A TEXTBOOK OF
General Physiology

PHILIP H. MITCHELL

Late Professor of Biology
Brown University

A TEXTBOOK OF GENERAL PHYSIOLOGY

McGraw-Hill Publications in the Zoological Sciences

E. J. Boell, Consulting Editor

There are also the related series of McGraw-Hill Publications in the Botanical Sciences, of which Edmund W. Sinnott is Consulting Editor, and in the Agricultural Sciences, of which R. A. Brink is Consulting Editor.

EDITOR'S PREFACE

The untimely death of Prof. Philip H. Mitchell occurred shortly after the manuscript for this edition had been submitted to the publishers. However, in correspondence with them and in discussions with some of his colleagues at Brown University the author had indicated the chief areas in which the text had been revised.

In the present volume, the general organization and chapter arrangement remain the same as in previous editions. However, every section of the book has been carefully worked over and modified, where necessary, in the light of new developments. Major changes or additions are found in the discussions of the relationship between resting and action potentials, the process of photosynthesis, the vitamins—particularly pantothenic acid and cyanocobalamine—the relationship between adrenaline and noradrenaline, and the action of cortisone. A completely new discussion of active transport across the plasma membrane has been added, and reference to this important process has been made where appropriate throughout the book.

Most of the illustrations have been redrawn, with a view to increasing their clarity and utility, and a number of new figures have been introduced. In addition, the type has been completely reset, which makes it possible to present the book in a more modern format.

The first edition of Mitchell's "General Physiology" appeared in 1923. For more than three decades, therefore, this book has been used by undergraduate and graduate students in physiology courses in this country. That it has exerted a genuine influence on the training of a large number of biologists goes without saying.

At the time when it first appeared, this book was unique in at least two respects:

In the first place, it reflected the author's conviction that a college course in physiology should represent something more than a watered-down version of the mammalian physiology taught in medical schools. Accordingly, Professor Mitchell stressed, as had Claude Bernard and Sir William Bayliss before him, those general principles that apply to functional activities of cells and tissues in a wide variety of organisms—invertebrate as well as vertebrate and plant as well as animal.

A second feature of the first edition of this book, and one that has

become increasingly apparent in later revisions, was the attempt to explain physiological events in terms of the physical and chemical processes that underlie them. Thus Mitchell endeavored "to describe physiological phenomena as energy transformations and to write, whenever possible, from the point of view of the law of mass action as it applies to dynamic equilibria." He recognized that this approach might conceivably be somewhat more difficult than a simple descriptive account, but he felt, as do now most teachers of physiology, that it represented the only means by which the student could obtain *fundamental* knowledge of the functional activities of organisms.

In comparing the textbooks available in a given field, one is often impressed by the fact that several books cover largely the same material. Yet only some of these are successful and pass through a number of revisions; others do not go beyond a first printing. Often the essential difference between books is not so much what subject matter is included but how the subject matter is presented. The many thousands of copies of Mitchell's "General Physiology" that have been used throughout the years in college courses testify eloquently that the facts and generalizations of physiology are effectively communicated to the student. It may be hoped that the present revised edition will continue to serve teachers and students of physiology in the way Professor Mitchell had planned.

E. J. BOELL

CONTENTS

EXCITATION AND INHIBITION

In attempting to decide what constitutes the difference between living matter and dead matter, one cannot avoid the observation that a special characteristic of living matter is its power to react to changes in its environment. Every living thing responds by some reaction to various physical or chemical changes in its environment. If an animal is alive, it responds to certain changes in pressure, heat, light, etc., by movements; if a seed is alive, it responds to increase in moisture and temperature by germination; if anything is alive, it will show some kind of physiological activity in response to some appropriate environmental change. This responsiveness is sometimes called the irritability of living matter, though the term excitability is preferable.

Dual Control. The response may take the form of an increase of some kind of activity, such as motion, growth, or secretion, or it may take the form of a decrease of these activities. If the response is an increased activity, the protoplasm is said to be excited; if the response is a decreased activity, the protoplasm is said to be inhibited. This dual responsiveness, which is found in numerous types of cells, would seem, at first thought, to be unnecessary, because decrease of activity would naturally follow any decrease of excitation. But just as the brakes of an automobile greatly increase its controllability, so inhibitions of living mechanisms make them respond sensitively to environmental changes. An environmental change causing excitation or inhibition is called a stimulus.

Response. The nature of the response is not always the same, even though the stimulus is identical, for the response depends upon the structure of the stimulated cells. Muscle cells respond by contraction; gland cells by secretion; nerve cells and their branches, nerve fibers, by conduction of nerve impulses; certain cells of the sensitive plant by changes in shape so as to cause drooping of the leaves; cells of all plants respond by changes in growth or other metabolic changes and by changes in the movements of their protoplasm. The responses to stimuli are often very complex in the higher animals, especially human beings, because even a localized stimulus can cause different kinds of cells to be excited or inhibited by means of the correlating action of the nervous system. But in any case the nature of the response to stimuli is of the same general charac-

ter in any given kind of cell, no matter what the nature of the stimulus may be, provided it acts in a normal, or physiological, manner and is applied to the same part of the cell.

Independent Excitability of Muscle. The universal excitability of living matter is not always apparent. For example, skeletal muscle might be regarded as responding only through the mediation of the nervous system since a muscle appears to be completely paralyzed when its functional connection with the nervous system is severed by nerve section or degeneration. A skeletal muscle, thus isolated, does indeed become useless and even degenerated from disuse. But this result is due to the fact that stimuli can no longer reach it effectively and not to a loss of excitability in the muscle cell, for if an electrical stimulus is applied to such muscle directly, or to the skin in such a way that the current passes through the muscle, a normal contractile response is obtained.

A classic experiment reported by Claude Bernard (1813–1878) may also be used to demonstrate the independent excitability of muscle. In this experiment, usually performed on a frog, the animal is injected with a small amount of the arrow poison concocted from plant juices by Indians of South America and called curare. The purified active principle, an alkaloid called curarine, is now available. Injected, curare seems to cause complete paralysis of skeletal muscles. But if the muscle is directly excited, it still responds, showing that the muscle itself is not poisoned. As one can also show that all nerves are still excitable, the paralysis must be due to an effect upon the structures (motor end plates) located between the nerve endings and the muscle fibers. The nature of this effect will be explained later (p. 13).

Excitability of All Living Matter. Because of the foregoing and many other similar observations, excitability has come to be regarded as an unfailing attribute of all living matter. The term excitability, or irritability, is sometimes used in a restricted sense to refer to the property of muscles, nerves, and a few other structures that respond to weak and diverse kinds of stimuli by showing especially rapid effects. Such structures are sometimes called the excitable (irritable) tissues. But modern opinion regards this distinction as only a matter of degree of excitability and as probably due to the manner in which the especially excitable portion of the protoplasm is placed in the cells. Every living cell is doubtless capable of responding to the right kind of stimuli properly applied. Even the seemingly inert cells of plants respond to slight and diverse kinds of stimuli by showing an electrical disturbance, the action current, to be described later. In some cases, e.g., leaf cells of the aquatic plant *Elodea*, excitation causes liberation of free calcium ions which react with oxalates of the cell to form microscopically visible crystals of calcium oxalate. Other similar plant responses could be cited.

Nonliving structures are also responsive to environmental changes,

mechanical, chemical, and physicochemical. Some man-made machines can even be set going by exceedingly minute disturbances once thought of as effective only upon sensitive living things. Thus a minute amount of light energy can activate a photoelectric cell, and the resulting current, duly amplified and acting through suitable relay switches, can start electric motors. It is still true, however, that the sensitivity of living things cannot always be imitated by artificial devices. No chemical detector equals the bloodhound's sense of smell when it trails a given individual by the scent of footprints.

Frog Muscle-Nerve Preparation. To a large extent, the facts of excitation have been established by experiments on the frog muscle-nerve preparation. As its behavior aptly illustrates many of the phenomena about to be discussed, a description of this preparation is necessary at this point. The gastrocnemius muscle and sciatic nerve constitute the preparation and have been widely used because this muscle is easily removed intact with the Achilles tendon attached to its lower end and a portion of the femur attached to its upper end, while the nerve can also be dissected out so as to yield a conveniently long stretch, extending from the pelvic plexus to the point where the nerve enters the gastrocnemius muscle. The completely excised muscle may be suspended without injury by a clamp attached to the fragment of femur, and the tendon may then be attached to a suitably weighted lever without any injury to the true muscle substance. As the movements of the lever magnify any contraction of the muscle, all responses to stimuli, applied to either nerve or muscle, are easily observed.

Several advantages in the use of frog muscles have made this preparation especially useful. Frogs are commonly available and can be kept in the laboratory for months without feeding. The dissections required for excising the preparation can be conveniently made on the living animal without the necessity of anesthesia because all sensibility is easily destroyed by the procedure known as *pithing*. This consists in destruction of the brain and spinal cord by thrusting a blunt needle into the cranium and into the spinal canal. For each of these brief operations, the needle is inserted through the same opening, a small cut made through the skin and other tissues that lie dorsally over the opening, between the cranium and spinal column, at the base of the skull. The accumulated store of nutrients in frog muscle permits use of the isolated preparation without the necessity of providing it with a nutrient solution. As the frog is poikilothermic (cold-blooded), its muscle is adapted to show irritability over a comparatively long range of temperature, so that a thermostat for maintenance of constant temperature is not required in experiments on frog muscle. Other excised muscles of the frog, especially the sartorius, also muscles of other cold-blooded animals, for example, the foot muscle of the slug, and even excised muscles of warm-blooded animals have been employed in physiological experimentation, but the frog gastrocnemius-sciatic preparation is especially convenient.

Certain precautions are required for satisfactory use of the muscle-nerve preparation. Drying of the tissues must be prevented. This is ensured by keeping the preparation moistened with isotonic salt solution. Water would, of course, cause disastrous changes in osmotic pressure. Ringer's solution has obvious advantages for the purpose,

because it preserves the balance of the concentration of physiologically important inorganic ions (Chap. 8). If, immediately after the preparation is dissected out, it is thoroughly moistened with Ringer's solution, it may be conveniently kept in an excitable condition during a prolonged experiment by enclosure in a moist chamber which prevents evaporation. Another necessary precaution is to use only those exciting stimuli which do not have destructive effects upon the tissues. This requirement is met by the use of electrical stimuli, applied to the tissues through nonpolarizable electrodes, described below.

Graphic Method. Physiological observations have depended largely upon the use of graphic recording. In one type of method, movements of levers, whether attached to muscles or to other moving mechanisms, are recorded. The point of the lever is made to bear with the least possible friction upon a recording surface. As the lever moves up or down, its point traces a curve upon the simultaneously moving surface. For this reason the recording apparatus is called a kymograph (curve writer). Its recording surface is covered before use with paper. Glazed paper, coated with a thin layer of soot from a smoky flame, is used to take the record of a swiftly moving lever in order to reduce friction. In some cases, levers that have pencil or pen points can make satisfactory records on unglazed paper. Abscissas of the kymograph curve are time intervals, and it is usually necessary to make a simultaneous time record during the tracing of the curve. For this purpose a writing point bears upon the recording surface directly below the point of the muscle lever and is given suitable vertical motion at definite time intervals by clockwork or by an electromagnet in circuit with a vibrating tuning fork or pendulum. The smoked kymograph record is made permanent by passing the paper bearing the completed curve through a bath of white shellac.

Recording levers have now been largely replaced by electronic apparatus. This has been possible because excitation, as now understood, seems always to be accompanied by an electrical disturbance. All living matter is so constituted as to produce measurable electrical potentials that change during excitation. Of course, the potentials and their changes are small, not measured in volts but in millivolts or fractions of millivolts. But the development of the oscilloscope (p. 23), first used for nerve-potential measurements by Erlanger and Gasser (1922), has made observation and recording of excitation by means of the accompanying electrical disturbances a process of great precision, because even when extremely small they can be amplified to the required extent and can be recorded not only to the thousandth part of a second (a millisecond, abbreviated msec) but even to the millionth of a second (a microsecond, abbreviated μsec).

Other modern advances include recording by the photographic method. Levers or other moving parts of apparatus may be placed in the path of a bright light in such manner that their shadows are focused by lenses upon the sensitized surface of a moving photographic plate or camera film that

is made to move past the camera slit at a uniform rate by means of a suitable motor. A modification of this method employs a small mirror attached to the moving part and reflecting a beam of light upon a moving photographic film. Friction and inertia of levers are thus eliminated. Certain types of physiological investigation, for example, those depending upon records of the movements of a sensitive galvanometer, the electron stream of an oscilloscope, or other electrical indicators, were made possible by developments of the photographic method of recording.

Nature of Stimuli. Inasmuch as living matter is very responsive in its phenomena of excitability, almost any environmental change may constitute a stimulus under some circumstances, at least for certain organisms. Examples of stimuli are (1) electrical changes, i.e., any change in the state of rest or motion of electrons, (2) pressure changes, i.e., mechanical stimuli, (3) electromagnetic changes as seen in the action of light, of ultraviolet rays, of X rays, of radio activity, etc., (4) chemical changes, such as changes in the abundance of food or water or substances of a foreign character, (5) changes in osmotic pressure, though these may be regarded as special cases of chemical changes, i.e., changes in concentration, (6) temperature changes.

In complex organisms, excitability does not always appear to be a response to an environmental change. The stimulus seems to arise from within. Hunger, thirst, emotions, and especially the dictates of the will, all seem to be inner stimuli, and, in one sense, they are; yet, in the last analysis, they may all be referred to environmental stimuli, even though the responses are delayed and are complex in character.

A given type of environmental change does not always act as a stimulus. This is due to the fact that the rate at which the change occurs is a large factor in determining its effectiveness as a stimulus. This has been proved for the action of various kinds of stimuli. The action of pressure, for example, upon the frog sciatic nerve constitutes a stimulus when pressure is suddenly applied as by striking or pinching. The resulting nerve impulse causes muscular contraction. But when pressure is gradually applied to the nerve while it is held between two glass plates, no response will be obtained even though pressure sufficient to injure the nerve permanently may be finally attained. Curiously enough, however, release of a pressure insufficient to injure the tissue and so gradually attained that it does not excite will cause a contractile response in the muscle when the pressure upon the nerve is released with sufficient suddenness. Change of pressure is thus seen to be a stimulus only when it is a sufficiently rapid change.

The best demonstration of this general principle is given in experiments that employ electrical stimuli. Such stimuli show that if the change in voltage or amperage of current passing through a nerve occurs at a sufficiently rapid rate, excitation results. But if the change of the current is at

a slower rate, it does not constitute a stimulus. One finds that a nerve applied to electrodes which are in circuit with a battery and a sufficiently high resistance will not be excited by the small current that the resistance permits to pass through it. Moreover, gradual increase of the current, obtained by slowly decreasing the resistance, does not stimulate. This is true even though the current finally attained is of such magnitude that, when it is suddenly broken by interrupting the battery circuit, excitation occurs. Any constant electrical current, passing steadily through a tissue, does not appear to excite it except at the time the current is made or broken. A change called electrotonus (p. 19) is produced in the tissue, and this may result in excitation of nervous structures in some cases; but under most circumstances, the constant current does not cause any visible excitation.

Electrical Stimuli. The use of electrical stimuli in physiological experiments has certain distinct advantages. Such stimuli can be accurately graduated in intensity and perfectly timed as to the moment of their application and their duration. An added advantage is the quick and complete recovery of the tissue from the effects of electrical stimuli. Since every response involves localized electrical changes, their external applications give a relatively good imitation of natural stimuli. Induction currents are especially convenient. Their intensity and timing are controllable. They may be repeated frequently without injury to protoplasm. The time during which rapidly repeated induction shocks are applied is satisfactorily controlled by a suitable key in the battery (primary) circuit of the induction machine. Many other types of electrical stimuli, such as the make and break of a steady current from a battery, condenser discharges, undulating currents, alternating currents, and some others, are used for special experimental studies. Works on physics must be consulted for a detailed account of the theory, construction, and use of electrical apparatus.

Accommodation in Relation to Stimuli. The fact that the tissue may not respond to a gradually increased disturbance, even though it may attain an energy level in excess of that required to excite at a more rapid rate of application of force, is described by saying that the tissue shows accommodation. It is as though the local excitatory disturbance, which the stimulus is causing in the tissue, is counteracted by an opposing change by which the apparent excitability of the tissue is decreased for the moment. For any type of stimulus, mechanical, electrical, etc., the minimum force required to excite at a given rate of increase can be determined. This is called the *threshold* of the tissue for that particular stimulus. One may say that accommodation is a rise of the threshold. Obviously, the threshold will be so variable with variation in the rate of application of the stimulating agent that it is not a satisfactory measure of the comparative excitability of the tissue.

The quantitative relations between the stimulus, the excitability of the tissue, and its accommodation have long been under investigation. What seems to be the most nearly complete formulation of these relations has been presented by A. V. Hill. He represents the variable threshold at any

given moment during the action of a stimulating agent by U and the threshold in the resting tissue by U_0. Then $U - U_0$ represents the extent of accommodation (rise of threshold) at any given moment. Correspondingly, the variable condition that causes excitation is represented by V. Hill calls this the "local potential" and points out that the nature of this potential, whether electrical, chemical, or of some other character, need not be stipulated in order to study the relation between stimulus and excitation. The "local potential" in the resting tissue would be V_0. Then $U_0 - V_0$ represents the minimum disturbance that would excite (true threshold), provided no accommodation occurred. This result can be very
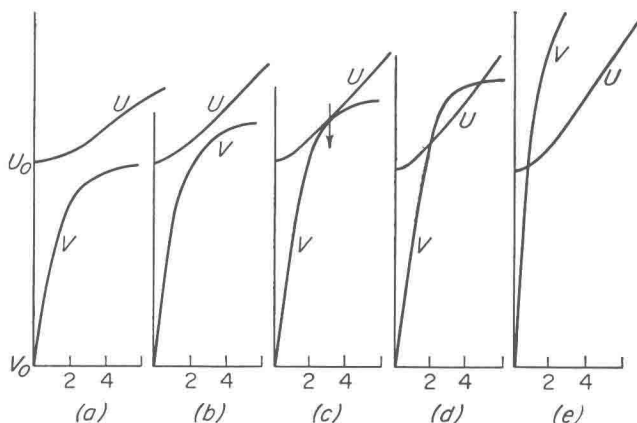

Fig. 1. Rise of "local potential" V and of "threshold" U at the cathode for constant current suddenly applied. Calculated from experiments on frog nerve at 40°C, very rapid "accommodation." Current 1, as used in (a), would be "rheobase" aside from accommodation. The actual rheobase is 1.29, and its utilization time is shown by an arrow in (c). Rapidly rising currents (d) and (e) excite in shorter times. (After Hill.)

nearly realized by stimulating with a very rapid discharge of an electrical condenser. $U - V$ represents the disturbance required for excitation at any moment during the application of the stimulus and is thus the reciprocal of the momentary excitability of the tissue. Hill postulates that when $V = U$, excitation occurs. The question of whether or not a given stimulating agent will actually excite thus becomes: Will V overtake U? If V barely reaches U without exceeding it, the current intensity employed, in the case of electrical excitation, is a rough index of the comparative excitability of the tissue. It is actually a measure of the *apparent* threshold under the specific conditions prevailing. It is commonly called the *rheobase* and may be defined as the current which, no matter how long it flows, is just barely sufficient to excite. The time during which it must flow until the tissue is excited is called the *utilization time*. If V increases more rapidly than U, excitation is bound to occur at or before the end of the utilization time, unless V reaches its maximum at a value less than U. These ideas are illustrated graphically in Fig. 1.

Stimuli Defined. Reversible excitation has been observed, experimentally, as the result of the use of all the kinds of forces mentioned above. Such experimental results, together with observations of the natural behavior of living things, make impossible any hard and fast limitation of the forces that are physiological stimuli.

At the outset of physiological studies it is well to become aware of the tendency of living matter to exist in what is called a "steady state." This means that any cell is apt to react to anything that would change a physical condition or a chemical equilibrium. Thus in mammals any tendency to lower or raise temperature may cause the body to react so as to return toward the constant body temperature. Similarly, any increase or decrease in blood sugar produces such reactions as tend to restore it to its normal level. Very many other tendencies to reach equilibrium, i.e., to attain a steady state, could be cited. They will be described in later chapters. In the particular case of excitation the steady state most frequently involved is probably (p. 36) the concentration and distribution of certain ions in and around the concentration cell.

This leads us to a flexible definition of a stimulus as an environmental or internal change occurring at such a rate as to disturb the steady state of living matter and thus excite it. The same changes occurring at a slower rate might fail to excite because of accommodation.

Even this flexible definition is not entirely satisfactory. As Loeb and others have pointed out, an environmental force as constant as that of gravity may constitute a stimulus in some cases. Plants respond to gravity so that their roots grow downward and their stems upward. This appears to be due to the influence of gravity in determining the relative concentrations of certain nutrients in specific parts of the plant. Any change in the mass (concentration) of any molecules or ions that take part in a physiological reaction may disturb an equilibrium and thereby become a stimulus. Constant forces, such as gravity and the constant electrical current, commonly appear to cause no excitation because, under their influence, the tendency of protoplasmic reactions to attain, in spite of a disturbance, an equilibrium (the tendency to maintain a steady state) is not overcome.

Chronaxie. The time during which a stimulus acts is significant, as well as the intensity and the character of the stimulus. This statement follows from the above discussion of accommodation. The time (duration) is most easily measured in the case of electrical stimuli. By varying the intensity of the current used to excite a tissue (nerve or muscle is most frequently used) and by measuring the time during which the current must flow in order to cause a response, one may obtain results from which a *strength-duration curve* may be constructed. The strengths of the current are plotted as ordinates against the measured time intervals as abscissas (Fig. 2). Among the numerous investigators of the relation of time to the

production of excitation Lapicque has been prominent. He recognized, as did earlier workers, especially Nernst, that the rheobase, which was called the threshold by earlier physiologists, is not always an accurate measure of the relative excitability of a tissue. This is due in part to accommodation in that its effects would vary with the rate of current rise as well as with the strength of the current. In an attempt to find a more accurate way to express quantitatively the relative excitability of any tissue, Lapicque proposed the measurement of what he calls chronaxie. This is defined *as the time that a current twice the strength of the rheobase requires to excite.* Chronaxie has the same meaning as "excitation time," a term proposed earlier by Lucas. In practice, currents of constant voltage and
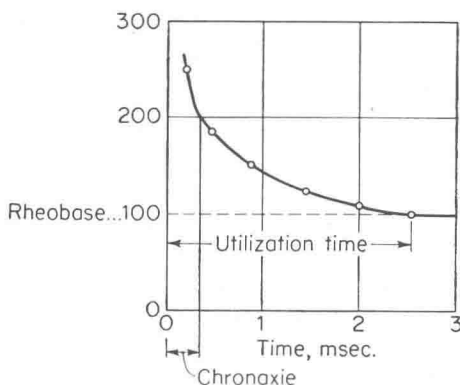

FIG. 2. Strength-duration curve for the frog gastrocnemius. Ordinates are comparative strengths of the current required to excite when flowing during the time intervals shown as abscissas (msec) the rheobasic current being regarded as 100. Utilization time is indicated for the rheobasic stimulus. The chronaxie is the time required for a current twice the strength of the rheobase to excite. (*After Lapicque.*)

amperage are usually varied by the resistance in the circuit, so that the chronaxie-measuring current has half the resistance of the rheobasic current. Chronaxie, then, is that abscissa of the strength-duration curve for which the ordinate is twice that of the rheobase and is assumed to vary inversely with the excitability.

Chronaxie measurements vary with the time characteristics of the stimulating current just as does the rheobase, but, of course, to a lesser degree since there is less time for accommodation to occur. Currents of rapid and constant rate of rise or condenser discharges are required for satisfactory measurement. Chronaxie is also a nonreproducible measurement unless the shape, size, and manner of application of the stimulating electrodes are standardized, probably because the current can vary in the extent to which it flows around the point on the tissue about to be excited rather than directly through it. Temperature has a marked effect upon chronaxie, as would be expected both on theoretical grounds and from the obvious effect of lowered temperatures in causing sluggishness (low-