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Neurophilosophy.
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Chapter 2
Modern Theory of Neurons

I doubt if we can even guess what Natural Selection has achieved, without some help from the way function has been embodied in actual structures. The reason is simple. Natural Selection is more ingenious than we are.
F. H. C. Crick, 1985

2.1 *Introduction*

If we are to understand how the mind-brain works, it is essential that we understand as much as possible about the fundamental elements of nervous systems, namely, neurons. Limits on the number of neurons, on the number of connections between neurons, and, perhaps most importantly, on the time course of neuronal events will highly constrain models of perception, memory, learning, and sensorimotor control. For example, it is worth dwelling on the constraints imposed by this temporal fact: events in the world of silicon chips happen in the *nanosecond* (10^{-9}) range, whereas events in the neuronal world happen in the *millisecond* (10^{-3}) range. Brain events are ponderously slow compared to silicon events, yet in a race to complete a perceptual recognition task, the brain leaves the computer far back in the dust. The brain routinely accomplishes perceptual recognition tasks in something on the order of 100–200 milliseconds, whereas tasks of much lesser complexity will take a huge conventional computer days. This immediately implies that however the brain accomplishes perceptual recognition, it cannot be by millions of steps arranged in sequence. There is simply not enough time. (This will be discussed in more detail in chapter 10. See also Feldman 1985.)

It is also worth dwelling on the fact that neurons are plastic, that their informationally relevant parts grow and shrink, that they are dynamic. Nor is their plasticity a nuisance or an ignorable nicety; it appears to be essential to their functioning as information-processing units. Again, as we search for models and theories to understand the nature of cognitive abilities, this fact will constrain our theorizing.

Moreover, considerations of plasticity in conjunction with limits on the number of neurons and the number of connections may be theoretically significant in the following way. Models of learning and memory that invest all the processing complexity in *connections*, and next to none in the neuron itself, may well find that the model must postulate many more units than the nervous system has. The number of neurons and their finite if large number of connections also restrict the range of possible models (Feldman and Ballard 1982).

Finally, it is useful to know that neurons and their modus operandi are essentially the same in all nervous systems—our neurons and the neurons of slugs, worms, and spiders share a fundamental similarity. There are differences between vertebrates and invertebrates, but these differences pale beside the preponderant similarities. Even our neurochemistry is fundamentally similar to that of the humblest organism slithering about on the ocean floor.

What matters here is not that this humbling thought pricks our eminently prickable vanity, but that it reminds us that we, in all our cognitive glory, *evolved*, and that our capacities, marvelous as they are, cannot be a bolt from the blue. Which means that models for human cognition are inadequate if they imply a thoroughgoing discontinuity with animal cognition. It is also a reminder that if we want to understand the nature of the information processing that underlies such functions as thinking and sensorimotor control, our theories must be constrained by how neurons are in fact orchestrated, and we cannot understand *that* without knowing a good deal about neurons themselves, about their connections to other neurons, and about how they form these connections. It is therefore a methodological constraint of the greatest importance (figure 2.1).

Nervous systems are information-processing machines, and in order to understand how they enable an organism to learn and remember, to see and problem solve, to care for the young and recognize danger, it is essential to understand the machine itself, both at the level of the basic elements that make up the machine and at the level of organization of elements. In this chapter the focus will be on neurons—on their structure and their manner of functioning.

2.2 *The Cellular Components of Nervous Systems*

The human brain weighs about three pounds and has a volume of about three pints. It contains some 10^{12} neurons, or perhaps as many as 10^{14}; the count is only an estimate. When the body is resting, the nervous system consumes about 20 percent of the body's oxygen supply, which is the lion's share, considering that the brain accounts

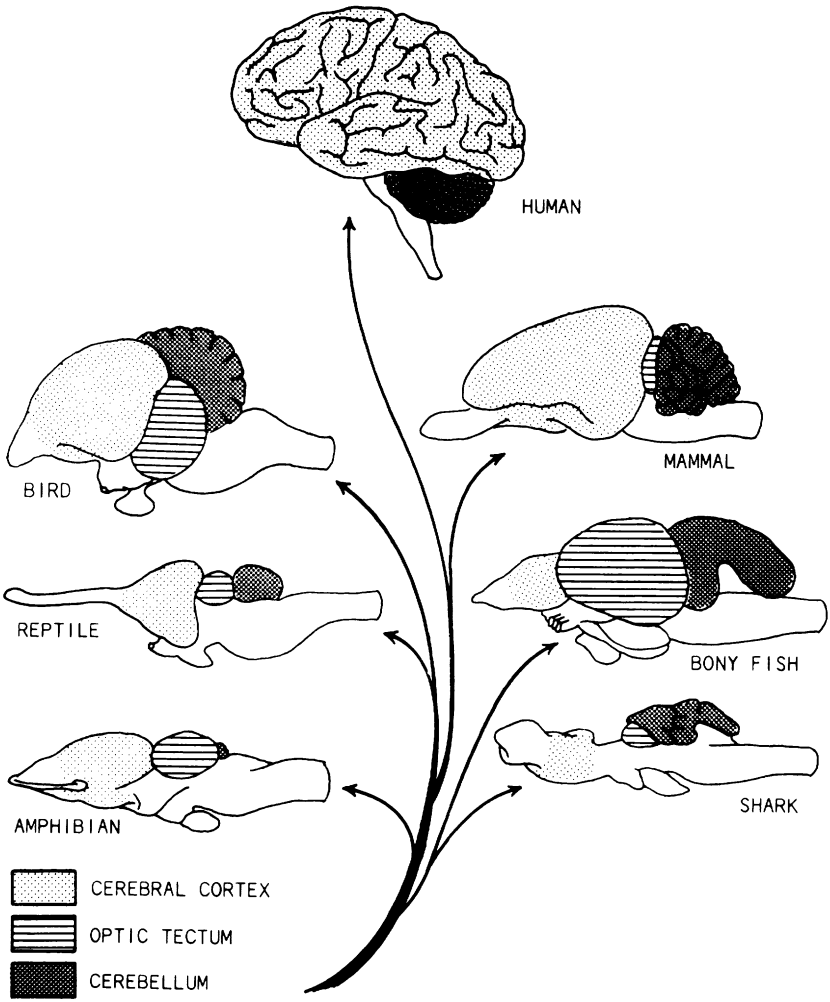


Figure 2.1
Lateral view of several vertebrate brains showing relative development of major brain divisions. Brains not drawn to scale. (Modified from Northcutt (1977). In *McGraw-Hill Encyclopedia of Science and Technology*. New York: McGraw-Hill.)

for only about 2 percent of the body's mass and that skeletal muscles, the kidneys, the heart, the liver, and so on, also demand oxygen. The central nervous system (CNS) consists of the brain and spinal cord; the peripheral nervous system (PNS) consists of all the nervous structures external to the brain and spinal cord, such as the fibers innervating the muscles and the sensory receptors in the skin. The retina is considered part of the CNS (figure 2.2).

Neurons

Neurons are the basic nervous elements and are differentiated into a cell body, or *soma,* and *processes*[1] (projections) extending out from the soma. The soma is the vital center of the cell, containing the nucleus and RNA, and it has structures that manufacture protein, much of which is shipped down the axon by a complex system of axonal transport. Processes are usually distinguished as *axons* or *dendrites,* but not all neurons have both. Axons are the principal output apparatus, and dendrites principally receive and integrate signals. Some sensory neurons in the skin have only an axon, and some neurons in the olfactory lobe have only dendrites. A single axon generally protrudes from the soma, and commonly it will branch extensively toward its end. In contrast, a dense arborization of dendrites often extends from the soma (figure 2.3). (See also figure 1.5.) In many types of neurons the dendrites are covered with stubby branchlets called *spines* that serve as the dominant points of contact with other neurons.

Neurons vary in size, but even the largest is exceedingly small. In the human nervous system, dendrites may be about 0.5 microns in diameter, and the soma of a motor neuron is about 20–70 microns wide. The largest axons are about 20 microns across, but they are long—some as long as the spinal cord. There is considerable variation between different types of neurons, with some showing fairly obvious specializations suited to their function. The squid was discovered to have motor neurons with relatively large axons (roughly one millimeter in diameter). Given its size, the giant axon of the squid could be impaled quite easily by recording and stimulating electrodes, allowing the electrochemical properties of axons to be investigated (Hodgkin and Huxley 1952). (These properties will be discussed in section 2.3.)

At birth, the primate nervous system has virtually all the neurons it will ever have. The only known exception is the olfactory system, in which neurons are continuously induced. Growth of axons and dendrites, as well as of the spines on dendrites, is prolific, especially in the first few years of life. In the midst of this luxuriant growth, how-

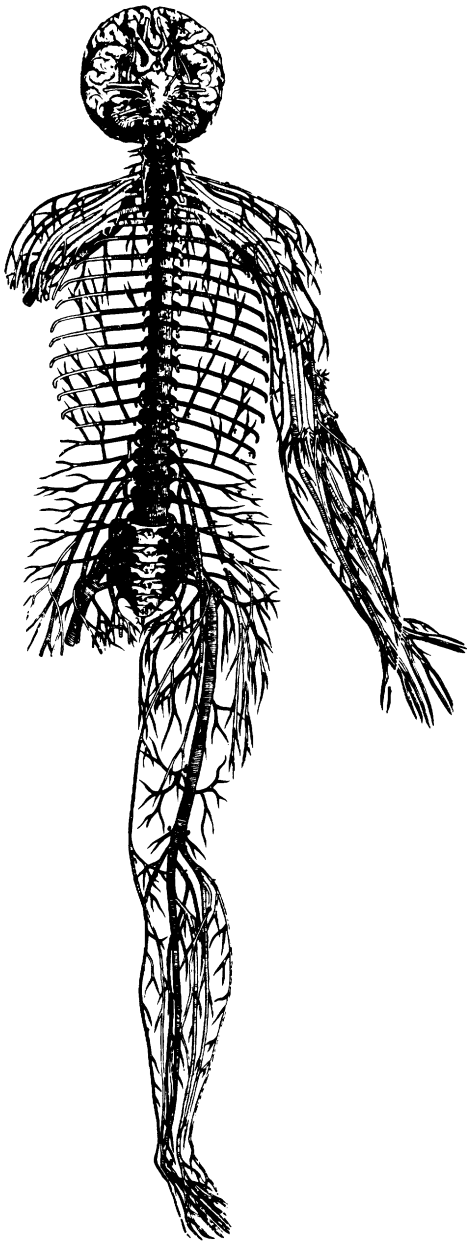


Figure 2.2
Drawing by Vesalius (1543) showing the brain, the spinal column, and the peripheral nerves, whose innervation of the trunk and limbs delineates the human form. (From Saunders and O'Malley 1950.)

ever, there is also massive selective death of neurons in early infancy, and between 15 and 85 percent of the original neuron pool is doomed. This appears to be a programmed death, and it is a crucial part of normal infant brain development, but exactly why it happens and precisely what are the principles of culling are not fully understood. (See also chapter 3.) There is additionally what one might call ordinary "grim reaper death," which fells about a thousand neurons per day in the adult brain after forty—a rather appalling statistic given the lack of replacements. Still, dendritic growth continues and surviving neurons apparently take up the slack. That the brain manages well enough even so is indicative of its plasticity.

Synapses are the points of communication between neurons, where processes make quasi-permanent junctions with the soma or processes of another neuron, and they appear to be highly specialized (figure 1.7, 1.8). It is usually presumed that signal transmission occurs only at synaptic junctions, but this is not known for sure. It may be that weak influences are transmitted at spots where the membranes lack specialized synaptic apparatus but are in close proximity. Commonly an axon will synapse on a dendrite or on the somas of other neurons, but it may synapse on other axons, and in some cases dendrites synapse on other dendrites and on somas. The number of synapses on each neuron varies widely, but it is large—approximately 5,000 on a mammalian motor neuron, and approximately 90,000 on a single Purkinje cell in the human cerebellar cortex (figure 2.4). Altogether, there are estimated to be about 10^{15} connections in the human nervous system, give or take an order of magnitude.

Functionally, neurons are classed as sensory neurons, motor neurons, or interneurons. Sensory neurons transduce physical signals, such as light or mechanical deformation, into electrical signals that they pass on. Motor neurons terminate on muscles to produce contractions. Interneurons are a mixed bag of everything else in between sensory neurons and motor neurons. Neurons come in a wide variety of types, and the types differ greatly in such properties as size, axonal length, and characteristic pattern of dendritic arborization (figure 2.4). In lower animals there is much less evidence of specialization, and in invertebrates the division of processes into axons and dendrites is not seen, dendrites being a later achievement than axons.

Neuroglia

Nervous tissue consists not only of neurons but also of special ancillary cells called *neuroglia*. These cells were first described and recog-

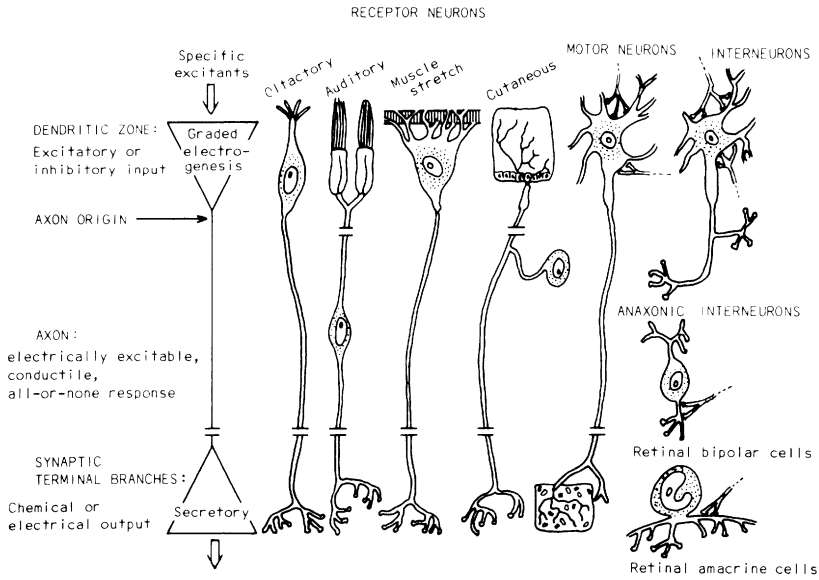


Figure 2.3
Basic functional and structural features of neurons, as shown in a variety of afferent (incoming) neurons, efferent (outgoing) neurons, and interneurons. The diagram illustrates the idea that impulse origin rather than cell-body position is the most reasonable focal point for the analysis of neuron structure in functional terms, at least for those neurons with an axon process. (Modified from Bodian 1967.)

nized as distinct from neurons in 1856 by Rudolf Virchow, who coined the term "neuroglia" because "glia" means glue, and he thought of them as a kind of glue in which nerve cells are planted. Their assorted properties, to the extent that they are known, turn out to be remarkable, though stickiness is not among them. One type of glial cell, the Schwann cell, wraps itself around and around the axonal process of a peripheral cell to provide an insulating sheath that permits faster conduction of the nervous impulse. The oligodendrocytes perform the same service for CNS axons. The sheath so formed is called *myelin*. Ensheathing is intensively cultivated during infancy and tapers off as the child approaches puberty; nevertheless, some myelinization in the cerebral cortex continues until about age forty (figures 2.5, 2.6).

True myelin is peculiar to vertebrates, though even in vertebrates not all neurons are myelinated. Phylogenetically older neurons, such as the thin C-fibers that innervate the skin and carry information about pain (and probably many other things as well) are not myelinated. The association between neurons and glial cells varies greatly,

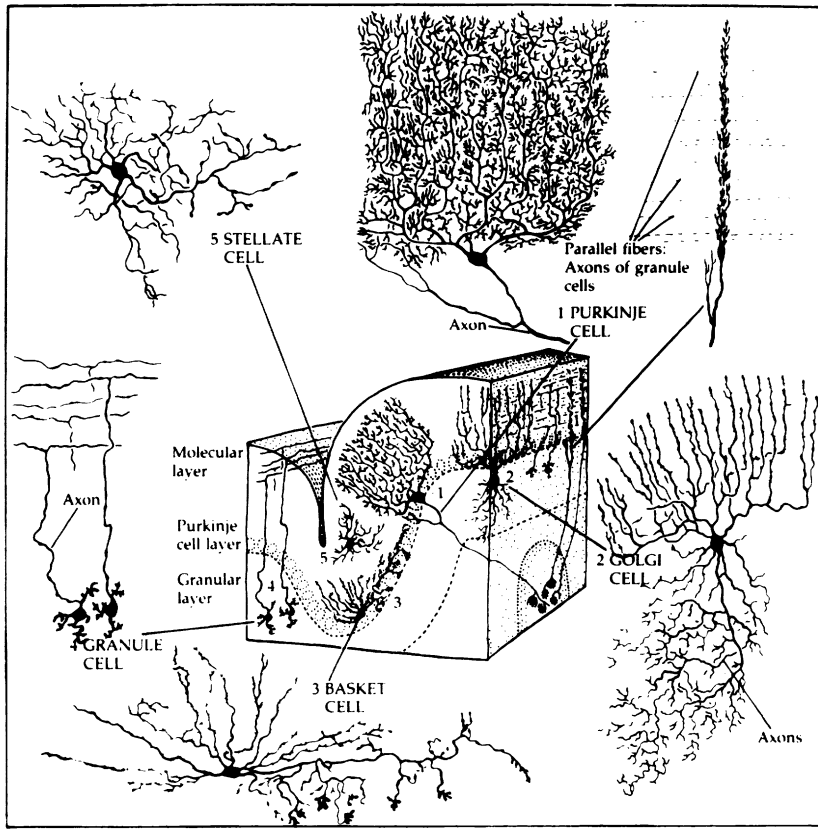


Figure 2.4
Types of neurons. The human cerebellum has over 10^{10} cells but only five neuronal types. Each type has its characteristic shape, branching pattern, connectivity pattern, and position. See figures 2.1 and 3.1 for the position of the cerebellum in relation to other brain divisions. (From Kuffler, Nicholls, and Martin (1984). *From Neuron to Brain.* 2nd ed. Sunderland, Mass.: Sinauer.)

and in some cases axons merely fit into a groove of a neighboring glial cell. Some neuroglia function as fences (astrocytes) and as filters (ependymal cells) in isolating neurons from blood but not from their special nutrient bath. Yet others, the microglia, function as phagocytes or scavengers, cleaning up dead neurons and assorted detritus. The operation of neurons is so dazzling that glial cells tend not to get their share of the limelight. Nevertheless, outnumbering neurons by about ten to one, they are crucial to the proper functioning of the nervous system, though research is only beginning to reveal just how many tasks they are relied upon to perform. Certainly degeneration

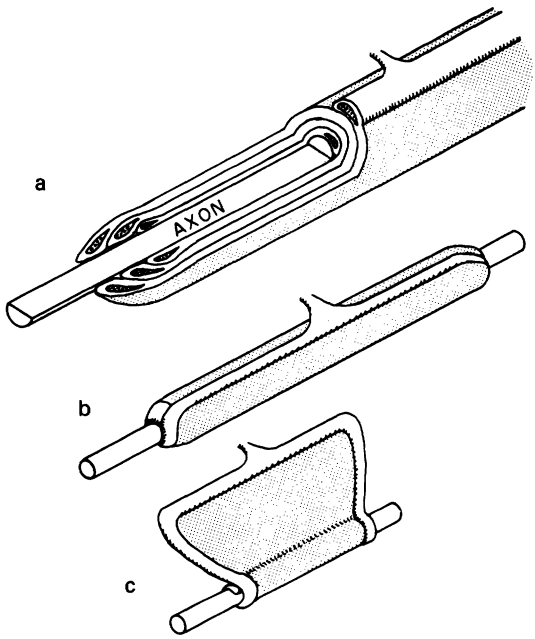


Figure 2.5
Diagram of a myelinated axon. (a) Part of the myelin is cut away to show the inner layers. (b) A glial cell that forms the myelin sheath is shown completely rolled up around a segment of axon. (c) Diagram of an axon segment and an unrolled glial cell. (Modified from Hirano and Dembitzer 1967.)

of the glia, for example of the Schwann cells and oligodendrocytes that make up the myelin sheaths, is devastating to proper sensorimotor control. Multiple sclerosis is one such demyelinating disease.

Where there are tracts of axons encased in myelin, the tissue appears lighter in color than where there are clumps of somas and their bushes of dendrites, which have a distinctly grayish (or pinkish) hue. It is the presence of myelin that makes the difference between white and gray matter, for only axons are myelinated. In a section of nervous tissue, this color difference is easily visible with the naked eye (figure 2.7).[2]

Receptors

Receptors hold a special fascination, perhaps because it is the range of stimuli to which receptors are sensitive that limits the kinds of things we sense in the world. Receptors are the interface between world and brain, and our conception of what the universe is like and what we

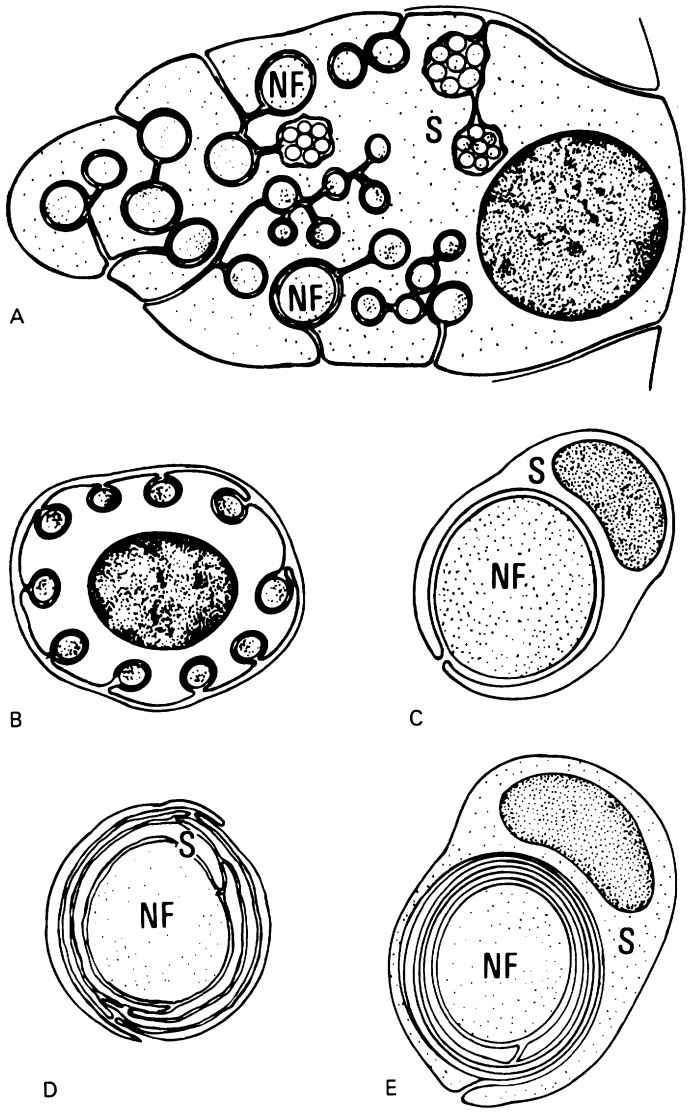
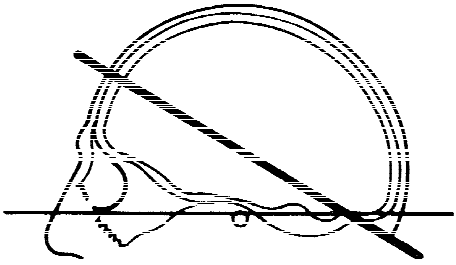


Figure 2.6
Schematic diagram of various forms of ensheathment known to occur in relation to neuron fibers. (A) Large glial cells ensheath axons singly or in groups (as in the leech). (B) Small undifferentiated nerve fibers may be enclosed in individual troughs of glial cell membrane (as in vertebrate peripheral nervous system). (C) Large nerve fibers may be surrounded by a single glial cell (as in insect peripheral nervous system). (D) Large nerve fibers may be surrounded by multiple layers of glial cell (as in insects). (E) Systematic spiralization and compaction lead to the myelin characteristic of the vertebrate peripheral nerve. (Modified from Bunge 1968.)



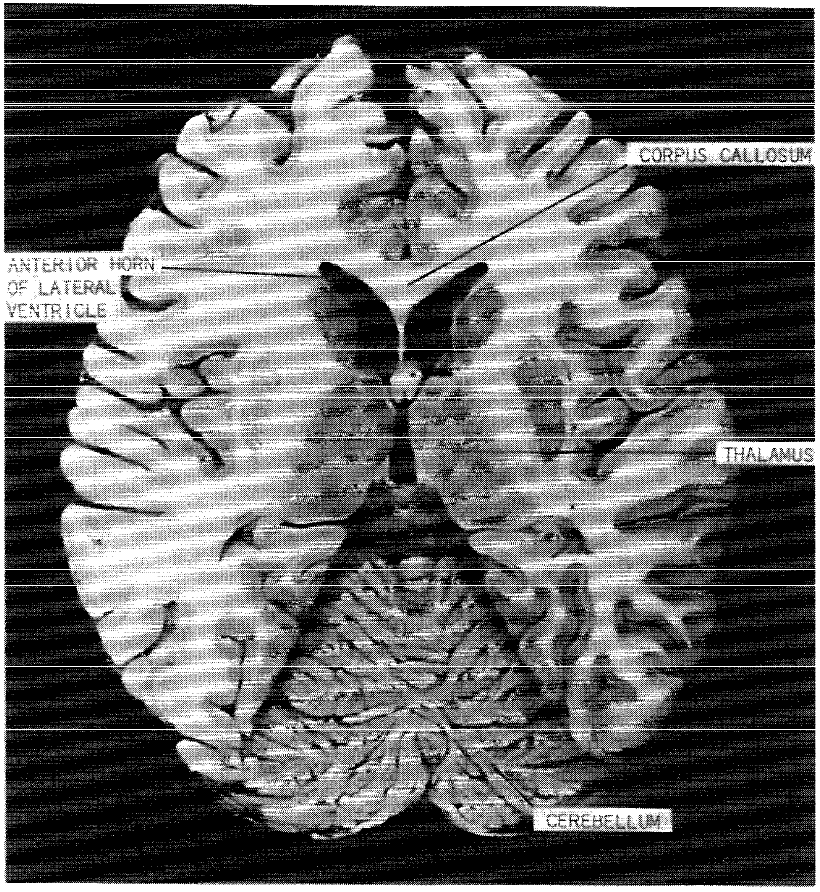


Figure 2.7
A section of the human brain at 20 degrees from the specified plane. The cerebral cortex shows as the gray rind on the outer surface, following the folds of tissue. The cerebellar cortex is also visible, as a rind following the very deep folds of the cerebellar white matter. The corpus callosum consists of myelinated nerve fibers, and so appears white. The thalamus contains a large consolidation of cell bodies and appears gray. (From Matsui and Hirano (1978). *An Atlas of the Human Brain for Computerized Tomography.* Copyright © Igaku-Shoin, Tokyo/New York.)

take to be the truth about the universe is inescapably connected to the response characteristics of cells at the periphery. This is what struck Magendie, and later Müller, in their experiments on the specificity of receptors in responding to distinct kinds of physical stimuli. It is probably also the source of the deep currents in Kant's plea for constraints in epistemology—constraints that would acknowledge that our access to the world is always *mediated* access, access via the nervous system. The human nervous system, after all, is a physical thing, with physical limits and physical modes of operation. Kant argued that we can know the world only as it appears to us—as it is presented to us—not as it is in itself. (See chapter 6.) When I open my eyes and look about me, it is as though I see the world as anything sees it, as it really is, in its nakedness and in its entirety. But what I see is a function not only of how the world is but also of how my visual receptors respond to one narrow parameter of the world's properties (electromagnetic radiation in the 0.4–0.75 micrometer range) and of how my brain is formed to manipulate those responses.

Nervous systems have evolved specialized receptors for detecting a wide range of physical parameters. The classical distinction into "five senses" is notoriously inept, since there are receptors not only for taste, smell, sound, sight, and touch but for a miscellany of other things as well. There are proprioceptors for detecting changes in position of the head, kinesthetic receptors in the muscles and the tendons to detect stretch, receptors for visceral distension and for lung stretch, and receptors in the carotid arteries to detect levels of oxygen in the arterial blood. Besides being incomplete, the classical taxonomy is imperspicuous. For example, the category "touch" rakes together diverse perceptions, including light touch, erotic sensations, light and deep pressure, vibration, a variety of temperature sensations, and a wide assortment of painful sensations.

Snug within the confines of our own perceptual world, it is jolting to realize that other animals are richly receptive where we are stony blind. Bees can detect ultraviolet light; snakes have pits for electromagnetic waves in the infrared range; flies have gyroscopic strain gauges; aquatic vertebrates can detect water displacement by means of lateral-line organs; pigeons have ferromagnets for orienting with respect to the earth's magnetic field, sharks can pick up and use low-frequency (0.1–20 Hz) electric fields; electric fish are sensitive to high frequency (50–5,000 Hz) current. A human submerging into the ocean depths finds an engulfing silence, but for an electric fish the watery world is rich in electromagnetic events, and it uses electrolocation and electrocommunication to great advantage (Bullock, Orkand,

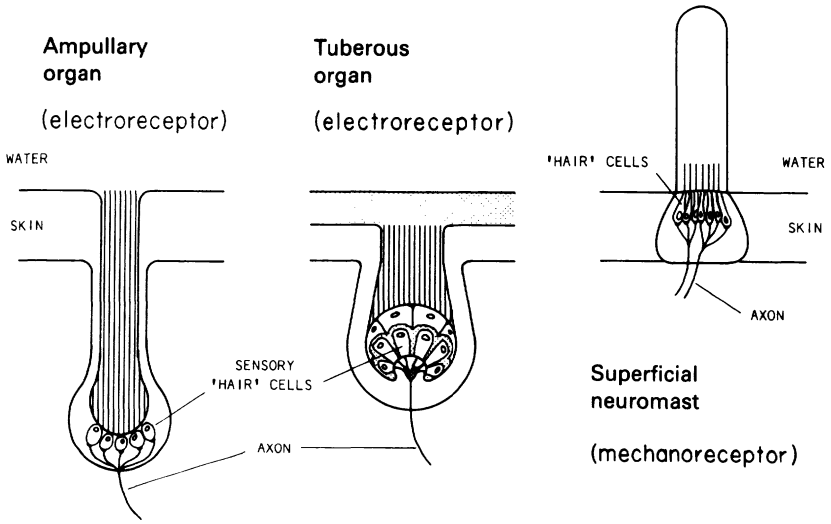


Figure 2.8
Diagram of two different electroreceptors and a mechanoreceptor found in the lateral line organs of fish. (Modified from Dijkgraaf 1967 and Szabo 1974.)

and Grinnell 1977). The world as perceived by humans is not the world as perceived by any organism. Rather, it is that narrow dimension of the world evolution has permitted our specialized receptors to detect (figure 2.8).

Even in very simple organisms, specialized receptors are found. The jellyfish, too far down the evolutionary ladder to have the benefit of organs for digestion and reproduction, nonetheless has complex eyes and statocysts (organs for detecting gravity, acceleration, and vibration). The jellyfish moves, and its first need is for receptors to inform its movement, since its survival depends on its moving in directed fashion. It does an organism no good to have a fancy digestive organ unless its movements ensure that things—and the right things—get put into it. It makes sense that the evolution of complex receptors to steer useful movement would be an early evolutionary development, and there is a correlation between the complexity of behavioral repertoire and specialization of central nervous tissue, on the one hand, and specialization of receptors and development of complex sense organs, on the other (Bullock, Orkand, and Grinnell 1977).

2.3 *How Do Neurons Work?*

Basic Electrical Effects

The distinctive thing about neurons is that they are instruments of communication; they receive, integrate, and send signals. Exactly how neurons do this is a complex story whose many subtleties are only beginning to be understood. Initially, the basic story will suffice, and the central elements in the basic story are fourfold: (1) *ions* in the extracellular and intracellular fluid, (2) a *voltage difference* across the cell membrane, (3) *single ion channels* distributed about the membrane that are specialized to control cross-membrane passage of distinct ion types, and (4) *voltage-sensitive changes* in single ion channels that transiently open the gates in the channels to permit ions to cross the cell membrane.

The cell membrane is a remarkable sort of sheet, dividing cytoplasm on the inside of the cell from the extracellular fluid on the outside. The membrane is nonuniformly dotted with tiny pores, specialized to control passage only of certain items. Both the intracellular and the extracellular fluids contain ions, which are molecules or atoms that have gained or lost electrons and consequently are negatively or positively charged. The plot of the basic electrochemical story depends on two general classes of ions: large negatively charged organic ions concentrated inside the cell, and inorganic ions with systematically changeable concentration profiles inside and outside the cell.

The large organic ions inside the cell cannot pass through the membrane, and their net charge is negative. Consequently, this affects the distribution of ions to which the membrane *is* permeable, since positively charged ions will tend to congregate inside the cell to balance the negative charge. The inorganic ions that figure in the story are potassium (K^+), sodium (Na^+), calcium (Ca^{++}), and chloride (Cl^-).

The high internal concentration of fixed negative charges is offset by just about the right number of cations. These are mainly K^+, because the membrane is much more permeable to K^+ than to either Na^+ or Ca^{++}, and because a sodium-potassium pump in the membrane draws in K^+ and dumps out Na^+. When the cell is at rest (that is, unless the membrane is stimulated), the Na^+ and Ca^{++} channels block the passage of Na^+ and Ca^{++}. Thus, K^+ concentrates inside the cell, and Na^+ and Ca^{++} concentrate outside (figures 2.9, 2.10). When the cell is stimulated, for example by an electric current or by a particular chemical, there is a change in membrane permeability to Na^+ and Ca^{++}. The principal instruments of this change reside in the structure of the single channel.

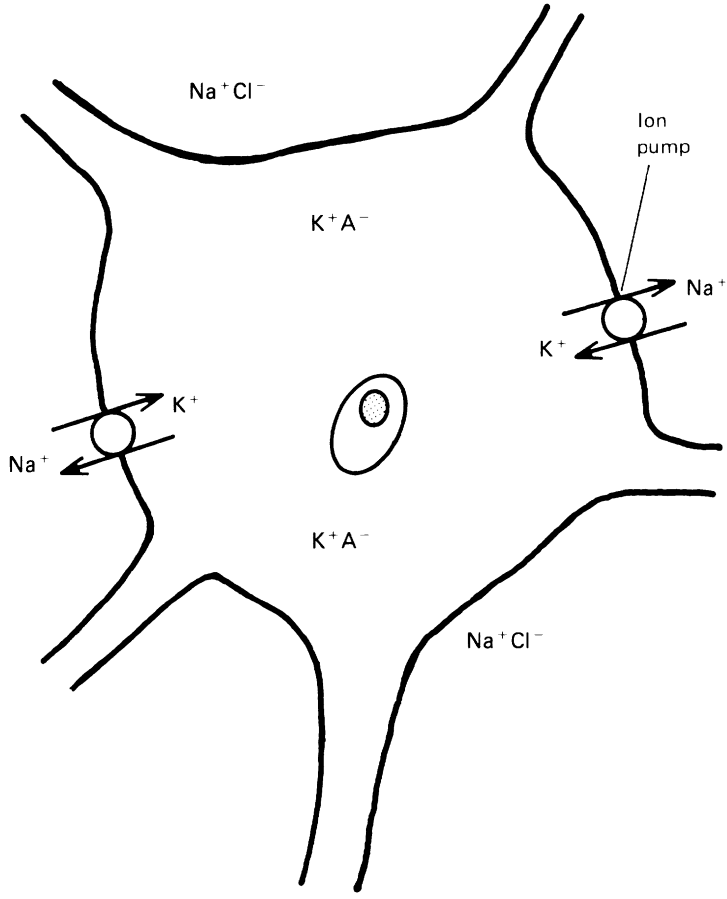


Figure 2.9
Schematic diagram of a neuron soma, showing the internal concentration of inorganic ions A^- and K^+, and the external concentration of NA^+ and Cl^-. The sodium-potassium pump in the membrane ejects Na^+ and hauls in K^+. (From Shepherd (1983). *Neurobiology*. New York: Oxford University Press.)

What accounts for the voltage drop across the membrane? Essentially, the organic anions together with the fact that among cations, only K^+ can cross the membrane to the cell's interior. Because the K^+ moves inward from areas of low K^+ concentration to areas of high K^+ concentration, it is said to move up its *concentration gradient*, and it does so because of the anion attraction inside. It therefore moves down its *electrical gradient*. At some point equilibrium between the two forces is achieved, in the sense that there is no net movement of K^+ across the membrane, and the electrical force required to keep K^+

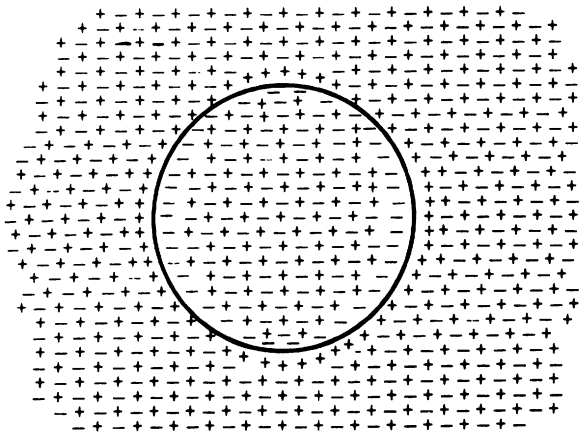


Figure 2.10
Schematic cross section of a neuron process showing the concentration of negative charges along the inside of the membrane and positive charges along the outside. (Reprinted with permission of the publisher from Koester (1981). Ch. 3 of *Principles of Neural Science,* ed. E. R. Kandel and J. H. Schwartz, pp. 27–35. Copyright © 1981 by Elsevier Science Publishing Co., Inc.)

at its concentration gradient can be calculated. This calculation yields the electrical *potential* for K^+ across the membrane. For example, in some neurons the equilibrium potential for K^+ (no *net* movement of K^+) is -70 millivolts (mv). The electromotive force is the force tending to equalize the charges, and the *electric potential* is a measure in volts of the electromotive force. In the neuron, accordingly, the organic anions exert an electromotive force of about -70 mv to pull K^+ up its concentration gradient. The actual recorded voltage across the membrane of the cell at rest is its *resting potential,* and this will be fairly close to the calculated potential for K^+.

Although -70 mv might seem to be an inconsequential voltage, in the cellular circumstances it is actually enormously powerful. This can be understood by observing that since a cross section of the membrane is only 50 angstroms thick, then its voltage equivalent across a one centimeter membrane thickness is 140,000 volts. An electric field of this magnitude is evidently capable of exerting a strong effect on macromolecules with a dipole moment, and it appears that single channels have as constituents precisely such macromolecules (Neher and Stevens 1979).

In sum, the consequence of the differential permeability of the membrane to the ions is that when the cell is at rest, there is a voltage across the membrane such that the inside of the cell membrane is negatively charged with respect to the outside (its resting potential).

Intracellular recording by microelectrode

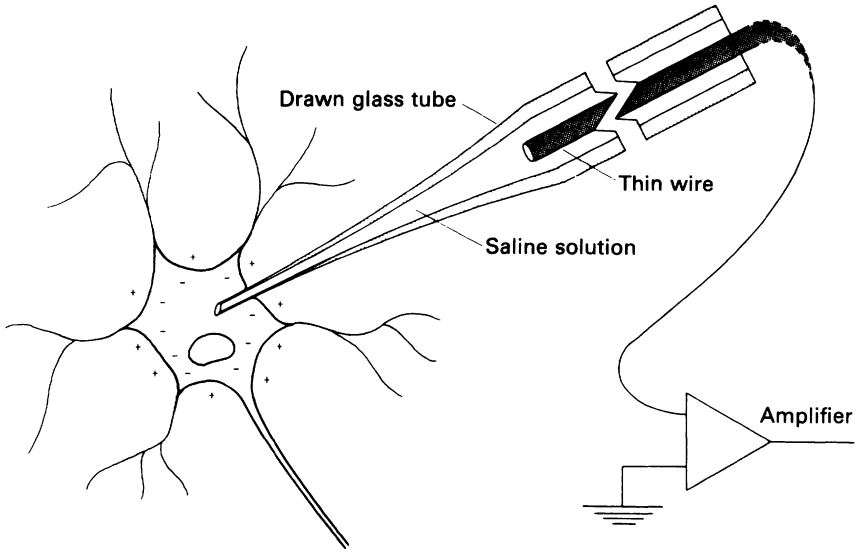


Figure 2.11
Idealized experiment for measuring the potential difference across the cell membrane. The electrode is a fine glass capillary with a tip no more than 0.1 micrometer in diameter filled with a saline solution.

By convention, the voltage is given as that of the inside relative to that of the outside, and since at rest the inside is negative relative to the outside, the voltage is expressed as a negative number of millivolts (e.g., −70 mv or −55 mv) (figure 2.11). The membrane is thus polarized, and the communicative functions of neurons depend on coordinated changes in the polarization of the membrane. The next step in the discussion will therefore concern how neurons exploit changes in potential so as to transmit information—from the outside world, to one another, and to the muscles and glands. The principal factor in the cell that is now believed to account for excitability, and hence for signaling, is the voltage-dependent conformational change in the molecular structure of single channels that permits a brief influx either of Na^+ or of Ca^{++}, depending on the channel type (Kuffler, Nicholls, and Martin 1984).

Synaptic Potentials

The dendrites and the soma of a neuron are bedizened with a profusion of synaptic connections (figure 2.12), and thousands of signals may be received at various places in the dendritic bush or on the cell

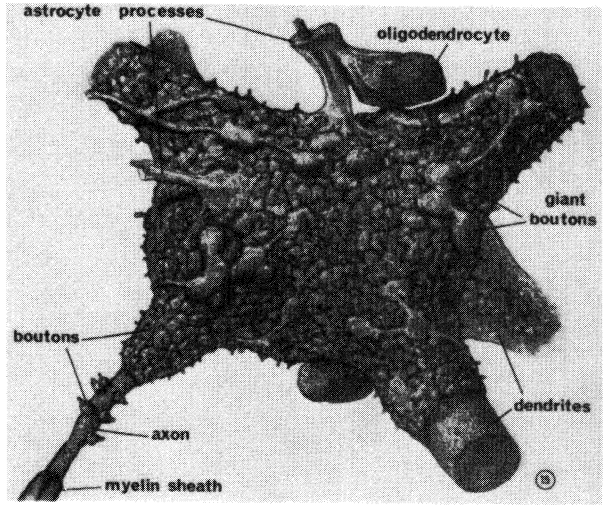


Figure 2.12
Synaptic end bulbs (boutons) on the surface of a motor neuron. (From Poritsky 1969.)

body during the space of a millisecond. The incoming signal is caused by a chemical acting on specialized membrane sites and it results in a change in the membrane's resting potential. The change in resting potential induced by an incoming signal at the synapse is the *synaptic potential.*

The postsynaptic response at any given site on the membrane may be a *decrease* in the membrane potential, for example from -70 mv to -60 mv. Such a membrane *depolarization* is brought about chiefly by changes in the permeability of the membrane that permit a brief influx of Na^+ or Ca^{++}. Alternatively, depending on the synaptic events, the postsynaptic response may be an *increase* in the membrane potential, for example, from -70 mv to -80 mv. This type of effect on membrane potential is referred to as *hyperpolarization* and can be achieved by the influx of Cl^-, the efflux of K^+, or both (figure 2.13).

The synaptic potential is transient, and the permeability profile of the membrane at its resting potential is quickly restored. The size of the synaptic potential is directly related to the number of single channels opened in response to the stimulating event and hence to the density of single channels in the vicinity of the stimulus; the greater the number of Na^+ channels, the higher the probability that a Na^+ channel will be opened after the depolarizing stimulus (Kuffler, Nicholls, and Martin 1984). At a given location a large stimulus will

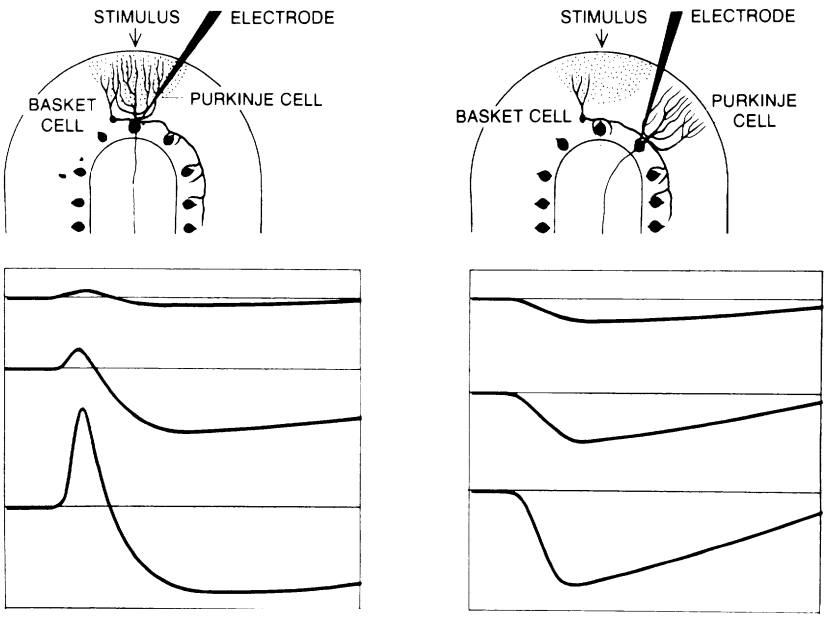


Figure 2.13
The soma of a Purkinje cell in the vicinity of stimulation is briefly depolarized (upward deflection), the degree of depolarization being a function of the stimulus intensity. A Purkinje cell outside that preferred area receives inhibitory input from the activated axon of a basket cell and is transiently hyperpolarized (downward deflection). (Courtesy R. Llinás.)

cause a potential with a greater amplitude than a small stimulus only if there is a greater number of single channels that it can affect.

The net movement of ions across the membrane constitutes a current, and this current spreads along the membrane from the focal site, decrementing with distance. The spread of current is affected by a number of factors, including the resistance of the cytoplasm, the resistance of the membrane, and the diameter of the dendrite. Since many synaptic potentials may be generated in close proximity within a narrow time slice, there arises the question of the nature of the interaction of synaptic potentials.

Suppose a dendrite's membrane is depolarized at some particular spot. As the current spreads, it will interact with current generated at that same place at a slightly earlier time, or with current generated elsewhere and elsewhen. For example, if it is adjacent to an area where the membrane is hyperpolarized, then the two effects will tend to cancel one another, or if it is adjacent to a depolarization, the

effects will summate. Potentials therefore interact as currents sum to create a larger depolarization; or, if the effects were hyperpolarizing, to prevent depolarization; or, if the effects are opposite, to interfere and cancel. Because the amplitude of synaptic potentials is determined by channel density, stimulus size, and summation, they are called *graded potentials*. In this respect they contrast, as we shall shortly see, with *action potentials*.

It is presumed that by means of this complex interfusion and integration of synaptic potentials in the soma and dendrites, information is processed, though complete understanding of what is going on still eludes us. (But see chapter 10 for discussion of a theory that addresses this matter.) Nevertheless, it is easy to see that the relative position of stimuli on the dendrites, the width of the fiber, the density of ionic channels, the availability of energy, and so on, will play a role in the overall character of the integration of signals. If, as it seems, dendritic growth and synaptogenesis are connected to learning, we will want to know what the rather bewildering interfusion of potentials comes to in informational terms.

If, after the integration of depolarizing and hyperpolarizing potentials, there is sufficient current to depolarize the membrane of the axon hillock by a certain critical amount known as the "firing level" (about 10 mv), then the cell produces a large and dramatic output. (The axon hillock is the region of the neuron where the axon emanates from the soma.) Under these conditions, the axon will relay a depolarizing signal—an *impulse*—from the hillock to its terminal bulbs, using a mechanism described below that typifies axons. Depolarizing synaptic potentials are called *excitatory* postsynaptic potentials (EPSPs) because they contribute to the generation of an impulse in axons by bringing the membrane potential closer to the firing level. Because hyperpolarizing potentials tend to diminish the probability of the generation of an impulse, they are called *inhibitory* postsynaptic potentials (IPSPs) (figure 2.14).

Action Potentials

Axons are long, thin projections, sometimes a few millimeters, sometimes a meter or more in length. If a message is to be sent from one end to the other, it is necessary to ensure that the signal does not peter out en route and that the same message reaches the end as was put in at the beginning. This capacity for long-distance transmission is achieved by an increase in the density of Na^+ channels all along the axon membrane. What makes these channels special is that they are voltage-sensitive, and with depolarization they cease briefly to gate Na^+, thereby permitting Na^+ to rush into the cell down its electrical

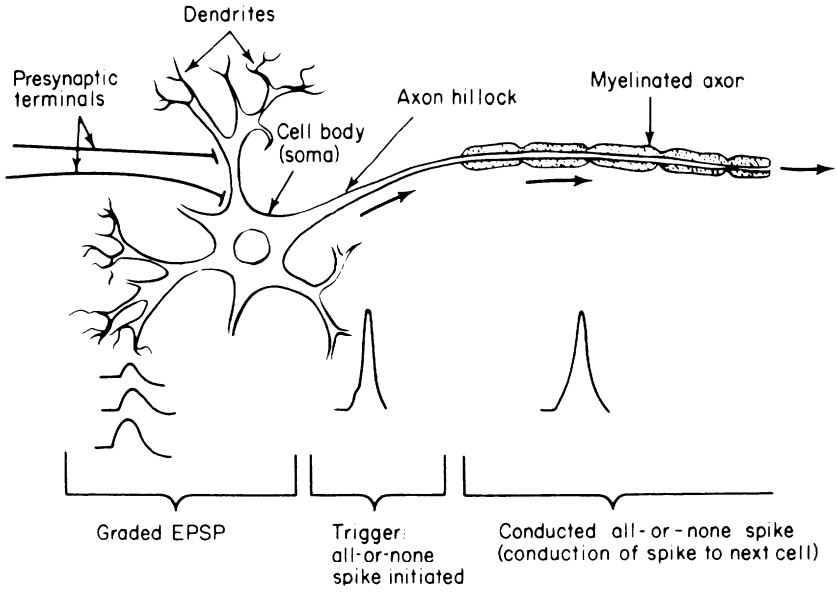


Figure 2.14
Summary diagram showing location on a motor neuron of the events responsible for impulse initiation. Dendrites and cell bodies respond with graded *excitatory synaptic potentials* (EPSPs) or *inhibitory synaptic potentials* (IPSPs); the action potential is triggered in the axon hillock and travels undiminished down the axon. IPSPs are not shown. (From Thompson (1967). *Foundations of Physiological Psychology*. New York: Harper and Row.)

and concentration gradients (figure 2.15). In the studied cases each channel has a mean channel current of about 1–2 picoamps and is open for a mean time of 0.7 msec (Sigworth and Neher 1980). When channel density is sufficiently great, therefore, the total current crossing a patch of membrane in a millisecond can be substantial, and because the channels are voltage-sensitive, this in itself can cause a special, self-amplifying effect.

Suppose incoming signals depolarize the membrane of the axon hillock by about 10 mv, as Na^+ ions move inside the cell. This inward Na^+ current results in a transient change in additional Na^+ channels in the axon membrane, thereby allowing even more Na^+ to enter the cell, depolarizing the membrane further, which then induces changes in yet more Na^+ channels to allow further Na^+ influx. Thus, a self-generating, explosive effect is produced. If the initial depolarizing current is large enough that the net influx of Na^+ is greater than the efflux of K^+ ions, the positive feedback results in a sudden large influx of Na^+ In absolute terms the number of ions crossing the

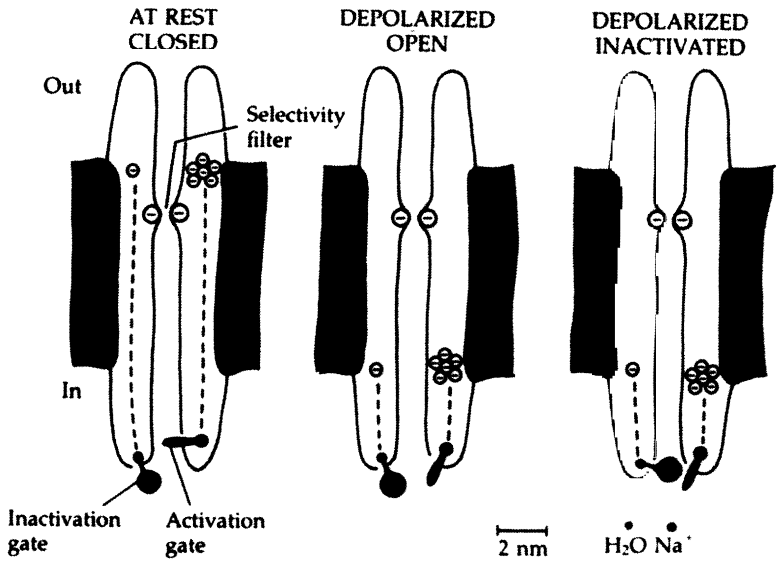


Figure 2.15
Voltage-sensitive sodium channel, drawn schematically to scale according to biochemical, electron microscopic, and electrophysiological information. Ionic selectivity is provided by a constriction lined with negative charges near the outer surface of the membrane. The activation gate near the inner surface opens in association with translocation of negative charges across the membrane from out to in. The inactivation gate blocks the inner mouth of the channel and prevents closing of the activation gate. Water molecule and hydrated sodium ion are drawn to scale for comparison. (Modified from Kuffler, Nicholls, and Martin (1984). *From Neuron to Brain.* 2nd ed. Sunderland, Mass.: Sinauer.)

membrane is actually quite small, but it is sufficient to change the membrane polarity dramatically from something on the order of -70 mv to something on the order of $+55$ mv (Kuffler, Nicholls, and Martin 1984).

Since the mean channel open time is only 0.7 msec, the summed increase in permeability to Na^+ of any given membrane patch is a very brief affair. As the membrane potential reverses from, say, -70 mv to $+55$ mv, Na^+ conductance is suddenly inactivated, and K^+ begins to move out of the cell, which initiates the restoration of the resting potential. Given a 10 mv depolarization, there is therefore a temporal *sequence* of voltage-sensitive changes in the membrane permeability: an abrupt increase in Na^+ permeability, followed by an abrupt inactivation of Na^+ permeability and an increase in outward K^+ current (figure 2.16). This precisely timed sequence of membrane events is a neuron *impulse,* and a membrane's capacity to generate

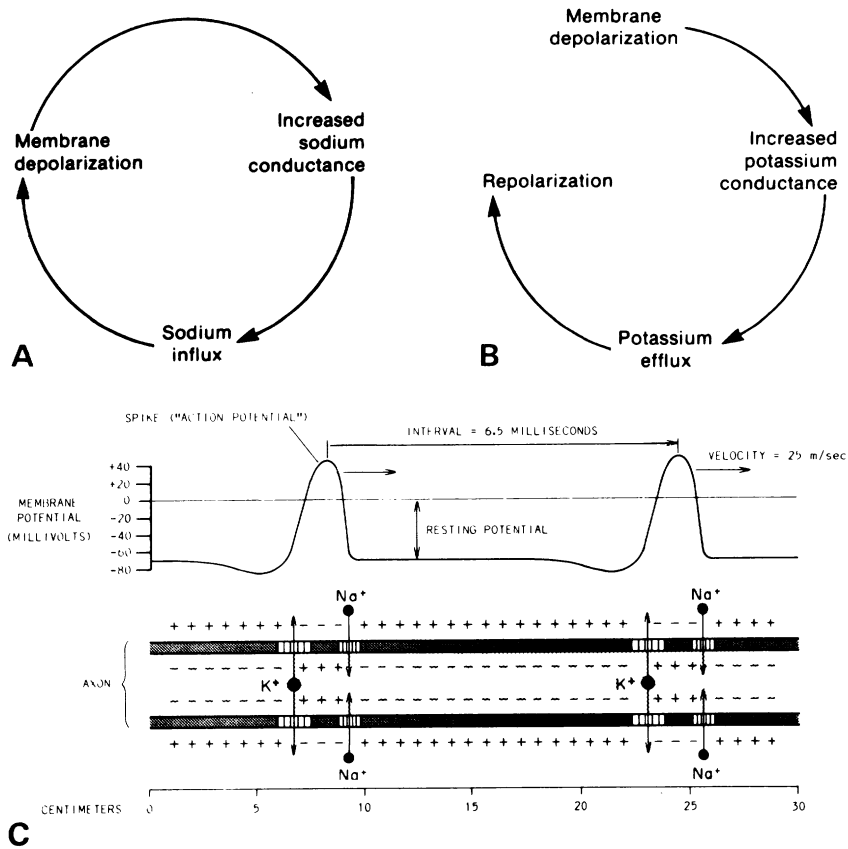


Figure 2.16
(A) Positive feedback effect resulting from above threshold depolarization of the membrane. (B) Restoration of the membrane's resting potential. (C) Propagation of a nerve impulse along the axon. The large change in potential is initiated by a small influx of sodium ions, which opens voltage-sensitive sodium channels, changing the potential further. The membrane's resting potential is restored as the sodium channels are inactivated, and potassium channels open to permit an outflow of potassium ions. This sequence of events begins at the axon hillock and continues down the length of the axon.

impulses is what is meant by excitability. (This gives only a simplified version of the sequence of membrane events. See Llinás 1984a.)

The impulse is also called an *action potential,* where the modifier "action" indicates that the large change in membrane polarization vastly exceeds the triggering depolarization contributed by the stimulus. If we put a recording electrode inside the axon and attach the recording electrode to an oscilloscope, the visual pattern pro-

duced by the impulse will appear on the screen as a spike; hence, impulses are also referred to as "spikes" (figure 2.16).

During the brief interval when the membrane is permeable to Na^+, the potential across the membrane at the relevant segment changes enormously as a consequence of the inward Na^+ current. This current will spread along the membrane, which will cause depolarization in the adjacent areas of the membrane, and Na^+ channels located there will, in their turn, undergo a conformational change to allow Na^+ current, thereby engaging the regenerative process to permit an influx of Na^+ ions in that region, and so on down the length of the membrane (figure 2.16). Therefore, the drama in the axon does not end with the production of a localized spike, for when an action potential is produced at the hillock, the spreading current depolarizes the neighboring membrane downstream, which in turn generates an action potential and consequently depolarizes *its* downstream neighborhood membrane, and so on.

In this fashion, a wave of depolarization and repolarization travels from the trigger zone in the axon hillock down the length of the axon. (It *could* travel the reverse direction, and can be made to do so in the laboratory, but in the untampered neuron it does not.) The signal does not alter in its journey down the axon, because the amplitude of the spike does not diminish as it travels. As long as there is one spike, this ensures that the adjacent membrane will be depolarized above its threshold, which means it will spike, and so on to the fiber end. During its spiking phase the axon cannot spike again; this is called its refractory period (figure 2.16). One might think of this by analogy with a slingshot that cannot fire again immediately but requires an interval for the sling to be repositioned and to regain a store of energy. The single channels have to be reconfigured, Na^+ has to be pumped out, and the neuron membrane has to regain its balance of electric potentials.

In view of the importance of time constraints imposed by the nervous system on modeling, it should be mentioned that the time course for a spike is some 0.2–5.0 msec, depending on the neuron, and this means that there is an upper limit on the spiking frequency of any given neuron. In humans some neurons can spike 500 times per second. For purposes of rough calculation, let us say that a spike takes about 1 msec. Now if a perceptual recognition task takes about 100 msec, then there can be *at most* 100 information-processing steps between input and output. Models that require ten thousand or a million steps are going to be out by several orders of magnitude.

The basic account of the electrophysiology of neurons was worked out by Hodgkin and Huxley in 1952, but not until recently has the

structural basis for these properties been understood. In what amounts to a revolution in understanding the nature of neurons (see Junge 1981, Kuffler, Nicholls, and Martin 1984), researchers have begun to reduce electrophysiologically defined properties such as spiking and synaptic potentials to the basic molecular biochemistry of cell membranes. More precisely, it appears that the framework is emerging for a reduction of the action potential, the synaptic potential, the refractory period, and so forth, as defined in terms of electrophysiological theory, to the "kinetics" of single-channel currents and single-channel macromolecule organization, as described by molecular biology. This is evidently a development of great significance, since it begins to forge reductive connections between neurophysiology and biochemistry. If we can also determine the neurophysiological basis for behavior (see below), then we shall actually begin to see the outlines of a general, unified framework for comprehending the nature of nervous system function (Llinás 1984a).

It should also be acknowledged that despite the discussion's generalized reference to "the neuron," in fact different types of neuron vary tremendously along a number of dimensions and there is no typical neuron. The observed differences presumably reflect such factors as differences in membrane properties, channel density, and channel properties and can be assumed to have an explainable functional significance. Moreover, as Llinás (1984a) has emphasized, there are not merely the Na^+, Ca^{++}, and K^+ conductances already discussed. In the soma, for example, one might find a Ca^{++}-dependent K^+ conductance and a "fast transient" K^+ conductance, as well as a voltage-dependent K^+ conductance. The number of voltage-dependent ionic conductances present in a particular neuron may be greater than ten.

The conventional wisdom until recently held that dendrites do not spike, but as a result of work originated by Llinás in the mid-1970s (Llinás and Hess 1976) it was discovered that Purkinje cells in the cerebellum do have spiking dendrites (figure 2.17). Since then, dendritic spiking has been discovered in a wide range of CNS neurons, including neurons in the hippocampus and the spinal cord. (For a discussion, see Llinás 1984a.) On the other side of the coin, there are neurons with short axons, for example amacrine cells in the retina, that do not spike at all. Thus, the criterion that identifies a neuronal process on the basis of whether or not it spikes has collapsed; there are both nonspiking axons and spiking dendrites.

The amplitude of the spike is largely invariant and does not increase or decrease with the size of the stimulus. Variation in signal can be produced by altering the *frequency* of spikes in a train or by

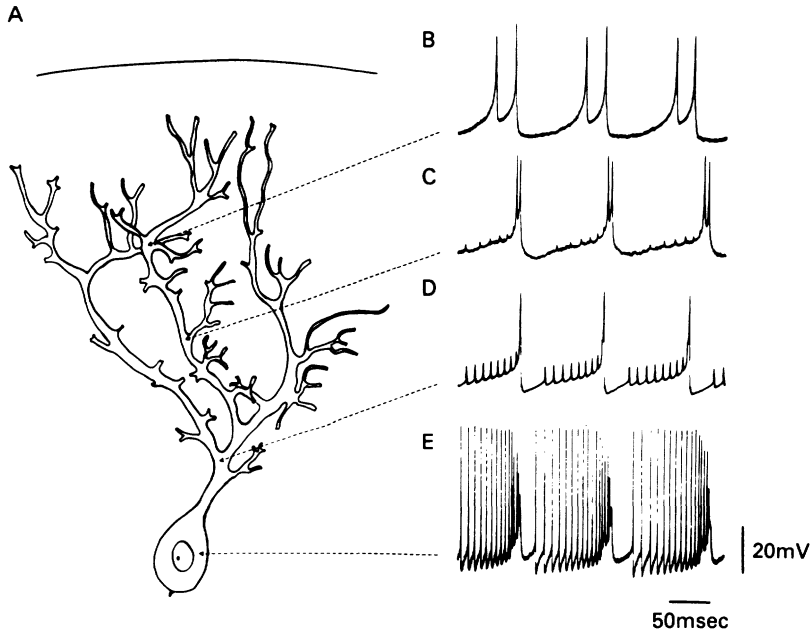


Figure 2.17
Sodium and calcium action potentials in (A) a Purkinje cell. (B) Depolarization of the dendrite produced long-duration calcium action potentials, and (E) depolarization of the soma produced high-frequency sodium action potentials, interrupted periodically by a calcium action potential that was followed by a transient hyperpolarization. (C) and (D) represent the effects of the passive spread of depolarization from the soma. (From Llinás and Sugimori 1980.)

producing special *patterns* in a train of impulses through the combined use of hyperpolarizing and depolarizing currents. Frequently neurons show a low rate of spontaneous spiking (spiking without externally induced depolarization, perhaps by inward leakage of Na^+ or Ca^{++}), and this base rate of firing is increased by depolarizing currents and decreased by hyperpolarizing currents (figures 2.18, 2.19).

Why the brain uses so much energy will now be evident. Neurons must continuously maintain the ionic gradients essential to receiving and sending information. If a neuron routinely handles a thousand depolarizing signals in the space of a second or so, and if it spikes several hundred times a second, its energy consumption will have to be lavish. Evolution stumbled upon one energy-saving device in myelin. The strategy here is that if glial cells ensheath the axon to form an insulating cover, then depolarizing current from one action poten-

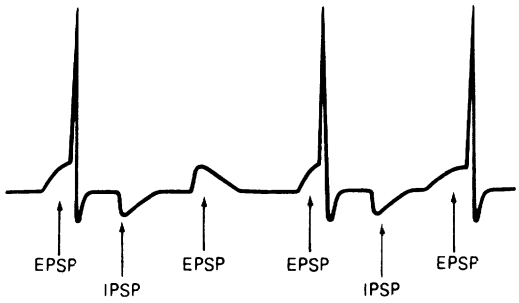


Figure 2.18
Interactions of excitatory and inhibitory synaptic potentials (EPSPs and IPSPs) in an otherwise silent cell. Each of the synaptic potentials illustrated here is usually produced by the synchronous action of many presynaptic neurons. (Reprinted with permission of the publisher from Kandel (1981a). Ch. 7 of *Principles of Neural Science,* ed. E. R. Kandel and J. H. Schwartz, pp. 63–80. Copyright © 1981 by Elsevier Science Publishing Co., Inc.)

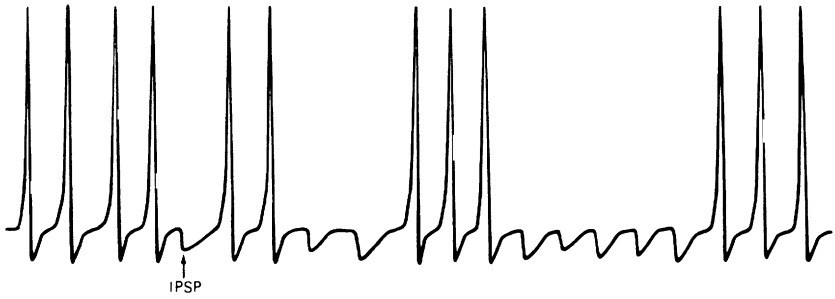


Figure 2.19
Sculpting role of inhibition, shown here to produce changes in the firing pattern of a spontaneously active neuron. (Reprinted with permission of the publisher from Kandel (1981a). Ch. 7 of *Principles of Neural Science,* ed. E. R. Kandel and J. H. Schwartz, pp. 63–80. Copyright © 1981 by Elsevier Science Publishing Co., Inc.)

tial will travel further down the axon and so the energy-intensive action potential need occur only at wider intervals. This is called *saltatory conduction,* because the spikes, as it were, jump down the axon in long strides (figure 2.14).

Rolled-up Schwann cells are strung along peripheral fibers like sausages on a string, and the action potentials occur only at the exposed membrane between the Schwann cells, the "nodes of Ranvier." A large, well-myelinated axon in a human motor neuron can conduct an impulse up to 130 meters per second, whereas an unmyelinated fiber is much slower, sending impulses at only about 0.5 meters per sec-

ond. These are factors concerning propagation of a signal within a neuron, but there is the additional matter of sending a signal from one neuron to another.

Neuronal Integration

There are two fundamental types of connection between neurons: electrical synapses and chemical synapses. Electrical synapses are of two types: (1) those generating *field potentials,* in which sending and receiving neurons are so closely positioned that current flow in one induces field changes in its neighbor, and (2) *gap junctions,* which consist of supremely thin protein tubes connecting the axon of one neuron to the dendrite or axon of another (figure 1.8). The tubes are so narrow as to permit the transfer of only very small ions such as Na^+ or K^+, and it is via the transfer of these ions that signals are transmitted from one neuron to the next.

Electrical synapses were for some time believed to be unique to primitive nervous systems, and though demonstrating their existence in the mammalian CNS is extremely difficult, research in the past ten years has shown electrical coupling in cells in the hippocampus and cells in the inferior olive that project to the cerebellum (Llinás, Baker, and Sotelo 1974). The intriguing question now is whether electrically coupled cells have a special functional significance in nervous systems.

The leading hypothesis focuses on the major difference between chemically coupled cells and electrically coupled cells, namely that the absence of synaptic delay (see below) in electrically coupled cells means that they can fire synchronously. Such synchronicity, along with positive feedback, appears to have an important role in generating rhythmic patterns typical of various CNS structures (Bower and Llinás 1983, MacVicar and Dudek 1980). In the case of the cells in the inferior olive, the electrical coupling may serve to establish synchronous firing of bands of Purkinje cells in the cerebellum. Since Purkinje cells are known to be crucial in subserving sensorimotor coordination, this general line of research has suggested that the synchronizing of rhythmic patterns in sets of neurons may embody a fundamental principle of neuronal organization underlying sensorimotor coordination (Llinás 1984b, 1984c).

Chemical synapses (figures 1.7, 2.20) have been most intensively studied in the giant synapse of the squid, and at the synaptic terminal it is Ca^{++} ions and Ca^{++} channels that play the crucial role (Llinás 1982). When a depolarizing wave reaches an end bulb of an axon, it opens voltage-sensitive Ca^{++} channels. Ca^{++} rushes into the cell and causes little vesicles containing neurotransmitter substance to fuse with the outer membrane at specialized zones (Heuser and Reese

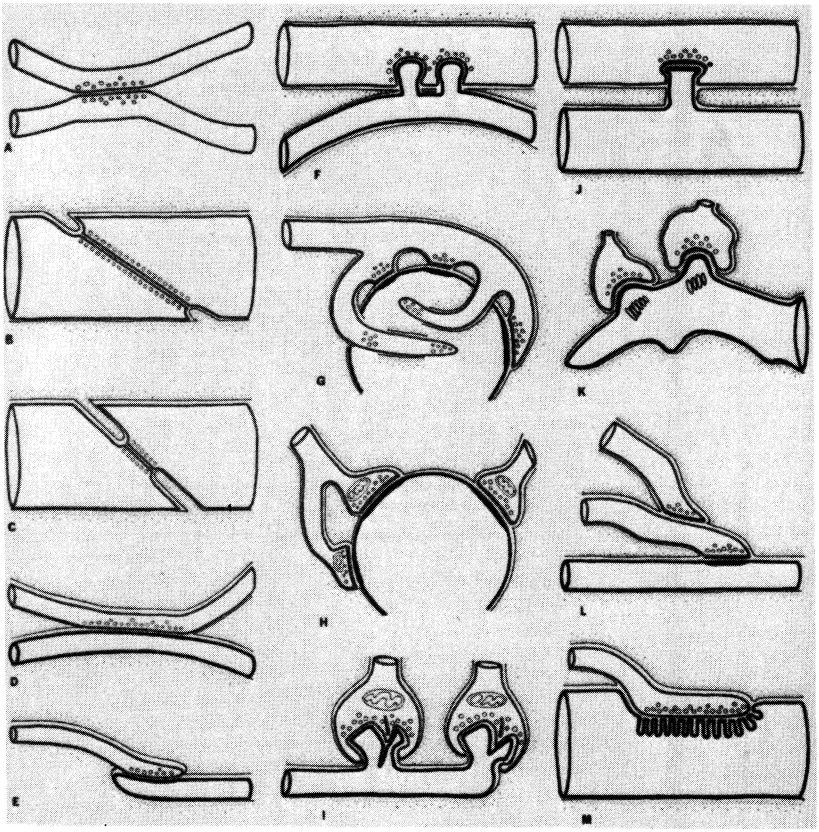


Figure 2.20
Types of synapses revealed by electron microscopy. (A) Axon-axon synapse in jellyfish. (B) Earthworm septal synapse with electrical transmission in either direction. (C) Crustacean synapse similar to (B). (D) Axon-axon synapse-in-passing, typical of invertebrates. (E) Axon terminal ending on a dendrite in invertebrate. (F) Crustacean giant-fiber-to-motor-neuron synapse, with postsynaptic motor fiber invaginated into the giant fiber. (G) Axon arborization-to-soma synapse typical of vertebrate brain cells. (H) Terminal buttons of axon arborizations typical of certain neurons in vertebrates. (I) Ribbon synapses between rod cell endings and dendrites of ganglion cells of vertebrate retina, with presynaptic specialization. (J) Synapse between giant fibers of squid stellate ganglion, postsynaptic invaginated into presynaptic. (K) Spine synapse (axon-dendrite) from cerebral cortical dendrite of vertebrates with postsynaptic specialization. (L) Serial synapse, permitting presynaptic inhibition. (M) Specialized neuromuscular endings found in vertebrate skeletal muscle, with postsynaptic grooves. (From Bullock and Horridge (1965). *Structure and Function in the Nervous Systems of Invertebrates.* W. H. Freeman and Co. Copyright © 1965.)

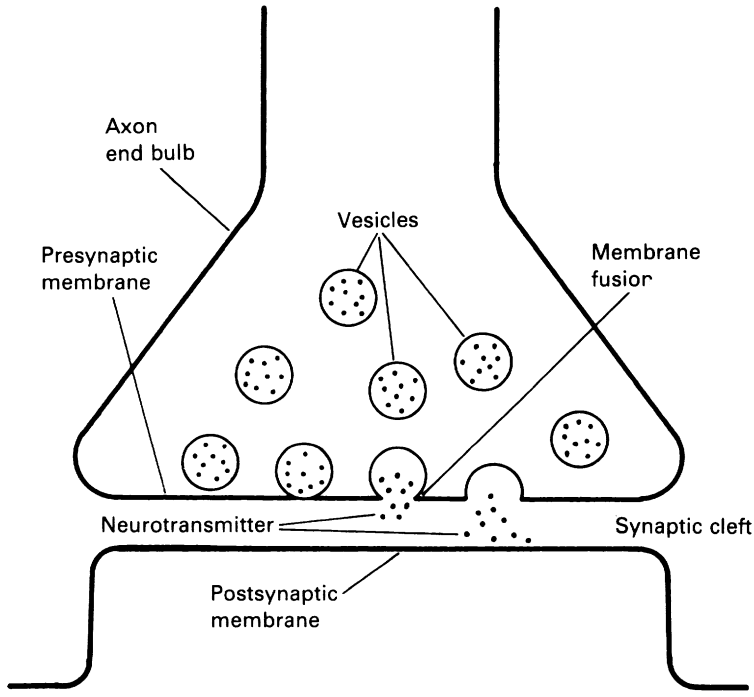


Figure 2.21
Schematic diagram showing release of neurotransmitter (synaptic vesicle exocytosis) a: vesicle membrane fuses with end bulb membrane. (After Heuser and Reese 1979.)

1979). As the vesicle membrane fuses with the cell membrane, the neurotransmitter substance is released into the extracellular space that separates the axon from the adjacent neuronal process. Some of the neurotransmitter diffuses across the synaptic cleft and binds itself to specialized sites on the receiving cell—the postsynaptic membrane (figures 2.21, 2.22).

The time between the arrival of the signal at the synaptic terminal and the onset of the generation of a postsynaptic potential is known as the *synaptic delay*. It comprises three component delays: the time it takes (1) for Ca^{++} channels to open, (2) for the vesicles to fuse and release neurotransmitter, and (3) for the transmitter to diffuse across the synaptic cleft. The actual time of the synaptic delay is about one millisecond, which is remarkably short considering the complex molecular scenario (Llinás 1982).

Depending on which transmitter is released and on the character of the receptor sites, the neurotransmitter may produce a depolarization (an EPSP) or a hyperpolarization (an IPSP). The process of interfusion

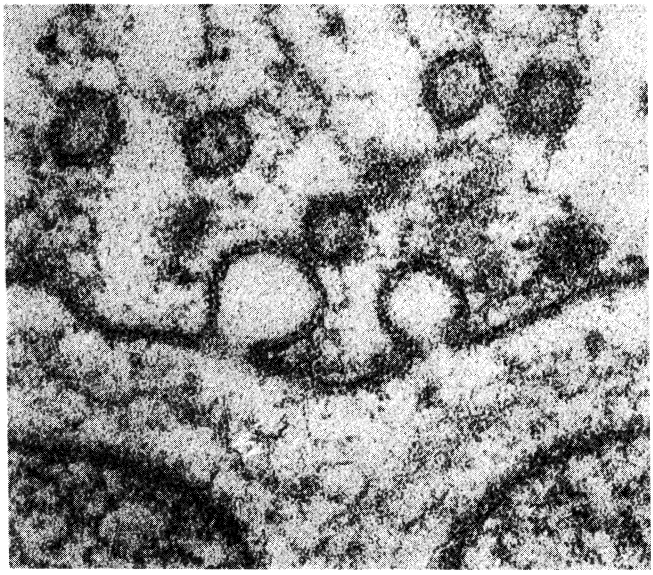


Figure 2.22
Electron micrograph showing how the synaptic vesicles fuse with the cell membrane as the neurotransmitter is discharged. (Micrograph produced by Dr. John E. Heuser of Washington University School of Medicine, St. Louis, Mo.)

and integration of current then begins in the receiving cell, as described earlier. In the studied cases unused transmitter is typically broken down and the components are retrieved by the presynaptic membrane for use next time, or sometimes they are retrieved by local glial cells. The transmitter that is bound to receptor sites must be quickly removed by enzymatic activity, if it is not to have a prolonged effect.

If the functional value of electrical coupling of cells is the synchronicity it permits, what is the distinct functional value to a nervous system of chemical synaptic coupling? Part of the answer is that it enables *amplification* of the signal. A current passed by electrical coupling from a small axon to a large soma is in danger of being ineffective. But if instead the signal in the axon causes at the end bulb the release of a flood of neurotransmitter molecules that depolarize the postsynaptic membrane across a substantial area, then the signal received will be nontrivial. In this fashion, a Ca^{++} current in the end bulb of one neuron can cause a substantial depolarization of another cell's membrane. Depending on the system's needs, therefore, the neurons may be coupled either electrically or chemically.

As outlined above, Ca^{++} is essential for synaptic transmission, and

in some cells dendritic spiking is dependent on Ca^{++}. Moreover, it turns out that Ca^{++} is also important in the spiking of embryonic neurons, and in the dynamics of the growth cone at the tip of embryonic neurons. These assorted roles of Ca^{++} are suggestive of a deeper connection, and the joint functions of Ca^{++} at the synapse and in the growth cone have prompted Llinás (1979, 1982) to hypothesize that synaptic terminals are modified growth cones. This is a unifying conception of considerable power, and a succinct version of the reasoning runs as follows: in development, Ca^{++} may regulate the addition of new membrane at the growth cone by promoting the fusion of vesicle membrane and cell membrane, similar to the process seen in synaptic transmission. In the mature neuron the growth is subdued, and new membrane introduced into the cell membrane at synaptic signaling is recycled rather than left in place (Llinás and Sugimori 1979).

Transmission at chemical synapses is susceptible to an assortment of types of influence, and the nervous system takes advantage of all of them under special conditions (Cooper, Bloom, and Roth 1982, Snyder 1980). It can be affected by changes in the amount of transmitter released from the presynaptic membrane, changes in the amount of transmitter retrieved and the efficiency of retrieval, changes in the synthesis of transmitter within the sending cell, the number of receptor sites available, and changes in the responding chemicals inside the receptor cell.

In what is perhaps the simplest form of memory, a neuron increases its concentration of intracellular Ca^{++} as a result of a high rate of impulses (tetanus) reaching the presynaptic terminal. This means that more transmitter is released, with consequent alteration in the response pattern of the postsynaptic membrane. This alteration shows itself in a steady increase in the amplitude of the EPSPs (figure 2.23). This phenomenon is called post-tetanic potentiation, and the modification may last for minutes, or even an hour in some cells. As to the number of receptor sites, the advent of the electron microscope has made it possible to count them, and it is important to note that with age and stimulation the number of synapses increases. In particular, it has been found that with high-frequency stimulation additional synapses will flower in short order, suggesting a further mechanism for memory (Lee et al. 1980). It should also be remarked that some chemicals may function not as specific neurotransmitters but as neuromodulators, affecting the sensitivity of the postsynaptic neuron without actually inducing postsynaptic potentials.

In one of the most celebrated discoveries concerning how synaptic events subserve plasticity in behavior, Kandel and his colleagues

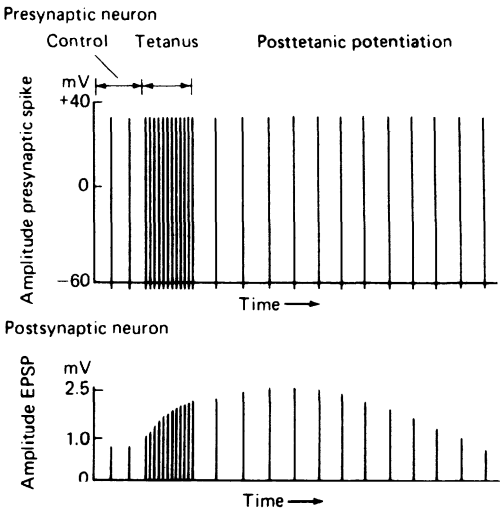


Figure 2.23
Post-tetanic potential: simultaneous recordings from a presynaptic neuron and its postsynaptic target cell. (In order to show events that occur over a long time, the sweep speed of this experiment has been compressed so that each presynaptic and postsynaptic potential appears as a simple line.) During the control period the presynaptic neuron is stimulated at a rate of 1/sec and produces a PSP of about 1 mv. The presynaptic neuron is then stimulated for several seconds at a higher rate of 5/sec. During this tetanus the PSP increases in size. After several seconds of tetanus, the presynaptic neuron is returned to its control rate of firing of 1/sec; however, the PSP it produces continues to be facilitated for many minutes and in some cells for several hours. (Reprinted with permission of the publisher from Kandel (1981b). Ch. 8 of *Principles of Neural Science*, ed. E. R. Kandel and J. H. Schwartz, pp. 81–90. Copyright © 1981 by Elsevier Science Publishing Co., Inc.)

(Kandel 1979, Hawkins and Kandel 1984) have shown that changes in Ca^{++} current (and hence changes in the amount of neurotransmitter released) are central in producing habituation and sensitization in the sea hare *Aplysia Californica* (This example will be discussed in more detail in the next subsection.)

The vulnerability of chemical synapses to modification by assorted chemicals has been exploited by organisms that have evolved the capacity to produce neurotoxins to be used as weapons. The snake venom alpha-bungarotoxin, like curare (the arrow poison used by Amazon Indians), works by binding to special receptor sites on muscles and resisting breakdown. This prevents the neurotransmitter acetylcholine from binding to produce depolarizing current to contract muscles. The muscles, therefore, are paralyzed. Botulinus toxin (a common cause of food poisoning) also produces paralysis, but

achieves this by preventing the release of acetylcholine from the presynaptic membrane. In this case receptor sites are available, but there is no acetylcholine to bind to them, so once again paralysis is the result. Other neurotoxins, such as black widow spider venom, increase the discharge from the presynaptic membrane, causing the muscle cells to be excessively stimulated, resulting in rigidity and tremor.

Although the human nervous system has not evolved venom pouches or poison sacs, we have learned how to synthesize certain neurochemicals in the laboratory and how to use them to intervene directly in the neurotransmitting affairs of neurons. Neuropharmacology is the study of chemicals that affect neurons, and in recent times it has become an area of intense research as scientists try to discover effective treatment for diseases of the nervous system. Perhaps because of its immediacy to clinical concerns, neuropharmacology has become a glamor discipline within the wider domain of neuroscience. Three discoveries in particular have propelled it into public attention.

First was the discovery in the 1950s that certain drugs dramatically curtailed psychotic symptoms in many patients, enabling them, if not to lead completely normal lives, at least to live outside the asylum walls. In the short run these drugs calm violent and wildly excitable patients, and in the long run they abolish hallucinations and ameliorate disorders of thought. Since schizophrenia is a devastating and widespread mental disease, finding even a consistently palliative drug has had profound social significance. Such findings naturally engendered the hope that knowledge of how the drugs worked would lead to knowledge of the disease and its etiology, and thereby to knowledge of prevention.

Second were discoveries, also in the 1950s, that led to the treatment of Parkinson's disease, also known as the shaking palsy. Parkinson's disease is characterized by muscular rigidity, tremor, and akinesia (a diminished ability to make voluntary movements). It was found in autopsies that the brains of patients with Parkinson's disease had abnormally low levels of the neurotransmitter dopamine and that one motor area rich in dopamine-producing neurons (the substantia nigra) had degenerated. This suggested that dopamine deficiency was the root cause of the disease and that the motor dysfunctions could be alleviated by giving the patients the drug L-dopa (which converts to dopamine in the brain). The idea was tried, with considerable though not unalloyed success, and L-dopa is now the drug of choice for reducing the effects of Parkinson's disease. This too was an important discovery, for Parkinson's disease afflicts large numbers of

people in their declining years. (For a short paper on recent developments in the treatment of Parkinson's disease, see Larsen and Calne 1982.)

Third was the revelation in the late 1970s that the nervous system manufactures and uses its own opiate-like substances—the *endogenous opiates,* as they came to be known (Hughes et al. 1975). It was found that there are at least five, three of which were classed as "endorphins" and two as "enkephalins." Though this discovery suggested a practical application in the relief of pain and of mood disorders, it also raised many questions. What are the opiates doing in the brain in the first place? Will we find endogenous tranquilizers and endogenous antidepressants?[3] Are certain diseases of the mind caused by imbalances in these chemicals? Can I be addicted to my own chemicals?

Investigation of the neurochemicals that have some role in the synaptic transmission of signals is accordingly important not only for determining what is going on at the cellular level. It is important also because it shows us that chemical events at the cellular level can have enormous effects on the brain's affairs as characterized at the psychological level of description. This is significant for those who oppose the idea of a unified science of the mind-brain, either because they believe the mind to be a distinct substance, because they believe mental properties to be emergent, or because they believe psychological theory to be irreducible to neurobiological theory. (See chapters 7–9.) Not that neuropharmacology can now yield anything like a decisive demonstration of the falsity of these views, but it can undermine certain favored theses about how very different and separate are brain states and mental states. By inches it helps to erode the metaphysical conviction that one's *self* is an affair apart from that mound of biological stuff hidden under the skull. It can help to shift the burden of proof to those who deny that there can be a science of the mind. Therefore, after a few simple illustrations of neurons as they participate in *networks,* I shall dwell a bit further on neuropharmacological considerations.

Some Simple Wiring Diagrams

To understand what the brain does, it is necessary to understand the connections between neurons at the sensory periphery and neurons at the motor periphery—that is, to understand how the neurons form a circuit to constitute an information-processing system. Because the intervening network is typically exceedingly complex, studying examples in which the neuronal connections between sensory input and behavioral output are very simple has been an important step in

seeing how input-output effects are achieved and in developing models of the intervening information processing. There are about twenty cases in invertebrate research in which the circuitry underlying a specific behavior pattern is known in great detail. These include swimming in the leech and the crayfish, walking in the locust, and a substantial number of behavior patterns in *Aplysia* such as inking, egg-laying, gill withdrawal, habituation, and sensitization (Bullock 1984).

To amplify the earlier mention of the cellular basis of simple habituation and sensitization, I shall illustrate the revolutionary discoveries in the neurobiology of behavior with the neuronal circuits in *Aplysia* (figure 2.24) that mediate gill withdrawal following stimulation of the siphon, habituation to a gentle stimulus, and sensitization after a painful stimulus to the head. Habituation is the decrement of a response to a repeated, benign stimulation. Sensitization consists in a heightened response to a benign stimulus following receipt of a painful stimulus.

In *Aplysia* the circuit leading from the siphon's sensory periphery to the motor periphery of the gill is very simple, as can be seen in the schematic wiring diagram in figure 2.25. It shows one of the 24 sensory neurons innervating the siphon in direct synaptic contact with the motor neurons innervating the gill. (Only one of the six gill motor neurons is shown.) The connection between the sensory neuron in the siphon and the motor in the gill muscle is *monosynaptic,* because only one synapse mediates input and output. There is also a second pathway formed by a branch of the sensory axon, which is disynaptic because it routes through the facilitating interneuron located between the sensory and motor neurons.

In the habituation experiments the animal's siphon is repeatedly stimulated with a gentle squirt of sea water, and after a few trials the gill withdrawal response decrements. Briefly, what Kandel and his colleagues found was that at the terminal bulbs of the sensory neuron the inward Ca^{++} current decreased during the habituation trials, which resulted in a decreased neurotransmitter release at the synaptic junction, with the result that the motor neuron was less depolarized and hence caused smaller contractions in the gill muscle.

In sensitization roughly the opposite happens; there is an increase in Ca^{++} current and hence an increase in the volume of neurotransmitter released into the synaptic cleft. However, this effect requires the mediation of the facilitatory interneuron, whose axon terminates on the end bulb of the sensory neuron (presynaptic facilitation) (figure 2.25). When the tail is given a noxious stimulus, the facilitatory interneuron releases serotonin, which then initiates a four-step

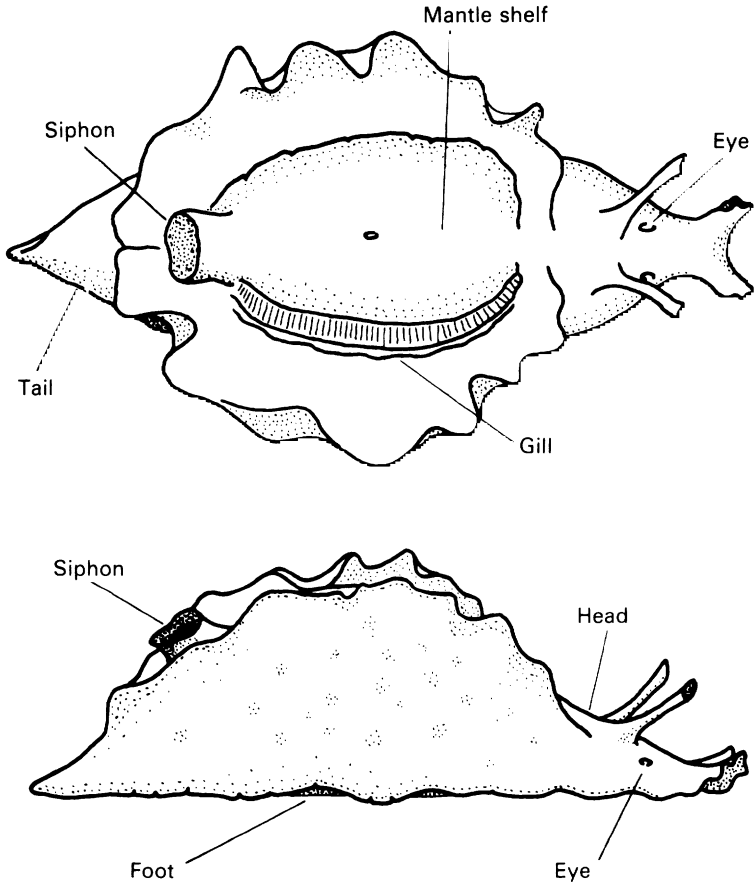


Figure 2.24
Top view and side view of the sea hare, *Aplysia Californica*. When the mantle shelf is stimulated, the gill contracts.

sequence of chemical events: (1) an elevation in the level of cyclic AMP (adenosine monophosphate) in the sensory neuron's end bulb, which causes (2) an elevation in an enzyme (cyclic AMP-dependent protein kinase), which causes (3) a decrease in the number of open K^+ channels, which causes (4) an increase in the number of open Ca^{++} channels.

Like sensitization, classical conditioning requires the facilitating interneuron. Conditioning is, however, more complex, because the close timing of the conditioned stimulus (CS) and the unconditioned stimulus (UCS) is essential in the system's selecting the particular

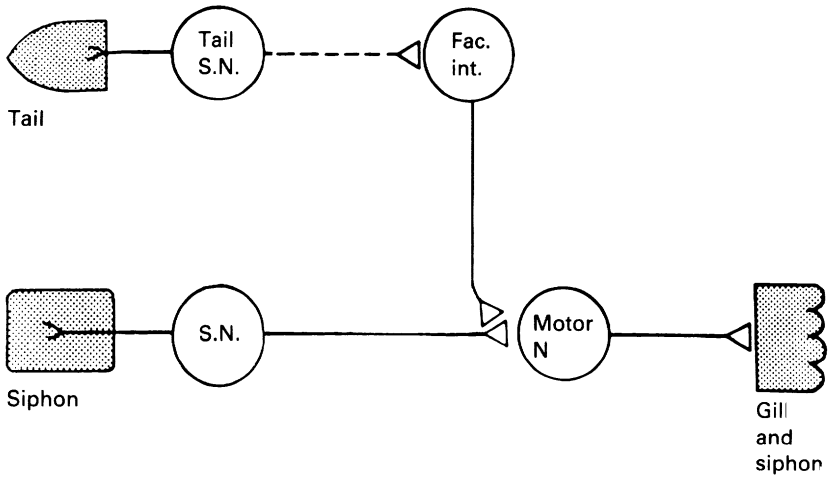


Figure 2.25
Partial neuronal circuit for the *Aplysia* gill and siphon withdrawal reflex and its modification. Mechanosensory neurons (S.N.) from the siphon make direct excitatory synaptic connections onto gill and siphon motor neurons. Tail sensory neurons excite facilitator interneurons, which produce presynaptic facilitation of the siphon sensory neurons. (From Hawkins and Kandel (1984). In *Neurobiology of Learning and Memory*, ed. G. Lynch, J. L. McGaugh, and N. M. Weinberger. New York: Guilford.)

stimulus to which it is sensitized. It appears that the temporal contiguity of CS and UCS causes an enhancement of Ca^{++} current in the sensory neurons on later occasions, though exactly how this happens is not yet understood.

Each of these forms of plasticity—habituation, sensitization, classical conditioning—appears to employ a relatively small set of specified cellular events, and Hawkins and Kandel (1984) have suggested that there might exist a general cellular "alphabet," in the sense that each of the various types of behavioral plasticity employs a distinct combination of the fundamental cellular event-types (figure 2.26). Possibly, they argue, other forms of plasticity such as associative learning, extinction, and stimulus generalization might have reductive explanations in terms of precise sequences of cellular events. They present for experimental evaluation models of kinds of plasticity based on that hypothesis.

To further illustrate how groups of neurons might be connected to yield a complex effect, consider the circuit in figure 2.27, which is a model for contrast enhancement. In every studied organism it has been found that sensory neurons typically send collaterals (axon branches) to interneurons that have an inhibitory effect on the neigh-

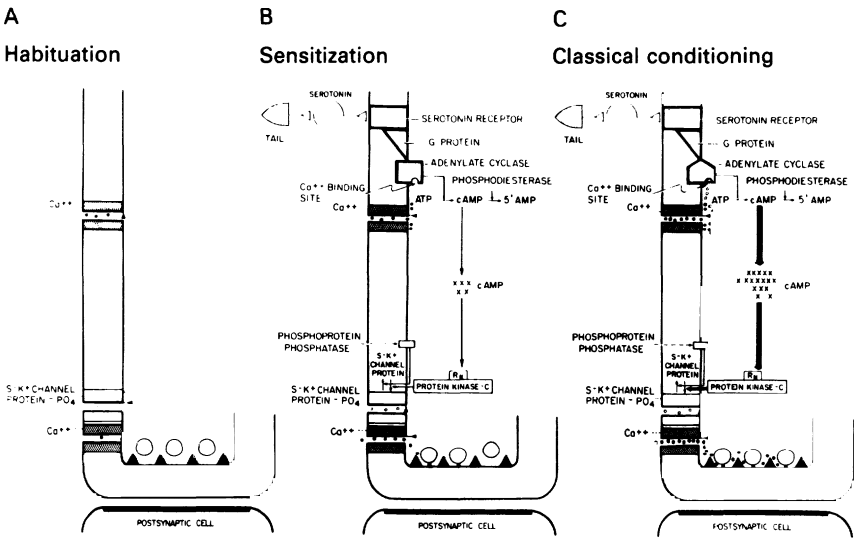


Figure 2.26
Cellular mechanisms of habituation, sensitization, and classical conditioning of the *Aplysia* gill and siphon withdrawal reflex. (A) Habituation: Repeated stimulation of a siphon sensory neuron (the presynaptic cell in the figure) produces prolonged inactivation of Ca^{++} channels in that neuron (represented by the closed gates), leading to a decrease in Ca^{++} influx during each action potential and decreased transmitter release. (B) Sensitization: Stimulation of the tail produces prolonged inactivation of K^+ channels in the siphon sensory neuron through a sequence of steps involving cAMP (cyclic adenosine monophosphate) and protein phosphorylation. Closing these channels produces broadening of subsequent action potentials, which in turn produces an increase in Ca^{++} influx and increased transmitter release. (C) Classical conditioning: Tail stimulation produces amplified facilitation of transmitter release from the siphon sensory neuron if the tail stimulation is preceded by action potentials in the sensory neuron. This effect may be due to "priming" of the adenyl cyclase by Ca^{++} that enters the sensory neuron during the action potentials, so that the cyclase produces more cAMP when it is activated by tail stimulation. (From Hawkins and Kandel (1984). In *Neurobiology of Learning and Memory*, ed. G. Lynch, J. L. McGaugh, and N. M. Weinberger. New York: Guilford.)

boring sensory neurons. This is called lateral inhibition, and it appears to be a common arrangement in nervous tissue, being found in the retina, the skin, the olfactory epithelium, and the gustatory epithelium. The effect of a lateral inhibition circuit is to enhance the contrast between highly stimulated neurons and their nonstimulated neighbors, since the stimulated cells fire at a high rate and the inhibited cells fire at a rate lower than their base rate. Some such arrangement in the retina is believed to figure in the perceptual effect known as "Mach bands." The effect is easily seen in figure 2.28. The

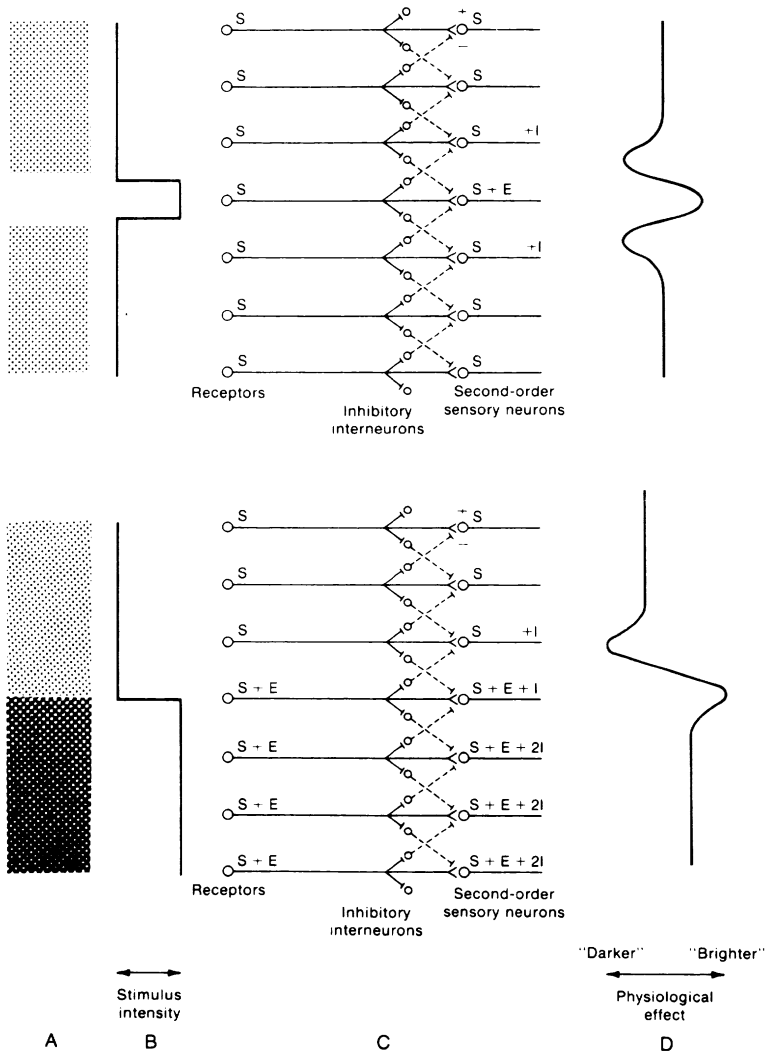


Figure 2.27
Lateral inhibition. (A) A pattern of uniformly gray areas with sharp edges, representing a visual field seen by an eye. (B) The stimulus plotted as intensity (horizontal) against spatial extent (vertical), emphasizing the uniformity of the physical intensity within each area. (C) A network of receptors and second-order neurons with reciprocal inhibitory connections via interneurons (broken lines). Spontaneous activity in the receptors (S) is augmented by excitation (E) due to light. The network causes the second-order neurons to show S activity augmented by E and/or reduced by inhibition (I) in single or double (2I) dose. (D) The output, equivalent to our sensation, plotted as darker or lighter than the background due to S. This sort of arrangement probably explains the Mach bands illusion seen in figure 2.28. (From Bullock, Orkand, and Grinnell (1977). *Introduction to Nervous Systems*. W. H. Freeman and Co. Copyright © 1977.)

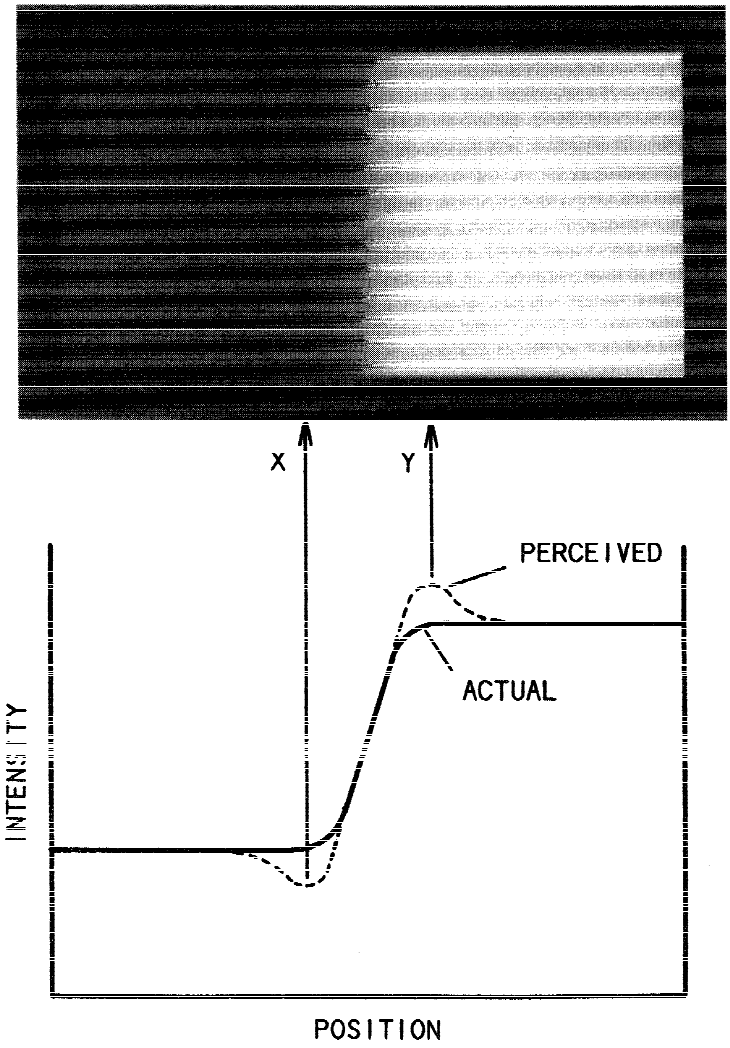


Figure 2.28
Although there is a smooth reduction in light intensity from right to left in the photograph, there appears to be a bright band at Y and a dark band at X. These are Mach band patterns. (Modified from Cornsweet (1970). *Visual Perception*. New York: Academic Press.)

Mach bands visible in the boundary area between a light region and a dark region appear as a sharper change in light intensity than actually obtains.

How contrast enhancement works in the hypothetical circuit can be observed in figure 2.27. All cells have a base firing rate, cells stimulated by the light have an increased firing rate, and each inhibitory neuron decreases the firing rate of its postsynaptic cell by some specified amount. Consider the cell that is on the boundary of the increase in stimulus intensity. Excited by the stimulus, it will fire at a higher than base rate, and it will therefore excite an inhibitory interneuron that synapses on the cells that are its immediate neighbors. One of its neighboring cells, unaffected by the light stimulus, will have its base rate decreased by the inhibitory interneuron, while the neighbor on the other side, despite being excited by the light stimulus, will fire less vigorously than the boundary cell because it receives inhibitory stimuli from excited neighbors on both sides. Since the cells at the boundary of the area receiving the stimulus are inhibited only by neighbors on one side, they have the highest firing rate. Although this is a highly simplified and schematic representation of how a network of neurons might interact to yield contrast enhancement, it illustrates how complex effects can be derived from appropriately connected simple units.

These examples of simple circuits are meant to provide only an introductory illustration of how neurons can be wired up to constitute an information-processing and a learning network. Nevertheless, they should help to make clear why neurobiologists have insisted it is necessary to understand the architectural and physiological properties of nervous systems. The reason is that such properties provide essential clues both to how networks can generate complex representations of the external world and of the internal nervous-system world and to the nature of the computations performed by large, interconnected arrays of neurons. In chapter 3 I will say more about some architectural properties of nervous systems believed to be especially significant in constructing a theory of the nature of neural network function. In chapter 10 I will discuss some theoretical developments arising out of, or at least directly inspired by, neuroanatomy and neurophysiology.

Concluding Remarks

Although the membranes of all body cells are polarized and have the ability to depolarize and repolarize, neurons are special both because their single channel configurations permit them to exploit this capacity in a *coordinated and systematic* fashion and because they are joined

together in a network. The result is that neurons can represent features of the world and can coordinate the occurrence of such features with muscular movement.

The fundamental principle is deadly simple, but at the same time almost endlessly versatile. Increased complexity will essentially be a matter of adding components of the same basic type; the neurons in a flatworm and the neurons in a human brain work on the same *fundamental* principles. From which it does not follow, however, that the capacities of the human brain are essentially just those of a densely packed conglomeration of flatworm ganglia. The marvelous thing about electrical circuits is that adding components is not merely a matter of enlarging the system, but sometimes means changing the system's capacities in novel and remarkable ways. In particular, the evolutionary step that interposes neurons between sensory neurons and motor neurons is revolutionary: it permits the building-in of a basic world-representation, and it can provide for increasingly fancy up-dating of that world-representation through learning. As the interneuron pool proliferates under evolutionary pressure for more competitive sensorimotor coordination, the innate world-representation improves and the dimensions of plasticity ramify.

2.4 *Neurotransmitters and Other Neurochemicals*

On a simple view of things it might have been predicted that the nervous system would need to produce just two chemicals to serve as neurotransmitters—one for excitation and one for inhibition. Even adjusted upward for Nature's tendency to scrounge, the prediction is not even close. There are at least forty known neurally active substances sloshing around in the nervous system, and it is a near certainty that more will be coaxed into revealing themselves. What are all these substances doing in the brain? Has Nature been wantonly extravagant in producing such variety, or does the variety reflect diversity in function?

These questions become especially fascinating in light of the synthesis of certain drugs that mimic, enhance, or obstruct the action of some of these substances and that moreover can have quite consistent and distinct psychological effects. Some may produce hallucinations, others reduce hallucinations; some alter moods to produce euphoria, others produce despair, anxiety, and hopelessness; some heighten arousal, others tranquilize; some are amnestic, others facilitate memory; some alleviate pain, others produce excessive drinking, eating, or unseemly sexual behavior. These drugs produce changes in the brain, mainly, it is believed, at synaptic junctions, and they provide a

means for interfering in the nervous system that may help us understand what various parts of the brain do.

The assorted endogenous neurochemicals are not distributed randomly in the brain. First to be considered is Dale's law, which says that any given neuron synthesizes and releases only one type of transmitter, though it may have receptor sites fitted for any number of diverse transmitters. The law seems to hold generally for adult neurons, but, interestingly enough, it is known to be violated by developing neurons in the very young. In any event, the accepted classification specifies neurons as *dopaminergic* if they typically release the transmitter dopamine, *cholinergic* if they typically release acetylcholine, and so on for the set of neurotransmitters.

Several techniques have been devised to locate neurons with a characteristic transmitter. For example, by treating a neurochemical so that it will fluoresce, researchers have been able to show areas of the brain where it is concentrated and thereby to identify the location of neurons releasing it. Dopamine has been found to concentrate in neurons in an area of the brain called the substantia nigra and in the midbrain tegmentum (figure 2.29). Some of these neurons project to the forebrain where, given behavioral evidence, they are thought to play some role in mood regulation. But dopamine is not found *exclusively* in these areas, and minute amounts are found hither and yon, including in the spinal cord.

It was hoped that particular neurochemicals might be found exclusively in certain tracts and areas whose function was more or less well defined, but these hopes have been disappointed. For example, it would perhaps have been easier if the enkephalins were found solely in tracts that carry pain information or mediate the pain response, but this has not turned out to be the case. Though enkephalin is concentrated in certain spots, these spots are not what one would expect if it were primarily a neurochemical for the nociceptive system. For example, it is found in the primary photoreceptors of the spiny lobster. It is also noteworthy that endorphins are found in a wide range of organisms, including leeches, spiders, lobsters, rats, and monkeys.

Additionally, it is evident now that there is no sharp division between the chemicals found in the brain and the hormones found elsewhere in the body. Consequently, the once sharp distinction between secretion of peptides by glands in the endocrine system and secretion of peptides at the synaptic terminal is fast losing its edge. All the peripheral peptide hormones—for example, the gut peptide cholecystokinin and the sex hormone estradiol—have been found in the brain, and peptides originally believed unique to the brain—for

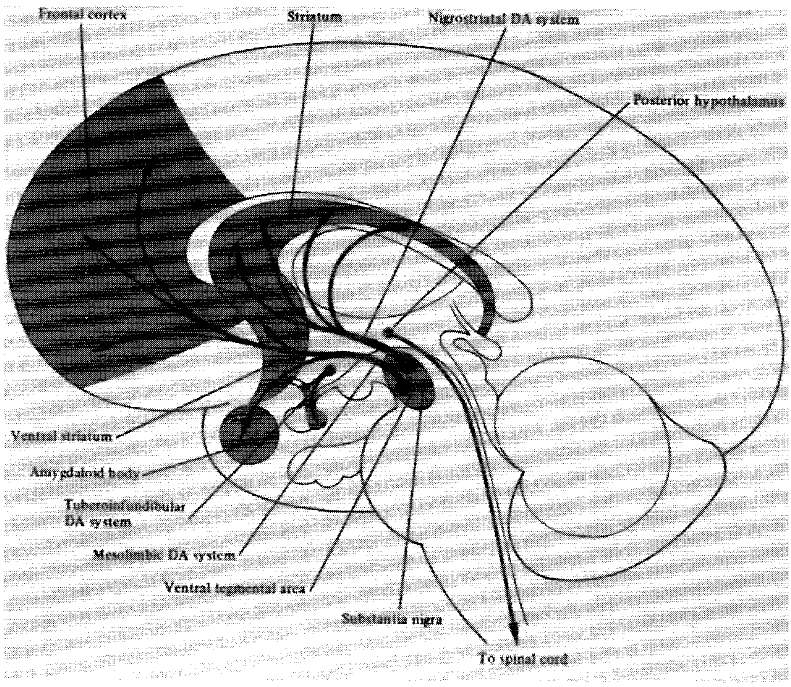


Figure 2.29
The nigrostriatal dopamine system originates in the substantia nigra and terminates in the main dorsal part of the striatum. Damage to this system results in Parkinsonian symptoms. The ventral tegmental area gives rise to the mesolimbic dopamine system, which terminates in the ventral striatum, amygdaloid body, frontal lobe, and some other basal forebrain areas. The tuberoinfundibular system innervates the intermediate lobes of the pituitary and the nearby median eminence, and dopamine neurons in the posterior hypothalamus project to the spinal cord. (From Heimer (1983). *The Human Brain and Spinal Cord*. Copyright © 1983 by Springer-Verlag.)

example, β-endorphin—are found outside the nervous system (Rehfeld 1980).

Moreover, the assumption that each transmitting substance has a one-trick profile, producing either just excitatory or just inhibitory effects on the postsynaptic neuron, is false. At least one neurotransmitter—serotonin—has been shown in *Aplysia* to cause either excitation or one of two styles of inhibition on the postsynaptic neurons, depending on the receptor structures. That this versatility is a general feature of transmitting substances is suspected but not yet proven (Paupardin-Tritsch and Gerschenfeld 1975).

Although each of the forty or so substances has been found to have some neural effect, especially at synaptic junctions, so far only eleven are demonstrated to function as transmitters. To count as a transmit-

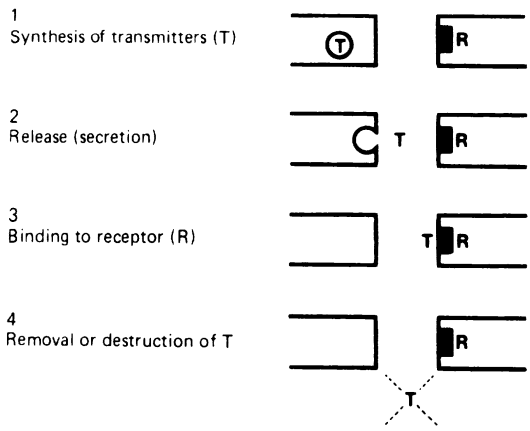


Figure 2.30
Four biochemical steps in synaptic transmission: (1) synthesis of the neurotransmitter substance (T), (2) release of transmitter into the synaptic cleft, (3) binding of the transmitter to the postsynaptic receptor (R), and (4) removal or destruction of the transmitter substance. (Reprinted with permission of the publisher from Schwartz (1981). Ch. 10 of *Principles of Neural Science*, ed. E. R. Kandel and J. H. Schwartz, pp. 106–120. Copyright © 1981 by Elsevier Science Publishing Co., Inc.)

ter, a substance must satisfy four conditions: (1) it must be synthesized in the presynaptic neurons, (2) it must be released from the presynaptic terminal, (3) it must be shown to cause EPSPs or IPSPs, and (4) there must be mechanisms for its removal from the scene of action (figure 2.30).

Demonstrating that a neurochemical passes muster on each of the four counts is exceedingly difficult, and to date only eleven have passed all four, though many others have been shown to pass some, and answers are awaited for many tests. The list of canonical transmitters includes acetylcholine (an excitatory substance released by motor neurons at the neuromuscular junctions, and by other neurons in the CNS as well), dopamine (so far found to be inhibitory), norepinephrine (also called noradrenalin), serotonin, and GABA (γ-aminobutyric acid, another inhibitory transmitter) (tables 2.1, 2.2).

Not all inhibitory transmitters have precisely the same causal profile, however. Norepinephrine appears to have a longer and slower course of action than, for example, serotonin (Taylor and Stone 1981). Some neurochemicals are thought to have a modulatory role in regulating the effects of a transmitter on the receiving cells, and there is evidence that some neurotransmitters act on voltage-sensitive channels as well as at the standard receptor sites, thus affecting the response properties of neurons in a range of subtle ways

Table 2.1
Canonical transmitter substances

Acetylcholine	γ-Aminobutyric acid (GABA)
Dopamine	Glycine
Norepinephrine	Glutamate
Epinephrine	Aspartate
Serotonin	Taurine
Histamine	

Source: Feldman and Quenzer (1984). *Fundamentals of Neuropsychopharmacology.*

Table 2.2
Neuroactive peptides

Gut-brain peptides
- vasoactive intestinal polypeptide (VIP)
- cholecystokinin octapeptide (CCK-8)
- substance P
- neurotensin
- methionine enkephalin
- leucine enkephalin
- insulin
- glucagon

Hypothalamic-releasing hormones
- thyrotropin-releasing hormone (TRH)
- luteinizing hormone-releasing hormone (LHRH)
- somatostatin (growth hormone release-inhibiting factor, SRIF)

Pituitary Peptides
- adrenocorticotropin (ACTH)
- β-endorphin
- α-Melanocyte-stimulating hormone (α-MSH)

Others
- angiotensin II
- bradykinin
- vasopressin
- oxytocin
- carnosine
- bombesin

Source: Snyder (1980). Brain peptides as neurotransmitters. *Science* 209:976–983.

(Nicoll 1982). The subtlety and complexity of interneuronal communication far outstrips the "excite-inhibit" repertoire, and we are only beginning to understand what the assorted chemicals do (Taylor and Stone 1981, Dismukes 1980).

Fine-grained detail has accumulated concerning such things as the molecular structure, location, synthesis, blocking agents, and enhancing agents of the various neurochemicals, but there is still nothing remotely resembling a comprehensive *theory* of what they do or of how the known psychological effects result from tinkering with them. We may know that cocaine acts by blocking the uptake of norepinephrine, leaving norepinephrine lying about in the synaptic cleft to continue its work unabated, but how that produces euphoria is a smooth-walled mystery.

The absence of theory here is not surprising. For one thing, until much more is known about the details of brain business and about how noradrenergic neurons fit into the grander scheme of things, merely focusing on the one change we happen to know cocaine produces cannot be expected to tell us much. Second, until we have higher-level concepts to describe what configurations of neurons are doing, we have no means of bridging the gap between molecular descriptions and molar descriptions. The mystery will not be solved merely by finding out about the molecular details of the slew of neurochemicals, but neither will it be solved without much of that detail. (See Miczek, Thompson, and Shuster 1982, Mayer 1975, Cooper, Bloom, and Roth 1982.)

Neuroleptics

Largely because of their clinical significance, the antipsychotic drugs (called *neuroleptics:* "that which takes the neuron") have been the focus of concentrated study. In the treatment of schizophrenia the phenothiazines, of which chlorpromazine is the most renowned, are extensively used, and it is estimated that some fifty million patients have been treated with them. For roughly a decade they were used without any clear idea of how they affected the CNS and were therefore prescribed mainly on the strength of their behavioral effects, much as antianxiety pills such as Librium and Valium are still used (Kolata 1979a).

Research now indicates that the phenothiazines block the dopamine receptor sites, and the evidence has come from the cellular as well as the behavioral level. In vitro studies show that chlorpromazine does bind to dopamine receptor sites, though it has as well been linked to an increase in norepinephrine turnover. A problematic side effect of chlorpromazine therapy that also points to dopamine

involvement is that patients on extended chlorpromazine treatment may eventually develop motor symptoms similar to those of patients suffering from Parkinson's disease. From another direction it has been found that amphetamine, which stimulates dopamine receptors, will induce "amphetamine psychosis" and in otherwise mild schizophrenics will induce acute psychotic symptoms. (See Feldman and Quenzer 1984.)

The possibility has been considered that the phenothiazines work not by zeroing in on the psychotic effects per se but rather by sedating or tranquilizing the brain. Though this possibility is not yet ruled out, some evidence against it was found in a comparison of the effects of sedatives such as barbiturates and of neuroleptics, which shows them to be quite distinct. Though neuroleptics are not widely regarded as a *cure* for schizophrenia, in virtue of their specific effects in treating a hitherto intractable disease they have engendered optimism for the discovery of a cure and even for the means to prevent the disease altogether.

Once the connection to dopamine was made, the hypothesis that naturally formed itself was this: if neuroleptics antagonize dopamine, then perhaps schizophrenia has its origin in the malfunction of dopaminergic neurons, such that there is an excessive amount of dopamine in the CNS. Schizophrenia, it might be said, is "hyperdopaminia." So far, efforts to prove this have been less than decisive, and the heady expectation of the early days that a simple solution was all but in hand has quietly given over to a tempered belief that an answer, probably not all that simple, will eventually be untangled as part of a more comprehensive theory of neurobiology.

Whether a dopamine flood is the root cause of schizophrenia is not yet established, and even assuming dopaminergic neurons are the culprits, there is an assortment of ways in which they might be malfunctioning. They might be too active and thus release too much dopamine, but alternatively the mechanisms for synthesis might be abnormally hearty, or the mechanisms for breakdown might be abnormally sluggish, or, in a different vein, the postsynaptic neurons might be overly sensitive to dopamine or might have cultivated too many receptor sites—all of which are consistent with chlorpromazine's demonstrated capacity to reduce symptoms. Though chlorpromazine alteration of dopaminergic transmission does of course make dopaminergic neurons prime suspects, the trouble is that such facts are entirely consistent with the possibility that some biochemical impropriety (e.g., an enzymatic muck-up) further upstream is the underlying cause (or, more difficult yet, one of several underlying causal factors). Additionally, it is likely that psychological

factors of a complex nature also play a role in altering the balance of the chemical soup, even as such alterations in the soup in turn affect the psychological states. Hence, an adequate account of schizophrenia, clinical depression, sociopathy, and so forth, would need to integrate biological and psychological descriptions (Kety 1978).

Still, the hopeful thing is that the array of possibilities is after all an array of empirical and testable possibilities. And the evidence is snowballing that schizophrenia is a somatogenically based disease, like, for example, Parkinson's disease or diabetes, rather than a disease that originates in strictly psychological elements such as guilt, shame, repression, and the like. A first source of evidence for this derives from comparison of the effectiveness of phenothiazine therapy with other therapeutic techniques such as psychotherapy. For very seriously afflicted patients, drug therapy is generally considered more effective in reducing symptoms than psychotherapy, more effective than placebos, and more effective than psychotherapy and placebos combined (Davis and Garver 1978). For milder afflictions, the case is far less clear.

Second, examination of the brains of schizophrenics in autopsies or by using three-dimensional scanning techniques (described in chapter 5) shows that there are some systematic differences between such brains and those of normal subjects. For example, the ventricles of chronic schizophrenics are typically larger, and the level of activity in the forebrain is substantially reduced. There are also distinct differences between normal subjects and chronic schizophrenics in the distribution of cerebral blood flow, in the gross electrical activity of the brain as measured by the electroencephalograph, and in glucose uptake patterns as measured by positron emission tomography (Ingvar 1982, Buchsbaum et al. 1982, Buchsbaum et al. 1984). (See chapter 5 for an explanation of these techniques.) Exactly what these findings mean is far from clear, but they do add another piece to the puzzle.

Third, there is strong evidence of familial susceptibility to schizophrenia. In one study it was found that if one monozygotic twin is schizophrenic, then there is about a 45 percent chance the second one will be so as well. The risk drops to about 13 percent if the twins are fraternal. The incidence of schizophrenia in the general population is roughly 1 percent. Additional studies on adopted children in Denmark also indicates an inherited susceptibility to the disease (Kety et al. 1975). Another study compared children born to schizophrenic parents but reared by normal parents with the opposite situation (children born to normal parents but reared by affected parents) and a control group (children born to normal parents and adopted by normal parents) (Wender, Rosenthal, and Kety 1974). The results

pointed to a genetic effect: roughly 18 percent of the first group became schizophrenic, whereas the incidence of schizophrenia in the second group and the control group was the same, about 10 percent. (For a collection of papers on schizophrenia as a somatogenic disease, see Henn and Nasrallah 1982.)

As a result of the work on familial histories and schizophrenia, the hypothesis that there is a genetic susceptibility to schizophrenia seems correct, though there is still considerable controversy concerning the adequacy of experimental controls and the interpretation of the data. No one has claimed that the genetic factor is all there is to it, for even assuming there is a gene implicated in the causal history of schizophrenia, environmental factors, whatever they are found to be, are certainly relevant. Otherwise the chance of a second monozygotic twin having schizophrenia if the first does would be 1 rather than .45. In this respect schizophrenia could be like phenylketonuria (PKU), a recessive disorder caused by a deficiency of an enzyme, which results in high levels of phenylalanine in the brain. It is a serious disease for those on a diet rich in protein, which contains phenylalanine, but it does not show up on a meat-restricted diet (Rosenberg 1980). Certain environmental conditions may trigger schizophrenic symptoms, whereas in an environment free of those factors a carrier of the gene may be largely free of the disease. For example, being raised by parents who are schizophrenic appears to be one relevant environmental condition.

Matters could be, and probably are, horrendously complicated. What is now classified as a single disorder—schizophrenia—may in fact be a number of causally unrelated types of disease (Crow et al. 1982), and even if some type of schizophrenia has a genetic basis, the modes of transmission and epigenetic factors have yet to be determined. It is worth bearing in mind that some genetically based diseases such as Sanfilippo's syndrome have essentially one clinical presentation but are producible by the presence of either of two distinct genes, and for all we know now this may be the case for schizophrenia. (For review papers, see Buchsbaum and Haier 1978 and Crowe 1982.)

This discussion of attempts to understand schizophrenia as a neurochemical disease has touched on only a sprinkling of current developments, and then only superficially. And schizophrenia is not the only mental disorder to be so studied; depressive disorders, the dementias, dyslexia, and sleep disorders are examples where genetic and neurochemical studies are bearing fruit. (For example, see Whitehouse et al. 1982.) Nor are *mental* disorders the only ones in this category; diseases involving the motor system (for example, Parkin-

son's disease, Huntington's chorea, and myasthenia gravis) are also instances where research in neurochemistry has been pursued with considerable success (Spokes 1981). For wider and more thorough discussions, the reader may consult works recommended in the reference section.

The discovery that it is possible to change the brain directly and alleviate the catastrophic effects of brain disease has far-reaching social importance. Brain disorders are widespread, and demographic distribution being what it is, the number of older citizens steadily increases—with the result that the number of patients with strokes, Parkinson's disease, Alzheimer's disease, and so forth, will also be on the upswing. The social and personal costs of brain disorders are enormous, and the possibility that we might really understand and manipulate some of the causally relevant conditions seems an increasingly real possibility. In this context it is useful to mention that a new technique for treating Parkinson's disease is being developed, a technique that presents an important moral issue, especially since it may conceivably be applied more generally to other disorders.

The issue is this. As a result of research in neural implants, it was found that foetal neurons extracted from a specified area of a rat's brain and injected into the same area of another rat's brain established themselves there as functioning elements in the nervous system. Thus, neurons extracted from the substantia nigra of a foetal rat and injected into the brain of a rat with lesions in the substantia nigra continued to live and began to produce dopamine, the neurotransmitter in deficit since the destruction of the substantia nigra. The dopamine deficiency suffered by the brain-lesioned rat was accordingly made good to some degree, and the motor deficits were diminished though not abolished. Because the brain is isolated from the immune system by the "blood-brain barrier" (the neurons are not directly nourished by the bloodstream but are "fed" by the intervening neuroglial cells), brain grafts are less susceptible to rejection by the immune system as a foreign invader. Although this immunological privilege, as it is called, has been demonstrated in the rat, it is not yet known whether primate brains enjoy the same property and will accept foreign neurons (Barker and Billingham 1977).

Now under study is the possibility that humans with Parkinson's disease might be treated by injecting foetal neurons into the brain. This would be far better than treatment with L-dopa, because the brain's need for dopamine is continuous but the drug can only be taken at discrete intervals, and because in the long term Parkinson's patients on this drug tend to develop psychiatric symptoms, some of the motor deficits reappear, and the drug seems to have declining

efficacy. A replacement of the atrophied neurons by healthy neurons would be a vast improvement. A similar case can now be made for treating diabetes with foetal cells from the pancreas, and it is possible that replacing neurons in the hippocampus may help patients with Alzheimer's disease. Foetal neurons implanted into the hippocampus even show a tendency to establish projections to the appropriate regions of the host brain, and more remarkably, they appear to establish functional synapses, though this is still under investigation (Bjorklund and Stenevi 1977 and 1984, Freed 1983).

The most effective implant cells are foetal cells, and if it should turn out that cell transplants in humans must use cells from human foetuses rather than from animal foetuses, the moral issue comes into focus. So far no human foetal cells have been used in neural implants, and the experiments with implants in the brain of humans with Parkinson's disease have all used cells from the patient's own adrenal medulla (Bjorklund and Stenevi 1984). These experiments have resulted in little if any restoration of capacity, but the belief is that human foetal cells would be more effective. One question to be raised here is this: is it acceptable to use neural tissue obtained from aborted human foetuses? Assuming for this discussion the moral propriety of abortion, should the cells be used to alleviate the ravages of cruel diseases such as Alzheimer's?

The issue may be sidestepped to some degree if some clever neurobiologist discovers how to produce the desired cells in tissue cultures. Even then, however, those who believe that the human soul is infused in the morula at the moment of conception may find the tissue culturing immoral on grounds that foetal neurons in tissue culture are "ensouled." Naturally neuroscientists are wary of undertaking any research that might provoke an imbroglio, however misguided its motivation. Thus, there is the further sociological and political issue concerning how to educate the public such that a rational, nonsuperstitious judgment can be made. (See also the discussion concerning materialism and dualism in chapters 7 and 8.) In any event, there is a real need for experimental studies on the efficacy of implantation of human foetal neurons in treatment of such disorders as Parkinson's and Alzheimer's disease.

Although these questions are intriguing, I shall take them no further in this book. My intent here is merely to flag the questions, partly for their intrinsic interest, and partly because the issue of the use of human foetuses will likely come to legislation in the near future. It is an issue of profound practical significance, and one on which cooperation between neuroscientists and philosophers will be essential. I do not believe there are any a priori answers, and the more empirical

information available in considering the question, the more informed will be the conclusions drawn.

Advances in our understanding of the biological factors in diseases such as schizophrenia also raise questions leading in a quite different direction. The developments in understanding madness that have shifted from the demonic possession theory popular from the sixteenth to eighteenth centuries, to the psychoanalytic theory advocated by Freud and widely practiced in the twentieth century, and now to biochemical theories, do not merely represent a change in clinical approach but penetrate to our everyday conception of ourselves.

Assuming that diseases such as schizophrenia do have a basis we can describe in biochemical terms, this invites the idea that we might enhance our knowledge generally, of the sane as well as the insane, should we acquire knowledge of the biochemical aspects of emotions, moods, and desires and of cognitive development and organization. If the desires, fears, inclinations, and dispositions of the insane are in some measure a function of the neurochemicals in the brain, then so are those of the sane. This line of thought leads to broad questions concerning the nature of the integration of psychological theory and neuroscientific theory, and the possibility of reduction. Because these questions require a substantial philosophical and neuroscientific setting, they will be deferred until chapters 8 through 10.

Sex and Neurochemicals

One dimension of the psychology of an organism where its neurochemistry is manifestly relevant is reproduction and the congeries of behavior patterns related to it. Gender identity is crucially connected to the presence of certain steroids, the gonadal hormones. Until rather recently it was widely supposed that the role of gonadal hormones did not include intervention in the business of the CNS, but it is now known that they are found in regionally specific parts of the brain and that sexual differentiation of the brain takes place at their behest (McEwen et al. 1974, Pfaff and McEwen 1983).

From the point of view of natural selection, sex is a good thing, since it provides the medium for mixing genetic material and hence for maximizing variation. Sexual reproduction requires dimorphism (two forms), and in many animals, including of course all mammals, there is a dimorphism of behavior as well as of reproductive organs and various other bodily features. Dimorphism in behavior is a method of ensuring that individuals recognize each other as appropriate mating partners and recognize that the timing is appropriate. It also ensures that coupling gets the reproductive parts where they

should be for successful reproduction. Parental nurturing behavior is also advantageous, and consequently many brains may have built-in dispositions for nest building, feeding the young, foiling predators, and so on.

In normal adult animals (rats and horses are well-known examples) priming by gonadal hormones—androgen for males and estrogen for females—activates reproductive behavior. In the developing organism the presence of gonadal hormones has a quite different effect, hidden from casual view. At this early stage the hormones function to set the brain's development on a course that establishes its gender. The brain of the developing organism thus becomes male or female, and subsequent influx of hormone in the adult organism will not be able to reverse the changes wrought in the brain.

An organism with an XY chromosome pair is a genetic male,[4] and at some point in his early development testosterone will be manufactured by his emerging testes and released in his body. Some will affect maturation of the gonads, and some will reach his CNS where, during a certain critical period in which particular neurons are maximally sensitive to testosterone, it will induce organizational changes in the brain that "masculinize" it. The critical period varies from species to species. In most animals studied it is confined to foetal stages, and in humans it is believed to encompass the third and fourth months of gestation. Rats, ever obliging to the experimenter, have a critical period that extends a few days beyond birth.

Until the influx of testosterone the brain is bipotential—that is, capable of becoming characteristically male or female. This means that brain sex is not simply a matter of genetic sex, and indeed the two can be dissociated such that a genetic male can have a female brain, and a genetic female can have a male brain. So-called experiments of nature are one indicator of this sort of dissociation. Freemartins are cows (genetic females) with a male twin. They are invariably infertile, and in the pasture behave more like bulls than like cows. Even before ultrastructural studies of brains revealed what differences there could be between male and female neuronal organization, the freemartin phenomenon suggested that there was a masculinization of the female's brain as a result of the foetal environment she shared with her male twin. In the human case a pathological condition called *androgen insensitivity* results in a genetic male who is phenotypically female both in external genitalia and in sexual orientation (Ehrhardt and Baker 1974).

In the laboratory male rats deprived of testosterone during their critical period never show male reproductive behavior (mounting, intromission), though they do show female reproductive behavior,

measured by frequency of lordosis (female presenting posture—raised rump, concave back). It is important to note that for such animals, priming with testosterone after the critical period fails to elicit mounting. Females exposed to testosterone during the critical period are masculinized; their adult behavior is characteristically male and their lordosis quotient is low and not much enhanced by priming with estrogen. The androgenization of the developing brain appears to be irreversible and enduring.

Taking such standard behavior patterns as mounting and intromission as an index of characteristic male reproductive behavior and lordosis as an index of female reproductive behavior, it is evident that genetic sex determines brain sex only via the intermediary auspices of gonadal hormones. Such indexes are admittedly rather restricted and other behavior profiles such as display patterns, offspring-care behavior, song, nest building, etc., can, where appropriate, be taken into account.

Establishing behavioral indexes for characteristically male or characteristically female behavior is notoriously difficult, and in the pioneering stages researchers have tended to adopt fairly conventional and crude descriptions. How to extend animal studies to the human case, how to refine and reconfigure the indexes of what is masculine and what is feminine, and how to extend studies to include nonreproductive behavior as well are questions for further research. However, the point of emphasis here is that, using narrowly defined indexes of the masculine and feminine in behavior, it is clear that such adult behavior is crucially affected by early exposure of the brain to testosterone and that this exposure determines whether exposure as an adult to gonadal hormones will be effective in producing characteristic reproductive behavior. There also seems to be a distinct feminizing of the brain, so that a female brain is not one that merely missed out on androgenization (Goy and McEwen 1977, Feder 1984).

What exactly does testosterone do in the brain, and what does brain androgenization mean in terms of neuronal structure and organization? To begin with, rat studies show selected areas in the brain where testosterone concentrates, and these areas include the hypothalamus, the pre-optic area, the amygdala, the midbrain, and the spinal cord. Within these regions are specialized neurons that contain protein receptors fitted for estradiol. Testosterone molecules enter such cells, convert to estradiol, and link up with the receptors. The protein-hormone pair migrate to the cell nucleus and enter it, where they interact with the genes to affect the program for protein synthesis (figures 2.31, 2.32).

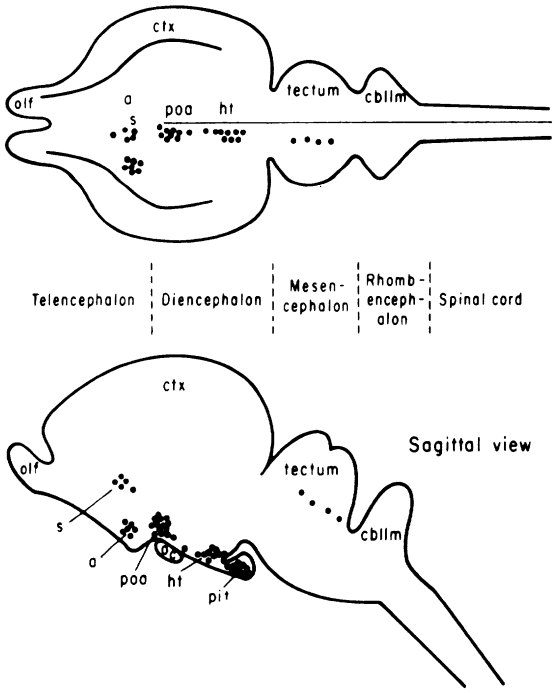


Figure 2.31
Abstract representation of a "generalized vertebrate brain," showing locations of estradiol- and testosterone-concentrating neurons common to all vertebrates so far studied. The top drawing is a horizontal view, and the bottom a sagittal view. Black dots represent groups of steroid-concentrating cells. Abbreviations: *a*, amygdala; *cbllm*, cerebellum; *ctx*, cortex; *ht*, nuclei in hypothalamus; *oc*, optic chiasm; *olf*, olfactory bulb; *pit*, pituitary; *poa*, pre-optic area; s, septum. (From Morrell and Pfaff 1981.)

Paradoxically, it is estradiol, a female hormone, to which testosterone converts and which articulates the androgenization of the brain. Why then, does the estradiol routinely produced by developing females not itself androgenize the brain? The answer is that in the foetus the liver produces a protective protein—alpha-fetoprotein—that binds estrogen in the blood and prevents it from entering the cerebrospinal fluid and so from reaching the brain. Testosterone is not so bound and accordingly is free to find its way unencumbered to the brain. This answer suggests the following test: administer estradiol directly to the brain of infant female rats to see whether it produces the characteristic androgenization seen in males. The outcome is that it does indeed androgenize the brain of the genetic female (McEwen 1976, McEwen et al. 1974).

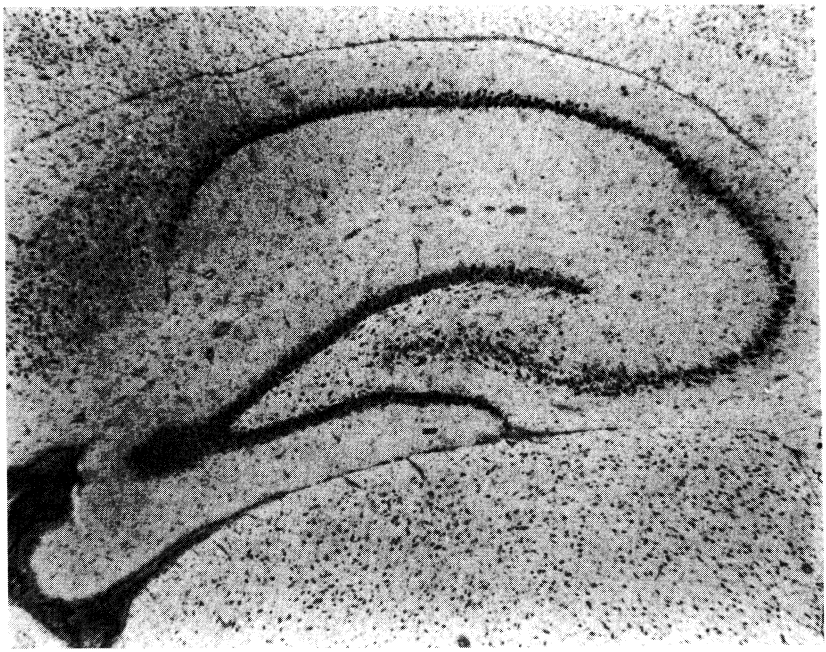


Figure 2.32
Steroid-hormone receptors in rat hippocampus, located by administering a radioactively tagged steroid. (Courtesy John Gerlach and Bruce McEwen.)

Precisely how the hormone-protein pair influence the genetic program for protein synthesis has not yet been uncovered, but it is suspected that there is a connection to neurotransmitter production. Heritage and Stumpf (1980) have found a proximity of hormone-sequestering cells and neurons that release transmitters such as dopamine and norepinephrine, and the project now is to divine the significance of that connection.

The possibility that arborization and connectivity patterns are altered is under exploration. Toran-Allerand (1978) found that hormone-sensitive neurons in vitro respond to application of estradiol by teeming growth of dendrites and axons. Raisman and Field (1973) found distinct patterns of synaptic connections in the pre-optic area of male rat brains. If genetic male rats were deprived of testosterone during their critical period, the synaptic connections of that area resembled the characteristic female pattern. The evidence points most convincingly in these cases to distinctions in circuitry and connectivity as a result of sexual differentiation induced by testosterone.

Morphological differences between male and female rat brains are

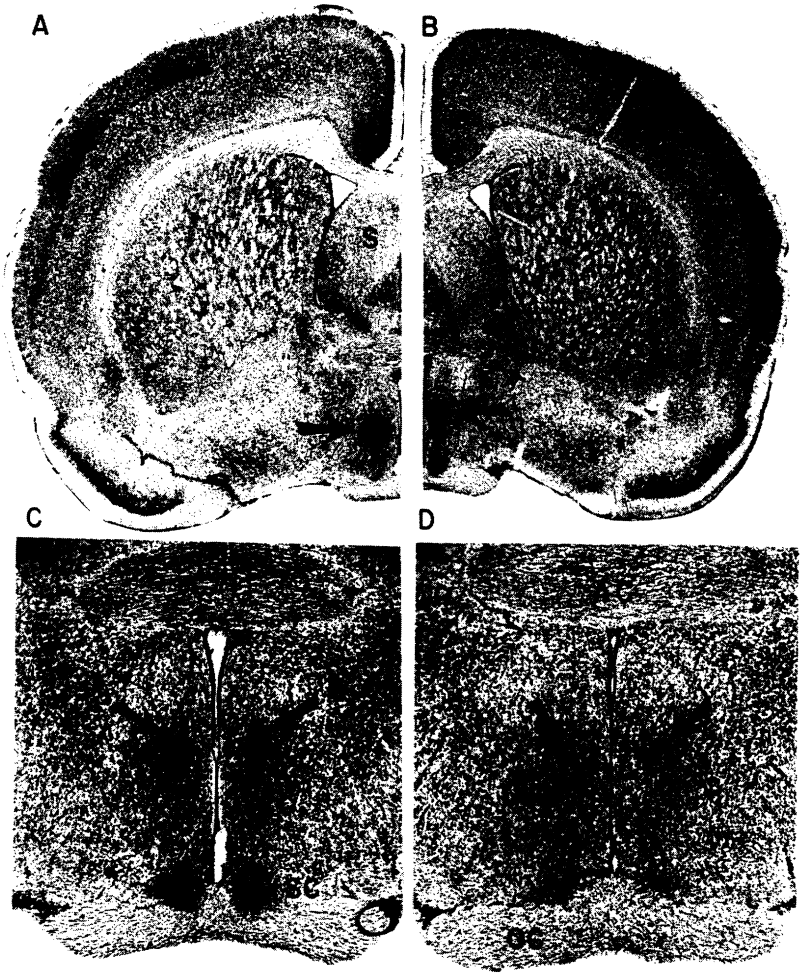


Figure 2.33
Visible differences in male (A and C) and female (B and D) rat brains. Tissue is stained with thionin, which stains acidic structures in cell bodies. Arrows point to medial preoptic nucleus (in the hypothalamus), which appears to be more densely packed and well defined in the male. (From R. A. Gorski 1979b.)

visible with the naked eye. Gorski et al. (1978) found an area near the hypothalamus that, when stained, shows a large, well-formed nucleus of cells in the male and a much smaller, diffuse pattern in the female (figure 2.33). Legions of outstanding questions present themselves here, not the least of which is how differentiation in neuronal morphology explains the dimorphism in behavior. Gradually answers are being pieced together, and the search for connections

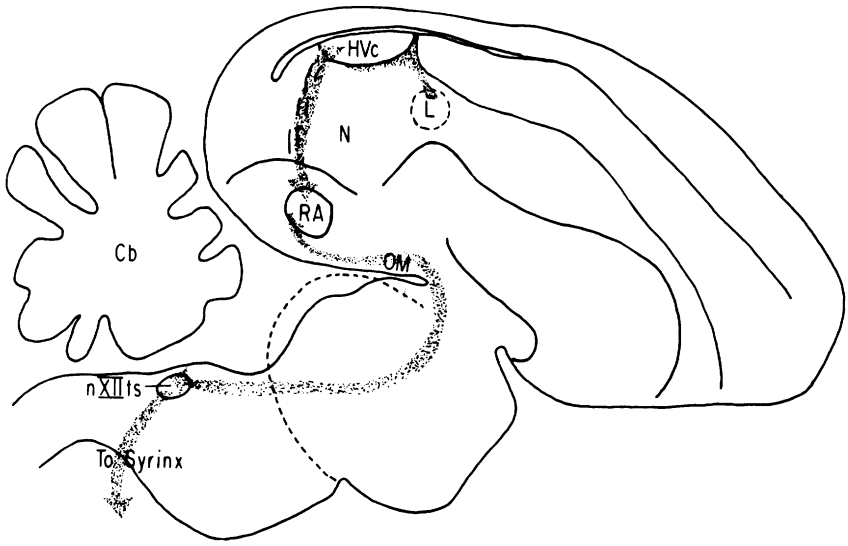


Figure 2.34
Drawing of a sagittal section of the brain of an adult male canary. HVc and RA are the two forebrain nuclei involved in song control. L, the auditory projection of the caudal neostriatum (N), sends fibers that end in a field apposed to ventral HVc, presumably enabling the learning of a song repertoire by reference to auditory information. nXII is the caudal half of the hypoglossal nucleus, formed by the motor neurons that innervate the muscles of the trachea and syrinx. Cb is the cerebellum. (From Nottebohm 1981.)

between steroid-sensitive neurons and reproductive behavior is beginning to yield impressive results. For example, male mating vocalizations in a range of different bird species are mediated by specialized nuclei whose neurons are steroid binding. Nottebohm has found in canary brains a pair of forebrain nuclei[5] that are large in males and small in females, and whose size can be manipulated by manipulating the availability of testosterone (figure 2.34) (Nottebohm 1981, DeVoogd and Nottebohm 1981). In canaries only the male is a songster, and Nottebohm has shown that well-developed nuclei are essential in the canary's learning and producing his song. Castrated males have diminished song-control nuclei and cease to sing; females ovarectomized and given testosterone grow song-control nuclei and learn to sing, albeit not with the customary virtuosity of intact males. Similar connections have been found in zebra finches by Konishi and Gurney (1982), in the oyster toadfish by Fine et al. (1982), and in frogs by Kelley (1980).

And what of our brains—do they too show sexual differentiation? By now it is evident that it is not so much a question of *whether* there is

sexual dimorphism in the brains of humans but of how much, what kind, whether there are any differences in cognitive capacities, and in what dimensions of behavior it shows up. Evolution is not likely to have been able to disengage the deeply embedded binding specificity of gonadal hormones in the brain from the rest of the program for brain development and maturation of gonads. Sex is nothing if not basic, and although small-scale modification of surface features of the reproductive package is not improbable (for example, receptivity of the female outside the estrus period—humans, pygmy chimpanzees, rhesus monkeys, macaque monkeys), modification of deep principles that are fundamental to a wide range of structural elements is wholly improbable. Moreover, what we know from pathological studies in human endocrinology confirms rather than falsifies the hypothesis that humans share with other animals a sexual differentiation of the brain.

Already mentioned was the condition known as androgen insensitivity, where the organism cannot use the testosterone it generates. Though there are no discernible effects on genetic females, genetic males with this condition are both phenotypically female and female in sexual preference. On the other hand, human females subjected to androgen in utero as a result of a genetically determined defect in the functioning of the adrenal gland have genitalia masculinized in varying degrees, though their internal reproductive organs are female. These females show varying degrees of masculinized behavior, as measured in terms of playmates preferred, initiation of rough-and-tumble fighting, and intense energy expenditure. These tendencies persist despite surgical correction of genitalia, hormone replacement therapy, and being raised as females, although most are heterosexual (Ehrhardt and Baker 1974).

Pioneer studies in lateralization of function also point to some behavioral differences between male and female children in the degree of hemispheric specialization, which has led to the speculation that male brains are more thoroughly lateralized than female brains (Witelson 1976, Waber 1976). In a study on rhesus monkeys in which an area of the prefrontal cortex was lesioned, Goldman and her colleagues (1974) found sex-dependent effects on a variety of tests requiring spatial discrimination. Male monkeys, both adults and infants, were impaired on the tests, whereas only female *adults* were impaired. Young females were unaffected. The results were taken to imply a dimorphism in the development of prefrontal cortex subserving the cognitive processes involved. This performance difference was abolished in females prenatally exposed to androgen. An anatomical difference in the caudal (rear) portion of the corpus callosum

of humans has been found; in females it tends to be larger and more bulbous than in males (de Lacoste-Utamsing and Holloway 1982). What this implies for psychological functions is not known.

Probably human male brains are androgenized in varying degrees and female brains are feminized in varying degrees, but how this shows itself in cognitive capacities, emotional responses, social interaction, and so on, is very much an open and empirically approachable question. It would not be surprising if the differences were found to have only a rough and approximate fit to current North American attitudes concerning what is masculine in behavior and what is feminine. Certainly the sheer existence of differentiation in neural morphology should not encourage a rejuvenation of the superstitions revered in some one culture or other. Folk tales specifying manliness as typified by sporting competitiveness and saloon camaraderie, and femininity as typified by lace and lullabies in the nursery, should not be mistaken for empirically tried and true theory.

Ethological studies are of tremendous importance to the enterprise, and it should not be assumed that available data confirm the prevailing conceits of folk sociology. Even among primates there is stunning diversity in sexually dimorphic behavior and in social structure. In some species, for example the hamadryas baboon, care of the offspring is a female task (Kummer 1968); in others, such as the marmoset, tending the young is, apart from suckling, a shared affair (Jolly 1972); in still others (the Barbary macaque) all males of the troop casually share in helping tend the infants. Some primates are largely solitary (orangutans), some have monogamous pair-bonding (marmosets), some have harems (hamadryas baboons), some are promiscuous (Anubis baboons), and in some species the females make a regular circuit of the appropriate males (Barbary macaques).

Competitiveness seen in females may be a function of species, social structure, the sex of an intruder, the availability of food and suitable males, and so on, but entirely absent it demonstrably is not. Sexual dimorphism tends to be accentuated in polygynous species, but it is too early to tell what, if anything, this implies about humans (Hrdy 1981, Krebs and Davies 1978).

The difficult thing about studying sexual dimorphism in humans is objectivity, for there is a fatal tendency to search selectively for facts to confirm a coddled hypothesis. Coddled science is bad science, and so it will be here. The degree to which culture and education overlie such hard-wired dispositions as exist is also an empirical question, not to be settled by culturally selective anthropology or species-selective ethology. Assuming that not all social behavior is hard wired, then the educational and cultural overlay we choose is a func-

tion of what we value, and this, finally, is a moral matter. All things considered, I believe we should welcome research on sexual differentiation in neuronal morphology, though the swill that can be expected from the popular press will doubtless smother some enthusiasm. Still, it is better to know than not to know.

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Neurophilosophy.
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