Teaching slides, chiefly captioned diagrams relating to the structure and function of nerve cells referenced as 'Dr Brown'

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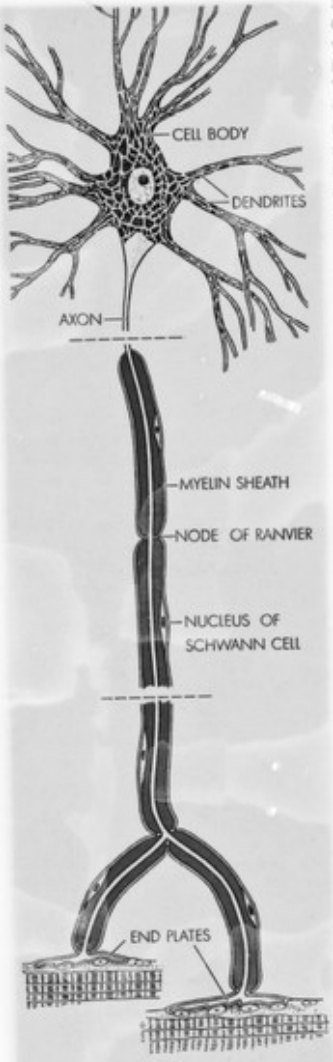


MOTOR NEURON is the nerve cell that carries electrical impulses to activate muscle fibers. The cell body (*top*) fans out into a number of twigs, the dendrites, which make synaptic contact with other nerve fibers (*see top illustration on opposite page*). Nerve impulses arising at the cell body travel through the axon to the motor-plate endings, which are embedded in muscle fibers. Myelin sheath is formed by Schwann cells as shown at bottom of opposite page. By insulating the axon the myelin wrapping increases the speed of signal transmission.

205], whose function is to monitor the organism's external and internal environments. The motor neurons carry impulses from the higher centers to the "working" cells, usually muscle cells, which provide the organism's response to changes in the two envi[illegible]nts. In simple reflex reactions the [illegible]fer of signals from senso[illegible]rons is automatic and inv[illegible]relat[illegible]imple synaptic mechan[illegible]whi[illegible] fairly well understood.

When a nerve [illegible] eith[illegible]tor or sensory, beg[illegible] di[illegible]ate in the embryo, the [illegible]body [illegible] out a long fiber—the ax[illegible]which [illegible]ne unknown way gr[illegible]ward [illegible]proper peripheral statio[illegible]make [illegible]t with muscle or skin. [illegible]n th[illegible]t axon may be several [illegible]long, [illegible]ugh it is less than .00[illegible]h thi[illegible] forms a kind of minia[illegible]able [illegible]nduct- ing messages [illegible]n th[illegible]iphery and the centra[illegible]inus[illegible]h lies protected toget[illegible]th th[illegible]ve-cell body inside th[illegible]al c[illegible]r the skull. Isolated [illegible]eral [illegible] fibers probably have [illegible]subject[illegible] more intense experim[illegible]tudy t[illegible]y oth- er tissue, in sp[illegible]the fa[illegible]t they are only fragme[illegible]cells [illegible]d from their central n[illegible]well [illegible]ir ter- minal connect[illegible]Even [illegible]olated axons are capa[illegible]condu[illegible]ens of thousands of in[illegible]befor[illegible]fail to work. This fac[illegible]other [illegible]ations make it clear th[illegible]nucle[illegible]ody of the nerve cell [illegible]cerned [illegible]long- term maintena[illegible]the n[illegible]bers— with growth at[illegible]ir rath[illegible]h with the immediate [illegible]ling me[illegible]m.

For years th[illegible]as contr[illegible]as to whether or not [illegible]ndamental concept of the existenc[illegible]dividual cell units could be appli[illegible]all to the nervous system and to it[illegible]tional connections. Some investiga[illegible]lieved that the de- veloping nerve [illegible]literally grows into the cytoplasm [illegible] cells with which it establishes [illegible]tional relationship. The matter c[illegible]ot be settled con- vincingly unt[illegible] advent of high- resolution elec[illegible]nicroscopy. It turns out that most [illegible]e surface of a nerve cell, includin[illegible]its extensions, is in- deed closely [illegible]ted and enveloped with other ce[illegible]t that the cytoplasm of adjacent c[illegible]mains separated by distinct mem[illegible]. Moreover, there is a small extra[illegible]r gap, usually of 100 to 200 angstrom units, between adjoin- ing cell membranes.

A fraction of these cell contacts are functional synapses: the points at which signals are transferred from one cell to

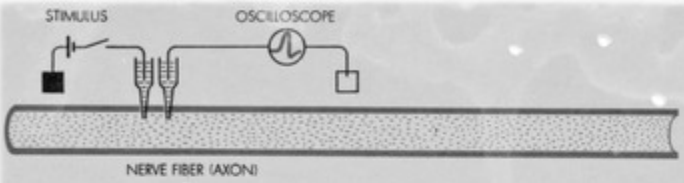
the next link in the chain[illegible] are found only at and ne[illegible] of the neuron or at the t[illegible] axon. Most of the inver[illegible] ticularly those clinging t[illegible] not nerve cells at all. T[illegible] still a puzzle. Some of th[illegible] are called Schwann c[illegible] cells; they do not app[illegible] part in the immediate pa[illegible] transmission except pe[illegible] to modify the pathway [illegible] flow around the axon. [illegible] for example, that ver[illegible] satellites are to be foun[illegible] cell surfaces of musc[illegible] closely resemble nerv[illegible] ability to conduct el[illegible] from one end to the ot[illegible]

One of the known [illegible] axon satellites is the [illegible] so-called myelin sheath[illegible] sulating jacket that in[illegible] ing efficiency of perip[illegible] in vertebrate animal[illegible] electron microscope st[illegible] Geren-Uzman and Fra[illegible] the Massachusetts In[illegible] ogy, we now know [illegible] segment is produced[illegible] Schwann cell that w[illegible] tightly around the s[illegible] forming a spiral envel[illegible] [*see bottom illustra*[illegible] *page*]. The segment[illegible] gaps—the nodes of R[illegible] the points along the a[illegible] trical signal is regene[illegible]

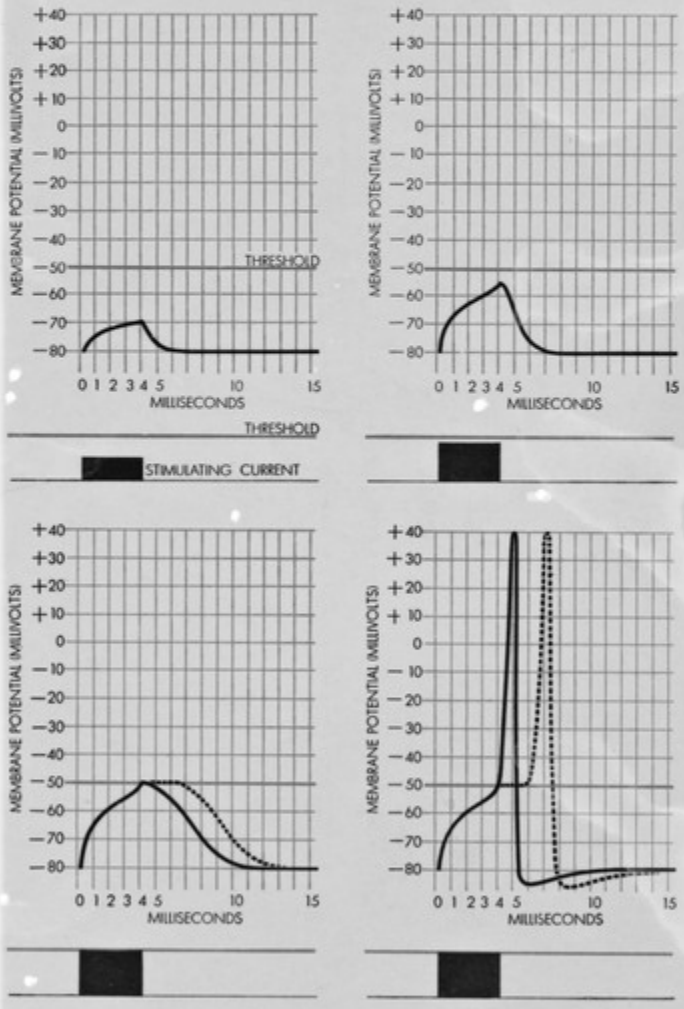
There are other t[illegible] that do not have a [illegible] even these are cover[illegible] of Schwann cells. F[illegible] axon extens[illegible]is so far [illegible] the nerve cell it rec[illegible] tion with nucleated[illegible] along its length. M[illegible] the isolated axons, [illegible]l axons, cells with nuclei dis[illegible] cytoplasm, which m[illegible] fibers can manage [illegible] investing layer of s[illegible] ever the function o[illegible] cannot maintain th[illegible] long once it has be[illegible] main cell body; aft[illegible] the peripheral segm[illegible] disintegrates. How [illegible] acts as a trophic [illegible]felong [illegible] brings its influence[illegible] tant parts of the a[illegible] of ordinary diffus[illegible] away—remains a m[illegible]

The experimenta[illegible] ogy have been mu[illegible] dealing with the [illegible] of nerve communi[illegible]

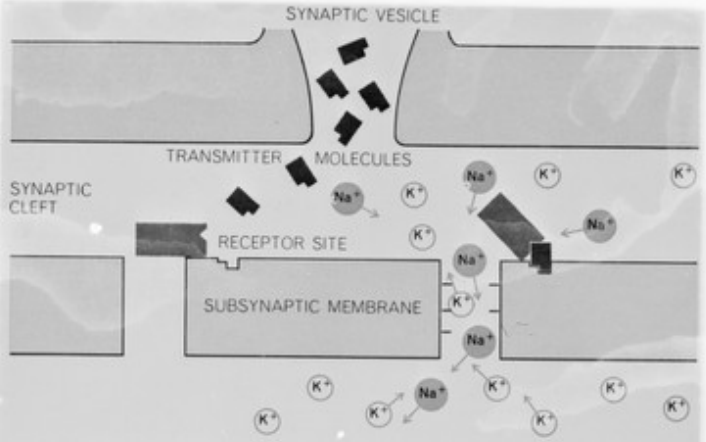
Dr. G. Brown



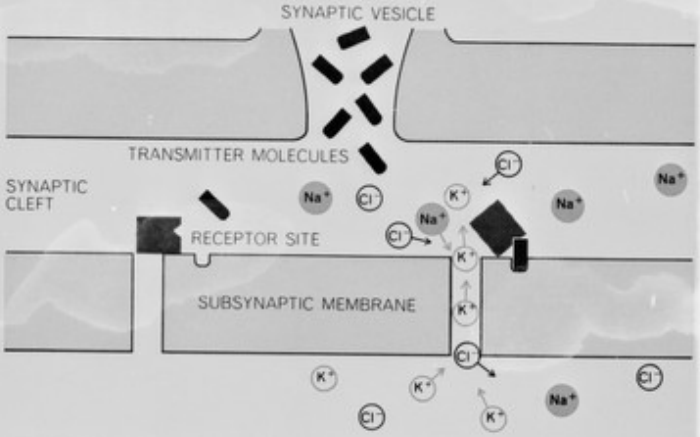
INVESTIGATION OF NERVE FIBER is carried out with two microelectrodes. One provides a stimulating pulse, the other measures changes in membrane potential (*see below*).



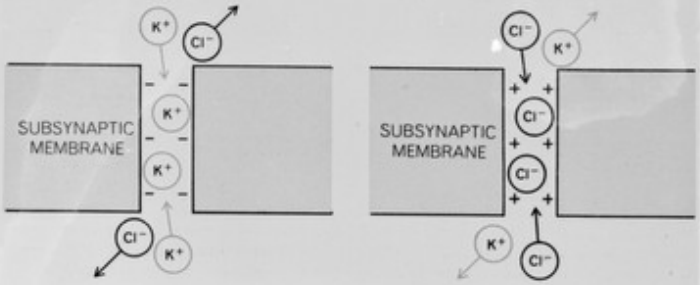
ELECTRICAL PROPERTIES OF NERVE FIBER are elucidated by measuring voltage changes across the axon membrane when stimulating pulses of varying size are applied. In the resting state the interior of the axon is about 80 millivolts negative. Subthreshold stimulating pulses (*top left and top right*) shift the potential upward momentarily. Larger pulses push the potential to its threshold, where it becomes unstable, either subsiding (*bottom left*) or flaring up into an "action potential" (*bottom right*) with a variable delay (*broken curve*).



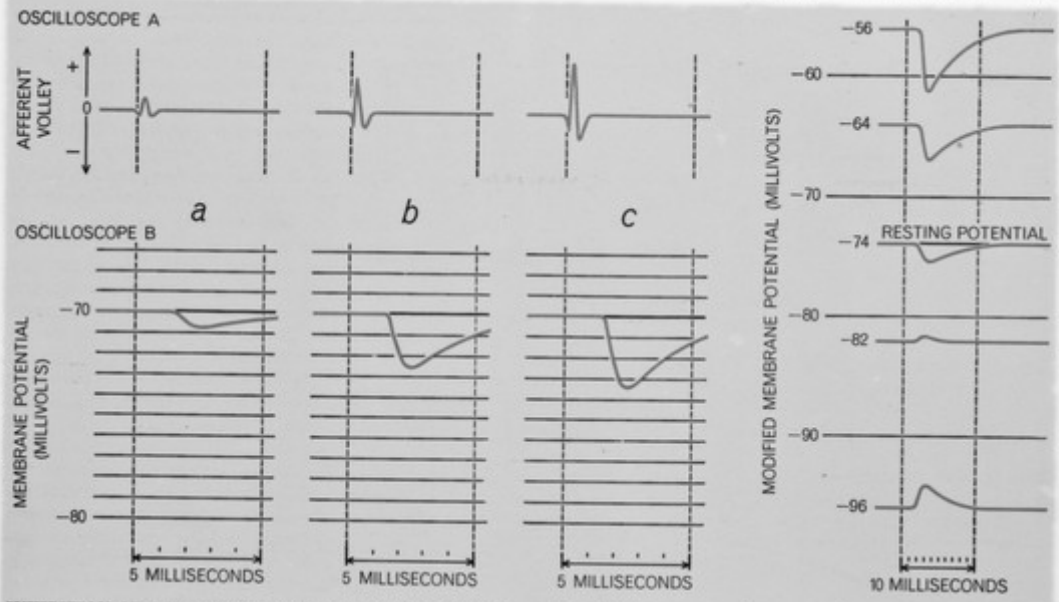
EXCITATORY SYNAPSE may employ transmitter molecules that open large channels in the nerve-cell membrane. This would permit sodium ions, which are plentiful outside the cell, to pour through the membrane freely. The outward flow of potassium ions, driven by a smaller potential gradient, would be at a much slower rate. Chloride ions (*not shown*) may be prevented from flowing by negative charges on the channel walls.



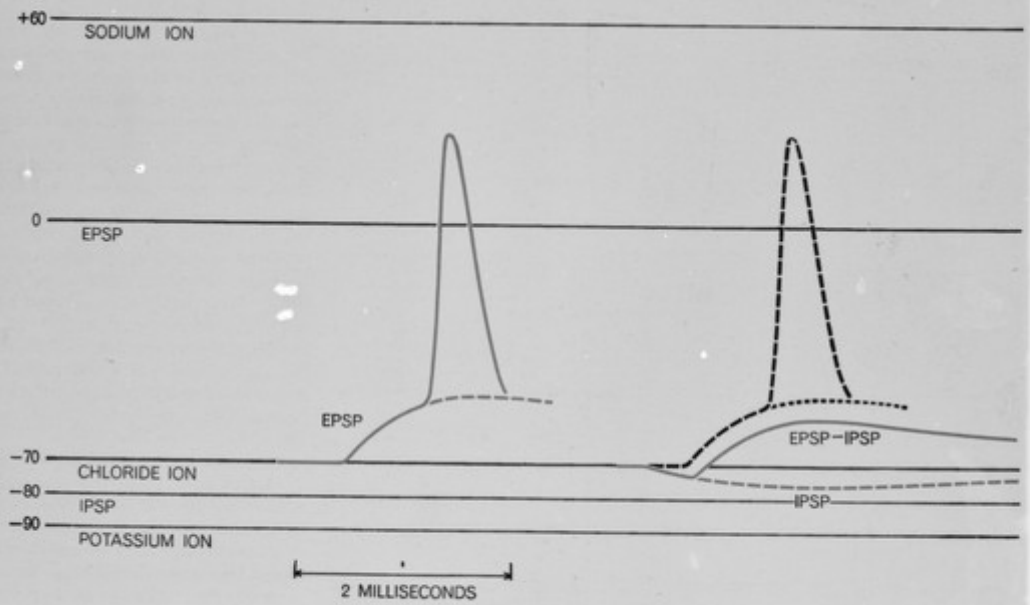
INHIBITORY SYNAPSE may employ another type of transmitter molecule that opens channels too small to pass sodium ions. The net outflow of potassium ions and inflow of chloride ions would account for the hyperpolarization that is observed as an IPSP.



MODIFICATIONS OF INHIBITORY SYNAPSE may involve channels that carry either negative or positive charges on their walls. Negative charges (*left*) would permit only potassium ions to pass. Positive charges (*right*) would permit only chloride ions to pass.



INHIBITION OF A MOTONEURON is investigated by methods like those used for studying the EPSP. The inhibitory counterpart of the EPSP is the IPSP: the inhibitory postsynaptic potential. Oscilloscope *A* records an afferent volley that travels to a number of inhibitory nerve cells whose axons form synapses on a nearby motoneuron (*see illustration on page 166*). A microelectrode in the motoneuron is connected to oscilloscope *B*. The sequence *a*, *b* and *c* shows how successively larger afferent volleys produce successively deeper IPSP's. Curves at right show how the IPSP is modified when a background current is used to change the motoneuron's resting potential. The equilibrium potential where the IPSP reverses direction is about minus 80 millivolts.



INHIBITION OF A SPIKE DISCHARGE is an electrical subtraction process. When a normal EPSP reaches a threshold (*left*), it will ordinarily produce a spike. An IPSP widens the gap between the cell's internal potential and the firing threshold. Thus if a cell is simultaneously subjected to both excitatory and inhibitory stimulation, the IPSP is subtracted from the EPSP (*right*) and no spike occurs. The five horizontal lines show equilibrium potentials for the three principal ions as well as for the EPSP and IPSP.

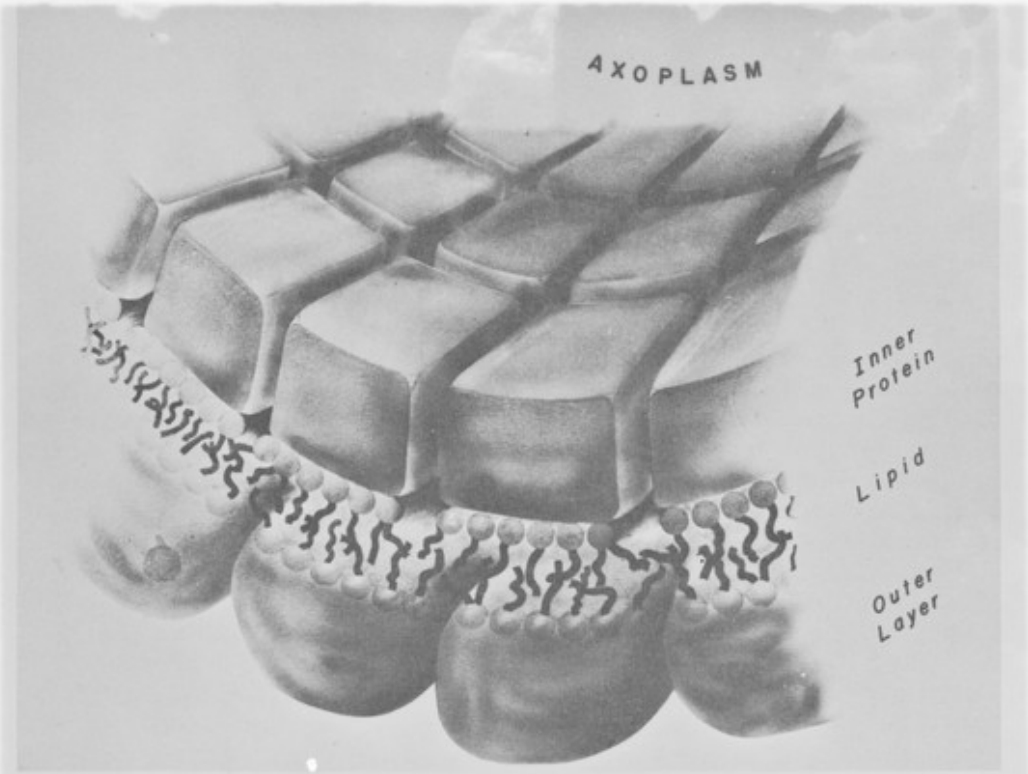


Figure 1. Diagram of axon surface membrane featuring 3 layers: (1) An inner monolayer of globular (shown as cuboidal) protein molecules forming a continuous, probably mosaic, sheet; proteins may be bound to the lipid layer through a shared layer of cationic counter-ions (e.g., Ca^{++}). (2) A bimolecular, liquid-expanded layer of mixed lipids with polar groups arrayed at both surfaces. (3) An outer monolayer of non-lipid molecules of unspecified nature possibly derived from the intercellular matrix.

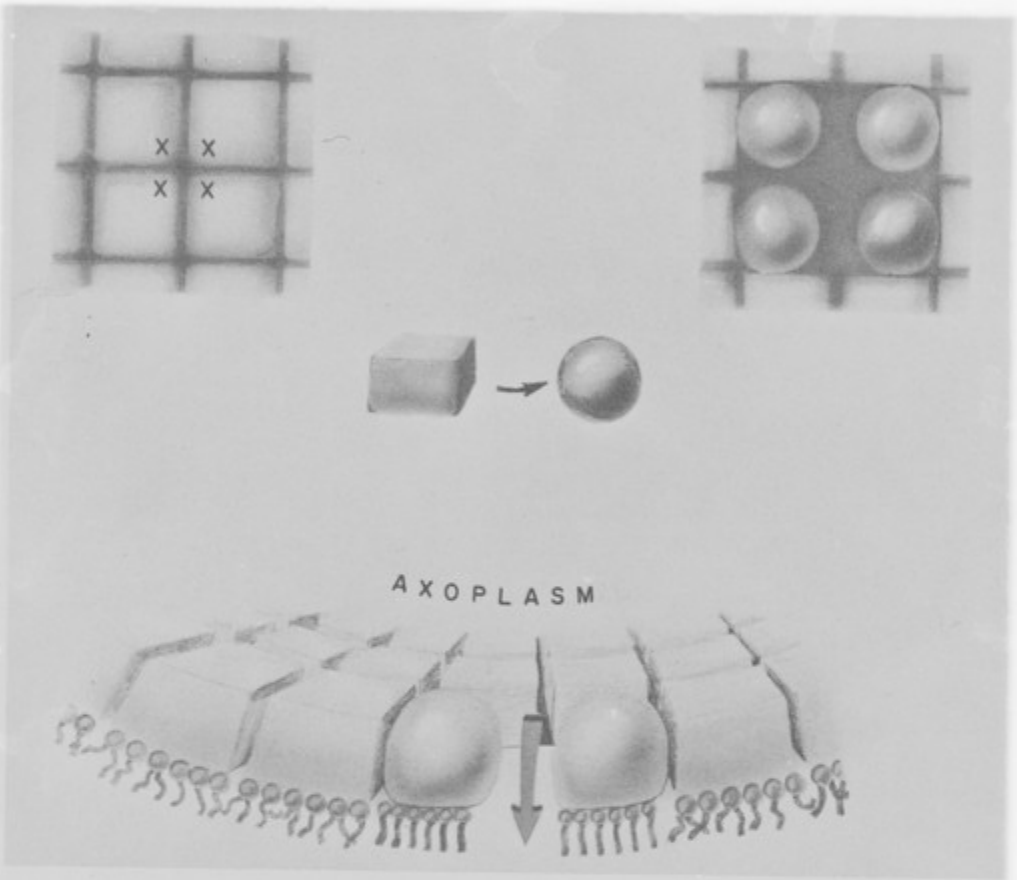


Figure 2. Reversible contractile conformation change of electrogenic protein produces pores through which, according to the ionic theory, ion effectors of the action potential could flow. Coupling of this contraction to lipid molecules of the bilayer leads to simultaneous local compaction of lipids from liquid-expanded to liquid-condensed (or solid) state and corresponding pores in the lipid phase. The conformational change of electrogenic protein could also be a cooperative change in quaternary conformation, i.e., an intermolecular interaction, of one or more proteins in the membrane mosaic.

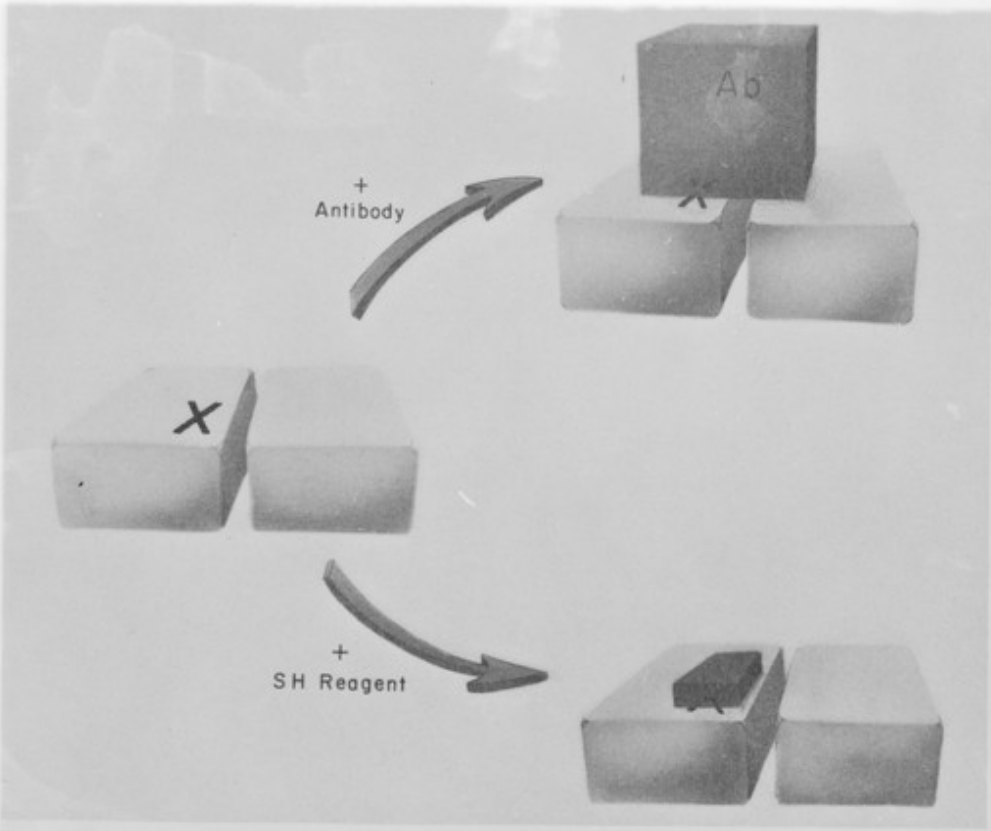
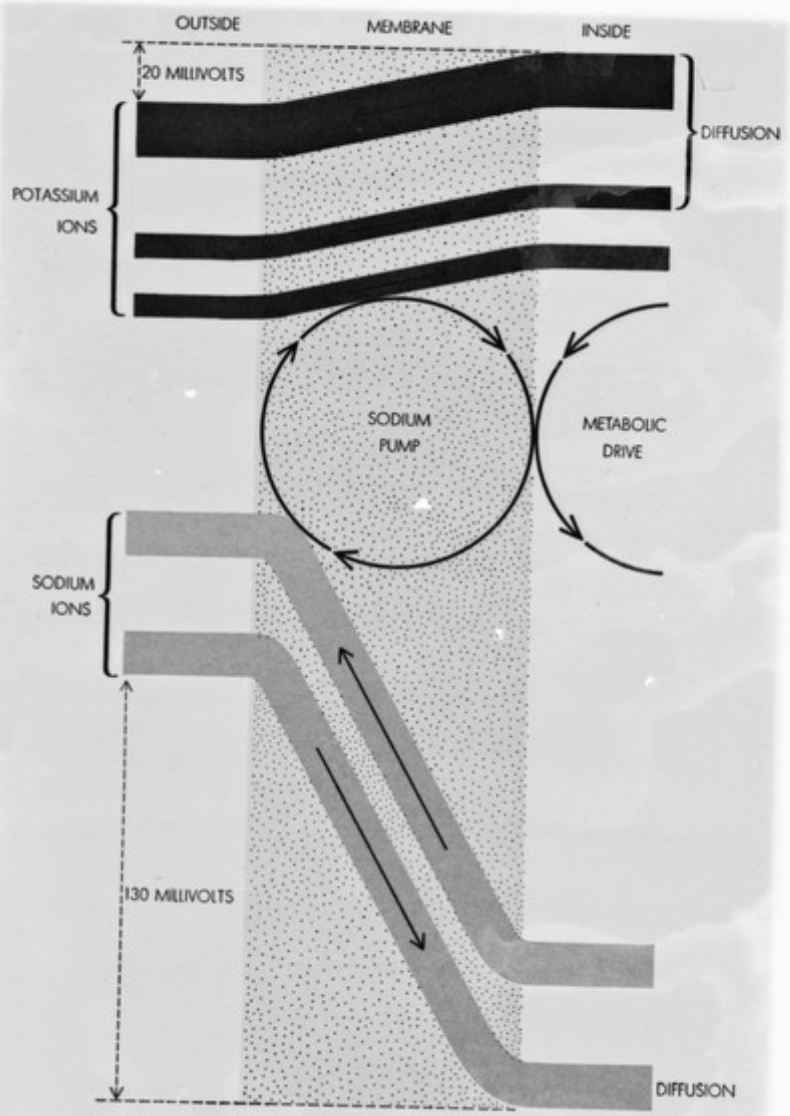


Figure 3. Action potential of perfused squid axon is blocked (with little effect on membrane potential) by antiserum against axon proteins or by -SH reagents. Reaction with antibody is ineffective unless the protein is reduced, suggesting that the protein conformation -- and electrogenic conformation change -- is critically dependent on the state of oxidation of -SH groups. Combination of antibody (upper) or -SH reagent (lower) with the electrogenic protein presumably prevents the conformation change and the triggering of pore formation.

the over-all internal composition of the axon is scarcely affected. Even without replenishment the store of potassium ions inside the axon is sufficient to provide tens of thousands of impulses. In repeated automatic boosting along the transmission path—provides the long-distance communication needs of our nervous system. It imposes a certain stereotyped form of "coding" on our signaling channels: brief pulses of almost



"SODIUM PUMP," details unknown, is required to expel sodium ions from the interior of the nerve axon so that the interior sodium-ion concentration is held to about 10 per cent that of the exterior fluid. At the same time the pump drives potassium ions "uphill" from a low external concentration to a 30-times-higher internal concentration. The pumping rate must keep up with the "downhill" leakage of the two kinds of ion. Since both are positively charged, sodium ions have the higher leakage rate (expressed in terms of millivolts of driving force) because they are attracted to the negatively charged interior of the axon, whereas potassium ions tend to be retained. But there is still a net outward leakage of potassium.

provided and ged in parallel. Fo
example, in th nerve trunk emer
ing from the ere are more than
million channe ning close togethe
all capable of nitting separate si
nals to the hig nters of the brain.

Let us now tu he question of wha
happens a napse, the point a
which the im reaches the end o
one cell and nters another nerve
cell. The self fying cable proces
that serves wi e borders of any one
cell is not desi o jump automatica
ly across the r to adjacent cells.
Indeed, if the re such "cross talk"
between adjac hannels, for instance
among the fib sely packed together
in our nerve s, the system would
become quite ss. It is true that at
functional syn contacts the separa
tion between ll membranes is only
100 to fred angstroms. But
from w of the dimensions of
the con nd of the insulating
propert nembranes, it is un
likely th ive cable connection
could e the terminal of one
nerve c interior of its neigh
bor. Th be demonstrated by
trying t threshold pulse—that
is, one ot trigger a spike—
across th at separates a motor
nerve fr e fiber. A recording
probe l nside the muscle de
tects no a weak pulse is ap
plied to nerve close to the
synapse. e cable linkage is
broken se and some other
process must t place.

The nature process was discov
ered some 25 ago by Sir Henry
Dale and his orators at the Na
tional Institut Medical Research
in London. In ways it resembles
the hormonal nism mentioned at
the beginning article. The motor
nerve terminal rather like glands
secreting a ch messenger. Upon
arrival of an i , the terminals re
lease a special nce, acetylcholine,
that quickly efficiently diffuses
across the sho aptic gap. Acetyl
choline molecul bine with receptor
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cle fiber and s w open its ionic
gates, allowing m to flow in and
trigger an impu e same result can
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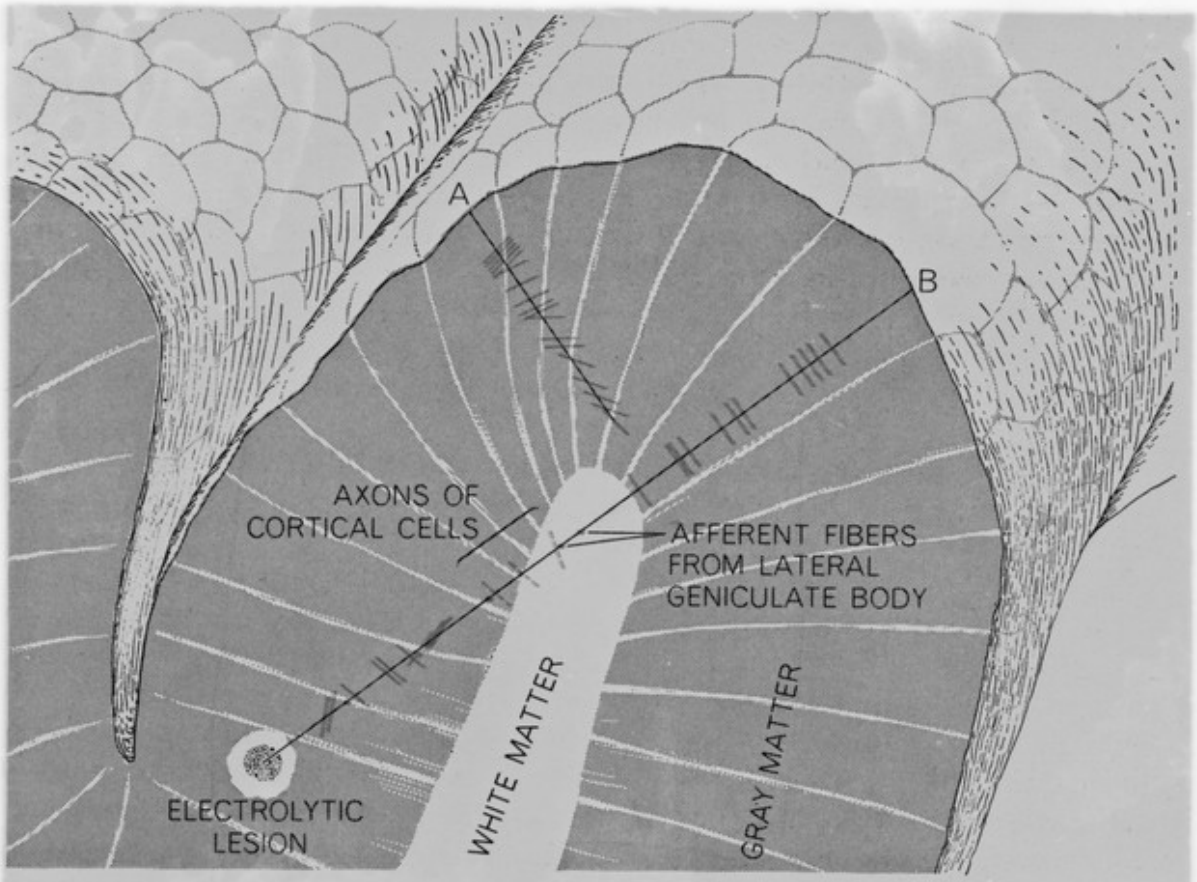
Dr. G. BROWN



FUNCTIONAL ARRANGEMENT of cells in visual cortex resembled columns, although columnar structure is not apparent under a microscope. Lines *A* and *B* show paths of two microelectrode penetrations; colored lines show receptive-field orientations encountered. Cells in a single column had same orientation; change of orientation showed new column.

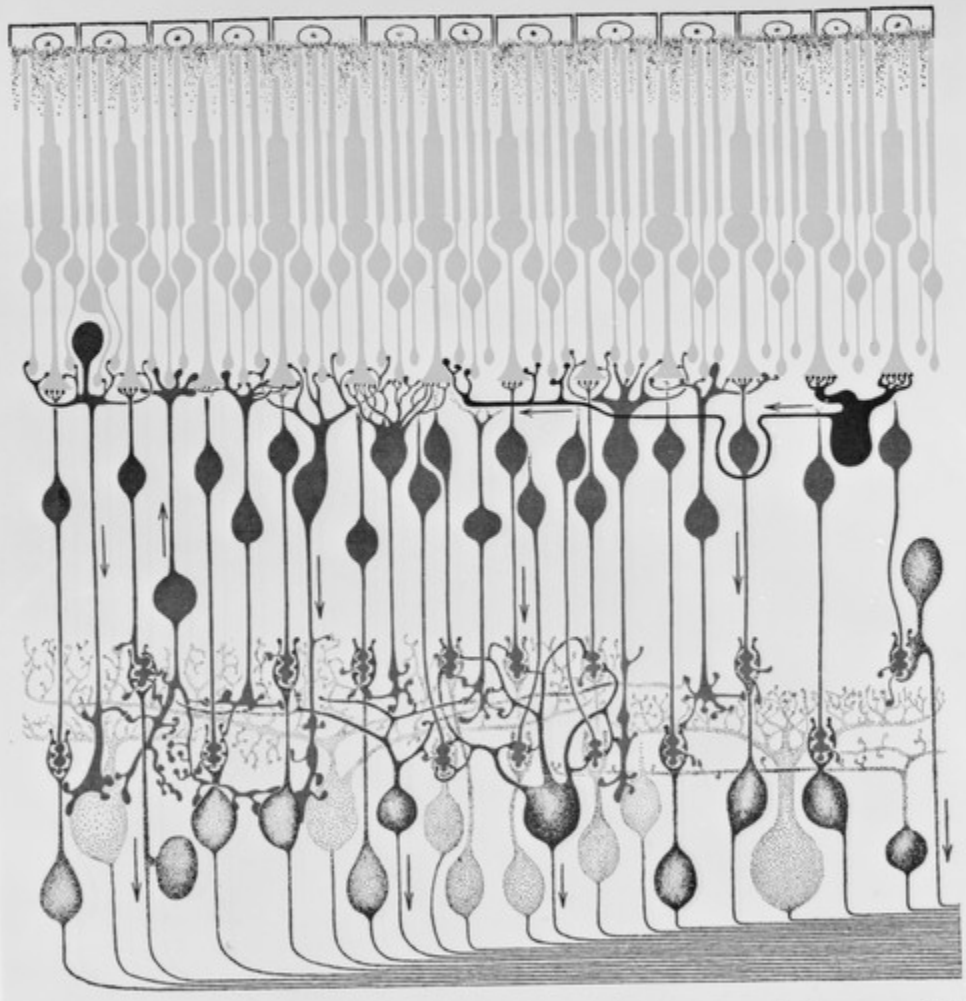
fined not by any anatomically obvious wall—no columns are visible under the

the anatomy that there are rich interconnections between neighboring cells

same receptive-field orientation. The evidence for this is that in a typical

the long, narrow, more or less cylindrical shape of the columns. This means

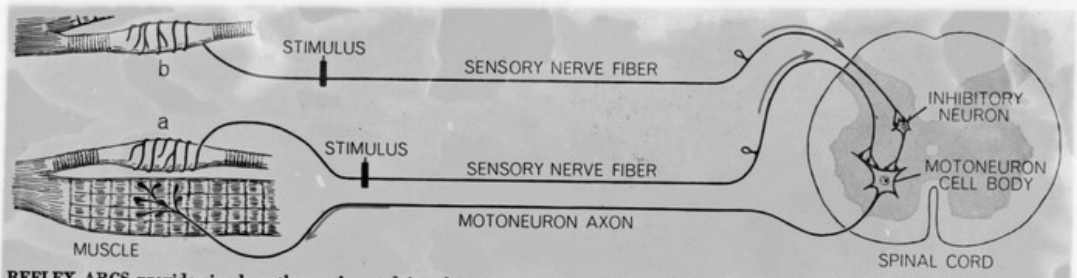
REFLEX ARC illustrates the minimum nerve circuit between stimulus and response. A sensory fiber arising in a muscle spindle enters the spinal cord, where it makes synaptic contact with a motor neuron whose axon returns to the muscle containing the spindle.



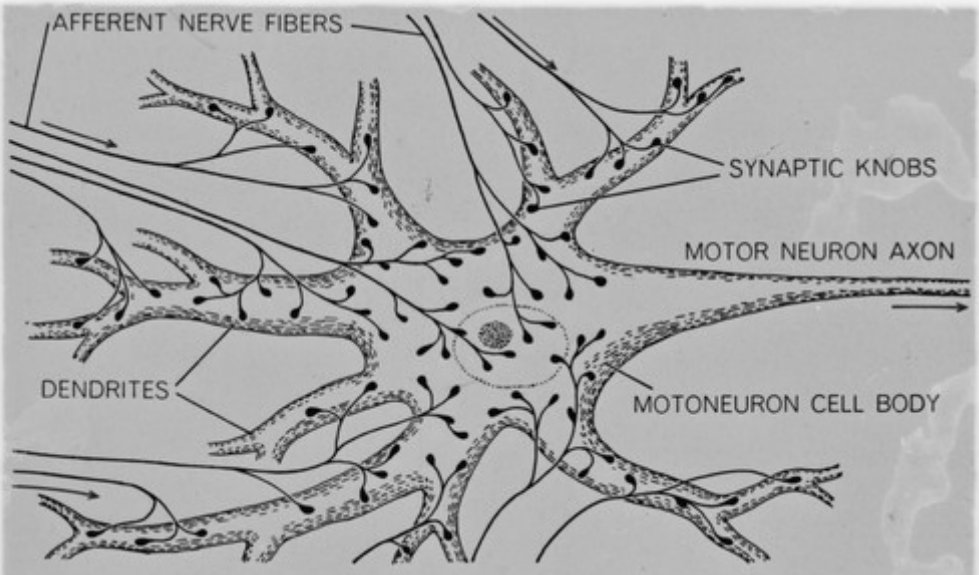
NERVE-CELL NETWORK IN THE RETINA, here magnified about 600 diameters, exemplifies the retinal complexity in man and apes. The photoreceptors are the densely packed cells shown in color; the thinner ones are rods, the thicker ones cones. To reach them the incoming light must traverse a dense but transparent layer of neurons *(dark shapes)* that have rich interconnections with the photoreceptors and with each other. The output of these neurons finally feeds into the optic nerve shown at the bottom of the diagram.

The first step in trying to understand the brain is to examine its structure in order to discover the components from which it is built and how they are related to one another. After that one can attempt to understand the mode of operation of the simplest components. These two modes of investigation—the morphological and the physiological—have now become complementary. In studying the nervous system with today's sensitive electri[illegible] ever, it is all too easy t[illegible] cal events that cannot be correlated with any known anatomical structure. Con[illegible] that receive nerve impulses from other nerve cells, and one relatively long branch—the axon—that transmits nerve impulses. Near its end the axon divides into branches that terminate at the dendrites or bodies of other nerve cells. The axon can be as short as a fraction of a millimeter or as long as a meter, depending on its place and function. It has many of the properties of an electric cable and is uniquely specialized to con[illegible] hard Katz, Offprint #98]. In very thin axons these impulses travel at less [illegible] continue beyond the synapse, it must be regenerated afresh on the other side. As recently as 15 years ago some physiologists held that transmission at the synapse was predominantly, if not exclusively, an electrical phenomenon. Now, however, there is abundant evidence that transmission is effectuated by the release of specific chemical substances that trigger a regeneration of the impulse. In fact, the first strong evidence [illegible] substance [illegible] provided [illegible] more than 40 years ago by Sir Henry Dale and Otto Loewi.

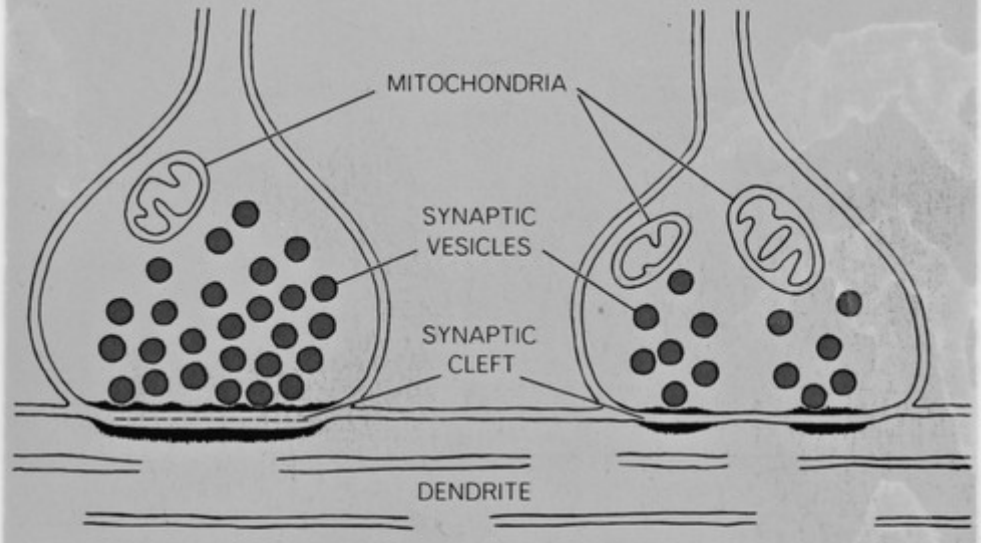
It has been estimated that the hu[illegible]



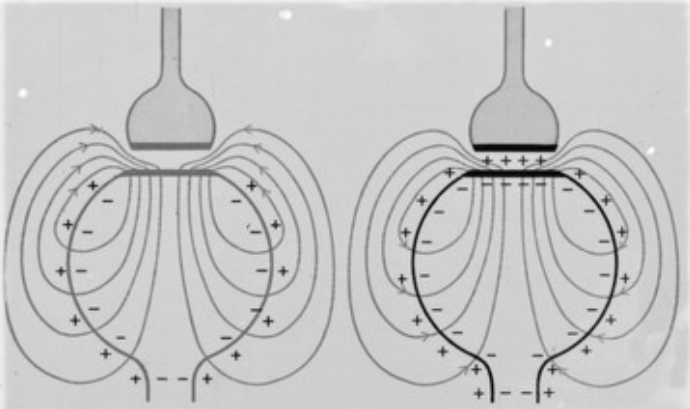
REFLEX ARCS provide simple pathways for studying the transmission of nerve impulses from one nerve cell to another. This transmission is effectuated at the junction points called synapses. In the illustration the sensory fiber from one muscle stretch receptor (*a*) makes direct synaptic contact with a motoneuron in the spinal cord. Nerve impulses generated by the motoneuron activate the muscle to which the stretch receptor is attached. Stretch receptor *b* responds to the tension in a neighboring antagonistic muscle and sends impulses to a nerve cell that can inhibit the firing of the motoneuron. By electrically stimulating the appropriate stretch-receptor fibers one can study the effect of excitatory and inhibitory impulses on motoneurons.



MOTONEURON CELL BODY and branches called dendrites are covered with synaptic knobs, which represent the terminals of axons, or impulse-carrying fibers, from other nerve cells. The axon of each motoneuron, in turn, terminates at a muscle fiber.



SYNAPTIC KNOBS are designed to deliver short bursts of a chemical transmitter substance into the synaptic cleft, where it can act on the surface of the nerve-cell membrane below. Before release, molecules of the chemical transmitter are stored in numerous vesicles, or sacs. Mitochondria are specialized structures that help to supply the cell with energy.



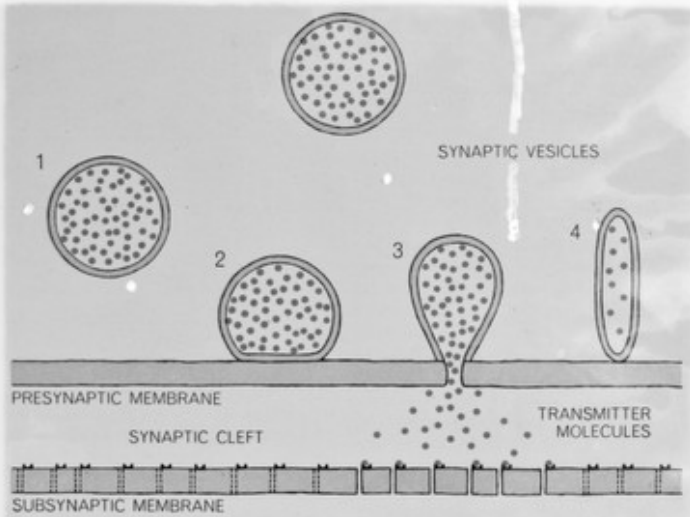
CURRENT FLOWS induced by excitatory and inhibitory synapses are respectively shown at left and right. When the nerve cell is at rest, the interior of the cell membrane is uniformly negative with respect to the exterior. The excitatory synapse releases a chemical substance that depolarizes the cell membrane below the synaptic cleft, thus letting current flow into the cell at that point. At an inhibitory synapse the current flow is reversed.

altering the potential inside the cell one can establish that there is no flow of ions, and therefore no EPSP, when the voltage drop across the membrane is zero.

How is the synaptic membrane converted from a strong ionic barrier into an ion-permeable state? It is currently accepted that the agency of conversion is the chemical transmitter substance contained in the vesicles inside the synaptic knob. When a nerve impulse reaches the synaptic knob, some of the vesicles are caused to eject the transmitter substance into the synaptic cleft [*see illustration below*]. The molecules of the substance would take only a few microseconds to diffuse across the cleft and become attached to specific receptor sites on the surface membrane of the adjacent nerve cell.

Presumably the receptor sites are associated with fine channels in the membrane that are opened in some way by the attachment of the transmitter substance molecules to the receptor sites. With the channels thus opened, sodium and potassium ions flow through the membrane thousands of times more readily than they normally do, thereby producing the intense ionic flux that depolarizes the cell membrane and produces the EPSP. In many synapses the current flows strongly for only about a millisecond before the transmitter substance is eliminated from the cleft, either by diffusion into surrounding regions or as a result of being destroyed by enzymes. The latter process is known to occur when the transmitter substance is acetylcholine, which is destroyed by the enzyme acetylcholinesterase.

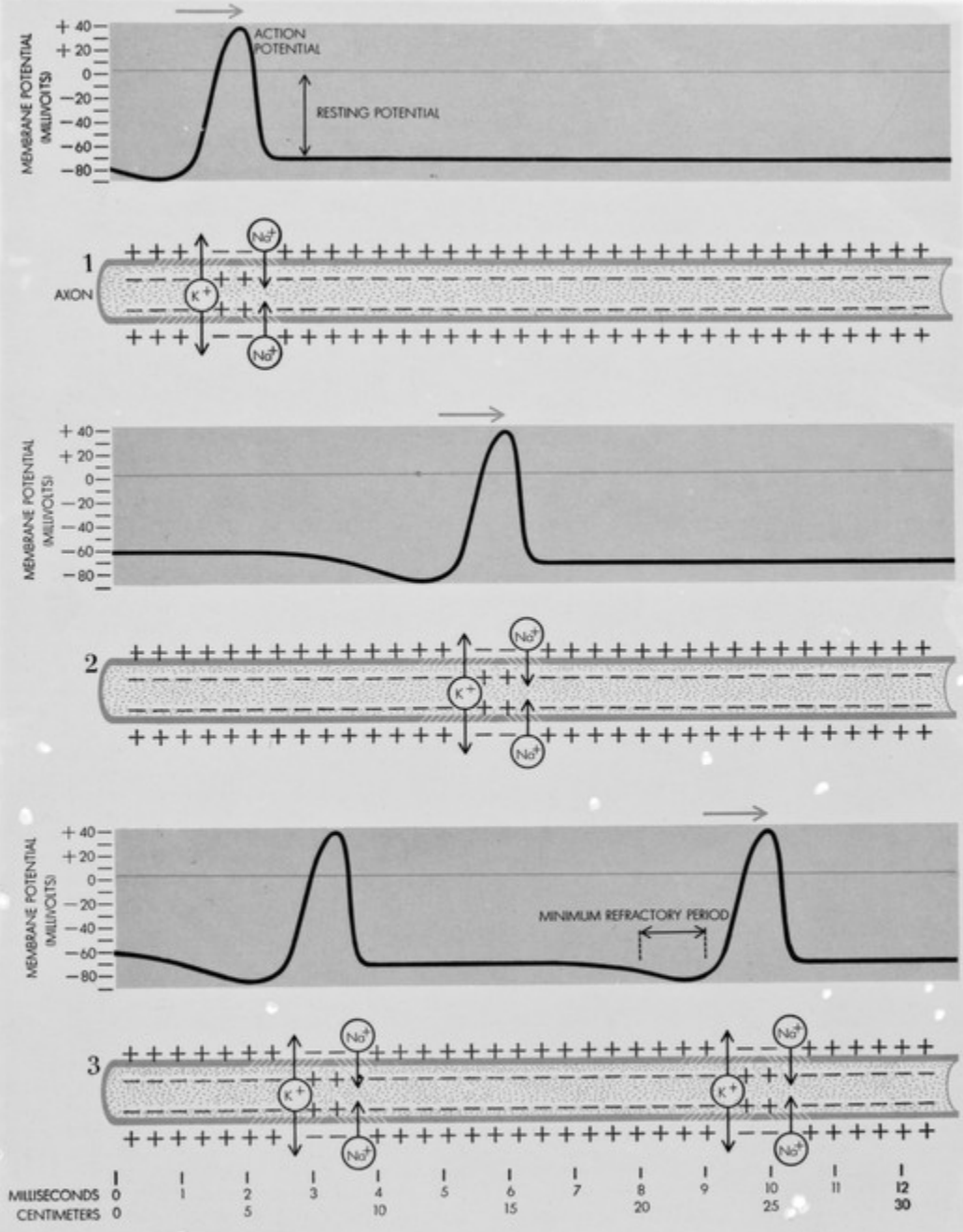
The substantiation of this general picture of synaptic transmission has required the solution of many fundamental problems. Since we do not know the specific transmitter substance for the majority of synapses in the nervous system we do not know if there are many different substances or only a few. The only one identified with reasonable certainty in the mammalian central nervous system is acetylcholine. We know practically nothing about the mechanism by which a presynaptic nerve impulse causes the transmitter substance to be injected into the synaptic cleft. Nor do we know how the synaptic vesicles, not immediately adjacent to the synaptic cleft are moved up to the firing zone to replace the emptied vesicles. It is conjectured that the vesicles contain the enzyme systems needed to recharge themselves. The entire process must be swift and efficient: the total amount of transmitter substance in synaptic terminals is enough for only a few minutes of synaptic activity at normal firing rates. There are also knotty problems to be solved on the other side of the synaptic cleft. What, for example, is the nature of the receptor sites? How are the ionic channels in the membrane opened up?



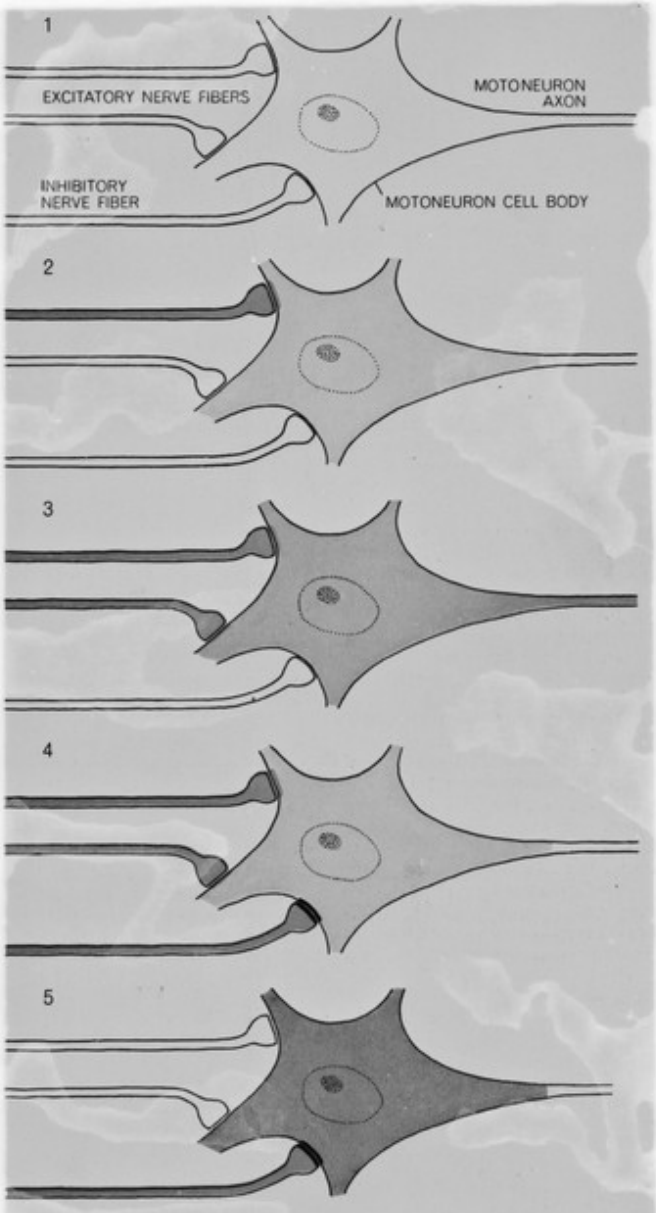
SYNAPTIC VESICLES containing a chemical transmitter are distributed throughout the synaptic knob. They are arranged here in a probable sequence, showing how they move up to the synaptic cleft, discharge their contents and return to the interior for recharging.

The Inhibitory Synapse

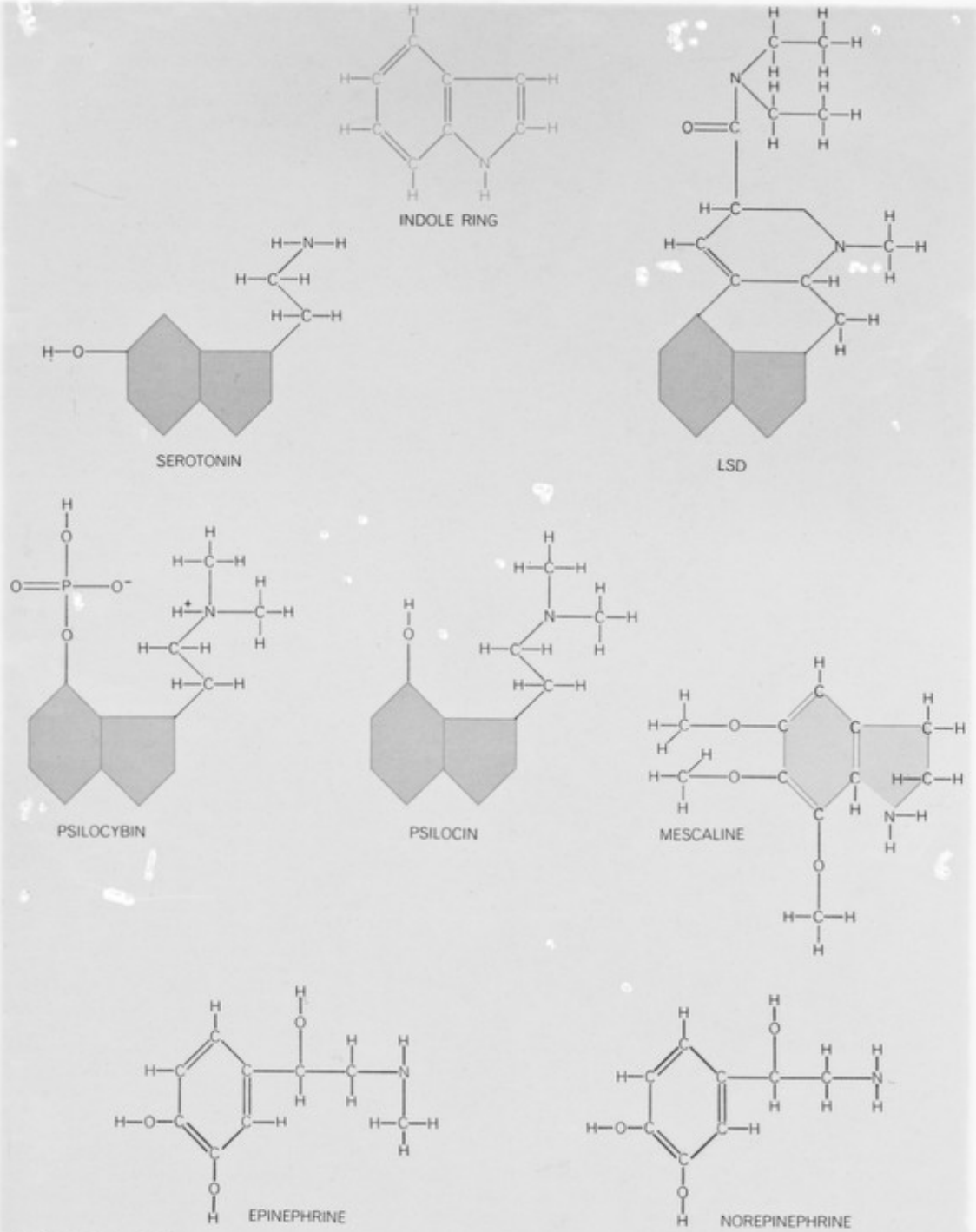
Let us turn now to the second type of synapse that has been identified in the nervous system. These are inhibitory synapses that can inhibit the firing of a nerve cell even though it may be receiving a volley of excitatory impulses. When inhibitory synapses are examined in the electron microscope, they look very much like excitatory synapses.



PROPAGATION OF NERVE IMPULSE coincides with changes in the permeability of the axon membrane. Normally the axon interior is rich in potassium ions and poor in sodium ions; the fluid outside has a reverse composition. When a nerve impulse arises, having been triggered in some fashion, a "gate" opens and lets sodium ions pour into the axon in advance of the impulse, making the axon interior locally positive. In the wake of the impulse the sodium gate closes and a potassium gate opens, allowing potassium ions to flow out, restoring the normal negative potential. As the nerve impulse moves along the axon (*1 and 2*) it leaves the axon in a refractory state briefly, after which a second impulse can follow (*3*). The impulse propagation speed is that of a squid axon.



EXCITATION AND INHIBITION of a nerve cell are accomplished by the nerve fibers that form synapses on its surface. Diagram *1* shows a motoneuron in the resting state. In *2* impulses received from one excitatory fiber are inadequate to cause the motoneuron to fire. In *3* impulses from a second excitatory fiber raise the motoneuron to firing threshold. In *4* impulses carried by an inhibitory fiber restore the subthreshold condition. In *5* the inhibitory fiber alone is carrying impulses. There is no difference in the electrical impulses carried by excitatory and inhibitory nerve fibers. They achieve opposite effects because they release different chemical transmitter substances at their synaptic endings.



CHEMICAL RELATIONS among several of the hallucinogens and neurohumors are indicated by these structural diagrams. The indole ring (*in color at top*) is a basic structural unit; it appears, as indicated by the colored shapes, in serotonin, LSD, psilocybin and psilocin. Mescaline does not have an indole ring but, as shown by the light color, can be represented so as to suggest its relation to the ring. The close relation between mescaline and the two catechol amines epinephrine and norepinephrine is also apparent here.