ADVANCES IN ELECTRONICS

—ADVANCES IN—
Electrocardiography

Edited by

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Library of Congress Catalog Card No. 58-8145

Printed in U. S. A.
(B)

Preface

FOR THE past quarter century it has been our custom at New York University to teach electrocardiography in the most quantitative manner that the sum total of knowledge permitted at the particular time. An empirical approach has been avoided, and the vicissitudes and pitfalls of electric-anatomic correlations have been repeatedly stressed. In 1935, when the editor first had the privilege of working as a Voluntary Assistant in the Heart Station at Ann Arbor, the fundamental basis of electrocardiography had already begun to unfold from the remarkable mind of Frank N. Wilson and his loyal associates. A field of endeavor which seemed to have come to a permanently sterile end when Lewis left it in the 1920's had a vigorous renaissance and a surge of growth which continues to the present day.

Immediately after World War II, with young physicians returning to civilian life avid for knowledge, it was our task to present in 1946 and again in 1947 in the new Post-Graduate Division of New York University College of Medicine a course which was titled "Advanced Electrocardiography" and advertised as being concerned with the fundamentals of electrocardiographic theory. Despite its emphasis on basic data and its content of analytical formulations, it was well attended and well received.

With the separation of the Post-Graduate Division from the undergraduate school, the former becoming the New York University Post-Graduate Medical School in December 1948, no further opportunity was presented to repeat the course, although others were and continue to be offered. In November 1955, the course was given by the editor alone in modified form under the auspices of the University of Miami and the Mt. Sinai Hospital of Greater Miami.

Late in 1955, a request was received from The American College of Physicians to prepare a course in electrocardiography for graduate physicians to be given at the New York University-Bellevue Medical Center. It was agreed to do this provided that a completely fundamental rather than clinical or empirical approach would be acceptable.

This qualification was inserted in the agreement for several reasons. The most important of these was the obvious need for narrowing the considerable gap which had developed in the previous decade between the clinician on the one hand and the biophysicist, the physiologic engineer, the cellular physiologist, the clinical investigator and the instrumentologist on the other. In the period 1946–1956, advances in all fields of science were so rapid and at times so complex that even the physician with an intense interest in electrocardiography had difficulty keeping abreast of and comprehending the advances pertinent to the method. The purpose of the course was to present, interpret, and integrate, so far as possible, these advances.

To be certain that prospective students understood what to expect, the following statement appeared in the announcement brochure:

> "The objective of the course will be to familiarize the student with the most recent advances in electrocardiography considered to be of the greatest immediate or future significance. Since most of these advances have been of a fundamental nature, the course itself must of necessity be on a relatively fundamental level. Although the clinical implications of the newer electrocardiographic knowledge will be discussed, exercises in clinical interpretation of records will not be included in the course."

Under the circumstances it was expected that few physicians would apply. Therefore, it was somewhat of a surprise when the course was oversubscribed within a few days of its initial announcement in the Spring of 1956. This was interpreted to mean that the average internist's desire for recently acquired, fundamental knowledge, at least in electrocardiography, had been seriously underestimated. Further, this knowledge was not easy to come by in any single publication. For these principal reasons, a decision was reached to make the lectures, with certain additions and deletions, available in this monograph.

The editor acknowledges his gratitude to the faculty of the course and co-authors of the monograph for their expert and indispensable help, and to Dr. J. Scott Butterworth who, during the course, presented his visual demonstration of the relationships between the origin of the cardiac potential and the potential of surface points. We were fortunate in having Dr. George Seiden, then at the University of Pennsylvania, as one of the students. He graciously presented a brief and lucid description of the cancellation technique for determining the electric heart center, a technique which he had used extensively (Chapter 6). Dr. Bertha Rader presented summary lectures on the Electrocardiogram and Serum Electrolytes and Electrocardiograms in Children but these have been omitted from the present monograph because of their availability in detailed form elsewhere.

Some of the original investigations reported were made possible by the generous and greatly appreciated support of the Electrocardiographic Laboratory at New York University College of Medicine at various times by the Knapp Foundation of New York, the New York Heart Association, the Western New York State Heart Association, the American Heart Association, and the National Heart Institute of the U.S.P.H.S.

Mr. Nathan Marchand kindly reviewed and corrected the mathematical and analytical portions of the manuscript. William Pasinosky made many of the line drawings and diagrams. Drs. Berger and Brumlík undertook the tasks of correcting proofs and making the index. The Misses Muriel Luken and Sally Anna Evans capably handled typing of the manuscript. The publishers were most generous in their help with the myriad of details concerned with publication.

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PART I. SOURCE OF POTENTIAL; BIOELECTRICS OF THE MYOCARDIAL CELL

1. The Transmembrane Potential

CHARLES E. KOSSMANN, M.D.

WHEN INTERPRETING an electrocardiogram there are four parameters to be considered (fig. 1) which determine the ultimate form of the record obtained. These are: (1) the source of potential (the heart); (2) the conductivity of the external medium (the body); (3) the size and shape of the boundaries of this medium (the surface of the body); and (4) the conductivity of the internal medium (the heart's blood).

The site of development of potential differences is the myocardial syncytial or cellular membrane. The source of potential is the dissipation or restitution of a gradient of ions during myocardial activity which normally exists across the resting "membranous" barrier (Chapter 2).

A record of the gradient of potential across the resting cell wall cannot be made by an external lead because there is no flow of current in the surrounding medium due to the high impedance of the membrane. As a consequence, there is no electric field and the potential, V, of any point in the medium is zero. On the other hand, if a discontinuity of the potential function can be achieved by passing an electrode into the myocardial fiber,[1] it will assume the potential of the interior. This can be demonstrated to be $-4\pi\phi$ where ϕ is the electrical moment of a unit area of the membrane.[2] In practice, the membrane resting potential (MRP), as it is called, can be measured either by inserting an exploring microelectrode into the cell, with an indifferent electrode in the surrounding conducting medium, or, less precisely, by injuring one end of the cell and pairing the indifferent electrode on that end with an exploring electrode on an uninjured portion (fig. 2). The former method yields an intracellular potential, whereas the latter yields an "injury" or "demarcation potential." To be noted in figure 2 is that similar polarity of the electrograms is obtained by opposite connections through the galvanometer in the two methods. This arises from the circumstance that the first method yields the negative side of the resting membrane potential and the second, in effect, the positive side.

With either method of recording, a reduction in the impedance of the membrane caused by activity of the cell results in a loss of the ionic gradient and of the initial polarity of the membrane (depolarization, activation,

invasion, accession). The resting potential disappears (fig. 3). A gradual restitution of the polarized state (repolarization, recovery, retreat, regression) restores the resting potential. The form of the record, obtained by either method, during this series of events is essentially monophasic in nature. When obtained with the microelectrode, it is called the monophasic action potential, the membrane action potential (MAP), or the transmembrane action potential.

In passing, it should be noted that the earlier method of leading which utilized an injured end of the cell as an "indifferent" electrode could easily have been interpreted as yielding a record of "negativity" of the exploring electrode when, in truth, it represented a decreased positivity of that electrode. This misinterpretation was probably the basis of the discredited "negativity hypothesis."

Resting potentials of cardiac membranes vary in magnitude from 40 to 110 mv., while the action potentials are some 20 to 50 mv. larger. The membrane action potential varies somewhat in form and duration depending upon the species studied,[4] the size of the orifice of the microelectrode[5] and the specific tissue studied (ventricular, atrial, or pacemaker tissue).

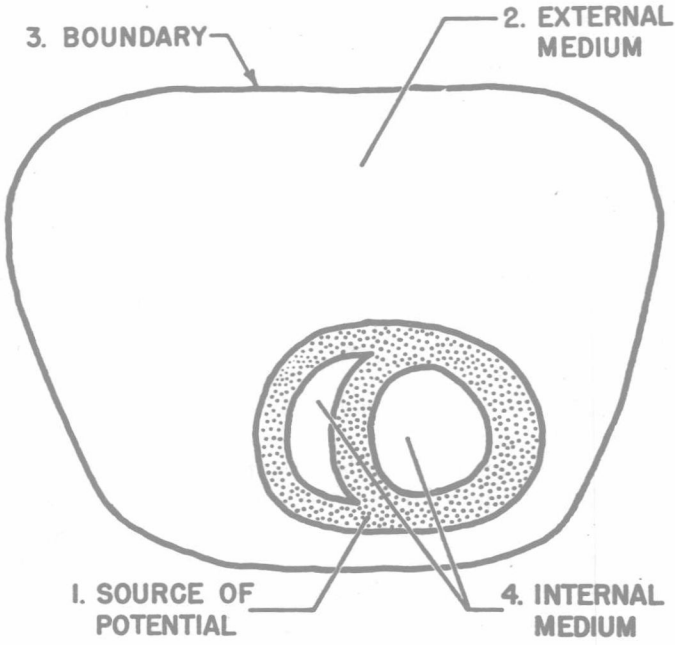

FIG. 1. Diagrammatic cross-section of the human thorax at the level of the heart, summarizing the four principal parameters which determine the form of the electrocardiogram. The internal medium, 4, is the heart's blood and the external medium, 2, the body tissues.

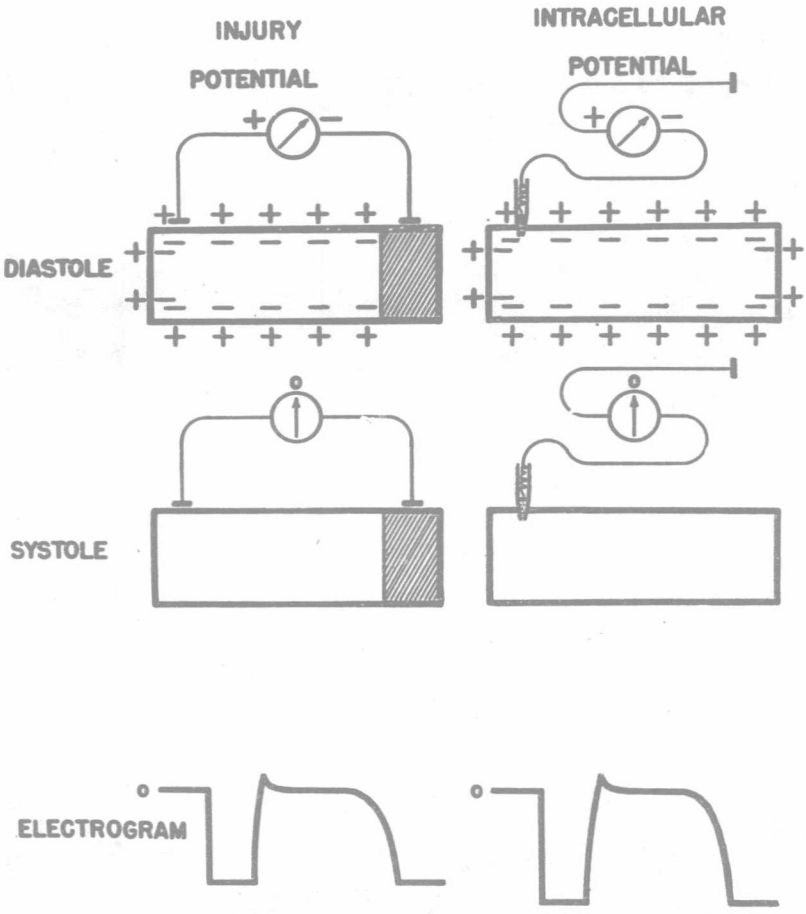

FIG. 2. Diagram to illustrate the similarity of electrograms obtained by recording the injury potential (shaded area of cell is injured, e.g., depolarized) and the intracellular potential. The second electrode, when recording the latter, is assumed to be in a surrounding conducting medium distant from the cell. The smaller magnitude of the injury electrogram is the result of loss of potential by short-circuit through the surrounding medium.

A typical ventricular transmembrane potential of the frog ventricle (Rana pipiens) recorded simultaneously with a bipolar lead from the forelegs is shown in figure 3. The monophasic action potential with a total duration inversely proportional to heart rate[3] may be subdivided into periods of depolarization (1–2 msec.), reversal spike (6–15 msec.), plateau, and repolarization (fig. 4). A short final phase of hyperpolarization (positive after-potential) or hypopolarization (negative after-potential) can probably exist, at least pathologically (Chapter 16).

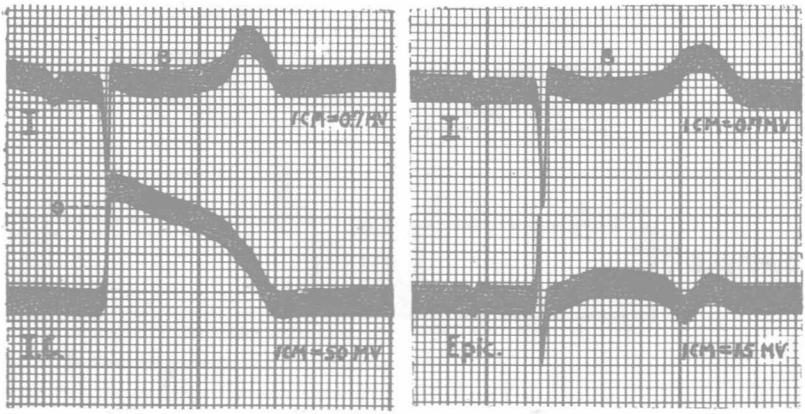

FIG. 3. Ventricular intracellular potential (I.C.) and epicardial lead (Epic) from the same area as the microneedle was withdrawn, recorded simultaneously with a bipolar lead from the forelegs (I) of Rana pipiens at 22° C. To be noted are: (1) the magnitude of the action potential (80 mv.) as compared to the epicardial potential (RS deflection = 3.0 mv.); (2) the three slopes of recovery of the action potential; (3) the chance form of lead I simulating a first derivative (axial current) and of the epicardial lead a second derivative (membrane current) of the action potential, with the S-T segment of the latter elevated probably due to injury caused by the microelectrode. The epicardial lead is distorted by AC pickup. B is the deflection caused by excitation of the bulbus cordis. Calibrations when recording are indicated on each record. The zero level (0) of the MAP is measured from the upper border of the trace.

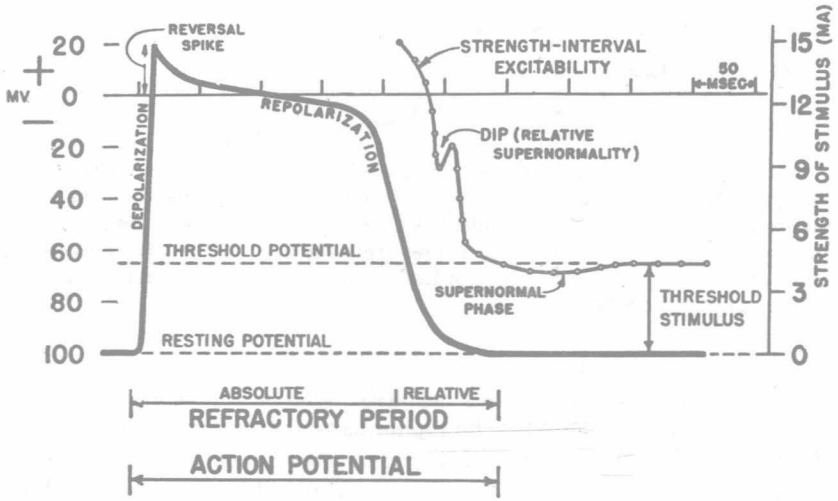

FIG. 4. Diagram of an intracellular myocardial potential and the strength-interval excitability curve of the same tissue (Chapter 15). The diagram is to serve as a concise glossary of terms rather than as an accurate representation of the transmembrane potential of any specific tissue or species. (Modified from Brooks et al.[4])

The "recovery" phase, regarded as beginning at the peak of the reversal spike and ending with the return to the resting potential, is incompletely understood from the viewpoint of what is happening in the membrane at the time (Chapter 2). Nevertheless, three different slopes of recovery can usually be recognized.[5] These phases of recovery are of different rapidity, the middle phase ("plateau") being the slowest. The first is the most sensitive to abnormal environments; the last the least sensitive. The different rates of recovery indicate different energy requirements for each of the phases.

Simultaneous intracellular potentials from the atrium and the ventricle of a frog (fig. 5) illustrate the shorter duration and steeper slope of repolarization in the former. In pacemaker tissue, the best-studied being the Purkinje fiber of the dog, depolarization is very rapid, the reversal

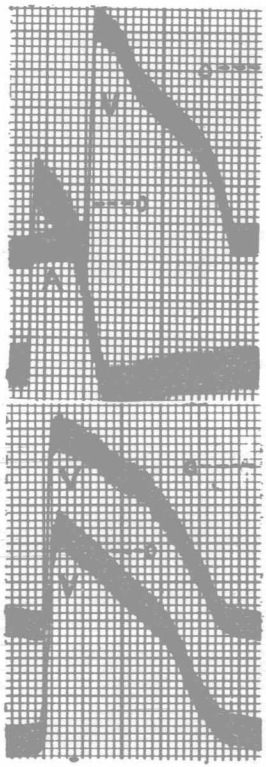

FIG. 5. Simultaneous intracellular records of a frog heart made with two microneedles. In the upper record, one needle was in ventricular tissue (V) and the other in atrial tissue (A); in the lower record, both needles were in ventricular tissue (V). Some artifacts are present but the figure does illustrate the different form of the MAP in atrial as compared to ventricular muscle. Calibration, 1 cm. = 60 mv. Time lines, 0.04 sec.

spike is higher and shorter, and the plateau is considerably longer at equivalent heart rates compared to myocardium. Most characteristic, however, is the occurrence in diastole of a gradual loss of the resting potential ("prepotential") until the "threshold" level is reached, when rapid depolarization begins again (Chapter 11). This diastolic loss of potential accounts for the tissue's automaticity. An example of the MAP of the sinoatrial node of the rabbit is shown in figure 6.

Kleinfeld and Stein, working in this laboratory, have recently demonstrated that the duration of the action potential is shorter in the left atrium than in the right of the guinea pig (fig. 7). This difference, if present in the human heart, probably accounts in part for the different behavior of these chambers in various hemodynamic states.

For purposes of future reference (Chapter 15) the absolute and relative refractory periods and the threshold potentials are shown diagramatically

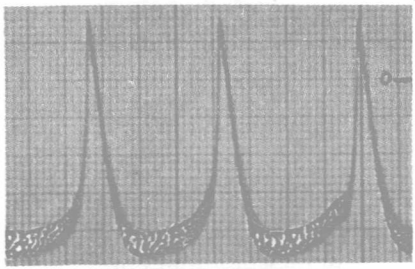

FIG. 6. An intracellular potential made from the region of the sinoatrial node of the rabbit to illustrate what is believed to be a gradual diastolic loss of the resting potential ("prepotential"). There is some alternating current distortion of the record. Calibration, 1 cm. = 25 mv. Time lines, 0.04 sec.

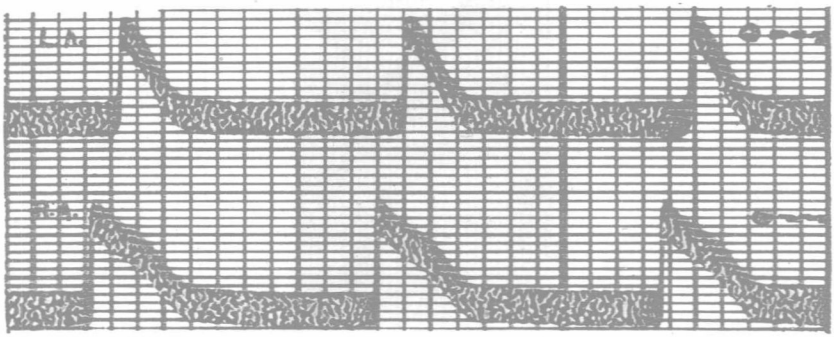

FIG. 7. Simultaneous intracellular potentials from the left (L.A.) and right (R.A.) atria of the guinea pig, illustrating the different forms obtained as a result, principally, of the shorter duration of the action potential in the left atrium. Calibration, 1 cm. = 60 mv. Time lines, 0.04 sec.

in figure 4. The durations of these periods vary not only with the species and with the tissue studied but also to some degree with the method used for testing refractoriness.[4]

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2. Ionic Basis of the Transmembrane Potential

STANLEY A. BRILLER, M.D.

A CELL retains its uniqueness in large measure due to its membrane, which allows it to achieve a chemical composition differing from its environment. The relationship between the electric potential or voltage and the ionic milieu on the two sides of the membrane may be understood by examining the effects of connecting a battery to two plates which dip into two compartments of a container separated by an inert, semipermeable membrane (fig. 1). If the solution in the compartments on either side of the membrane contains equimolar concentrations of a salt such as KCl, it is apparent that the potassium cations will drift to the compartment containing the negative plate, and the chloride anions to the positive plate. If we could arrange matters so that no chemical reactions would take place at either the anode or cathode, it can be appreciated that after a given amount of time the concentration of potassium surrounding the cathode would be much greater than that about the anode (fig. 2). An opposite situation would apply to the distribution of the chloride ions. The point at which no further separation of ion species can be attained is a function of the voltage applied. This relationship is expressed by the Nernst equation:

$$E = -\frac{RT}{ZF} \operatorname{Log}_e \frac{Q_1}{Q_2} \tag{1}$$

where E is the battery potential, R is the gas constant (1.987 calories per mole per degree), T is the absolute temperature, Z is the valency, F the Farad (96,500 coulombs per equivalent), e is the natural logarithmic base, and Q_1 and Q_2 are the ionic concentrations in compartments 1 and 2 respectively.

This equation applies to anions as well as cations. As given, it will indicate the polarity in the Q_1 compartment due to the cationic disposition. The sign must be changed if predictions due to anionic displacement are to be made, or if cationic measurements are made in the Q_2 compartment. Although the following statements apply with equal validity to both anions and cations, for simplicity only the potential measured in compartment Q_1 due to the cationic distribution (potassium ion) will be described. Movements and concentration of chloride are opposite but equal to potassium in this case.

In the example cited the equation applies only when a steady state of differential concentrations is attained. When the battery is first switched

on, the concentrations of potassium within the compartments are equal and the calculated voltage (0) does not agree with that applied. Accordingly, it is necessary to apply equation (1) only when equilibrium has been reached or else add expressions to indicate the effects of movement or flux of the ions across the membrane, as follows:

$$E = -\frac{RT}{ZF} \operatorname{Log}_e \frac{Q_1 F_1}{Q_2 F_2} \tag{2}$$

The symbolization in equation (2) is similar to that in equation (1). F_1 represents the flow of any one ion toward Q_1, F_2 flow in the opposite direction (fig. 3). When the battery in figure 1 is switched on, F_1 for potassium greatly exceeds F_2 and the equation will predict the voltage of the battery although the concentrations of ions have not had time to change appreciably.

In the example cited, energy from the battery was supplied to the model and it should be noted that one of three possible situations may be detected: (1) $Q_1 = Q_2$ but F_1 is greater than F_2 ; (2) Q_1 is greater than Q_2 and F_1 is greater than F_2 ; (3) Q_1 is greater than Q_2 and $F_1 = F_2$. These dispositions of ionic concentration and flow are characteristic of systems which are receiving energy from an outside source, such as a battery.

When the battery is disconnected from the system, the ions tend to flow in such a direction that equal concentration of ions in both compartments ultimately will be obtained. Until the latter situation is attained, the polarity of the system remains unchanged. In the case of the potassium ion in the model system, the flux ratio is reversed, and F_2 becomes greater than F_1 . Since the flux ratio is disposed oppositely to the concentration ratio, the potential will be somewhat less than when F_1 was equal to F_2 in the equilibrium state. It is conceivable that if a battery were connected to this system in such a manner that the negative pole is attached to the Q_2 compartment, the potassium ions would be driven out of the Q_1 compartment at a greater rate than they tend to flow naturally. Under these circumstances, the flux ratio will exceed the inverted concentration ratio and the polarity of the system will be reversed.

The discussion thus far indicates: (1) in general, the polarity of an ionic system will be the opposite of the most highly concentrated ion contained in the compartment where the measurement is made; (2) if energy is delivered to such a system, the net flow will be toward the greatest or potentially greatest concentration of ion specie, until equilibrium is reached; (3) if the system is delivering energy, the net ionic flow will be away from the most concentrated ionic milieu. The potential will be lower in this case than in the equilibrium state; (4) if energy is supplied to a system in such a way that the flow away from the more concentrated environment is hastened, the polarity may be reversed.

It has been assumed that there is a known and fixed value for the permeability of the membrane for the potassium ion. However, it must be appreciated that another species of ions might have more or less difficulty in penetrating such a membrane by virtue of a difference in size as compared to potassium. Moreover, as will be seen, a membrane may at times vary in its physical ability to restrain specific ionic movement. In general, if several ionic systems are compared, that in which the permeabilities are greatest can supply the greatest ionic current or flux. The freely moving ion in a complex system may thus swamp the effects due to the more sluggish members of the population.

The Resting Biological System

The major charged constituents of cells are arranged as indicated in figure 4. It might be supposed that the cell membrane is completely impermeable to protein and sodium, at least in the resting state, and that

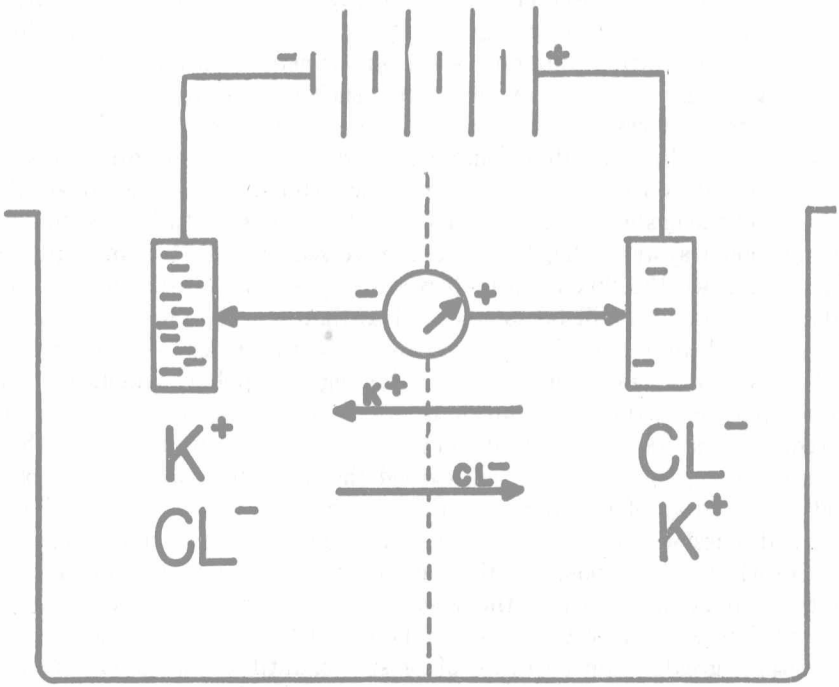

Fig. 1. Disposition of ions at the instant of application of potential across a semipermeable membrane (dashed vertical line) separating equimolar concentrations of potassium chloride. Compartment Q_1 (see text) is to the left. Dashes within electrodes indicate relative electron concentrations. Circle containing arrow represents a polarity indicating galvanometer. Horizontal arrows indicate *net* flow.