying processes.

Recently we have distinguished another property which is of importance in permitting repetitive firing in response to a single presynaptic impulse in the cardiac ganglion of lobsters (Hagiwara and Bullock, 1955). This may be described as a *safety factor* of much less than one so that the postsynaptic impulse, once initiated in the axon, cannot invade the cell body (antidromically). This protects the latter from the possibility of loss of any partial depolarization it may have built up. Its significance depends on the asymmetrical relation between cell body and axon—the slow synaptic potential of the soma can spread electronically into the axon with less

attenuation for any given time constant of the membrane than the brief spike potential of the axon can spread into the soma; thus the soma can excite repetitive discharge of the axon with a single, long-lasting synaptic potential, while the resulting spikes are seen in the soma as tiny, five millivolt electrotonic deflections (Fig. 3). This case also illustrates the interaction of several factors in determining when a neuron fires. It is obvious that a fixed threshold voltage across the membrane of the soma does not exist; something else interacts with voltage so that successive spikes occur at smaller depolarizations.

A somewhat similar situation may account for the activity of dendrites as analyzed by Clare and Bishop (1955a,b). Dendrites in the vertebrate cortex appear not to conduct all-or-none impulses toward the cell body, as has been classically supposed from the law of dynamic polarity of Cajal (1909). Instead slow potentials generated in dendrites and spread electrotonically may influence the spike-initiating region of the soma. One can think of two interacting regions of integration, the dendrites and the soma; in this way the vertebrate cortex differs from most invertebrate nervous tissue where the soma probably plays little rôle and cell-free neuropiles are responsible for integration (Bullock, 1952).

The last property to which we will allude here is *spontaneity*. This varies not only in the degree to which it is developed but also in the form by which it is manifest, and the question is still unanswered whether these several forms are different in underlying mechanism. Spontaneous subthreshold activity seems to be of two kinds but these are possibly basically the same. In some cases it is quasi-sinusoidal, in others it rises (depolarization) more or less linearly to a point where it reaches a threshold and initiates a spike the repolarization of which carries the membrane back to the high level from which the so-called generator potential can begin again. These two forms of subthreshold change differ at least superficially as a sine wave oscillation from a relaxation oscillation; that is, one form can continue to go through successive cycles without an all-or-none discharge, the other requires such a discharge to restart the cycle.[1] The generator potential is best known in certain sense organs and in the specialized muscle cells pacing the vertebrate heart, but it is also present in integrative neurons which control other neurons, i.e., pacemaker interneurons in the lobster cardiac ganglion.

Spontaneous activity may be relatively rhythmic or nonrhythmic. Even in the same unit a continuous spectrum may be shown between very small and very large standard deviations of the intervals between spikes—the

[1] We have recently found, in spontaneous ganglion cells of the lobster cardiac ganglion, that a propagated spike is not necessary to repolarize the soma to a high level and restart the cycle. An active but graded form of soma potential suffices.

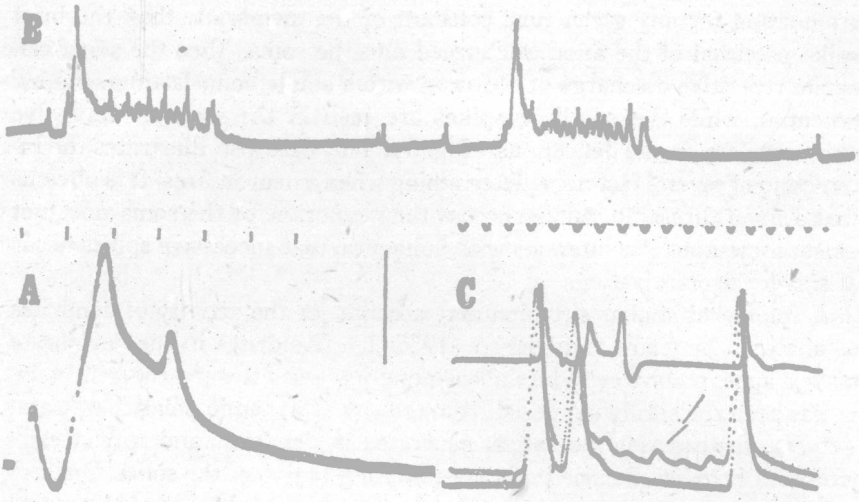

Fig. 3. A. Intracellular potential of the soma of a large neuron of the cardiac ganglion of a lobster. The activity results from stimulation applied to the ganglion a few mm. away. The first deflection is an antidromically conducted spike. The large deflection is interpreted as a synaptic potential resulting from arrival of an impulse in a presynaptic fiber; it is all or none by this form of presynaptic stimulation. The record shows two spikes arising from the synaptic potential, one at its peak and one on the falling phase; other records show from one to five, the number apparently determined by the condition of the postsynaptic element, not by a difference in the number of presynaptic elements. Time marks, 10 msec.; vertical calibration, 10 mv.

B. Intracellular potential of the soma of a large neuron of the cardiac ganglion of a lobster. The activity is spontaneous in the ganglion and in the form of bursts, one for each heart beat. The large deflection is regarded as a synaptic potential resulting from arrival of presynaptic impulses, and the smaller slower deflections are interpreted similarly. The sharp spikes (7-9 per burst) are the impulses in the axon leaving this soma; they arise from or near the crest of a synaptic potential. Note that, as in A and C, they do not have a fixed voltage threshold but a threshold which depends on other factors, e.g., time, even in naturally occurring repetitive firing. The spikes between bursts are preceded by a slow depolarization or generator potential; these are regarded as spontaneous activity of the cell we are in. The record illustrates the complexity of the interaction of integrative properties in a simple ganglion. The record is 3.6 seconds long.

C. Intracellular potentials of a median giant fiber of an earthworm. Two microelectrodes are inside the fiber, 11.3 mm. apart, the one farther from the stimulating electrodes is the lowest beam, the nearer one is the middle beam. The top beam is an extracellular monitor still farther down the fiber. Two shocks are given, 2 msec. apart. The first elicits action potentials of 98 and 110 mV. on resting potentials of 72 and 74 mV. The second elicits smaller direct spikes plus complex small potentials in the nearer penetration only (arrow), regarded as synaptic potentials from small fiber bombardment eventually leading to a spike which propagates. (There is also a lateral giant spike on the external leads, in the middle of the sweep, but this has no reflection in the internal median giant leads.) Like the preceding, the record shows the interaction of prepotentials and a complex recovery of excitability in determining firing. Time in msec. (The experiment a[illegible] permission to us[illegible] the record are due to the kindness of C. Y. Kao.)

former at high average frequency and the latter at low frequency of firing. But at any given average frequency there are types of neurons which are markedly regular and others which are markedly irregular in successive intervals. This suggests intracellular variables of importance in effective magnitude, such as fluctuating spike threshold, fluctuating amplitude of sinusoidal potential or of rate of rise of generator potential, fluctuating area of nonpropagated or decrementally propagated activity, and the presence of multiple loci of origin of spontaneous subthreshold activity (Wiersma, 1952a).

Besides these short-term changes in the frequency of firing there are in some cases long-term changes in average frequency on the scale of minutes. We will consider their significance below.

Eyzaguirre and Kuffler (1955) have just described a puzzling case of repetitive firing in the cell body of a neuron which has recently received an antidromic spike. Whatever the explanation—and these authors propose a tenable one based on differing local delays or partial blocks in the several dendrites—it is germane as an indication of the degrees of freedom present, and our purpose here is only to review the available ways in which the neuron can exhibit the several variables whose interaction could accomplish integration. In our present state of knowledge this means we have to include some observations whose "explanation" is less obvious than that of others. Eyzaguirre and Kuffler's interpretation of the intracellular afterdischarge in the stretch receptor cell of the dorsal muscle sense organ of crayfish may be correct; but Bullock and Turner (1950) reported a similar phenomenon in the giant fiber of the earthworm, so the phenomenon does not depend on the particular anatomy in the crayfish receptor. In the earthworm, a spike initiated at stimulating electrodes and conducted a long distance down the giant fiber arrived at a locus of partial or complete block (anode of a polarizing circuit) where it hesitated before proceeding or died out; after five or more milliseconds a burst of several impulses at high frequency originated at that locus or immediately adjacent to it.

One of the consequences of spontaneity may be *sensitivity to weak electric fields*. At any rate one can control the frequency of discharge of spontaneous integrating centers by passing a fraction of a microampere through a mass of tissue of a few ten-thousands of an ohm resistance, where the voltage drop along the length of a single cell must be a fraction of a millivolt (Bullock, Burr, and Nims, 1943, on *Limulus*; Maynard, 1956b, and Terzuolo and Bullock, 1956, on lobster cardiac ganglion; Hagiwara, Oomura, and Takagi, unpub., on citrated squid axon). The voltage drop across the membrane must be still smaller. Either an excitable mechanism not familiar to us is operating or the curve of membrane potential against firing interval is exceedingly steep, which means the threshold is very critical and constant.

The evidence against electrical transmission, based on the absence or minute size of the voltage change across the postsynaptic membrane produced by the arrival of the presynaptic impulse (del Castillo and Katz, 1954, on muscle; Bullock and Hagiwara, 1955, on squid) may be conclusive. But this does not mean, as some have supposed, that weak electric fields are without influence on poised or already active neurons. The experiments cited on cardiac ganglia, as well as many others of the same sort, classical and recent, are direct and pertinent and, when considered quantitatively, impressive in the sensitivity they bespeak.

The significance of this sensitivity is the enormous integrating potentiality, in complex centers, of the fields of current interacting among small and large groups of neurons. Here ordinary synaptic pathways give way in importance to architectonics. And synchronization and desynchronization of graded subthreshold activity of somata and dendrites take on a paramount significance both in producing fields effective upon other units and in sensitizing the somata and dendrites themselves to *effects en masse* (cf. Fessard, 1954).

Taken together with our earlier conclusion (see above under subthreshold excitability) about tonic subthreshold influence, these considerations also lead us to the suggestion that much of normal nervous function *occurs without impulses* but mediated by graded activity, not only as response but also as stimulus.

Pattern Formation in the Discharge of Groups of Neurons

As a special case of the most general interest we may examine the integrative mechanisms capable of organizing patterned bursts of impulses in which the serial order is determined centrally and in which several efferent neurons are coordinated. Since overt behavior consists in just such coordinated bursts of impulses, as far as its neurophysiology is concerned, this problem is a large segment of the problem of behavior. It is too much to expect that we can enunciate a satisfactory general solution or even a complete solution of a single case. But I believe there are some things we can say which will carry us quite a way in accounting for simple patterns with only the properties outlined above. Actually there is little difficulty in drawing hypothetical circuit diagrams of neurons with connections and properties within known limits which will produce a given pattern of output impulses in space and time. But there has been little effort to discover what actual neurons and connections are employed in real cases, perhaps because the enormous neuron pools in the familiar cases are too complex in sheer number of cells and impulses. A few cases have been studied recently in which a very small number of nerve cells control a large muscula-

ture and in which physiologically initiated movements or impulse bursts can be nearly completely accounted for in the neurograms.

In the simplest case there is a cell which has a fixed frequency of firing and this cell is simply turned on and off by input from the periphery or from higher centers. This has been found in the control of (neurogenic) sound production in a cicada (Hagiwara and Watanabe, 1956) and in the control of electric organ discharge in *Torpedo* (Albe-Fessard and Szabo, 1954.) In both the pacemaker cell is an interneuron, not a motoneuron, and the fixed frequency is high—200 per second in the former, 100 in the latter. The frequency or intensity of stimuli to sensory nerves does nothing in the cicada but determine how long the pacemaker will buzz and how promptly it will start. The system is like an oscillator controlled by a switch which can be only on or off but which can be turned on with various speeds due to the finite distance the switch must be moved before it changes its state. In *Torpedo* it does not yet seem clear whether the 100 per second frequency is independent of the input. In both cases the frequency-determining interneuron is penultimate—it controls the motoneuron directly, one motoneuron on each side in the cicada, about 70,000 on each side or 100 for each interneuron in the electric lobe of *Torpedo*. There is one other step in the cicada. Whereas the electric-lobe motoneurons follow the interneurons 1:1 after the first impulse of a series, the cicada motoneurons follow every other interneuron impulse, therefore firing the muscles at 100 per second. Moreover, the two sides are always 180 degrees out of phase, so that there must be some reciprocal inhibition of the two sides.

The only other preparation which I will discuss here is the lobster heart ganglion (Fig. 4), which is somewhat more complicated. This is largely based on the work of my former associate, Dr. Donald Maynard, but some aspects have been extended by Dr. Hagiwara and myself (Maynard, 1953 a,b,c, 1956a,b,c; Bullock, Cohen, and Maynard, 1954; Hagiwara and Bullock, 1955). Here a pattern is repeated at regular intervals, corresponding to each heart beat; and normally the heart beat, or as we shall call it the burst, is paced by the activity of certain of the four small posterior cells. Here, as in the system we have just examined, each of the follower cells responds to the pacemaker, or to some other cell triggered in turn by the pacer, with a train of impulses whose frequency is not the same as that of any other cell but is peculiar to the cell. But this frequency is not fixed. It starts high or quickly rises to a maximum and then falls along a curve characteristic for the cell over some hundreds of heart beats. This frequency/time curve could conceivably be determined entirely by the properties of the given cell since the cell can respond to a single incoming impulse by a repetitive discharge, as we have seen happen in intracellular records. A single large, slowly decaying synaptic potential can, by the