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The Electrical Activity of the Nervous System

Electrical signals are the neurophysiologist's clue to coding in the nervous system.

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The single most important discovery in the exploration of nervous mechanisms was that the nerve impulse is identifiable with an electrical change. This electrical sign of activity has given the investigator a means of studying the functioning nervous system—a tracer by which he can follow impulses in the living organism through the complexity of structure that the microscope can reveal only in dead tissue. It is also the only clue he has as to how messages may be coded in the nervous system.

But it was not in the whole organism that the pioneers made the first observations, nor their followers the analyses of the basic characteristics of nerve action. It was from the most readily accessible nervous structure, the large peripheral nerve trunks of an animal's limbs, that this fundamental knowledge was first acquired. The fact that these nerve trunks, themselves formed of numbers of parallel nerve fibers, could retain their function for a limited time if maintained in a moist atmosphere set the experimental pattern for all the early workers; only much later were techniques developed for recording the electrical activity of the nerve in vivo.

The first unequivocal demonstration of the electrical potential of nerve by Du Bois-Reymond (*1*) in the 1840's, gave the death-blow to the vitalist's concept of "animal spirits" as the activator of sensation and movement, and provided a restitution of Galvani's belief in animal electricity (*2*).

As with many phenomena in the biological field, demonstration and proof had to await the development of an adequate technology. The primitive electroscopes, which were the only detectors of electricity available to Galvani in the 18th century, could not register the small changes in potential which accompany activity in nerve, and it was to Oersted's discovery of electromagnetism in 1820 (*3*) that the early period of electrophysiology owed its development. The string galvanometer based on electromagnetic principles remained the principal tool of the neurophysiologist until the invention of the cathode ray oscilloscope.

But even before vacuum tube amplifiers (*4*) and inertialess electronic recording devices (*5*) were introduced into the physiological laboratory in the early 1920's, brilliant minds had perceived that the characteristics of the membrane of the nerve are the basic determinants of its electrical properties, for the nerve impulse is not an electric current flowing down the length of the fiber as through a passive conductor but is itself an active process. The action potential, as the electrical sign of nervous excitation is called, reflects a progression of ionic changes traveling along the nerve and deriving energy for transmission from the metabolism of the nerve itself.

There have been many hypotheses about this traveling wave of excitation, almost all of which derive from the membrane theory originally framed at the turn of the century by Bernstein (*6*) for the muscle fiber, but subsequently applied to nerve. Later work has shown that some modification and extension of this theory is necessary, but the essentials of Bernstein's original concept still stand. They are that the membrane of the nerve when inactive is polarized, the inside of the neuron being negative to the outside, and that the action potential is a self-propagating depolarization of this membrane.

The degree by which the inside of a neuron is negative to the outside is far from negligible; in some cells it may reach as much as 90 millivolts. This ionic imbalance is brought about by the high ratio of external sodium to internal (10:1) and by the high ratio of internal potassium to external (30:1 in some nerves), the potassium being held there by the strong electrostatic attraction of organic anions too large to pass out through the membrane.

If one follows the unfolding of knowledge about the electrical activity of the nervous system one finds that it developed in a sequence from that of the largest and most accessible structure to the smallest and most difficult of access: from the one which primitive apparatus could explore, to the fine structure that only modern technology could aid. This progression has, then, been from studies of the large nerves in the limbs, to the large motor neurons of the spinal cord and their junction with the muscles; then to the synapses of the central nervous system and the cells of the brain itself.

As will be seen, the knowledge obtained at each stage has been the stepping stone to the next; this sequence will therefore be followed here.

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Electrical Activity in Axons

What are the basic electrical characteristics of the conducting fiber, the axon that runs out from the parent cell to effect action on some other structure—perhaps another nerve cell in the brain or spinal cord; perhaps a muscle fiber in a blood vessel or in a limb; perhaps a gland to cause it to secrete?

In answer one must rank, first, the all-or-nothing character of its discharges (*7*). Provided a nerve impulse is strong enough to be propagated, the action potential and the speed of its conduction down the fiber will be independent of the intensity of the stimulus. The nerve gives all the response it can at that moment and nothing less. This famous characteristic, which became known rather rashly as a "law," was thought for years to apply to all electrical activity in neurons—to the nerve cell itself, to the receptor and effector endings, and to the dendrites. Happily for those who strive to find the mechanisms that code the subtle reactions of the nervous system, it is now known that in the mammalian nervous system this restrictive behavior is confined only to the propagated discharge and many finer electrical changes of a graded sort have been detected and defined at both the peripheral and central ends of these connecting fibers as well as in the receptor organs (*8*), thus providing greater plasticity of reaction.

The all-or-nothing principle still stands, however, for the propagated discharge in the conducting portion of the axon. It follows, therefore, that the state of the fiber at the point where it receives a stimulus becomes all important in deciding the size of the action potential. Should the fiber be exhausted by the recent passage of an impulse it will be refractory; should the fiber have an inadequate oxygen supply or be narcotized by some drug, then the size of the response may be reduced, for the energy necessary for transmission of the impulse comes from metabolic processes within the nerve itself and not from the stimulus. The occurrence of an all-or-nothing action potential in the conductile part of the neuron carries the message that an adequate stimulus has been received, but is not in itself proportional in size to the stimulus strength.

In the vertebrates the typical axon in the peripheral nervous system begins, at a short distance from the parent cell, to be surrounded by a fatty insulating substance; this is the myelin sheath which is wound round the nerve like a helix. This sheath, protruding from Schwann cells lying on the surface of these nerves, is interrupted at intervals by gaps where the electrical potential is regenerated as it travels down the nerve. The gaps are called the nodes of Ranvier, and the phenomenon of the action potential as it leaps from node to node is known as saltatory conduction (*9*), although perhaps it should be noted that, as discussed by Tasaki (*10*), not all electrophysiologists are in agreement that the internodal segments act merely in a passive way. It is agreed, however, that the impulse emitted from each activated region reaches the next one by the current flow in its local circuit.

Even in the peripheral nervous system not all nerves are segmented in this way, for not all are provided with sheaths; in these unmyelinated nerves the progress of the action potential is more sedate, being by smooth progression rather than by jumps. In both types of nerve, however, there is sufficient insulation to avoid leakage of discharge to parallel fibers, and in both types of nerve the action potential proceeds on its way in an all-or-nothing fashion, without decrement and at a constant velocity. The speed of conduction is related to the diameter of the fiber and may reach more than 100 meters per second in the large mammalian motor fibers serving the limbs. In cold-blooded animals the velocity of conduction is much less. In the central nervous system a great variety of axons is encountered and many of their electrical characteristics have been assessed by analogy rather than by direct recording, since their structure is so small.

Direct measurements of the electrical properties of the membrane in mammalian species have only been possible so far in the large motor neurons, where the resistivity has been found to be of the order of 1000 ohms (*11*) per centimeter and the capacitance about 3 microfarads.

Bernstein held that the action potential represented a breakdown in the selective permeability of the membrane which, when not conducting activity, maintains a greater concentration of potassium ions inside the nerve than is present in the surrounding medium where sodium ions, unable to enter, predominate. More modern work (*12*) has shown that the prevention of sodium entry cannot be laid to permeability factors alone and that, when not discharging, the nerve cell exerts a "sodium pump" continually forcing the extrusion of sodium ions against their electrochemical gradient and using, for this, energy derived from its internal metabolism. Coupled with this extrusion of sodium is a potassium transport system continually carrying potassium into the cell.

Bernstein's theory was formulated before techniques had been developed for examining single nerve fibers (*13*) when only the action potential of the whole nerve trunk, consisting of many fibers, was known. Nearly 40 years later the first direct readings of the potential difference across the membrane of a single nerve fiber were made by Curtis and Cole (*14*) in the United States and by Hodgkin and Huxley in England (*15*). Both teams took advantage of the large axon of the squid—large enough to permit the insertion of one electrode into the core of the nerve fiber and allow the other to rest on the external surface. This technique, later successful in mammalian neurons, led to many new findings which necessitated some modification of Bernstein's theory. Mere breakdown of the permeability of the membrane cannot account for the whole of the action potential, for the electrical charges do not immediately become equalized when the impulse passes but in fact are briefly reversed. In other words, the potential change overshoots the equilibrium line.

Electrical Activity at the Neuromuscular Junction and at Central Synapses

At the end of the line of a motor nerve where an impulse has to cross over to a muscle fiber (that is, at a neuromuscular junction), the recordable electrical activity is of a different nature.

At the junction of motor nerves with skeletal muscles, fine electrodes can detect the repetitive eruption of a brief potential change at the postsynaptic membrane, even in the absence of muscle activity (*16*). These miniature endplate potentials have been shown each to accompany the release of a small amount of acetylcholine from the terminals of the motor nerve (*17*). This is a kind of "priming of the pump" for, when an impulse arrives in the terminals of the nerve fiber, a

great increase in acetylcholine floods out at the nerve endings; this so alters the ionic balance of the muscle fiber's membrane that its threshold for electrical discharge is lowered, the muscle cell fires, and activity is achieved.

This important function of acetylcholine at the skeletal neuromuscular junction (*18*) has led to a continuing search for the identity of transmitters at other types of neuromuscular junction and at synaptic junctions between nerve and nerve in the central nervous system. A chemical substance known to be a transmitter in the autonomic system is norepinephrine (*19*) but whether or not it functions as a transmitter in the brain or spinal cord is still *sub judice*. And, as a matter of fact, the evidence for acetylcholine being a transmitter in the central nervous system is at present only indirect even where it is most convincing, namely for the Renshaw cells of the spinal cord, cells which have been shown to have an inhibitory rather than an excitatory influence (*20*).

The word "transmitter" is perhaps unfortunately chosen, for it suggests that the chemical compound itself carries the code in its molecular structure, whereas its action is to modify the electrical characteristics of the receptor membrane and influence the threshold of that membrane for discharge of an electrical (code-carrying) signal.

At the neuromuscular junction, the postsynaptic potential is always excitatory, but in synapses within the nervous system, between nerve and nerve, this modification by the transmitter may be to render the membrane more excitable or it may be to make it less so. In the first case one speaks of an excitatory transmitter, in the latter of an inhibitory one. The first evokes an excitatory postsynaptic potential (EPSP), the latter an inhibitory postsynaptic potential (IPSP). At present a controversy rages as to whether or not a generalization can be made that chemically excitable postsynaptic membranes are electrically inexcitable (*21*).

Even though the transmitters still remain unidentified, reasonably complete descriptions can be given of the electrical characteristics of these EPSP's and IPSP's, for microelectrodes have revealed their properties. The critical determinant of whether or not a cell will fire is the state of its membrane and the potential difference across it.

As mentioned earlier, any change that tends to decrease the potential drop across the membrane will increase the probability of firing—that is, will be excitatory by virtue of its depolarizing action. Any change that tends to increase the potential difference between the inside and the outside will hyperpolarize the membrane and decrease the tendency of the neuron to fire—that is, will be inhibitory.

Basically this means that the outcome depends on the ionic state of the neuron's interior relative to its surrounding medium. If the permeability of the membrane is in such a state that sodium ions cannot flow in to reduce the internal negativity, firing will be inhibited. In fact, this happens naturally after every firing of the neuron (*22*) for, following the first depolarizing afterpotential, there is a brief period when potassium ions flow out and sodium is blocked from entry; this is the cause of the hyperpolarizing afterpotential that follows the action spike and gives the appearance, as recorded by an electrode external to the cell, of a positive afterpotential. Although the identity of inhibitory transmitters remains a mystery, there is little doubt that a similar shift of ions is the basic mechanism they evoke.

There has been considerable controversy (*23*) over the identity of the neurons in the central nervous system whose activity causes postsynaptic inhibition rather than excitation, and evicence has accumulated for the necessary presence of an interneuron between the primary nerve and its postsynaptic counterpart. The evidence, based largely on the longer latency for IPSP's (suggestive of an indirect pathway), came first from studies of spinal reflexes (*24*) but has more recently received support from centrally evoked motor neuron activity—that is, by pyramidal stimulation in the primate (*25*) which delivers an EPSP to the motor neuron in the lumbar spinal region 1.3 msec before the IPSP reaches it (*26*).

A formulation of this kind carries with it the concept that the EPSP's are generated at different loci (*27*) on the postsynaptic membrane from the IPSP's since they arrive in different presynaptic fibers and this, together with other evidence, has brought the realization that a single generalizing statement cannot be made about the electrical characteristics of the entire soma membrane of the cell. A patchwork of independent activities may be taking place on the receptive membrane of an individual neuron.

The electrical signs that accompany these excitatory depolarizations and inhibitory hyperpolarizations have become available for study by the technical development of fine microelectrodes inserted into the very body of the nerve cell itself. This procedure was first successful in the large motor neurons of the spinal cord (*28*) but soon was achieved in the Betz cells of the brain (*29*). Since then, hyperpolarizing inhibitory postsynaptic potentials have been recorded from many other types of brain cell, including the pyramidal cells of the hippocampus.

The excitatory postsynaptic potentials of mammalian nerve cells differ from the propagated action potential of the axon in their characteristics. On subliminal stimulation, they are monophasic in form and show a relatively rapid decrease in internal negativity followed by a slow return to the resting level. Inhibitory postsynaptic potentials are their mirror image and show a corresponding increase in internal negativity as the membrane becomes hyperpolarized with a similar slow decay. Both types have been demonstrated in cortical synapses where the duration of their decay may be as long as 80 to 100 msec (*30*) if no further presynaptic activation interrupts. Neither type of postsynaptic potential propagates away from the locus on the membrane at which it forms, its only action at a distance being by passive electrotonic spread.

Strikingly unlike the action potential, excitatory postsynaptic potentials have no refractory period but are cumulative and reflect the strength of the stimulus; under either temporal or spatial bombardment from the presynaptic fibers, they can sum to the threshold the degree of depolarization necessary for discharge of a spike. When an EPSP does not reach the threshold for spike discharge but dies out for want of reinforcement, only a very brief period of hyperpolarization follows—that is, a short-lasting drop in excitability.

Electrical Activity of Nerve Cell Bodies

When one turns to the electrical discharge from the nerve cell itself (as distinct from its long fiber) the evidence is that the propagated spike discharge originates in the junction between the soma and its axon, in the region comprising the axon hillock and the short segment of bare axon before

myelin sheath encloses it (*31*). This portion of the membrane has a significantly lower threshold for depolarization than that of the soma or dendrites (*32*). In general this holds for most nerve cells including those of the mammalian cortex (*33*), and accounts for the generally recognized efficacy of surface anodal stimulation of the cortex (*25, 34*) since the cathodal effects can then operate on the deeper, more vulnerable initial segments of the descending axons.

The recent supportive evidence for emerging axons having a significantly lower threshold excitability than cell bodies to an imposed electrical stimulus [both in the spinal cord (*31*) and the brain (*35*)] has implications for all experiments in which attempts are made to identify the function and connections of specific nerve cell aggregates by stimulation in their midst with threshold currents. By virtue of the higher threshold of cell bodies for excitation, the effects produced may have been evoked by flow of current reaching low-threshold axon segments of more distant cells.

The relatively higher membrane resistance of the soma and dendrites compared with the initial segment has the result that excitation arriving by fibers which synapse onto dendritic or soma surface will cause a depolarization that fires the segment by electrotonic spread from the point of contact before the cell membrane itself reaches its threshold for discharge. Recordings from inside the cell reveal this sequence of segment spike and soma spike quite clearly, as well as situations in which only the firing threshold of the segment is reached, so that no discharge of the cell body follows.

After the spike discharge has taken place, the depolarization of the initial segment, from whatever source it has been fired, spreads backward into the soma of the cell and electrotonically into its dendrites, depolarizing their membranes.

Just before the *status quo ante* is fully reestablished, a prolonged hyperpolarization sweeps over the soma membrane (*29*) lowering its excitability and giving the appearance, when recorded by an electrode outside the cell, of a "positive" afterpotential. The effect of this hyperpolarization is to limit the rate at which a nerve cell can fire and to impose a rhythm on its discharge when maximally stimulated. This is a factor that has to be taken into account in all models of coding in the nervous system where frequency of discharge is considered as one of the parameters of the code, for not all neurons exhibit the same duration of hyperpolarization; in other words, this limiting factor on the parameters of their rhythm varies for different types of nerve cell.

Coding in the Nervous System

Of great current interest is the exploration of the codes by which information is transmitted in the brain. Features of a stimulus which need to be conveyed by the nervous system may be regarded as falling into five main categories: intensity, duration, frequency, locus, and form, though many finer distinctions will have to be made once the clues to these rough divisions have been found.

The earliest hint as to how *intensity* is signaled came from Adrian and Matthews' (*36*) demonstration that intensity of stimulus may be signaled by frequency of discharge. But when the single nerve fiber is examined, for example in the single ommatidium of the *Limulus* eye, it appears that, in this instance at least, both intensity and *duration* of a light flash are signaled by frequency of discharge. One moves then to the hypothesis that it is the patterning in space, as well as in time—that is, the spatio-temporal configuration of activity in aggregates of neurons—that differentiates the messages. Thus, even in the first neuron serving a receptor, the problem is not simple; across a synapse it is even more complex, for already it is known that no single transfer function will serve all synapses.

To cite some of the problems facing the worker in this field, a nerve cell may continue to fire repetitively even though the presynaptic fiber which detonated it may have fired only once. This type of after-discharge would appear to be generated in the postsynaptic cell for, in such a case, only the first spike in the series is seen to arise from a postsynaptic potential (*37*). Furthermore, some single mammalian motor neurons discharge rhythmically in response to arhythmic presynaptic stimulation, the control presumably being exerted by the characteristics of the rise and decline of EPSP's (*38*). Yet this does not hold for interneurons of the spinal cord (*39*) or for many other neurons whose inter-spike intervals have been examined.

Considerable advance has, however, been made toward elucidation of coding of intensity by studies in the afferent somatic pathway (*40*). For each of its three stations (cuneate nucleus, thalamus, and cortex) increase in intensity of a brief peripheral stimulus evokes an increase in the number of spikes elicited and shortens the latency, though the numerical correlations are far from simple. Computer analyses of number of discharges, inter-spike intervals, and latencies are greatly aiding this type of research and are no doubt essential if the code is to be cracked.

When one turns to the question of how *frequency* of stimulation is coded, one finds that the more central the neuron, the less the response follows in a one-to-one manner. Characteristic of the failure to follow in the time domain is the inability (because of their slower recovery time) of thalamocortical neurons to respond to as rapid repetitive stimulation as can the primary neurons that lead to them. This fact has been demonstrated in all the specific afferent systems (*41, 42*). In the primitive visual system in the brain stem (the superior colliculus) the recovery rate is even slower than in the specific afferent path, for only low rates of repetitive flash can be followed (*43*).

In the case of the visual system, the failure of the one-to-one code at high frequencies reveals itself in the psychophysiological phenomenon of critical flicker fusion, a state in which the brain receives the message that the eye is exposed to steady illumination whereas, in fact, the flash is intermittent but of too high a frequency for the central neurons to follow.

The clue to the coding must therefore lie not in frequency of discharge only, and one is drawn to the view that the distribution of excitation and inhibition among the fibers of the central pathways may be a crucial factor in getting the message through.

When the signaling of *locus* of stimulation is considered, it must be recognized that, in the synaptic systems of higher species, the terminals of each presynaptic fiber usually make synaptic contact with a multitude of other neurons, and each postsynaptic neuron receives impulses from a vast number of presynaptic fibers. Thus, preservation of the code as it passes from a first-order neuron in the periphery to a

second-order neuron in the spinal cord and then to yet a third in the thalamus, whose axon leads to the cortex, depends very largely on the degree of specificity maintained in the pathway.

This varies very greatly in different systems of the brain, the relations being much more precisely held in the great specific afferent systems, such as the somatic (*44*), visual (*45*), and auditory (*46*) systems than in the midline nonspecific ascending system (*47*) whose function is of a different kind and whose neurons receive synaptic contacts from a variety of sources.

For example, in the synapses that the neurons of the medial lemniscus make with the cells in the ventrobasal thalamus, it has been shown that individual units are as specific for modality and topography of the stimulus as are the primary neurons in the skin and joints (*42*). The axodendritic synapses in the pathway are presumably held very rigidly to neurons subserving specific functions.

Recent work on the signaling of *form* and movement (*48*) has contributed important information indicating a high degree of specificity even of individual neurons in the visual cortex.

No such consistency of message is carried by the ascending pathways in the brain stem and midline thalamus, whose function is not the reporting of the modality of point of origin of a stimulus but the alerting of the organism to awareness that the stimulus has been received. Even in the deepest anesthesia the specific afferent systems deliver their signals to the cortex, but they go unobserved, for anesthesia suppresses the activity of the nonspecific ascending system and awareness of their arrival is lost (*49*).

However, even in the specific systems, although they carry such clear reports of the locus and modality of the stimulus received in the periphery, the actual characteristics of the signals fail to follow through consecutive relays in any linear fashion, and the code for information carried in the temporal domain undergoes a transformation at each synapse in the pathway.

Some of these transformations may well be from "space into time"; in other words, primary receiving neurons scattered over an area may converge on a synapse and an increase in the number of them receiving the stimulus (that is, the extent of the area stimulated) may be signaled in the postsynaptic neuron by such signs as: decrease in latency, increase in rate of firing, or number of discharges per stimulus. It is, however, doubtful that any of these are linearly related, and considerable current effort is being given to study of the transfer functions involved.

The nervous system has several other very potent mechanisms for introducing more information into the centrally directed pathways, and one of these is feedback from the cortex. Control by descending systems modulating input have been identified for many sensory pathways as has the modulating influence of the ascending reticular system on the cortical response to a peripheral stimulus (*50*).

In the somatic system a descending inhibitory action has been shown to act on the interneurons that lie between the incoming dorsal root fibers and the ascending fibers of the dorsal column in the spinal cord (*51*). There is strong evidence that this descending inhibitory influence may play a role in "editing" the flow of information by acting to suppress some of the input from the periphery of the receptive field and thereby producing an effective inhibitory surround to the main focus. Inhibitory surrounds to an excitatory focus have been demonstrated also in the retina (*52*), and evidence for centrifugal control of input has been identified also in the auditory system (*46*), the olfactory system (*53*), and in the efferent gamma fiber system innervating muscle spindles (*54*).

The temporal characteristics of the neural code are now being studied intensively in many laboratories, not only in terms of rate of firing, or the number of discharges, or their latency, but in terms of the patterns of incidence of cell-firing. Such studies have been greatly aided by computer analysis and, in fact, physiologists have come to realize that the information they seek requires that experimentation must enter a phase of increasing sophistication that may well prove out of reach without the help of the computer.

The Electroencephalogram

Many decades before technology provided the electrophysiologist with the electronic amplifiers which have enabled him to explore the electrical activity of the single cell, it had been observed that oscillatory activity could be recorded from the surface of the brain (*55*); 54 years later this phenomenon was demonstrated in man (*56*). More modern exploration has shown that these waves are not the envelopes of spike discharges but probably reflect the waxing and waning of electrotonic potentials in dendrites of cortical cells.

Only in those regions of the brain where the geometry of dendrites—that is, their orientation to the surface—is such that they mass to produce a synchronized field can their combined effect produce a smooth oscillation. Outstanding among the regions whose cytoarchitecture is such that the dendrites lie parallel to each other are the visual cortex of man and the hippocampal cortex where the long apical dendrites of the pyramidal cells are optimally oriented.

As described previously, an electrotonic depolarizing invasion of the dendrites follows discharge of the initial segment of the axon, this in turn being followed by a long-lasting wave of hyperpolarization which limits the rate at which the individual dendrite can again become depolarized. Since microelectrodes at the level of the initial segment of pyramidal cells in the cortex have shown these cells to be firing continuously in the unanesthetized animal (*57*), it seems possible that the electrotonic flow along the dendrites may well be paced by this alternation of depolarization and hyperpolarization imposed by the time-constants of their membranes.

The practice of electroencephalography in man has been hampered in general by the necessity of recording through his scalp and skull. Electrodes so placed can record only from the most superficial layers of the convexity of the brain and can thus only imply activity in the depth if the structures involved can cause changing behavior of the cortical cells, transmitted through projection pathways to the surface. Among the physiologically normal changes in the cortical electroencephalogram caused by activity in deep structures are, for example, the variations emanating from the brain stem in sleep and wakefulness and projected to the surface through the diffuse projection system.

In disease states where a lesion is in a deep structure that has projections to the cortex, or where cortical cells are themselves damaged, or where an

expanding lesion, by mechanical pressure on the cortical cells, forces them to behave abnormally, the electroencephalogram can be of great help in diagnosis. But where the lesion is in a center that has no direct pathway to the cortical convexity, for example the amygdala (a nuclear mass in the depths of the temporal lobe), dismayingly abnormal discharges may take place without disturbance of the electroencephalogram recorded from the scalp (*58*). Such is the case in certain patients suffering from temporal lobe epilepsy, whose cortical neurons may give no hint of the hidden abnormality. The safe development of recording from fine electrodes implanted under anesthesia in the depths of the brain and left in place for several days or even weeks has enabled the electroencephalographer to gain much information of diagnostic and therapeutic help in such cases. But even here there may be a hidden code that signals the presence of disturbances at a depth. At this laboratory, investigators are currently exploring the possibility of predicting by computer analysis the probability of a change in the electroencephalogram of the scalp (previously regarded as normal) being triggered by a focus of abnormality deep in the brain.

Conclusion

Whether the goal of the electrophysiologist be to seek the codes that carry the messages in the physiologically normal brain or those that signal some hidden disease process, it is strikingly apparent that investigators are giving increasing attention to probabilistic models rather than to deterministic ones. It has occurred to many that discriminations may be made by the brain on a statistical basis: that is, on the probability that the afferent patterns are significantly different from those which are currently taking place in the brain or which its past experience has set its neurons to "expect" (*59*).

The statistical viewpoint may be defined as the "probabilistic" model in contrast to a "deterministic" one in which a given stimulus elicits a stereotyped response irrespective of the likelihood of its occurrence. Such a viewpoint releases the investigator from seeking the rigidity of arithmetic relationships and adds another dimension to the neural code.

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