NEUROPHYSIOLOGY, AN OVERVIEW

Neurophysiology is a study of **neurons**, **nerves**, and **nervous systems**, what they do and how they do it. A neuron is a cell that is specialized in two of the fundamental properties of living matter, namely **excitability** and **conductivity**. Excitability is the ability to respond to changes in the environment; conductivity is the ability to convey an impulse or action potential from one part of the cell to another. In most neurons the portion of the cell which carries action potentials away from the cell body is called the **axon** or **nerve fiber**. Some axons are very short, a few micrometers in length; some axons are long, in man up to six feet in length. A **nerve** is a bundle of these axons originating in various cells. Finally, a **nervous system** is the aggregate of all nerve cells within a single organism. It happened that, in the course of evolution, all but the simplest animals have resorted to the use of a nervous system of some sort to organize and carry out their behaviors. So it is that the study of the nervous system, in other words **neurophysiology**, is fundamental to the study of behavior.

In the discussion of any phenomenon as complex as the nervous system, it is nearly impossible to present every topic in appropriate sequence without mentioning some ideas, events, or structures out of order. A brief overview of the topics to be discussed may help the reader maintain a sense of order even when topics are mentioned before they are discussed in detail. The nervous system is composed of billions of individual nerve cells, each having its own membrane that separates electrical charges; in biological tissues those charges are in the form of ions. The result is that each cell has a resting membrane voltage, or potential, that acts as a source of potential energy for the workings of the cell. Membrane voltages of nerve cells can change with time, and these changes can be communicated as signals to other nerve cells or to effector organs such as glands and muscles. In fact, this is one of the major activities of the nervous system.

If the distances for communication are short, the local changes in voltage can be communicated directly; however, because the nerve membrane is a poor conductor of electricity, the local voltage signals would not span distances greater than a millimeter or two. Thus, a special communication device, the action potential, is used to communicate over great distances, in large animals over many meters. The action potential is well suited to this purpose because of its short duration (0.5 msec or so) and rapid conduction (at 1-120 m/sec) without decrement. The short duration of the action potential allows it to be generated at high frequencies, 500/sec or more.

Cells communicate with each other by way of special junctions, called **synapses**. Synapses are of two types: chemical and electrical. At **chemical synapses**, the voltage signal in one cell triggers the release of a chemical transmitter substance onto another cell. This transmitter substance can either increase the activity of the receiving cell, i.e., increase the likelihood that it will discharge action potentials, or decrease the activity of the receiving cell, i.e., decrease the likelihood that it will discharge action potentials. We refer to the former effect as **excitation**, the latter effect as **inhibition**. In addition to these obvious and direct effects, transmitter substances also can affect neurons indirectly, affecting neurons at some distance from the point of release of the substance or changing the effectiveness of other transmitter substances.

Electrical synapses do not use transmitter substances, but communicate changes in membrane voltage directly, and they usually only involve excitation. In mammals, chemical synapses seem to form the majority of synaptic junctions, but this may simply be because they have received more study.

The receiving cell is usually influenced synaptically not by one cell but by many. It integrates the excitatory and inhibitory influences from a number of other cells and, based on this integration, generates its own signals that, in turn, influence other cells. Understanding this integrative property of nerve cells is extremely important to understanding how the nervous system behaves normally and how it malfunctions. Some cells require a lot of synaptic influences to generate an output; others do not. Most nerve cells require a lot of synaptic input to generate an output; muscle cells do not. A single action potential arriving at the synaptic junction of an axon on a muscle, the neuromuscular junction, always causes the healthy muscle to generate a single action potential of its own and to contract.

Some nervous structures, the **receptors**, are specialized to receive signals from the external environment or from the internal environment, i.e., signals about the condition of the body itself. Receptors use the potential energy of their membrane voltages to respond to these environmental signals and to generate coded signals of their own that tell the rest of the nervous system what has been sensed in the environment. The signals are normally trains of action potentials that vary in pattern or frequency depending upon the qualities of the environmental signals. These action potential signals are sent over axons into the central nervous system (CNS). Part of the code of the signal is determined by which particular axon or which particular pathway in the central nervous system it traverses. Signals in particular pathways are often associated with particular kinds of sensory events. Much of the study of neurophysiology is a consideration of how sensory systems code sensory information.

The sensitivity of receptors is variable. It is variable between individuals and between genders. It is variable with the time of day or the time of the month. It depends upon the conscious state of the individual and what he is doing. What we sense is, therefore, not a constant, but we, nevertheless, perceive that we and our world are relatively constant. The visual world is made by several million tiny point-receivers of light (the rods and cones), but we perceive the visual world as if it were continuous. The brain is responsible for this transformation.

Movements are generated within the central nervous system, both as direct, automatic responses to sensory signals (the reflexes) and as responses to the environment, more independent of particular sensory signals. The spinal cord plays a big role in both kinds of movement, both because it supplies the only effective connection between the nervous system and skeletal muscles and because it contains the neural machinery that generates most of the reflex activity and other more complicated activity, such as walking.

However, the spinal cord does not normally work independently of the rest of the nervous system. Important deficits in movement and behavior occur with disruption of activity at a great many places in the nervous system. These deficits can range anywhere from small changes in fine tuning of movements, as occur following some damage to the pyramidal tract, to lack of coordination and synergy of muscle contraction, as occur with lesions of the cerebellum, to complete absence of any normal activity, as occur with small vascular lesions of the brain stem.

The "higher functions"–learning, emotion, speaking, thinking–presumably are produced using the same cellular processes that are involved in simple reflex behavior, but involving these processes in many different structures.

In dealing with the nervous system, it is natural to ask why animals, including man, have resorted to the use of nerves instead of some other mechanism for directing their activities. It is not difficult to conjure up a variety of alternate schemes, some of which are, in fact, found in nature, but it soon becomes clear that for large organisms, the only practical way, other than a nervous system, to communicate with or activate a distant part of the body is through the use of chemical substances, called hormones, that are carried in the blood.

Let's briefly compare both nervous and hormonal systems with respect to some of the essential features of the nervous system. A primary function of both the nervous system and the hormonal system is to communicate information from one part of the body to another. Nerve cells are capable of carrying a signal from the toe of a six foot man to his cerebral cortex in about 25 msec, that is, in about 25/1000 of a second. If a hormone were secreted into the blood at the toes, it would not be able to reach the cerebral cortex in less than 17 seconds. <u>Speed</u> is at a premium in the behavior of most animals, and clearly the speed advantage lies with the nervous system. Can you imagine what would happen to a cat whose righting reflex was mediated by hormones? A hormone secreted by the vestibular apparatus, which senses orientation, would reach the muscles of the neck, where righting begins, in let's say about two seconds. In earth's gravity, an object falls 64 feet in two seconds. This means that a cat would not be able to correctly right itself if dropped from less than 64 feet above the ground. Clearly, the performance of normal cats exceeds this level. Of course, where speed is not essential, such as in the regulation of growth, the hormonal system works perfectly well and, indeed, is used for that purpose.

The same functions served by hormonal systems in a slow organism, or one that does not need rapid responses, may be served by a neural system in an organism that does need to respond rapidly. For example, the sensitivity of the eye is variable in most organisms in such a way that, in bright light, it is less sensitive and, in dim light, it is more sensitive. In relatively slow-moving crustacea that do not respond rapidly to changes in light intensity, this sensitivity is under hormonal control, whereas in man and relatively fast-moving insects that do need to respond rapidly to changes in light intensity, the same mechanism is controlled by the nervous system.

Another major function of the nervous system is to <u>coordinate</u> precisely the contraction of the various muscles in the body. The hormonal systems also play a role in coordination, but only for activities that do not require very close timing or abrupt onset and offset. The nervous system uses very brief action potentials to send signals. Because these signals last only a fraction of a second and travel at high speeds: movements can be started and stopped in a fraction of a second. In contrast, hormones have half-lives of seconds or minutes and travel about a thousand times more slowly, because they must be conveyed to the tissues through the vascular system. Therefore, they cannot start actions quickly or end them quickly. On the other hand, where speed of response is not essential, hormones can adequately coordinate activity in many tissues in different places, as they do, for example, in the case of the events surrounding ovulation. Where prolonged activity is required, hormones again have the advantage. They can act for a long time, because hormones have long half-lives compared to action potentials. To do the same job, prolonged nervous activity would be required, which means continuous generation of action potentials at perhaps higher metabolic costs.

Another difference between nervous control and hormonal control lies in number of target organs activated at one time. If a given behavior requires the action of several organs to provide a generalized response, a hormonal system may be well suited, but if only one or a few organs are required to respond in a specific manner, then nervous control may be better suited. Were it necessary to control every movement of a normal human with hormones, a hormone or combination of hormones would be required for every movement, and receptor sites would be required for several hormones on the same effector organ. Otherwise, an organ would not know what kind of response to give–small or large, fast or slow. Clearly, the number hormones would be immense and the system impractical. On the other hand. if it were necessary to regulate growth with the nervous system, it would require a neural connection to each cell of the body, also an impractical condition. The nervous system does participate in some generalized responses, but, in general, the nervous system provides highly specific control of only one or a few organs.

Another essential function of the nervous system is to collect and <u>integrate</u> sensory information, that is, to combine, analyze, and process information about the environment both inside and outside the body in order to execute an appropriate response. Because the common denominator of activity in all sensory systems is changes in electrical potential, it is no problem to add them together. It is easy to sum electrical potentials. If integration were to be accomplished by a chemical system, the matter would be much more complicated. One would, for example, want to distinguish visual events from auditory events, so each sense must use a separate hormone. Then there is the problem of how to add them together, something like adding apples and oranges; molecules would have to combine chemically, and then different cells would be required to respond to all possible ways of combining the hormones. This kind of chemical integration does occur in hormonal systems, for example, in the control of fat cell activity, but the number of hormones involved and the total repertoire of responses of the organ is limited compared to the number of different ways a neuron can respond and the total behavior of an organism. On the level of a whole organism, the thorny problem for chemical integration is how to handle something like mathematical computations. It is no doubt obvious by now that nervous control of behavior does provide certain advantages over all the alternatives. These are:

(1) increased speed of performance,

(2) increased precision of performance related not only to speed and control of onset and offset, but also to the way neurons are connected to the organs,
(3) economy of chemistry with no need to synthesize large numbers of hormones.

Nervous control of behavior is least efficient in the initiation and organization of generalized or prolonged responses.

Up to this point in our discussion, we have dealt with the nervous system and neurons as if their only function was to produce action potentials. Many textbooks, in fact many neurophysiologists, deal with the nervous system as if this were true. There is now a lot of evidence of other functions. For example, removing the innervation of a striated muscle results ultimately in wasting or atrophy of the muscle. This implies that the contact of the nerve is required for the muscle to maintain its integrity. Not only that, but the nerve determines, at least to some extent, the contractile properties of the muscle. The characteristic rate of contraction of a muscle can be altered in a systematic way by denervating it and reinnervating it with the nerve from a different muscle. It also appears that it is the neuron that induces the formation of myelin around the axon by the Schwann cells. In addition, the axons probably supply nutrients or some other factors vital to the maintenance of myelin. The nervous system also interacts intimately with the immune system.

Another function of neurons is secretion. We will learn that most neurons communicate with each other by way of chemical transmitter substances. These substances are synthesized in the cell body of the neuron, probably stored in the Golgi apparatus, and then transported down the axon. There are two rates of transport in this orthograde direction; one is very rapid, of the order of 410 mm/day (this is amongst the fastest rates of cellular transport for all cells in the body), and the other is relatively slow, of the order of 1-12 mm/day. In the terminal portion of the axon, the transmitter substance is stored for later release by action potentials onto nearby neurons, whose activity it influences in characteristic ways. In addition, it is now known that axons transport substances in the retrograde direction, i.e., from the terminals back to the soma, at a rate of 40-100 mm/day. The terminal portions of the axon pick up substances from their environment; proteins are taken up by nerve terminals and transported back to the soma where they may be used in making other compounds or broken down and used in further synthesis or eliminated as waste products. It is fascinating that an axon can transport two different substances in opposite directions along its axon at the same time.

There is also the possibility that neurons may play a role in disease control processes. For example, sectioning the trigeminal nerve or a part of it for the treatment of chronic pain or for any other reason is often followed by an outbreak of Herpes zoster virus infection in the area of the face served by that nerve. Some investigators believe that the virus may be controlled by uptake into the neurons, and when the neurons are damaged they release their captive viruses into their terminals in the skin. (My friend, Dr. Robert Grimm, calls this the garbage dump theory.) This notion receives some support from the recurrence of cold sores (Herpes viral infections) at the same site or at nearby sites over a period of many years. There, of course, may be other explanations, but the possibility exists that the nerves play some role in disease control.

How important these nonspike activities of the neurons are to the functioning of the nervous system is not known. It is possible that they are a major route for interneuronal communication. It is also possible that they are only manifestations of basic cellular metabolic processes. The near future may hold the answer.

How did the nervous system of the human come about? The nervous system is subject to evolutionary pressures in the same way as any other part of an organism. Its structure may be altered or added to in order to allow the species to survive in a changed or new environment that requires a new life style. Thus, we might expect to be able to trace the evolution of nervous systems in fossil records. This has proven difficult to do because nervous tissue is soft, and it is not preserved the way bones are. However, we do have some idea of the development of nervous systems. The first organisms were very likely single cells like the amoeba. Because single-celled animals have all of the characteristics of matter, they must have conductivity and excitability. In this way, these first single-celled organisms were also the first nervous systems, doing many of the things more complex systems do. As animals became more complex, it became more efficient to differentiate cells into functional types. Different tissues appeared and, with them, nerve cells. At first, nerve cells may have been poorly organized, perhaps in loose bundles with no obvious order; later, they associated more closely in organized groups called ganglia. Still later the ganglia became interconnected and coalesced to form what we know as the spinal cord and brain stem. In the course of phylogeny, some new groups of cells or nuclei were added; later, in different animals, these nuclei increased in size and complexity, while others decreased or stayed the same. The cerebral cortex made its first appearance in evolution among the reptiles and then gradually changed in size and complexity to reach its current configuration in the human brain.

The phylogenetic development of the nervous system may be characterized by analogy to the wooden blocks you played with as a child. At first, there were just a few blocks strewn on the floor, but you quickly put them in order to form a framework. Then you reached into the box and picked out a few more blocks and added them to your construction as they were needed. The basic foundation remained, you just added more blocks on top. In the same way, the framework of the spinal cord evolved with its basic neural connections that provide the **reflexes**. As environments changed, for example from wet to dry as previously aquatic species emerged onto the land, pressures were applied to the species, forcing them to change their behavior or die out. In many successful species, this meant modification of the basic framework in the spinal cord and brain stem and, in some cases, the addition of new structures. Each new structure was capable of modifying the activity of the basic framework. Even in the human brain, so-called higher centers, such as the cerebral cortex, work by modifying the activity of lower centers, but these higher centers are not capable of controlling behavior by themselves. It is this modification of the basic reflex activity and not direct control of muscle contraction, that leads to the fluid, continuous activity characteristic of the higher mammals, including man.

To summarize, the functions of the nervous system are as follows:

1. Communication
2. Sensation

3. Integration
4. Coordination
5. Movement or secretion
6. Behavior

In our study of the nervous system, we consider these functions more or less in this order. By the term communication, we mean simply getting information from one place in the body to another, usually by transmission of nerve impulses. In order to understand this process, we must know how impulses are generated and propagated, i.e., how nerve cells carry signals and transmit information to other nerve cells, muscles and glands. The study of sensation involves consideration of what features in our environment can be sensed, of the different organs used to sense; of the process of transduction, i.e., converting energy (be it mechanical, thermal or light) into a form that can be used by the nervous system, namely the action potential; and of how these processes finally lead to a "sensation." This last topic includes some consideration of how the activity of the nervous system relates to what we sense. Integration is the combination and comparison of information from various sensory organs and from memory to be used in making decisions about behavior. Movement and secretion are, of course, the end products of all the machinations of the nervous system, and when numerous movements or secretions are assembled together into complex patterns that are modifiable by experience over time, the result is termed **behavior**. It is the understanding of behavior that is the final goal of neurophysiology and, as such, it is the topic about which the least can be said, in the inclusive sense. We will discuss stereotyped behaviors like the reflexes and a few more complex behaviors like sleeping, speaking, and learning, but what we can say about them will be superficial compared to the complexity of behaviors themselves. We know relatively little about the learning process or the coordination that allows a swift to fly at 140 miles per hour through a slit in a wall only slightly larger than its body. Neither can we say much about the mechanisms of personality or of consciousness. Though our understanding of these phenomena is in its infancy, new "facts" are being turned up all the time; and existing knowledge is, at the same time, perplexing and fascinating.