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The Electrochemistry of Porous Membranes, with Particular Reference to Ion Exchange Membranes and Their Use in Model Studies of Biophysical Interest

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The Electrochemistry of Porous Membranes, with Particular Reference to Ion Exchange Membranes and Their Use in Model Studies of Biophysical Interest

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INTRODUCTION

Some Basic Considerations Concerning the Nature of Membranes as Barriers and Transducers; Classes of Membranes

The purpose of this paper is twofold: to present the basic facts and concepts of the electrochemistry of membranes in a manner designed to be interesting and useful to readers unfamiliar with this field, and to give a selective bird's-eye view of some of the less widely known and in part somewhat unconventional ramifications of the electrochemistry of membranes which should be of interest to a wide circle of biological investigators.

First, the two-sided character of membranes, which gives them their particular interest, will be pointed out, namely, their nature as restrictive barriers and as physicochemical machines, i.e., as transducers; thereafter, we will touch briefly upon the conventional classification of membranes according to the mechanisms of their barrier actions.

The second section will show how the basic experimental facts and concepts of the electrochemistry of membranes have evolved from the classical physical chemistry of electrolytic solutions under the powerful stimulus of electrophysiological interest. The basic electrochemistry of membranes will be outlined, including the state of the art of preparing membranes with prestated properties; also, the use of certain such membranes as membrane electrodes and in a variety of preparative and industrial operations will be indicated.

The third section will deal with some special, relatively little-known cross-membrane transport processes and with some membrane transport model studies in systems with composite membranes, such as model systems in which, as in living cells, an accumulation of electrolytes occurs against concentration differences.

The most characteristic feature of membranes is their function as selective barriers to the cross-membrane penetration of the various species of particles, molecules, ions, or colloidal particles contained in the two phases or compartments separated by the membrane, in other words, their selective permeability. While acting as barriers, membranes regulate the movement of particles and the flow of energy across their thickness and thereby cause a great variety of effects, such as movement of solute, the closely related development of (not necessarily static) hydrostatic pressures, and the partial or complete separation of solutes from the solvent. With solutions of electrolytes, numerous additional effects of particular interest in biology may arise, such as static or dynamic membrane potentials, anomalous osmosis, movement of third ions against concentration gradients, electro-osmosis, etc. In all these cases the membranes act as physicochemical machines, that is as transducers, transforming by various mechanisms the free energy of the adjacent phases (or energy applied through them) into other forms of energy (mechanical, concentration, electrical, etc.), sometimes in a reversible but ordinarily in an irreversible manner. "Physicochemical membranes" regulate energetic processes, essentially without being changed, exhausted, or consumed. They cannot by expenditure of energy of their own bring about any transport phenomena [1, 2].

The mechanism or mechanisms by which membranes act are of no importance in the thermodynamic treatment of reversible processes in systems with ideally semipermeable membranes; this was emphasized by van't Hoff [3] in elaborating his classical theory of solutions, and was clearly recognized by Donnan [4] in his treatment of electrolytic membrane equilibria and of membrane potentials. However, in the study of the dynamics of membrane systems, the twin questions of membrane structure and of the mechanisms of the barrier action of the membranes become of paramount importance. This is equally true whether the membrane systems under consideration involve semipermeable membranes or, the much more frequent case, membranes of differential degrees of restricted permeabilities for the various species of particles in solution.

The dynamics of membrane systems can be understood only to the extent to which the mechanism(s) of the restrictive actions of the membranes under the given situations are known, and only on this basis does it become possible to create at will membranes with properties "tailor-made" for a great variety of investigative and technological purposes.

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Membranes are commonly classified into two basic groups "oil" or "liquid" membranes and porous membranes. The study of these two groups has followed separate lines. The former are essentially outside the scope of the present paper and will be mentioned here only in the most general terms. Liquid membranes exert their typical functions by means of the differential solubilities in them of the various species of particles contained in the phases separated by the membrane: Particles, molecules, or the ions of electrolytes which are soluble in a membrane can pass across it.†

The principles of the electrochemistry of oil membranes, particularly the electromotive behavior of oil phases, were developed between 1896 and 1910 by Luther [5], Nernst and Riesenfeld [6, 7], and Haber and collaborators [8, 9], particularly Beutner [10, 11]. Many of the liquid membranes studied by Haber and Beutner act electromotively in a manner similar to that of the solid electrolyte phases, such as the glass electrode, investigated by these authors. As we know today, this electromotive action of liquid membranes is due to the ion exchange characteristics, however weakly developed, of these membranes. More recently, much improved Haber-Beutner-type "liquid ion exchange membranes" of extreme ionic selectivity and high transmissivity of the permeable ions have been prepared [13-20] which are closely similar in many ways to the "permselective" ion sieve membranes which will be treated extensively in this paper. The literature on the electrochemistry of liquid membranes up to 1960 was reviewed briefly but critically by Kahlweit [12].

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† The terms "oil" and "liquid" membranes were obvious choices when they were introduced by the early investigators; they referred to the most manifest characteristic of these membranes, their liquid nature, which set them apart from the ubiquitous solid membranes —solid at least in the macroscopic sense—having porous structures. We realize now that the functionally most important property of the "oil" membranes is not their liquid nature but the mechanism of their selective barrier action, namely, their propensity to selectively dissolve different solutes, often to very remarkable degrees. Therefore, the terms "dissolution," "solubility," or "solvent" membranes would be more fitting for membranes of this type in general. These designations would also obliterate the artificial semantic barrier between the classical dissolution-type liquid membranes and the vast group of macroscopically solid membranes—mostly consisting of high polymers and plastics—which exert their typical membrane functions in the same manner by selective dissolution. These latter membranes fittingly might be designated as solid dissolution, solubility, or solvent-type membranes. The familiar terms "oil" and "liquid" membranes are used in this paper primarily to maintain continuity with the literature.

The membranes to be discussed here belong to the other main group of membranes, the "porous," "structural," or "sieve membranes," whose barrier actions are due to the screening out of the various species of solute particles according to their different sizes and, to some extent, their different adsorbabilities, and, in the case of ions, also according to the sign and magnitude of their charge. This latter factor is predominant with small ions, particularly with the (solid) ion exchange membranes which are the main topic of this paper.

THE ELECTROCHEMISTRY OF POROUS MEMBRANES

Early Developments

In the context of this symposium it would be of considerable interest to demonstrate to experts in the biological-medical sciences and in chemistry how their respective fields of endeavor have fruitfully interacted with each other for more than 100 years to create the contemporary science of membranes, especially the electrochemistry of ion exchange membranes, and the molecular basis of electrophysiology [21]. Though lack of space precludes delving in detail into this historical development, the author hopes that the subsequent paragraphs will convey to the reader an impression of the interweaving, multidisciplinary lines of experimental and theoretical work which have contributed to our knowledge in these fields.

The "muscle" and "nerve currents," the "action potentials" and "action currents" which arise between the injured site and the undisturbed surface of cells and tissues, were the main topic of interest of the 19th century electrobiologists [22-24]. More than 100 years ago, du Bois-Reymond [22] hypothesized, correctly, as we know today, that the source of these potentials are not the injured sites but the undisturbed surfaces of the living structures. According to du Bois-Reymond, the bioelectric potentials originate there at a membrane to which he ascribed electromotive properties qualitatively analogous to those of the Zn-Cu couple. More than 50 years had to elapse, however, before this suggestion was taken up productively by Bernstein [25] (see below).

In retrospect, it is easy to realize that any successful attempt to understand the molecular mechanisms of these bioelectric effects had to be preceded by the development of the physical chemistry of electrolytic solutions. This occurred during the 1870s and '80s and led to the classical theory of ionic solutions [26-29], which in 1889 found its capstone in Nernst's paper [30] on the electromotive action of ions in solution, in which he developed the theory of the "liquid junction" or "diffusion potential."

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The electrochemistry of membranes can be said to have begun in 1890 with an essentially speculative paper by Ostwald [31] concerning the electromotive properties of "semipermeable" membranes. According to Ostwald, a membrane, in order to be impermeable to an electrolyte, need not necessarily be impermeable both to its anions and its cations. It is sufficient if it is impermeable either to the cations or the anions, because cations and anions cannot be separated from each other in chemically measurable quantities; macroscopic electroneutrality must be maintained. However, a minute quantity of the permeable ions penetrates from a more concentrated to a more dilute solution whereby, according to Ostwald, a static electrical double layer is established at the membrane, the permeable ions impressing their charge on the more dilute solution. This membrane potential across "semipermeable" membranes is the limiting case of a liquid junction potential in which the mobility of the nonpermeable ions in the membranes is zero. Ostwald surmised that "not only the currents in muscles and nerves but also the puzzling actions of the electric fishes will find their explanation in the... outlined properties of semipermeable membranes" (author's translation).

In 1899 Nernst [32], in the context of proposing a quantitative theory of the mechanism of the electrical excitation of tissues by alternating current, developed the concept of the polarization effects which arise when a current is passed across membranes. Nernst pointed out that all component parts of tissues, including the membranes, are electrolytic conductors, and that the contributions of the various species of ions to the transportation of current in different electrolytic conductors are ordinarily different. Accordingly, changes in electrolyte concentration arise at the phase boundaries when a current is passed. These concentration changes were considered by Nernst as the cause of electrical excitation, an idea which later was confirmed experimentally.

The really effective and permanent intussusception of the classical electrochemistry of solutions into electrobiology was brought about by the physiologist Bernstein [25, 33], who proposed in 1902 the now universally accepted "membrane theory" of the electromotive action of living cells and tissues. In doing this he attacked, in a highly knowledgeable and skillful manner, the two most fundamental physical problems of electrophysiology, namely, the molecular mechanisms and the locale of the processes which give rise to all bioelectrical effects. Bernstein based the strictly electrochemical part of his considerations on the Nernst-Planck conception of the liquid junction potential [30, 34]. He pointed out how differences between the transport numbers of ions in a membrane and those observed in free solution must lead to membrane diffusion potentials which are different, ordinarily higher, from those in free solution. The limiting maximum values of these membrane diffu-

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sion potentials are given by Ostwald's [31] considerations. By the measurement of the temperature coefficient of bioelectric potentials, Bernstein proved that these effects are of an osmotic, not a biochemical, nature, their magnitude being essentially proportional to the absolute temperature. He also demonstrated that it is overwhelmingly probable that the bioelectric potentials originate at the uninjured rather than the injured surfaces of cells and tissues, thus confirming with modern electrochemical methods this most important electrobiological fact, which, as stated above, had already been considered by du Bois-Reymond [22] as a most probable supposition. Bernstein [25, 33] further suggested the now generally accepted idea that most bioelectrical potentials are essentially cross-membrane concentration potentials. While the electrobiological importance of Bernstein's "membrane theory" is universally recognized, it is frequently forgotten that many of his strictly physicochemical considerations represent also a major contribution to the electrochemistry of membranes per se.

The manifest importance of the electrochemistry of membranes for electrobiology induced many noted biologists, such as Girard [35], Bethe [36-38], Loeb [39-45], Michaelis et al. [46-52], and Höber et al. [53-55], during the first third of this century to pioneer in this field, thereby providing the basis for the "modern" era of electrochemical membrane studies, which started in 1935.

The few physical chemists who took some interest in the electrochemistry of porous membranes were mainly concerned with specific problems, such as nerve excitation [56], the mechanics of anomalous osmosis [57-64] (see below), and other effects [65-69] which seemed not to fit readily into the framework of classical electrochemistry. The outstanding exception was Donnan [4], who, leaning on Ostwald's [31] ideas concerning the electromotive action of semipermeable membranes, developed in 1911 his well-known theory of ion distribution equilibria and the concomitant electromotive effects which arise in membrane systems in which two or more species of ions can permeate across the membrane while one species of ions cannot permeate across it. Donnan derived his theory on a thermodynamic basis from the principles of the classical electrochemistry of solutions; it therefore does not stipulate any particular molecular mechanism. However, in the present context it is of interest that in testing the theory, Donnan and collaborators [4, 70] and other investigators [71, 72] used porous membranes nearly exclusively; accordingly, Donnan called the nonpermeating ionic species the "colloidal ion."

Donnan's work is one of the most important milestones in the development of the electrochemistry of membranes. A systematic presentation of Donnan's theory of "membrane equilibria" ("Donnan equilibria") and of the concomitant equilibrium "membrane potentials" ("Donnan potentials") would, however, require an inordinate

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amount of space; therefore, it is presented here only in a condensed form.

Following Donnan, we assume a (completely dissociated) binary electrolyte, NaR, with the nondiffusible, "colloidal" anion, R^-, which might be visualized as a large dyestuff ion. A compartment of invariant size is filled with the solution of NaR at concentration c_1 and separated from pure water by an R^--impermeable membrane which is permeable to all small ions. The electrolyte NaR cannot permeate across the membrane because macroscopic electroneutrality is maintained. However, when the pure water phase is replaced by an aqueous solution of, for instance, NaCl at concentration c_2, both Na^+ and Cl^- can move across the membrane, as long as electroneutrality is maintained. Calling the R^--containing solution Solution 1 and the R^--free solution Solution 2, and assuming equal volumes of the two solutions, we suppose that the equilibrium is reached when x mols of Na^+ and x mols of Cl^- have passed from Solution 2 into Solution 1. This equilibrium may be represented in the following manner:

Solution 1	Solution 2
$[R^-] = c_1$	$[Cl^-] = c_2 - x$
$[Cl^-] = x$	$[Na^+] = c_2 - x$
$[Na^+] = c_1 + x$	

Since NaCl (meaning equivalent amounts of Na^+ and Cl^-) can move across the membrane without violating the law of electroneutrality, the chemical potential of NaCl in the equilibrium state must be the same in both compartments. Accordingly, we may write:

$$\left(a_{Na^+}\right)_1 \cdot \left(a_{Cl^-}\right)_1 = \left(a_{Na^+}\right)_2 \cdot \left(a_{Cl^-}\right)_2 \qquad (1)$$

The treatment is simplified if we replace the activities by concentrations and write with Donnan:

$$[Na^+]_1 \times [Cl^-]_1 = [Na^+]_2 \times [Cl^-]_2 \qquad (1a)$$

Accordingly, the equilibrium in the above system prevails when

$$x(c_1 + x) = (c_2 - x)^2 \qquad (2)$$

From Eq. (2) we obtain:

$$x = (c_2)^2/(c_1 + 2c_2) \qquad (3)$$

$$c_2 - x = \frac{c_2(c_1 + c_2)}{c_1 + 2c_2} \tag{4}$$

$$c_1 + x = \frac{(c_1 + c_2)^2}{c_1 + 2c_2} \tag{5}$$

$$\frac{c_2 - x}{x} = \frac{[Cl^-]_2}{[Cl^-]_1} = \frac{[Na^+]_1}{[Na^+]_2} = \frac{c_1 + x}{c_2 - x} = \frac{c_1 + c_2}{c_2} \tag{6}$$

If c_2 is small compared with c_1, x is small compared with c_2; that means that only a very small quantity of NaCl has moved from the outer to the inner solution. If, however, c_1 is small compared with c_2, the value of x approaches the limit $c_2/2$, and NaCl is distributed between the two solutions nearly evenly. As shown in readily available reference books, Eqs. (3) and (6) can be utilized to calculate from experimentally determined osmotic pressures the osmotic pressure which the R^- ions would exert if they were uncharged particles, an approach routinely used for the determination of the molecular weights of proteins and polyelectrolytes.

Of much greater importance in the present context are the potential differences which arise between the inner and the outer solutions due to the uneven distribution of the diffusable ions, in our example, Na^+ and Cl^-. The difference in the equilibrium concentrations of any permeable species of ions on opposite sides of the membrane can only be maintained through an electromotive force of the appropriate direction and magnitude. In our example, the R^--free Solution 2 which has the lower Na^+ concentration is positive with respect to the other solution; the same conclusion is reached if we consider the concentration of Cl^- which is higher in Solution 2. The electromotive force, E, arising between the two solutions is given by:

$$E = \frac{RT}{F} \ln \frac{\left(a_{Na^+}\right)_1}{\left(a_{Na^+}\right)_2} = \frac{RT}{F} \ln \frac{\left(a_{Cl^-}\right)_2}{\left(a_{Cl^-}\right)_1} \tag{7}$$

Since the solvent H_2O is an electrolyte, the equilibrium of Eq. (7) must also be extended to the H^+ and OH^- ions, and we may write:

$$E = \frac{RT}{F} \ln \frac{[Na^+]_1}{[Na^+]_2} = \frac{RT}{F} \ln \frac{[Cl^-]_2}{[Cl^-]_1} = \frac{RT}{F} \ln \frac{[H^+]_1}{[H^+]_2} = \frac{RT}{F} \ln \frac{[OH^-]_2}{[OH^-]_1} \tag{7a}$$

or, more rigorously, the corresponding equations in terms of activities. Equations (7) and (7a) state that "membrane hydrolysis" arises

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in Donnan membrane systems. Quite generally, if several species of diffusible cations, A^+, B^+, C^+, ..., and anions, L^-, M^-, N^-, ..., exist in a Donnan system the ratio of the equilibrium distribution of these ions is implicitly given by Eqs. (7) and (7a), and we may write:

$$\frac{[A^+]_1}{[A^+]_2} = \frac{[B^+]_1}{[B^+]_2} = \frac{[C^+]_1}{[C^+]_2} \cdots = \frac{[L^-]_2}{[L^-]_1} = \frac{[M^-]_2}{[M^-]_1} = \frac{[N^-]_2}{[N^-]_1} \cdots \qquad (8)$$

Experimental studies, mainly by Donnan and collaborators [70, 71] and others [72, 73], proved the essential correctness of Donnan's theory; other investigations, particularly those by Procter and Wilson [74, 75] and Loeb [45, 76], have dealt with its applications to various physicochemical and biological systems. This literature was reviewed by Bolam [72] and commented on by Donnan [77, 78]. The theory was redeveloped on a more rigorous basis by Donnan [79, 80] and others [81-83].

It is now universally realized that any kinetic theory of electrical membrane effects which, when applied to equilibrium conditions, leads to conclusions contradicting Donnan's equations, must be erroneous. However, at the time of its publication in 1911, Donnan's work [4] was seemingly so far ahead of its time that its influence on the development of the systematic electrochemistry of membranes remained very limited for many years. Donnan's papers did not offer any direct help in the development of a kinetic theory, and they were even less helpful in the experimental study of systems with porous membranes and solutions of electrolytes consisting of small ions only, on which the other investigators [35-69] focused their attention. The further development of the electrochemistry of membranes, to which we shall turn presently, stems from the study of systems of this latter type.

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The Systematic Electrochemistry of Porous Membranes and the Fixed Charge Theory of Ionic Membranes

The most conspicuous and most readily studied electrical membrane effect is the electromotive force, EMF, which arises when a membrane separates two solutions which are not identical with respect to their electrolyte content. The simplest systems of this nature are membrane concentration cells, which were the object of most fundamental studies.

If a natural or artificial membrane consisting of almost any material, such as collodion, silicates, or proteins, is interposed, for instance, between two solutions of different concentrations of the same electrolyte, an electromotive force arises that is different in most instances from the liquid junction potential which would arise between the same two solutions on free diffusion, that is, in the absence of a membrane. The electromotive forces arising in such membrane concentration cells customarily are referred to as "membrane concentration potentials" or "concentration potentials." Concomitant with this and related electrical effects that are observed in the various types of membrane cells, there arises also the translocation of liquid across the membrane. With membranes of the highly porous, dialyzing type, the "osmotic" flows of liquid can be very pronounced, being in many instances much larger than those arising with solutions of nonelectrolytes. In some instances the translocations of liquid across the membrane are even in the opposite direction from that expected on the basis of the concentration gradient across the membrane. These anomalous effects, called "anomalous osmosis" [57-64], will be discussed below.

The above mentioned membrane concentration potentials, like all types of cross-membrane potentials, are measured most conveniently in cells with two identical calomel half-cells and KCl bridges, the scheme for a concentration cell with A^+L^- as electrolyte being:

	KCl	A^+L^-		A^+L^-	KCl	
$HgCl_2$			membrane			$HgCl_2$
	sat.	c_1		c_2	sat.	

The sign and the magnitude of the concentration potential depend on the absolute concentrations and the concentration ratio of the electrolyte in the two adjacent solutions, on the nature of the electrolyte, and on the nature of the membrane.

With membranes of highest porosity the concentration potentials are identical with, or not much different from, the corresponding liquid junction potentials. The concentration potentials deviate more and more from the liquid junction potential as denser membranes are used.

Bethe and Toropoff [36, 37], in two most remarkable papers that anticipated the ideas and results of many later publications by other investigators, pointed out that the direction of the deviation of the concentration potential from the liquid junction potential is functionally correlated to the electrokinetic charge of the membrane as determined in electro-osmotic experiments. With electronegative membranes, the dilute solution is more positive than on free diffusion; with electropositive membranes, it is more negative. The interpretation of these observations in terms of ionic processes leads immediately to the conclusion that with electronegative membranes the cross-membrane permeation of cations is favored, and that with electropositive membranes the permeation of anions is favored. This conclusion is expressed commonly in the statement that electronegative membranes are preferentially cation permeable and electropositive membranes preferentially anion permeable. This

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general conclusion, which is readily confirmed by appropriate permeability studies (see below), is the most fundamental fact in the whole electrochemistry of membranes of porous character.

With certain membranes of low porosity, as shown mainly by Michaelis et al. [46, 47, 51, 52], the concentration potential may nearly reach the magnitude of the potential difference which would arise between the two solutions if the membrane were replaced by a pair of reversible electrodes, specific for the permeable ions. This "thermodynamically possible maximum value" of the concentration potential is physically and conceptually identical with the Donnan potential, the nonpermeating ion playing the role of the "colloidal" ion. The Donnan potential thus represents the upper limit of the possible membrane concentration potentials, the liquid junction potential being the other limit.

The correlation of ionic membrane selectivity and concentration potential in formal electrochemical terms is the basic concept in the electrochemistry of membranes. The virtual transportation of electricity across the membranes is divided between anions and cations in a proportion which is different from the ratio of the transference numbers of these ions in free solution, as was pointed out by Michaelis et al. [47, 51, 52]. In electronegative membranes, a greater fraction of the current is transported across the membrane by cations than in free solution; the transference number of the cations in the pores of the membrane, τ_+, is larger than the transference number t_+ of the cations in free solution: ($\tau_+ > t_+$, and $\tau_- < t_-$), the sum of τ_+ plus τ_-, like t_+ plus t_-, being unity by definition. With positive membranes the inverse is true; $\tau_+ < t_+$, and $\tau_- > t_-$.

The correlation of membrane concentration potential, E, and the transference numbers τ_+ and τ_-, may be expressed quantitatively by substituting transference numbers for ionic mobilities in the Nernst equation for the diffusion (liquid junction) potential [47, 51, 52]. For the case of a uni-univalent electrolyte and a negative membrane, and substituting mean ionic activities, $a_\pm^{(1)}$ and $a_\pm^{(2)}$, for concentrations, we may write:

$$E = \frac{\tau_+ - \tau_-}{\tau_+ + \tau_-} \frac{RT}{F} \ln \frac{a_\pm^{(1)}}{a_\pm^{(2)}} \qquad (9)$$

where the sign of E refers to the more dilute Solution 2; for a positive membrane, Eq. (1) becomes:

$$E = \frac{\tau_- - \tau_+}{\tau_- + \tau_+} \frac{-RT}{F} \ln \frac{a_\pm^{(1)}}{a_\pm^{(2)}} \qquad (9a)$$

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If a membrane is exclusively permeable to cations, the transference number of the cation in the membrane, τ_+, is unity. It is an electronegative membrane of ideal ionic selectivity. Correspondingly, an electropositive membrane of ideal ionic selectivity is permeable exclusively to anions, τ_- being unity. With such membranes of ideal ionic selectivity Eqs. (9) and (9a) become:

$$E = \frac{\pm RT}{F} \ln \frac{a_\pm^{(1)}}{a_\pm^{(2)}} \tag{10}$$

the Nernst equation for the difference in electrode potential as function of the activity of the "potential determining" ion in solution. Equation (10), which is identical to Donnan's equation for the membrane potential, Eq. (7), is the formal expression for the thermodynamically possible maximum of the concentration potential across membranes of ideal ionic selectivity.†

The cause of the close correlation of the electrokinetic charge of a membrane and its electromotive action was first clearly visualized by Bethe and Toropoff [36, 37] and was also recognized by Bartell et al. [57], Loeb [39-45], Michaelis et al. [46-52], and all later investigators. At the pore wall | solution interface an electrical double layer is formed. The charges (ions) which form the immovable part of the electric double layer at the pore wall | solution interface are attached firmly to the pore walls and determine the electrokinetic charge of the membrane. They are unable to move and thus cannot participate in diffusive processes or in the transportation of electricity across the membrane. The counterions of the fixed wall charges are dissociated off into the liquid in the pores and are freely movable; they are therefore able to diffuse and to participate in the transportation of electricity, the current being transported across the membrane by these ions and by whatever other electrolyte, both anions and cations, may be present in the pores. The counterions of the fixed wall charges are a larger and larger fraction of the ions which are able to move across the membrane, as membranes of decreasing porosity are considered. According to this concept, ions of the same charge as the membrane are prevented by electric repulsion from approaching the

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† The derivation given in the text follows the presentation given by the various earlier authors mentioned in the text. It disregards certain minor factors, mainly the water transport due to the hydration of the ions which penetrate across the membrane [84]. The influence of the concomitant electrophoretic effects on the EMF of membrane cells has been discussed by Scatchard [85]. With fairly dense membranes the influence of these factors is, under many conditions, not detectable, or just barely so.

spots at the pore walls where the fixed charges of the same sign are located. From sufficiently narrow pores such ions are virtually excluded. In this case, the membrane acts as a "membrane of ideal ionic selectivity," with all the possible pathways across it blocked completely for the ions in solution which carry the same charge as the membrane.

The dependence of the membrane selectivity on the pore diameter, at a given solution concentration, is shown in the highly schematic Figs. 1a to 1c for electronegative pores. In these figures the crosshatched parts indicate the solid wall material; the protuberances on the latter which carry a minus sign denote the negative charges, anions, or anionic groups that are fixed to the pore walls and form the immovable part of an electrical double layer. The plus and minus signs in the pore water represent the movable (univalent) cations and anions.

In the widest pore (Fig. 1a) there are 15 movable cations and eight movable anions; in the next narrower pore (Fig. 1b) the numbers are eight and one, respectively. The narrowest pore (Fig. 1c) contains only the seven movable counterions of the fixed wall charges; it behaves, therefore, as a pore of ideal ionic selectivity.

With increasing concentration of the outside electrolyte solutions, an increasing quantity of electrolyte tends to enter the pores. The specific influence of the pores is thereby decreased; in other words,

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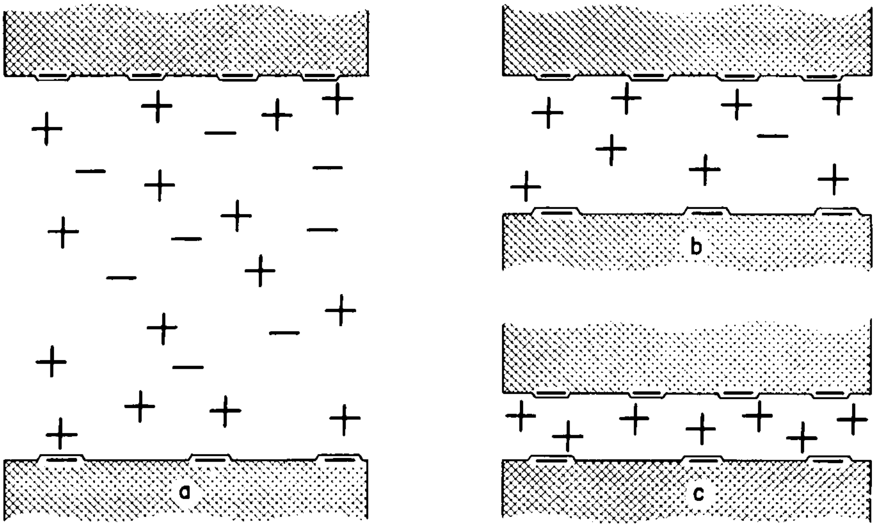

Fig. 1. The distribution of ions in three pores of different diameter at the same concentration of the outside electrolyte solution.

the ionic selectivity of the membrane is reduced. At sufficiently high concentrations some electrolyte may enter even rather narrow pores, such as the one shown in Fig. 1c, which thereby would lose their perfect ionic selectivity.

Polyvalent ions with a charge of the same sign as the membrane are much more restricted in their permeation across the membrane than univalent ions, not only because of their ordinarily larger size but also because of their higher charge, which prevents them by electric repulsion from entering pores which are accessible to univalent ions of the same sign.

The pores of real membranes are, of course, not regular, cylindrical, and perpendicular to the membrane surfaces as indicated in the highly schematic Fig. 1, but they are the irregular interstices between the more or less randomly arranged micelles or polymer molecules of which the membrane consists. Membranes consisting of organic polymeric materials in many instances may be visualized as brush-heap structures or as more or less dense gels of intertwining fibrous molecules or bundles of such molecules which might or might not be interconnected by primary chemical bonds as in ion exchange resins. The pore systems of all artificial membranes heretofore studied are networks of more or less irregular, branching, and interconnected channels whose cross sections vary in size and shape from one spot to the next. Such a pore system may also include dead-end cavities which are nonfunctional for cross-membrane diffusion or electromigration of ions. There is little doubt that the degree of this type of heteroporosity [60-64, 86] differs greatly according to the matrix material of which the membrane consists and the preparation method used. The extent to which very thin, natural or artificial membranes, perhaps of a semicrystalline or mesophase nature, may approach a fair degree of homeoporosity is still an open question.

The availability of any particular pathway across a membrane for nonelectrolytes of a given molecular size is obviously determined by its narrowest spot; with electrolytes or, more correctly, with ions the availability of a pathway depends upon a combination of this geometrical factor and the electrical factor, the repelling action of the fixed wall charges on ions of the same sign. Figures 2a and 2b indicate how, in geometrically identical pores, the location of fixed charges may determine the ion permeability and thereby also the electric characteristics of the pore. The continuous circles around the plus or minus signs represent here the size of the ions including their effective shell of hydration; the broken lines indicate the effective range of the electrical force of repulsion which, at the given ionic strength, acts between the charges situated on the pore walls and ions of identical signs in the pore water. The tips of the arrows show how far the ions identical in sign with the charged wall groups may move from the left side toward the right.

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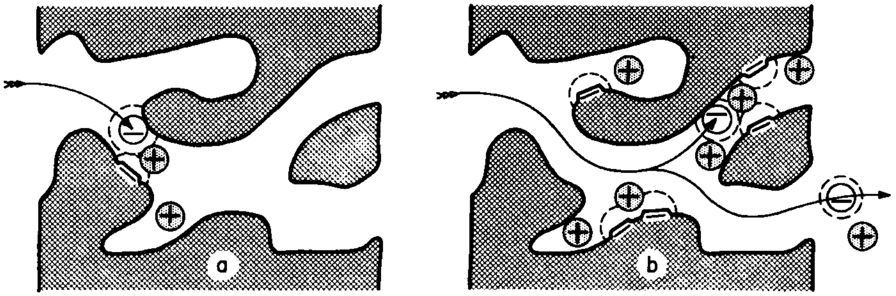

Fig. 2. The influence of the location of fixed charges at the pore walls of irregular and branched pore upon the blockage of ions of the same sign.

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A single fixed wall charge located at a fairly narrow part of the pore with no alternate pathway blocks this pore to ions of the same sign of charge as the membrane (Fig. 2a), while several less strategically located wall charges leave the pore permeable to these ions (Fig. 2b).

We now return to the question of the origin of the electrokinetic charge of membranes. Of the early workers, seemingly only Bethe and Toropoff dealt with this problem explicitly [36]: "The charge of the immovable liquid at the pore walls may be visualized as being due either to adsorption or, in appropriate cases, e.g., with protein, gelatin, etc., as due to the dissociation of the wall material. The nature of the proteins as amphoteric electrolytes, yields for this latter view a particularly clearly visualisable possibility, whereas with all other materials, e.g., collodion, one would have to rely on the still rather unclear hypothesis of ion adsorption. In principle, the result is the same in both instances" (author's translation). Loeb's view [41-44] on the origin of the charge of "proteinized" collodion membranes, that is, membranes whose pore walls are covered by proteins adsorbed from solution, was essentially identical to that of Bethe and Toropoff. This view, which we now know is correct, was not generally accepted. As late as 1933 Michaelis [52] still considered as unsolved the vexing question of the origin of the charge of membranes consisting of such supposedly inert materials as collodion.

With rare exceptions, mainly some of Loeb's proteinized membranes in acidic solutions, electropositive membranes were not available for study since nearly all natural and artificial membranes, including the collodion membranes, are charged negative in most electrolyte solutions. Making use of the well-known fact that basic dyestuffs impress their positive charge on almost any material, several investigators prepared positive collodion matrix membranes by casting membranes from collodion solutions containing basic dyestuffs [44, 55, 87], and alkaloids [87]. Dense, "dried" membranes of very high resistance prepared in this manner in some instances retain their fairly satisfactory electropositive characteristics for prolonged periods. Wide-pored membranes activated with these substances, however, soon lose these materials to the adjacent solutions and thereby also lose their electropositive charge and their permeability characteristics.

Another basic problem in the electrochemistry of porous membranes is the exact location of the ionic process or processes which give rise to the electromotive forces of membrane cells, that is, whether or to what extent these processes occur at the membrane-solution interfaces or in the body of the membranes.

The above-outlined treatment of the membrane potentials across porous membranes is based on the Nernst-Planck [30, 34] concept of the liquid junction potential and thus seems to imply that a single electromotive process occurs throughout the thickness of the membrane. Michaelis [49, 52], though aware of the conceptual difficulties which arise from the application of this approach to porous membranes, did not try to resolve them.

The question of the location of the electromotive membrane processes had been clarified in principle for the case of "oil" membranes by Luther [5], Nernst [6, 7], and Haber [9, 10] and their collaborators, who showed that in one of two conceivable limiting cases the measurable EMF is solely the liquid junction potential within the bulk of the liquid membrane phase, while in the other limiting case the membrane potential is solely the difference between the two phase boundary potentials which arise at the two membrane-solution interfaces.

Sollner in 1930 [60], on the basis of the work of these investigators, came to the conclusion that the measurable membrane potentials across porous membranes consist ordinarily of three parts—the two phase boundary potentials at the two membrane-solution interfaces and a diffusion potential within the membrane. The magnitudes of the potentials arising at the membrane-solution interfaces were considered to be determined by the concentrations of the two solutions separated by the membrane and the assumed corresponding equilibrium distribution concentrations within the immediately adjacent layers of the water within the pores: these latter concentrations also determine the magnitude of the cross-membrane diffusion potential. No attempt was made to cast these ideas into a quantitative framework. Similar views on "mixed" membrane potentials were developed independently by Wilbrandt [87].

Teorell [88], in 1935, was the first to express the idea of "mixed" potentials in a quantitative manner. Following the example of the earlier investigators, he based his considerations on the classical

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concept of the diffusion potential [90] as developed by Nernst [30], Planck [34], and Henderson [91].

> "Consider a membrane which carries electrical charge. This charge may be due to an electrolyte character of the membrane substance itself, or the charge may be caused by 'adsorption' or polar groups, etc. For simplicity we may represent the membrane by X^- behaving as an *immobile*, negative ion uniformly distributed within the membrane. Then NaCl is placed on both sides of the membrane. What will happen? The very beginning is hard to account for, but ultimately an ionic distribution according to the sketch [Fig. 3] may be attained. Two Donnan distributions are obtained, one at each phase boundary (where Na > Cl). At the same time two potential jumps appear, φ_1 and φ_2 [each being of the form 58. log ($Na_{bulk}/Na_{membr.}$)]. Besides these two boundary potentials, there must arise a common diffusion potential, π. This can be easily calculated according to Henderson's formula, because all concentration gradients are likely to be linear. The complete formula for the total membrane P.D., i.e., the 'mixed' potential, is written
>
> $$\text{Total P.D.} = 58\left[\underbrace{\log \frac{a_1 \cdot Na_2}{a_2 \cdot Na_1}}_{\text{Donnan}} + \underbrace{\frac{u-v}{u+v} \log \frac{Na_1\,(u+v) - X \cdot v}{Na_2\,(u+v) - X \cdot v}}_{\text{Henderson}}\right] \qquad (11)$$
>
> Here a_1 and a_2 are the bulk concentrations of the NaCl, Na_1 and Na_2 the boundary concentrations due to the Donnan distribution and u and v the mobility of Na and Cl. If X denotes the 'membrane concentration,' then Na_1 (and Na_2) can be evaluated from Donnan equations $a_1 \cdot a_1 = Na_1 \cdot Cl_1$ (after substitution of Cl_1 by ($Na_1 - X$) one finds that
>
> $Na_1 = \sqrt{a_1^2 + 0.25\,X^2} + 0.5\,X)$."

Shortly after Teorell, Meyer and Sievers [92] presented independently and in much greater detail essentially the same theoretical approach to the tripartite origin of the membrane potential. Most important, both from the conceptual and the experimental point of view, these authors incorporated into their presentation the assumption that the number and distribution of the fixed wall charges in the membrane are independent of the nature and concentration of the outside solution. In other words, Meyer and Sievers state—and emphatically so—that the characteristic electrochemical properties of porous membranes ordinarily are due to their ion exchange characteristics, which stem from the polyelectrolyte nature of the material of which most membranes consist; they proved this point

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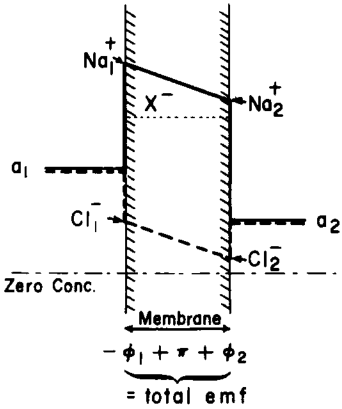

Fig. 3. Concentration profile across an ionic membrane (after Teorell [89]).

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in a simultaneous experimental study [93] of fundamental importance for the further development of the electrochemistry of membranes (see below).

A really adequate presentation of the mathematical formulation of the Meyer-Sievers theory is not possible in the limited space available and it must suffice to present here a condensed outline in Meyer's own words [94]:

> "Consider a membrane consisting of an acid high-molecular substance, for instance of pectin chains, of which the carboxyl groups have been neutralised with metallic cations, e.g., potassium ions. The membrane then possesses fixed anions and mobile cations. The cations may therefore be displaced if a supply of others is maintained from one side: the membrane is cation permeable. The concentration of the fixed anions, calculated in gram equivalents per litre of the imbibed liquid, is a quantity characteristic for each membrane which we will call the 'selectivity constant,' A. If now the membrane be immersed in a salt solution, both ions of the salt will penetrate into it; the equilibria then obtaining may be calculated from the Donnan equation: the actual membrane behaves like a solution bounded by two ideal Donnan membranes through which the fixed ions cannot pass....
>
> "If a current is passed across the membrane, the transport of the electricity will be divided between the two kinds of mobile ions in accordance with the relative numbers of ions passing through the membrane. The ratio, n_C/n_A, between the numbers of cations and of anions traversing the membrane,

which we will call the ratio of the transport or 'traversal' numbers, may be determined by the same methods as those used for the determination of transport numbers in a solution. n_C/n_A depends on the rates of migration of the mobile ions and on their number; as mentioned above, the latter is dependent on the concentration of the ions in the surrounding liquid. We then obtain

$$\frac{n_C}{n_A} = \frac{U_C \cdot (y + A)}{U_A \cdot y} = \frac{U_C}{U_A} \cdot \frac{\sqrt{4c^2 + A^2} + A}{\sqrt{4c^2 + A^2} - A} = \frac{U_C}{U_A} \cdot R \qquad (12)$$

where U_C and U_A are the rates of migration, c the molar concentration of the salt in the surrounding liquid, and A the selectivity constant...." [y is the concentration of mobile anions in the membrane.] "The dependence of the selectivity, i.e. of the quantity n_C/n_A, on the concentration is expressed by the factor R. Its dependence on the ratio c/A is shown by the following table:

c/A	10	1	0.1	0.01	0.001
R	1.1	2.6	101	10,000	1,000,000

"If we therefore take a membrane with wide pores such that the concentration of the fixed ions in its aqueous parts is normal ($A = 1$, $c^2/A = c^2$) and surround it with a salt solution the ions of which have equal mobilities, then R will equal the selectivity n_C/n_A. The dependence of n_C/n_A on the external concentration has, as mentioned above, been long known (the 'concentration effect'), but so far without having been explained.

"Ionic selectivity is not, however, the sole factor governing ionic permeability: in a network the 'sieve effect' can also occur, its importance being the greater the finer the mesh of the net; this will in general be the case with membranes which contain little liquid of imbibition. Finally the 'solubility' of the ions in the membrane may also play a part. By this we mean that, as a result of the attractive influences of the organic groups of the membrane, some, say organic, ions may attain a greater concentration in the aqueous liquid of imbibition of an organic membrane than in pure water. The complete equation therefore reads

$$\frac{n_C}{n_A} = \frac{U_C}{U_A} \cdot \frac{\sqrt{4c^2 \, l_C \, l_A + A^2} + A}{\sqrt{4c^2 \, l_C \, l_A + A^2} - A} \qquad (13)$$

where U_C/U_A is the ratio of the rates of migration in the membrane under the influence of the sieve effect, and l_C and l_A the

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> solubility coefficients (partition coefficients) of the ions with respect to membrane and water.
>
> "Now these two essential properties of the membrane—its sieve action with respect to different ions (as expressed by the quotient U_C/U_A) and its selectivity constant, can be determined by measuring the traversal numbers at different concentrations. The potentiometric method is the best; the potential set up when the membrane separates two solutions of the same salt, but of different concentrations is measured, the absolute concentrations being varied in such a way that their ratio is kept constant. When there is no ionic selectivity the potential is determined only by the quantity U_C/U_A, which is dependent on the absolute concentration; the greater the value of A as compared with the external concentration, the more marked will be the ionic selectivity.
>
> "A, the selectivity constant, and U_C/U_A, which includes the expression for the sieve effect, can be quantitatively determined either by calculation or graphically..." [on the basis of EMF measurements in concentration cells].

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This selectivity constant of Meyer and Sievers, A, is much less constant [95] than was assumed by these authors. Its true, physical meaning has also been questioned [96]; nevertheless, it is useful in the rough characterization of membranes. Meyer and collaborators soon tried to extend their theory to various systems and tested it under a variety of conditions [97-99].

Meyer and Sievers [93, 99] concluded that the ion exchanger properties of most natural and artificial membranes are the cause of their charge in systems with solutions of the common, strong, inorganic electrolytes. For the special case of collodion membranes this conclusion was confirmed in detail and quantitatively in the author's laboratory [96, 100, 101]. However, one must not forget that with solutions containing heavy metal, polyvalent, or other strongly adsorbable ions including proteins and many polyelectrolytes, the sign and the magnitude of the charge of membranes are ordinarily determined by the (concentration-dependent) adsorption of these ions.

The further development of the theory of ionic membranes stems from several sources. There was the intensified interest of biophysicists and neurophysiologists in the dynamics of cross-membrane ionic processes which showed up clearly in papers by Cole and Curtis, in 1939 [102], and by Goldman [103]. This line of reasoning in a more or less modified form is currently used by most neurophysiologists, as exemplified by the classical work of Hodgkin and Huxley [104]. Teorell [105-107], too, renewed and intensified his interest in the theory of ionic membranes and gave some rather elaborate treatments which consider the details of the ionic fluxes across membranes: membrane conductance, membrane rectification, membrane capacitance and reactance, the spatial distribution of ions (i.e., the ionic concentration profiles and the concomitant potential profiles within the membrane), water flow, electro-osmosis, and, more recently, periodic phenomena [108].

Another factor which indirectly furthered the development of the theory was the creation in 1944 of "permselective membranes" (discussed in the next section), which combine extreme ionic selectivity with high transmissivity for the nominally permeable ions and thus represented new, desirable objects for experimental work. The subsequent preparation of a variety of such permselective membranes by various investigators thoroughly familiar with the theory and practice of ion exchangers was a most powerful stimulus to the ever-accelerating study of the electrochemistry of membranes. Since the early 1950s, when ion exchanger chemistry had already reached a considerable degree of sophistication, a large part of the theoretical work on ion exchangers has been incorporated into the systematic physical chemistry of ion exchange membranes, as is most clearly evident from Helfferich's [109] excellent monograph on ion exchangers.

Space would not permit, and the purpose of this paper makes it unnecessary, to go into the details of the theory of ionic membranes. However, at least a few of the most productive investigators in the field in addition to Teorell [105-108] must be mentioned: Schmid [110], Scatchard [85, 111], Mackie and Meares [112], Helfferich [109, 113], and Schlögl [114, 115]; also Sollner and Dray [116, 117] and Wyllie [118]. Staverman [119], Spiegler [120], Kedem and Katchalsky [121], and others have applied with increasing success the methods of irreversible thermodynamics to the kinetics of the various effects arising within and across ionic membranes. Caplan and Mikulecky [122], two of the most active workers in this field, have recently presented an exhaustive review on these and related problems.

Several synoptic reviews with copious references, primarily those by Lakshminarayanaiah [123], Schlögl [115], and Helfferich [109], summarize in a critical manner the current state of electrochemistry of membranes in general. Tasaki [21] has recently surveyed the properties and functions of ionic membranes from the point of view of the neurophysiologist.

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The Preparation of Ion Exchange Membranes of High Electrochemical Activity; "Permselective" Membranes of Highest Ionic Selectivity and Transmissivity

The previously rudimentary art of preparing membranes of considerable electrochemical activity received a novel, and in the long run most productive, stimulus when Meyer and Sievers [93], in the experimental study which accompanied their theoretical paper, utilized the methods of the just emerging polyelectrolyte chemistry for the preparation of membranes. These authors synthesized several polyacids and polybases for the preparation of electrochemically active membranes by the known adsorption and dissolution methods. They further described some new methods for the preparation of ion exchange membranes; they created dissociable groups on preformed membranes by a chemical reaction, the oxidative formation of carboxyl groups on cellulosic membranes, and made membranes by synthetic methods akin to those used now in the preparation of commercial ion exchange resins, thereby laying the groundwork of an art that about 15 years later started to attract industrial interest. In this context it is of interest to recall that the first synthetic ion exchange resins had been described just one year earlier in 1935, by Adams and Holmes [124].

The work of Meyer and Sievers on the preparation of ionic membranes [93, 98] was more important for its demonstration that the preparative methods of the (then) new polyelectrolyte and ion exchange resin chemistry open up new possibilities of membrane preparation, than for the quality of their membranes, many of which were of poor stability. Meyer's laboratory, however, showed only limited interest in the improvement of the methods of membrane preparation [98]. Further progress in this direction was slow and laborious; years elapsed before other investigators [125-130] made use of Meyer's most fruitful example of using the methods of synthetic polymer chemistry for the preparation of ion exchange membranes, which today dominate all industrial work in this field.

Marshall et al. [131-133], in 1939, were seemingly the first to take up the ideas of the Teorell and Meyer-Sievers theory. Their limited purpose, from the point of view of the electrochemistry of membranes per se, was the preparation of membranes of high ionic selectivity from zeolitic silicates, particularly from clays, for use as "membrane electrodes" in the determination of activities of cations in solution. These membranes were rather fragile, mostly of inherently limited stability, of high electrical resistance, and rather slow in their electromotive response. Nevertheless, these membranes enabled Marshall and collaborators to determine the activities of the alkali ions and of Ca^{2+} and Mg^{2+}, primarily in single-electrolyte solutions but also in mixed solutions. In his later papers, Marshall seems inclined to consider his clay membranes as physically more akin to the solid electrolyte phases studied by Haber et al. [8, 9], such as the pH glass electrode [9], than to the porous structures considered here. The experimental difficulties in the use of the clay membranes are probably the reason that Marshall's great experimental and theoretical contributions to the electrochemistry of membranes have not received the deserved recognition. Most of Marshall's original goal has been reached in recent years by the development of glass membrane electrodes which are responsive specifically to the various alkali ions [134].

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The author and his collaborators started their systematic investigations on the electrochemistry of porous membranes in 1939. It soon became apparent [135] that the first objective must be the development of methods for the preparation of membranes which would show the characteristic electrical effects and permeability properties to very pronounced degrees. From the beginning it was clear that, other things being equal, the electrochemical activity of membranes of porous character of a given porosity will be higher, the greater the number of potentially dissociable groups per unit area on the walls of the pores. For most purposes it is necessary that the membranes be chemically and mechanically stable so that their properties remain constant during prolonged serial experiments, that they be reasonably uniform over their whole area, and that they can be reproduced by dependable procedures; and last but not least, it is highly desirable for most exploratory work that the membrane porosity can be readily varied over wide ranges so that families of chemically identical membranes of different, graded degrees of porosity may be studied.

Following the example of Bethe and Toropoff [36, 37], Loeb [39-44], and Michaelis et al. [46-52], we chose collodion as the matrix material for our membranes. Collodion was one of the very few materials (all cellulose derivatives) then available from which membranes of graded porosities could be prepared readily and reproducibly by simple laboratory methods [136-141], a property in which the cellulose derivatives still seem to outrank all other materials.

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For the preparation of membranes these materials are dissolved at suitable concentrations in appropriate solvents or solvent mixtures, and these solutions are spread on smooth supports, ordinarily glass or mercury. Next, the solvent is allowed to evaporate to a predetermined extent under controlled conditions [136-141]. When the concentration of the matrix material in the film has reached the desired concentration and the film itself a suitable degree of cohesion, the foil thus formed and its support are immersed in water. Thereby the matrix material is precipitated in the form of a film and the nonaqueous solvent replaced by water. Thus a coherent hydrogel of the matrix material with the desired degree of porosity, the membrane, is obtained which now can readily be removed from the support on which it was cast. The porosity of this primary membrane may later be adjusted by further drying or by swelling in a suitable organic swelling agent.

Our membranes were prepared from ether-alcohol solutions of collodion or of collodion plus polyelectrolyte. Initially [100, 135], we cast them in the conventional manner on the inside of test tubes; later [142-145], to increase the macroscopic homogeneity of the membranes and to improve the reproducibility of their preparation, we cast them by pouring the collodion solutions over horizontally rotating test tubes and drying the resulting films for carefully stan-

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dardized periods. In most instances a second and a third layer of collodion were added. The porosity of these membranes depends primarily on the length of time they are dried prior to their immersion in water. In this manner, membranes may be obtained whose porosities were varied at will from wide-pored, dialyzing-type membranes to very dense, molecular sieve membranes. Reproducible variations in and near this latter range of porosities were achieved by controlling the temperature and relative humidity during the drying process and in some instances by reswelling in alcohol of controlled water content. The details of these procedures can be omitted here, though they are of utmost importance in the preparation of membranes of optimal prespecified properties. One of the major problems in the preparation of dissolution-type membranes is the rarity of compatibility of the activating polyelectrolyte and the matrix material in the solution from which membranes are cast. This is a difficulty which arises with all matrix materials, not only with collodion.

Acidic, electronegative membranes of high electrochemical activity have been prepared by the use of collodion which had been oxidized in bulk and by the oxidation of formed collodion membranes [96, 100, 101, 142, 144]; by the dissolution of polyacids such as sulfonated polystyrene in the collodion solution from which the membranes are prepared [146-148]; and by the adsorption of polyelectrolytes on formed membranes [146-148].

Basic, electropositive membranes of high electrochemical activity have been first obtained by the adsorption, on highly porous collodion membranes, of protamine, a basic protein with an isoelectric point higher than pH 12 and a molecular weight of around 3000 [143, 145, 149, 150]. These membranes, the first really satisfactory positive membranes described in the literature, are extremely stable and fully maintain their essential characteristics over a wide pH range, about 2.8-8.5. Similar to these are membranes prepared by the adsorption method with poly-2-vinyl-N-methyl-pyridinium bromide as activating polyelectrolyte [151].

The dialyzing-type, high-porosity membranes of high electrochemical activity prepared by the indicated procedures have thus far met with little interest, while the generically similar, dense, ion sieve-type membranes have attracted widespread attention, as we shall see shortly. It therefore seems best to present here a few experimental data which characterize the former type of membranes.

The two basic electrochemical parameters for the characterization of membranes of high porosity are the membrane concentration potential and the rate of electro-osmosis across them. The differences in electrochemical behavior between low-charge-density and high-charge-density membranes are more conspicuous at medium and high concentrations than at very low concentrations, for the reasons stated before in the discussion of Fig. 1. The higher the concentration potential and the higher the rate of electro-osmosis, the greater is the "electrochemical activity" of a membrane of given porosity. A meaningful comparison of membranes of different electrochemical activities can, of course, be made only if their geometrical pore structures are similar. In this context it is important to note that the osmotic and permeability properties of highly porous collodion membranes are not significantly altered by oxidation [152]. This indicates that oxidation does not grossly affect the geometrical structure of collodion membranes. Thus we can compare the electrochemical properties of objects which structurally are very similar, namely, a membrane in the nonoxidized, electrochemically rather inactive state and the same membrane in the electrochemically active state after numerous dissociable groups have been formed throughout its microstructure.

A membrane of the dialyzing type, before oxidation, gave, in the concentration cell KCl 0.1 M | membrane | KCl 0.01 M, a concentration potential of 1.6 mV, after oxidation of 25.0 mV [152]. With protamine collodion membranes (of the same hydraulic properties) the result of activation is analogous [149].

The influence of activation by oxidation on electro-osmosis can be seen in columns 1-3 of the self-explanatory Table 1 [152].

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Table 1. Electro-osmosis through a Typical Unoxidized Collodion Matrix Membrane of High Porosity, the Same Membrane after Oxidation, and a Protamine Collodion Matrix Membrane of about Equal Porosity

1	2	3	4
	Electro-osmotic flow in $mm^3/100\ cm^2$ per hr with a current intensity of 0.1 mA/cm^2 [a]		
Concn. of KCl solution, equivalents/liter	Unoxidized collodion membrane, mm^3	Oxidized collodion membrane, mm^3	Protamine collodion membrane, mm^3
0.00100	+2840	+4640	—4380
0.0100	+360	+1800	—1680
0.100	±0	+210	—80

[a] A plus sign indicates transport toward the cathode, a minus sign transport toward the anode.

Column 4 of this table shows the analogous effect of activation by the adsorption of protamine on a collodion membrane of closely similar porosity [149].

Another rather sensitive and very convenient way to compare the electrochemical activity of membranes of high porosity is the study of the rate of "anomalous osmosis" across them, a topic that will be taken up in the next section when discussing anomalous osmosis per se as an effect of particular biophysical interest.

We turn now to the dense, ion sieve-type membranes prepared by the above-outlined methods, which combine formerly unknown degrees of highest ionic selectivity over fairly wide concentration ranges with electrical conductances several orders of magnitude higher than those of any previous membranes of reasonably high ionic selectivity. These membranes, for which we have coined the term "permselective" membranes [142], facilitate under the proper conditions high rates of diffusive through-fluxes of the permeable species of ions and high rates of their electromigration across them under the influence of an applied electromotive force. Likewise, the rates of exchange across permselective membranes of two (or more) different species of permeable ions of the same charge may be high, corresponding to the relatively high conductance of these membranes (see below). For these reasons, as pointed out in a lecture in 1949, such membranes are suitable for various preparative and industrial operations [84].

The anticipated industrial usefulness of permselective-type membranes, particularly in electrodialytic water desalination [153] (quite aside from their value as membrane electrodes [19, 154, 155] discussed below), was obviously the main reason why, since 1950 [125-127], an ever-increasing number of publications has appeared which deal with the preparation, properties, and various uses of permselective membranes which are not based on a collodion matrix [128-130, 156-170]. Most of these membranes were prepared by the use of ion exchange resins or by the techniques used in the preparation of commercial ion exchange resins.

The literature on the preparation of permselective membranes, which contains numerous patents, is too voluminous and repetitive to be discussed here in detail. In a rather oblique terminology, so-called "heterogeneous" and "homogeneous" membranes are distinguished. "Heterogeneous" membranes are prepared by embedding macroscopic or microscopic particles of ion exchange resins in an inert polymer binder, which provides the cohesion and mechanical strength required in a membrane. The swelling and shrinking, however, which the ion exchanger particles undergo with changes of the composition of the milieu, severely limit the stability of such "heterogeneous" membranes.

Many types of "homogeneous" membranes are obtained by polymerization processes of the type which lead to the formation of ion

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exchange resins, but carried out under such conditions that the products are in the shape of membranes—a feat which seemingly has been achieved only with a limited number of materials, as emphasized by Helfferich [109]. Some such membranes are reinforced by various supports (e.g., woven fabrics), are over 1 mm thick, and have high exchange capacities per square centimeter, a feature decidedly undesirable in many types of exchange studies [171]. Gregor and collaborators [162], using the dissolution method, prepared most promising "homogeneous interpolymer" membranes of rather uniform structure from solutions containing a linear polyelectrolyte and an inert linear polymer as matrix materials of very high mechanical strength and chemical inertness, such as Dynel. Somewhat similar "homogeneous" membranes were prepared by Chen et al. [161] by a process of graft polymerization—a fairly flexible and promising method.

For the last 16 years, many types of highly selective ion exchange membranes manufactured for specific industrial purposes, mainly electrodialysis, have been available from various manufacturers in this country and abroad. Most of these membranes are vastly superior to collodion matrix membranes both in mechanical ruggedness and resistance to alkaline solutions. While membranes of different brands differ considerably in their properties, each brand comes in very few grades, the properties of which, including porosity, cannot be modified by the user. The ionic selectivities of many types are lower than those of our permselective collodion matrix membranes. Many of the commerical types of ion exchange membranes described in the literature, including some of the most desirable types, particularly the Dynel interpolymer membranes, are unfortunately not obtainable anymore. Reviews on the preparation of ion exchange membranes have been given by Spiegler and Wyllie [172], Helfferich [109], Lakshminarayanaiah [123], and, very briefly, by Hills [173]. These authors also mention several of the then-existing sources of supply of commercial permselective membranes.

In spite of the great amount of work that has gone into the preparation of permselective membranes, there are still many problems which need the attention of polymer chemists of a high degree of inventiveness and ingenuity. The most urgent problems include: the preparation of membranes of high stability in alkaline surroundings, a feature of great importance in the technological use of such membranes; methods for the production of families of membranes of identical chemical compositions with graded porosities; and last but not least, of primary scientific importance and considerable technological potentialities, the problem of the preparation of membranes of considerable ionic specificity—this means the creation of membranes able to distinguish to very pronounced degrees between ions of the same charge but of different chemical nature (aside from the effect of ionic size). This problem, of course, is closely related to

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the question of ion specificity in ion exchangers in general, which has been found to be most refractory. That it is not hopeless, however, can be concluded from the fact that many living membranes of undoubted ion exchange character show very high degrees of ionic specificity, the best-known instance being the extreme K^+ specificity of many cell membranes.

The Basic Electrochemical Properties of Permselective Membranes

This section reviews the fundamental electrochemical properties of permselective membranes. The specific data were obtained in the author's laboratory with collodion matrix membranes, the original and still representative examples of permselective membranes in general. Other types of permselective membranes tend to follow the same general pattern, except for the unit area exchange capacity and water content, which are much higher with most brands of ion exchanger resin-type membranes.

Our membranes are test tube-shaped, glass clear, and perfectly smooth. For easy handling they may be tied with linen thread to wide glass rings which fit inside their open end. Their thickness can be varied at will; ordinarily we used two- or three-layer membranes with a thickness in the dry state of 30-40 μ [142-151].

In more recent years we have characterized our membranes routinely [147, 150, 151] by measuring the following parameters: their exchange capacity in microequivalents per square centimeter, their water content, the rate of osmotic water movement across them, their resistance per square centimeter when equilibrated with 0.1 M KCl, ρ^*, and the concentration potentials which they yield in cells 0.4 M KCl | membrane | 0.2 M KCl. Membranes selected for special purposes were characterized more closely by the determination of the concentration potentials $c_1:c_2 = 2:1$ over a wide range of concentrations [147, 150, 151], and by the direct measurement of the relative leakage of noncritical ions.

The exchange capacity of the membranes was measured by the conventional methods of ion exchange chemistry with rectangles cut from the cylindrical part of the membranes. To measure the water content, these flat membranes were blotted, and weighed in the wet state. They were then dried over phosphorus pentoxide in vacuo. The loss in weight was taken as the water content. The results are expressed as g of water/100 g of wet membrane. To measure the rate of osmotic water movement across a membrane, it was filled with a 0.2 M solution of sucrose (for which the membranes are virtually impermeable), fitted with a rubber stopper carrying a graduated capillary manometer tube, and placed in a beaker of water at 25.00 ± 0.05°C; the rise in the meniscus in the capillary was measured at intervals.

The ohmic resistance of the membranes in 0.1 M KCl solution, ρ^*, was measured at 25.00 ± 0.05°C by the Kohlrausch method using test tube-shaped electrodes [144].

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The membrane concentration potentials were determined in cells with the concentration ratio $c_1:c_2 = 2:1$. (The sign in the tables refers to the solution with the lower concentration c_2.†) Most measurements were made with saturated calomel electrodes with saturated potassium chloride agar bridges; the raw experimental data were corrected for the asymmetry of the liquid junction potentials at the tips of these bridges [144-147, 150, 151]. When the electrolyte used was a chloride, the measurements in some instances were made with silver-silver chloride electrodes. The accuracy was in most instances better than ±0.05 mV. The theoretical maximum values of the concentration potential were computed from Eq. (7), using standard activity data converted from the molality to a molarity scale. The accuracy of the calculated E_{max} values might be estimated to be of the order of ±0.05 mV except with the highest concentrations where the error might be appreciably greater.

Table 2 summarizes the properties of a series of representative permselective polystyrene sulfonic acid (PSSA) collodion matrix membranes prepared by the sorption method [147]. Data obtained with other types of collodion matrix membranes, such as permselective poly-2-vinyl-N-methyl pyridinium (PVMP) membranes [151] and protamine collodion membranes [150], are very similar.

The low unit area-exchange capacities (Table 2, column 2) are helpful in many physicochemical experiments where it is desirable to have membranes with exchange capacities which are low relative to the number of equivalents of exchangeable ionic constituents in the surrounding solutions. The water content of the membranes (Table 2, column 3) is higher, the higher the loading of the membrane with polyelectrolyte. The rate of osmotic water movement across the membranes (Table 2, column 4), which is measured under a driving force corresponding to 50 m of water pressure, is low except in the case of those with the highest content of polyelectrolyte. It is greater the higher the water content of the membranes (Table 2, column 3). Low water permeabilities are helpful in studies where it is necessary to keep solutions of different water activity separate for long periods.

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†Ion exchange membranes respond electromotively in a proper manner only if their "critical" ions are the same as those contained in the outside solutions. To assure correct results it is best to equilibrate the membrane with the outside solution or solutions; the period required for this varies with permselective collodion matrix membranes from less than half an hour to several hours [174-176]. However, if a membrane saturated with a particular species of critical ions is transferred to solutions of different concentrations containing the same critical ion, its electromotive response in most instances is immediately correct and reproducible [174-176].

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Table 2. The Properties of a Series of Representative Polystyrene Sulfonic Acid (PSSA) Collodion Matrix Membranes Prepared by the Dissolution Method[a]

1	2	3	4	5	6
Concn. of PSSA in collodion solution, g/liter	Cation exchange capacity, μeq/cm^2	Water content, %	Av. rate of osmotic water movement (0.2 M sucrose), mm^3/hr 100 cm^2	Av. unit area resistance[b] in 0.1 M KCl, ρ^* (t = 25.00°C) Ω cm^2	Av. concn. potential[b] 0.4/0.2 M KCl (t = 25.00°C), mV[c]
0.30	0.19	5.0	5.3	50,100 (11,000)	15.16 (0.22)
0.50	0.32	5.6	8.4	2,030 (350)	15.45 (0.10)
0.70	0.50	5.7	13.7	435 (80)	15.48 (0.02)
1.0	0.69	7.0	57	54.5 (10.5)	15.32 (0.01)
1.4	1.14	10.3	190	26.3 (3.7)	15.09 (0.04)
2.5	3.20	26.8	2000	18.5 (3.5)	13.9 (0.2)

[a] After Neihof [147].

[b] Figures in parentheses indicate maximum deviations from the mean value obtained with sets of 12 membranes each.

[c] The theoretically possible maximum potential is 15.95 mV.

The resistance of the membranes (Table 2, column 5) depends on the loading of the membrane with polyelectrolyte; it decreases steeply with higher polyelectrolyte contents. The resistance varies with the concentration of the ambient solution. At higher concentrations the resistance decreases as "nonexchange" electrolyte enters the pore systems. This effect is less pronounced, the denser the membranes and the higher the charge density in their pore systems [147, 171]. With some membranes the resistance in the concentration range below 0.1 M may not vary by more than 10 or 20%, and is only twice as high with 2.0 M as with 0.01 M solution [147]. In the presence of slower and larger critical ions the membrane resistance is higher [177].

A comparison of the concentration potentials (Table 2, column 6) with the corresponding resistances (column 5) shows that the highest potentials, and thus the highest ionic selectivities, are reached with membranes in a medium resistance range; too low a content of polyelectrolyte does not provide a sufficient number of dissociable wall groups in all pores to prevent the leakage of noncritical ions. Membranes with rather high contents of polyelectrolyte tend to be too porous for optimal ionic selectivity.

Table 3 gives the concentration potentials obtained in KCl cells with two cation-selective and two anion-selective permselective collodion matrix membranes. It shows to what degree and in which concentration ranges various permselective membranes of moderately low resistance approach electromotive ideality. The oxidized collodion membrane, particularly in the range of higher concentrations, is decidedly inferior to the three other types. With these latter membranes the concentration potentials in cells with low and medium concentrations either reach the calculated maximum values within the accuracy of the data or are barely significantly lower. Membranes of somewhat higher resistance than those shown in Table 3 regularly give slightly higher potentials, particularly at the higher concentrations. The correlation of membrane resistance and membrane selectivity as determined by the concentration potential measurements is also evident from Fig. 4 [150]. The differences in the electromotive behaviour of different critical ions in concentration cells are small, as becomes evident when comparing the calculated theoretical maximum values, E_{max}, and (corrected) experimental values, E_{exp}, of the concentration potential shown in Table 4 [150].

With electrolytes having bivalent "noncritical" ions (not shown in the tables), the range of closest agreement between the experimental and the calculated values of the concentration potential is found to extend to much higher concentrations, well above 0.5 M [178, 179].

The deviation of these membranes from electromotive ideality in the range of low and medium-high concentration, as will be seen below, cannot be accounted for by the leakage of noncritical ions.

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Table 3. Concentration Potentials ($c_1 : c_2 = 2 : 1$) with Solutions of KCl across some Representative Permselective Collodion Matrix Membranes ($t = 25.00 \pm 0.05$°C)

1	2	3	4	5	6
Concn. of electrolyte soln. c_1/c_2, eq/liter	Theoretical maximum, mV	PSSA collodion membrane[a], mV	Oxidized collodion membrane[b], mV	PVMP collodion membrane[c], mV	Protamine collodion membrane[d], mV
0.002/0.001	±17.45	+17.25	±17.20	−17.17	−17.23
0.004/0.002	±17.31	+17.19	+17.04	−17.15	−17.13
0.01/0.005	±17.10	+16.97	+16.95	−17.09	−17.09
0.02/0.01	±16.86	+16.74	+16.74	−16.73	−16.81
0.04/0.02	±16.63	+16.52	+16.47	−16.48	−16.51
0.1/0.05	±16.30	+16.10	+15.80	−16.09	−16.12
0.2/0.1	±16.11	+15.74	+15.09	−15.73	−15.81
0.4/0.2	±15.95	+15.40	+13.90	−15.37	−15.30
1.0/0.5	±16.32	+14.58	+10.93	−14.48	−14.49
2.0/1.0	±17.34	+13.86	+8.01	−13.31	−13.33

[a] Polystyrene sulfonic acid membrane; $\rho^* = 80\ \Omega\ \mathrm{cm}^2$.
[b] $\rho^* = 300\ \Omega\ \mathrm{cm}^2$.
[c] Poly-2 vinyl-N-methyl pyridinium collodion membrane; $\rho^* = 70\ \Omega\ \mathrm{cm}^2$.
[d] $\rho^* = 21.5\ \Omega\ \mathrm{cm}^2$.

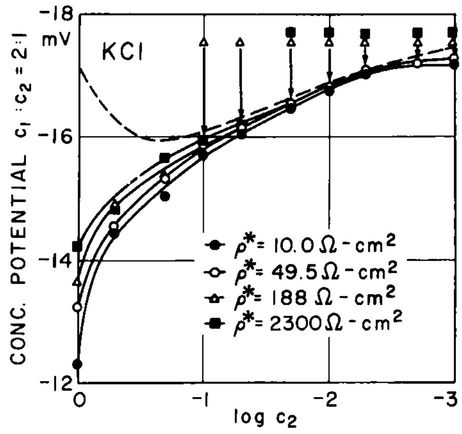

Fig. 4. Concentration potentials with KCl solutions ($c_1 : c_2 = 2:1$) across typical permselective protamine collodion matrix membranes of different standard resistances, ρ^*.

Table 4. Concentration Potentials ($c_1 : c_2 = 2:1$) of Several Electrolytes across a Permselective Protamine Matrix Membrane ($\rho^* = 660\ \Omega\ \text{cm}^2$) ($t = 25.00$ • $0.05°C$)

Concn. of solutions c_1/c_2, eq/liter	Concn. potential, mV					
	Potassium iodate		Potassium nitrate		Potassium acetate	
	E_{max}	E_{exp}	E_{max}	E_{exp}	E_{max}	E_{exp}
0.002/0.001	−17.5	−17.0	−17.52	−16.98	−17.43	−17.02
0.004/0.002	−17.3	−16.8	−17.40	−16.92	−17.34	−17.13
0.010/0.005	−16.9	−16.8	−17.12	−16.76	−17.16	−16.94
0.020/0.010	−16.7	−16.6	−16.72	−16.50	−16.97	−16.85
0.040/0.020	−16.1	−16.0	−16.27	−16.12	−16.82	−16.77
0.100/0.050	−15.1	−14.9	−15.58	−15.26	−16.79	−16.63
0.200/0.100	−14.1	−13.8	−15.02	−14.92	−16.85	−16.55
0.400/0.200	—	—	−14.19	−13.95	−17.27	−16.20

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The available evidence indicates that at least a major part of it is due to the fact that the critical ions pass across the membrane in a hydrated state [84,85].

Proper values of the ionic selectivity of highly ion selective membranes therefore cannot be calculated by use of Eqs. (9) and (9a) [179]. These data must be obtained by the direct measurement of the rates of exchange across the membranes of the critical ions and of the noncritical ions (for which the membranes are nominally impermeable) [147, 150, 151]. From these two measurements we compute the ratio (rate of exchange of critical ions)/(rate of exchange of noncritical ions) which is the true quantitative measure of the ionic selectivity of the membranes. The reciprocal of this ratio is the true measure of the degree of deviation from ideality of the membrane (under the conditions of the experiment), that is, of the relative "leakage" of noncritical ions.

The rate of exchange studies were carried out wherever possible with the aid of radioactive tracers. Representative data obtained with anion-selective membranes are shown in Table 5 [150, 151].

The methods used in these experiments were as follows: A membrane filled with a KCl solution containing radioactive ^{36}Cl was placed in a large volume of solution of nonradioactive KCl of the same concentration. Both solutions were stirred. Aliquots of the outer solution were periodically withdrawn and their radioactivity determined. The initial rate of anion exchange was calculated from the fraction of the radioactive chloride exchanging for stable chloride per unit time. The strictly comparable initial rate of exchange of the nominally nonpermeating cations can be obtained from analogous experiments only with membranes of very low resistance and relatively high rates of leakage of these ions because of the short half-life ($t_{1/2}$ = 12.4 hr) of the available potassium isotope ^{42}K. Instead, with the membranes of the extremely low cation leakage of particular interest here, the rate of exchange of cations between NH_4Cl and a KCl solution of equal concentration was determined by conventional microanalysis. This seems permissible in view of the great similarity in behavior of NH_4^+ and K^+ in solution as well as in cation selective membranes, and of the fact that the rates of exchange $^{39}K^+ \rightleftarrows {}^{42}K^+$ and $NH_4^+ \rightleftarrows K^+$ agreed satisfactorily in the case of those membranes with which both rates could be determined.

The various interrelationships of the data in the several columns of Table 5 cannot be discussed here. We note, in agreement with intuitive expectation, that the rates of self-exchange are in a rough manner inversely proportional to the membrane resistance (see below). The degrees of ionic selectivity of membranes prepared with different polyelectrolytes differ significantly, as is evident from Table 5. The highest selectivities that we observed were obtained with cation-selective sulfonated polystyrene (PSSA) mem-

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Table 5. The Rates of Movement of Critical and Noncritical Ions Across Several Anion-Selective Permselective Collodion Matrix Membranes at Various Concentration Levels in the System $^{36}KCl\ c_1 \parallel NH_4Cl\ c_1$

1	2	3	4	5	6	7	8	9	10
	Concentration								
	1.0 N			0.1 N			0.01 N		
Membrane ρ^* Ω cm^2	Initial rate of movement of Cl^-, μeq/hr per cm^2	Initial rate of movement of NH_4^+, μeq/hr per cm^2	Ratio of initial rates of movement of Cl^- to NH_4^+	Initial rate of movement of Cl^- μeq/hr per cm^2	Initial rate of movement of NH_4^+, μeq/hr per cm^2	Ratio of initial rates of movement of Cl^- to NH_4^+	Initial rate of movement of Cl^- μeq/hr per cm^2	Initial rate of movement of NH_4^+, μeq/hr per cm^2	Ratio of initial rates of movement of Cl^- to NH_4^+
a. Poly-2-vinyl-N-methyl pyridinium membranes									
9500	0.146	5.8×10^{-3}	25	0.133	19×10^{-5}	700	0.114	8.1×10^{-6}	14,000
900	4.42	0.37	12	2.96	5.4×10^{-3}	550	1.88	3.4×10^{-4}	5,600
330	6.55	0.16	41	5.08	3.9×10^{-3}	1300	3.15	9.8×10^{-5}	32,000
160	27.2	2.47	11	18.2	3.8×10^{-2}	480	8.7	1.05×10^{-3}	8,300
16	218	59	3.7	107	7.7×10^{-1}	140	43	1.43×10^{-2}	3,000
b. Protamine membranes									
5040	0.366	0.025	14.6	0.192	7.8×10^{-4}	250	0.180	5.8×10^{-5}	3,100
2780	0.638	0.034	18.7	0.376	1.1×10^{-3}	340	0.304	4.6×10^{-5}	6,600
450	4.64	0.380	12.2	2.46	5.6×10^{-3}	450	1.71	2.00×10^{-4}	8,550
113	17.9	1.09	16.4	8.34	2.10×10^{-2}	400	5.56	4.6×10^{-4}	12,000
24.5	121	16.7	7.2	42.8	2.09×10^{-1}	160	15.00	6.5×10^{-3}	2,300
9.5	267	33.6	7.9	110	1.18	93	17.2	1.36×10^{-2}	1,250

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branes [147] (which are not shown in Table 5). For example, with one such membrane with a $\rho^* = 80\ \Omega\ \text{cm}^2$, the selectivities were 40 : 1, 1280 : 1, and 67, 000 : 1 in 1.0 M, 0.1 M, and 0.01 M KCl solution, respectively [147]. The acidic groups of protamine and acidic impurities in the poly-2-vinyl-N-methyl pyridinium (PVMP) preparation used may explain the lower selectivities observed with the membranes prepared with the basic polyelectrolytes as activating materials. The ionic selectivities of permselective membranes with electrolytes having univalent critical and bivalent noncritical ions are, in 0.1 M solution, of the order of several hundred thousand to one [147, 150, 151]. With more dilute solutions these selectivities can be safely assumed to be even higher.

We turn now briefly to the relationship between the rates of ionic self-exchange across membranes and their resistances measured under the same conditions. According to the concepts of classical electrochemistry, as embodied in the Nernst-Einstein relationship between the diffusion coefficient and the equivalent conductance of an ion, there should exist a predictable quantitative relationship between the resistance of a membrane of extreme ionic selectivity and the rate of self-exchange of the permeable, critical species of ions at the same concentration. This matter is too complex to be discussed here in detail [171]. Suffice it to state that the consensus of experts in ion exchangers is that, due to electrophoretic effects, the exchange rates calculated from resistance data should be somewhat greater, of the order of 20 or 30% higher, than the experimentally determined rates of self-exchange [171]; this was borne out in the few instances reported in the literature. When we studied this matter more closely, it was found that oxidized collodion, protamine collodion, and PSSA collodion membranes behaved in the anticipated manner, as is shown for the example of three PSSA membranes in Fig. 5a [171]. However, with the PVMP collodion membranes there appeared substantial anomalies, as shown in Fig. 5b; here, the experimental rates of exchange are at low concentrations several times higher than those calculated from resistance measurements at the same concentrations. The cause of this apparent anomaly is not known; it is the object of current work.

The importance from a wider point of view of the data presented in the Tables 2-5 and in Fig. 4 is that truly permselective membranes (in general, not only the collodion matrix prototypes) are of a degree of ionic selectivity several orders of magnitude higher than those of ion-selective membranes available to the classical investigators, such as Michaelis, and that the resistances per unit area of the permselective membranes are several orders of magnitude lower. Ionic processes across permselective membranes therefore occur in a much more clear-cut manner and at rates which may be orders of magnitude greater than those obtainable with the older types of membranes. The permselective membranes

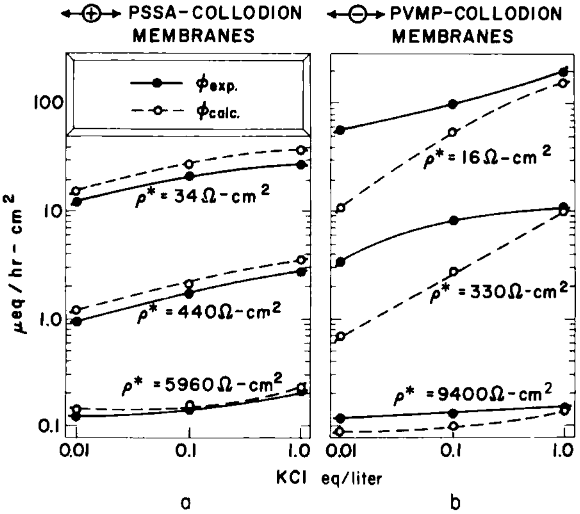

Fig. 5. A comparison of the experimental rates of self-exchange of critical ions across permselective membranes and of the rates calculated from the membrane resistances, (a) K^+ exchange across PSSA collodion matrix membranes, (b) Cl^- exchange across PVMP collodion matrix membranes.

therefore facilitate a great variety of studies which formerly were not in the realm of experimental possibility.

From the point of view of systematic electrochemistry, the permselective membranes may be considered as a special type of cationic and anionic conductors [84], in common with all other dense ion exchangers in which invasion by "nonexchange electrolyte" is minimal. In limited concentration ranges permselective membranes behave electromotively closely akin to layers of certain solid electrolytes having either anionic or cationic conductance only [84]. However, there are two fundamental differences between solid electrolytes and the permselective membranes. The former have a definite composition which is independent of the presence of other ions in the adjacent solutions, and the phase boundary potentials solid-liquid are, under ordinary conditions, determined solely by the activities in the adjacent solution of those species of ions of which the solid phase consists. This is in sharp contrast to the situation prevailing with permselective membranes, whose composition in mixed electrolyte solutions is a function of the nature and concentrations of the exchangeable ions in solution; therefore, in contact with mixed electrolyte solutions, permselective membranes are ordinarily not specific for only a single species of critical ions.

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The second fundamental difference between solid electrolytes and the permselective membranes is that within the former the potential determining species of ions are not solvated, whereas they are hydrated in the latter [84, 85].

Permselective Membranes in Systems with More than One Species of Critical Ions; Bi-Ionic and Polyionic Potentials

Of great physicochemical interest and perhaps of still greater biophysical interest are the dynamics of membrane systems with permselective membranes and more than one species of permeable, critical ions. The simplest systems of this general type, aside from the previously treated border line case of ionic self-exchange, are cells which for the case of a cation-selective permselective membrane are represented by the following scheme:

	$\longleftarrow \oplus \longrightarrow$	
Solution 1	Exclusively	Solution 2
Electrolyte A^+L^-	cation-permeable	Electrolyte B^+L^-
c_1	permselective	c_1
	membrane	

Here A^+ and B^+ represent univalent cations which are able to exchange freely across the membrane, referred to as "critical" ions, and L^- represents the "noncritical" anions which are unable to penetrate across the membrane. The exchange of critical ions across the membranes leads to the progressing degradation of the system, with increasing quantities of B^+ showing up in Solution 1 while an equivalent quantity of A^+ appears in Solution 2, until ultimately the final state, a Donnan membrane equilibrium, would be reached.

The potential which arises in the above system is designated as the bi-ionic potential, BIP [116], which must be measured in cells which are in a virtually nondegraded stationary state. This can be readily achieved under the proper experimental conditions, namely, the use of membranes of moderate transmissivity, solutions of appropriate—not too low—concentrations, large solution compartments or flowing solutions, and adequate stirring.

Table 6 gives bi-ionic potentials, E_{BIP}, across two representative permselective membranes [176]; columns 1-3 and 5-7 are self-explanatory. When arranged according to the magnitude of the bi-ionic potentials which are caused by their presence, the various critical cations and anions yield two ionic sequences which coincide with the two lyotropic, so-called Hofmeister series [48,51,52,55,180]. These sequences are, of course, the same whatever cation or anion may be chosen as reference, as K^+ and Cl^- are chosen in Table 6. The influence of the noncritical ions on the BIP is ordinarily very

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Table 6. Several Representative Bi-ionic Potentials, E_{BIP}, across a Typical Cation-Selective and a Typical Anion-Selective Permselective Collodion Matrix Membrane (t = 25.0 ± 0.1°C)

1	2	3	4	5	6	7	8
	Oxidized collodion membrane ($\rho^* = 1550\ \Omega\ cm^2$)				Protamine collodion membrane ($\rho^* = 1250\ \Omega\ cm^2$)		
Solution 1 0.0100 M	Solution 2 0.0100 M	E_{BIP}[a], mV	$\frac{\tau^0_{B^+}(2)}{\tau^0_{K^+}(1)}$	Solution 1 0.0250 M	Solution 2 0.0250 M	E_{BIP}[a], mV	$\frac{\tau^0_{M^-}(2)}{\tau^0_{Cl^-}(1)}$
KCl	CsCl	−8.7	1.41	NaCl	NaCNS	+32.0	3.48
KI	NH_4I	−6.8	1.30	NaCl	$NaNO_3$	+23.1	2.46
KCl	RbCl	−5.6	1.25	NaCl	NaI	+12.2	1.61
KCl	KCl	±0.0	1.00	NaCl	NaBr	+7.2	1.32
KI	NaI	+35.4	0.252	NaCl	NaCl	±0.0	1.00
KCl	NaCl	+35.5	0.251	NaCl	$NaBrO_3$	−2.2	0.918
KCl	LiCl	+63.7	0.084	NaCl	NaFormate	−7.6	0.744
KI	$(CH_3)_4NI$	+81.6	0.042	NaCl	NaSalicylate	−12.3	0.619
KI	$(C_2H_5)_4NI$	+110.0	0.014	NaCl	NaBenzoate	−38.6	0.222
				NaCl	$NaIO_3$	−45.1	0.173
				NaCl	NaAcetate	−46.2	0.165
				NaCl	NaPropionate	−59.3	0.099
				NaCl	NaButyrate	−65.9	0.077
				NaCl	NaLactate	−68.6	0.069

[a] The sign refers to Solution 2.

small. The reader will notice that the BIPs arising with the various pairs of three (or more) ions, e.g., A^+, B^+, and C^+, show consistently, with only very small deviations, the following regularity:

$$E_{BIP_{A^+/B^+}} + E_{BIP_{B^+/C^+}} = E_{BIP_{A^+/C^+}}$$

From the formal electrochemical point of view, as was pointed out by Michaelis, the sign and the magnitude of the BIP must depend on the relative ease with which the two species of critical ions can penetrate across the membrane [48, 51, 52]. The more readily permeable critical ions impress on the other solution a potential, the BIP, which is identical in sign with that of their own charge.

In order to obtain quantitative information concerning the relative ionic "mobilities" of the two critical cations in the membranes, Michaelis [48, 51, 52] employed—not without misgivings—the Planck-Henderson equation for the liquid junction potential [90], and wrote, for the case of ideally cation-selective membrane,

$$E_{BIP} = \pm \frac{RT}{F} \ln \frac{u_{A^+}}{u_{B^+}} \qquad (14)$$

where E is the bi-ionic potential and u_{A^+} and u_{B^+} the ionic "mobilities" of A^+ and B^+ in the membrane.

The concept of ionic "mobilities" in the membrane, if understood in analogy with the concept of ionic mobilities in free solution, is not applicable to the solution within porous membranes. The magnitude of E_{BIP} must be considered a function of the relative contributions of the two species of critical ions toward the (virtual) transportation of current across the membrane, that is, the ratio of their transport numbers, which depends not only on the ratio of the ionic mobilities but also on the ratio of the concentrations of the two species of critical ions in the membrane.

In order to evaluate quantitatively, from the magnitude of the BIP, the true relative contributions of the different ions to the virtual transportation of current across the membrane, Gregor and Sollner [144, 145] expressed Eq. (14) in the more basic terms of transference numbers, $\tau^0_{A^+}$ and $\tau^0_{B^+}$ [144, 145] instead of Michaelis' "ionic mobilities," and Eq. (14) became the expression

$$E_{BIP} = \frac{+RT}{F} \ln \frac{\tau^0_{A^+}(1)}{\tau^0_{B^+}(2)} \qquad (14a)$$

the sign referring to the charge of Solution 2.

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In order to visualize in a quantitative way the differences in the behavior of various ions in the experimental cells referred to in Table 6, the ratios $\tau^0{}_{B^+}{}^{(2)}/\tau^0{}_{K^+}{}^{(1)}$ and $\tau^0{}_{M^-}{}^{(2)}/\tau^0{}_{Cl^-}{}^{(1)}$ were calculated from Eq. (14a) and its analogue for anion-selective membranes; they are given in columns 4 and 8 of Table 6. These figures may be considered as a quantitative measure of the ratio of the intrinsic competitive permeabilities of the two ions across a given membrane when present in the same system.

In a first attempt to arrive at a physical picture that could explain the data of Table 6, the author considered the membranes as ion exchange bodies according to the fixed charge theory [116]. The two exchangeable (critical) species of ions compete, according to their ion exchange specificity, for positions as counterions of the fixed dissociable groups of the membrane. Thus the transport numbers of the two competing species of critical ions were assumed to be determined by their relative abundance, multiplied by their degrees of dissociation and relative diffusion velocities (and valencies) [116]. Wyllie [118] developed these ideas in a more rigorous treatment and formulated equations for the bi-ionic and polyionic potentials which incorporate the named parameters in an explicit manner, thereby returning closely to the starting point of the considerations of Michaelis [50-52] and Gregor and Sollner [144, 145], the conventional form of the Nernst-Planck-Henderson equation. Successful experimental work along these lines was reported by Wyllie and Kanaan [181].

A more rigorous approach to the theory of the origin of the BIP than that taken by the aforementioned investigators was presented by Helfferich [109], who considered the BIP explicity in terms of the two membrane-solution phase boundary potentials and a diffusion potential within the membrane.

The ionic specificity which is evident from columns 4 and 8 of Table 6 is a matter of considerable biophysical interest. The differences between the various univalent cations can be increased considerably by using very dense membranes [176, 182] due to the fact that hydrated ionic sizes vary considerably and steric exclusion occurs. The specificity observed with the anions is much less influenced by the porosity of the membranes. It therefore must be assumed to be due primarily to the chemical differences between the various anions. It would be of great interest if membranes with specific differential binding ability, particularly for cations, could be developed. Membranes of high ionic specificity, of course, might also turn out to be useful in preparative and industrial applications.

The above treatment of the bi-ionic potential leads directly to the study of the dynamics of polyionic membrane systems with permselective membranes in general, that is, systems with two or more species of critical ions which may be present in the two solutions separated by the membrane in pure or mixed solutions at the

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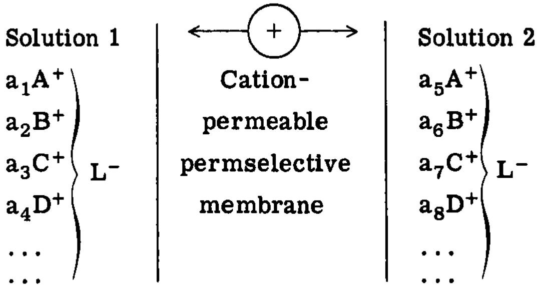
same or at different activities [117]. Systems of this type are represented in the following general scheme:



The dynamic membrane potentials which arise in such polyionic systems are denoted as "polycationic" and "polyanionic" potentials.

The most fundamental question in dealing with polyionic systems in general is the quantitative correlation of the potentials that arise with any ratio of activities of two or more species of critical ions in the two solutions, and the potential in some standard systems. As in the case of the BIP, the solution of this problem was found in the use of the Planck-Henderson equation expressed in terms of transference numbers [117, 182].

The simplest cases of a polyionic potential, next to the bi-ionic potential, are systems in which each of the two solutions separated by the membrane contain only one of two species of critical ions but at different activities. The Planck-Henderson equation may be applied to these systems, $a_1A^+L^- | \text{membrane} | a_2B^+L^-$, in a manner analogous to that used with the bi-ionic systems:

$$E = \frac{\pm RT}{F} \ln \frac{\tau_{A^+}}{\tau_{B^+}} \tag{15}$$

The simplest possible assumption is that the ratio of the transference numbers of the two critical ions τ_{A^+}/τ_{B^+} in the system $a_1A^+L^- | a_2B^+L^-$ is equal to the ratio of the transference numbers of the two critical ions in the corresponding bi-ionic potential system, $\tau^0_{A^+}$ and $\tau^0_{B^+}$, multiplied by the ratio of the activities of the two critical ions in the two external solutions of the system under discussion. Thus, this ratio of transference numbers in the stated two-ionic system can be expressed as

$$\frac{\tau_{A^+}}{\tau_{B^+}} = \frac{a_{A^+(1)}\tau^0_{A^+}}{a_{B^+(2)}\tau^0_{B^+}} \tag{16}$$

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Combining Eqs. (15) and (16) we obtain for the two-ionic potential, E_{2IP}, in the cell $a_1A^+L^-|a_2B^+L^-$:

$$E_{2IP} = \frac{\pm RT}{F} \ln \frac{a_{A^+(1)}\tau^0_{A^+}}{a_{B^+(2)}\tau^0_{B^+}} \tag{17}$$

The application of the Planck-Henderson equation to the most general type of polyionic system, in which any number of species of critical ions are present in any arbitrary combination of concentrations on each side of a permselective membrane, leads to an equation too involved to be presented here [117, 182]. For two-ionic systems [183] with both species of critical ions in either solution, $a_{A^+(1)}, a_{B^+(1)} | a_{A^+(2)}, a_{B^+(2)}$, this general question reduces to:

$$E_{2IP} = \frac{RT}{F} \ln \frac{a_{A^+(1)}\tau^0_{A^+} + a_{B^+(1)}\tau^0_{B^+}}{a_{A^+(2)}\tau^0_{A^+} + a_{B^+(2)}\tau^0_{B^+}} \tag{18}$$

which reduces to Eq. (17), when the solutions each contain only a single species of critical ions.

Table 7 gives a comparison of several experimental potentials for a few representative three- and four-ionic systems with mixed electrolyte solutions at various concentrations across some typical permselective collodion matrix membranes and the values calculated from the appropriate equations (omitted here) [184]. With two-ionic systems [183], not shown in Table 7, the agreement of the experimental potential values and those calculated from Eq. 18 is somewhat better than with the three-ionic and four-ionic systems shown in the table. The signs in this table refer to Solution 2.

Thus it is evident that two-, three-, and four-ionic potentials can be calculated with a satisfactory degree of accuracy on the basis of one, two, and three bi-ionic potential measurements, respectively, with the same membrane in the appropriate reference bi-ionic systems [182-184].

Some Uses of Permselective Membranes; Permselective Membranes as Membrane Electrodes, in the Study of Membrane Equilibria, and in Preparative and Industrial Operations

The unique electrochemical properties of permselective membranes invite a host of applications, some already realized and some still lying in the future.

In 1943 it became apparent that permselective membranes could be used as membrane electrodes at least in dilute single-electrolyte solutions, since under this condition they act electromotively virtually as reversible electrodes for the critical species of ions [154]. Thus it was shown that by means of permselective membrane elec-

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Table 7. A Comparison of Several Calculated and Experimental Polyionic Potentials with Mixed Electrolyte Solutions at Various Concentrations Across Some Representative Permselective Collodion Matrix Membranes (t = 25.0 ± 0.1°C)

Membrane	Solution 1, c, M	Solution 2, c, M	Polyionic potentials mV	
			Calculated	Experimental
	a. Three-cationic systems			
PSSA collodion; $\rho^* = 800\ \Omega\ \text{cm}^2$; $\frac{\tau^0_{K^+}}{\tau^0_{Li^+}} = 6.28$, $\frac{\tau^0_{Na^+}}{\tau^0_{Li^+}} = 2.33$	0.010 KCl 0.040 NaCl	0.400 LiCl	−21.6	−23.8
	0.025 KCl 0.025 LiCl	0.020 NaCl	+33.1	+34.4
	0.160 KCl 0.040 NaCl	0.010 NaCl 0.040 LiCl	+70.4	+69.4
	0.060 KCl 0.030 NaCl 0.010 LiCl	0.050 NaCl	+33.3	+34.5
	0.060 KCl 0.030 NaCl 0.010 LiCl	0.010 KCl 0.010 NaCl 0.080 LiCl	+25.5	+24.9
	b. Four-anionic systems			
Protamine collodion; $\rho^* = 1180\ \Omega\ \text{cm}^2$; $\frac{\tau^0_{Cl^-}}{\tau^0_{Ac^-}} = 5.71$, $\frac{\tau^0_{NO_3^-}}{\tau^0_{Ac^-}} = 15.52$, $\frac{\tau^0_{CNS^-}}{\tau^0_{Ac^-}} = 22.25$	0.010 NaCNS 0.040 NaCl	0.160 $NaNO_3$ 0.040 NaAc	+40.2	+38.7
	0.010 NaCNS 0.010 NaCl 0.080 NaAc	0.040 $NaNO_3$ 0.060 NaAc	+15.5	+15.5
	0.080 NaCNS 0.010 $NaNO_3$ 0.010 NaCl	0.100 NaCl 0.200 NaAc	−26.6	−26.8
	0.080 NaCNS 0.010 $NaNO_3$ 0.010 NaCl	0.020 $NaNO_3$ 0.020 NaCl 0.060 NaAc	−36.8	−36.4
	0.010 NaCNS 0.020 $NaNO_3$ 0.030 NaCl 0.040 NaAc	0.100 NaCl 0.200 NaAc	−1.0	−1.3
	0.100 NaCNS 0.080 $NaNO_3$ 0.080 NaCl 0.040 NaAc	0.010 NaCNS 0.010 NaCl 0.080 NaAc	−58.9	−56.7
	0.080 NaCNS 0.060 $NaNO_3$ 0.040 NaCl 0.020 NaAc	0.010 NaCNS 0.020 $NaNO_3$ 0.030 NaCl 0.040 NaAc	−33.5	−33.0

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trodes it becomes possible to determine the activities of many ions for which specific reversible electrodes do not exist, as is the case with many anions, NO_3^-, acetate, ClO_3^-, ClO_4^-, IO_3^-, etc., or where the only available electrodes involve considerable experimental difficulties, as, for example, the alkali and alkaline earth amalgam electrodes [154, 155]. The use of permselective membranes for the determination of several of these cations has been rendered obsolescent by the introduction of ion-specific glass electrodes [134]. The topic of "membrane electrodes" in general has recently been reviewed extensively by the author [19]. Here, it must suffice to say briefly that activity determinations with the membrane electrodes may be made in various ways. The potential difference which arises between a known solution on one side of the membrane and the solution of unknown concentration on the other side may be evaluated by reference to some calculated standard curve; by reference to an empirical curve determined for a specific membrane in advance; or by electrometric titration through the zero point, a zero potential indicating that the activity of the critical ion is the same on both sides of the membrane [155]. Such activity determinations can be made within a few minutes with an error of considerably less than ±1.0% [155]. The aforementioned review [19] also discusses the use of membrane electrodes in mixed solutions.

The experimental study of Gibbs-Donnan membrane equilibria was restricted in the past to systems containing colloidal or semicolloidal ions as nondiffusible ions and a few systems in which the cyanoferrate (II) ion acted as the nondiffusible ion in conjunction with a copper-cyanoferrate membrane [71]. Except for this latter case, Donnan equilibria involving only strong inorganic electrolytes, in which relatively small ions act as "nondiffusible" ions, could not be studied. These restrictions were removed by the creation of the permselective membranes of extreme ionic selectivity and high ionic transmissivity, and Sollner and Gregor [73] soon tested the Donnan principle, expressed in Eq. (8), in systems involving only the ions of common uni-univalent strong electrolytes. In properly selected systems it is permissible, for obvious reasons, to consider concentration ratios instead of activity ratios. The results of Sollner and Gregor [73], obtained with a cation-selective oxidized collodion membrane, are summarized in Table 8.

Anion-selective permselective membranes are equally useful in the study of anionic Donnan equilibria, as was shown in a later, as yet unpublished, series of experiments in systems with greater ratios in the concentrations of the various diffusible ions.

The significance for the pure physical chemistry of electrolytic solutions, as well as for the investigation of colloidal systems, of the possibility of the experimental study of membrane equilibria which may involve almost any desired combination of uni-univalent and many combinations of unipolyvalent strong electrolytes, hardly requires emphasis.

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Table 8. Gibbs-Donnan Equilibria Across Permselective Collodion Matrix Membranes that Involve Only Strong Inorganic Electrolytes (the Anions Are the Nondiffusible Ions)

Ratio of volumes in solution in/solution out	Solute	Original state, millimoles/liter		Equilibrium state: Experimental, millimoles/liter		Equilibrium state: Calculated, millimoles/liter		Concentration ratio, in/out	
		In	Out	In	Out	In	Out	Experimental	Calculated
1:1	NH_4^+	20.0	10.0	22.4	7.5	22.5	7.5	2.99 ± 0.05	3.00
	K^+	10.0	—	7.4	2.4	7.5	2.5	3.08 ± 0.10	3.00
	Cl^-	30.0	10.0	30.0	10.2	30.0	10.0	2.94 ± 0.05	3.00
	Sucrose	—	33	—	(33)	—	(33)	—	—
1:1	NH_4^+	30.0	—	22.4	7.5	22.5	7.5	2.99 ± 0.05	3.00
	K^+	—	10.0	7.5	2.5	7.5	2.5	3.00 ± 0.10	3.00
	Cl^-	30.0	10.0	29.8	10.1	30.0	10.0	2.95 ± 0.05	3.00
	Sucrose	—	33	—	(33)	—	(33)	—	—
1:10	NH_4^+	50.2	2.51	37.4	3.79	37.5	3.78	9.9 ± 0.3	9.9
	K^+	—	2.56	12.0	1.27	12.7	1.29	9.4 ± 0.4	9.9
	$C_2O_4^-$	25.1	2.54	24.7	2.53	25.1	2.54	9.8 ± 0.2	9.9
	Sucrose	—	39	—	(39)	—	(39)	—	—

The Donnan equilibrium can be utilized in an analytical method for the determination of ion activities in mixed electrolyte solutions [185]. This approach is based on the consideration of the ion distribution which exists in the equilibrium state between the "unknown" and an appropriately chosen reference solution of known concentration of the ions under investigation, and of the concomitant membrane potential. This method would be applicable and uniquely useful with systems containing more than two species of critical ions, or ions which are very similar in character, such as the sodium, potassium, and ammonium ions. The low-resistance permselective membranes, which facilitate a fast equilibration between solutions across them, are the obvious choice with this method, which is likely to be of considerable help in the elucidation of numerous problems in colloid chemistry, biochemistry, and physiology.

The use of permselective membranes in preparative and industrial chemistry was suggested in 1949 at a meeting of the Electrochemical Society and is illustrated by a few examples [84]:

> "The use of permselective membranes for the purpose of the exchange, between solutions, of ions (including the exchange of the ions of water) in preparative chemistry and in industrial operations has not been explored as yet. It might prove to be of great practical significance that the ion exchange operations might be performed between phases of different water activity without a disturbing extent of osmotic solvent movement. Industrial chemists might be interested in the numerous possibilities in this field.
>
> "To give just a few examples: The salts of pH sensitive organic acids may be converted into the free acid either by membrane hydrolysis or by dialytic ion exchange against an acid without ever coming into contact with the latter as occurs in precipitation reactions.
>
> "The regeneration of certain industrial waste liquids seems feasible. For instance, in the system: fairly concentrated (c_1) solution of sodium sulfate | negative permselective membrane | dilute (c_2) sulfuric acid, ($c_1 \gg c_2$), the hydrogen and the sodium ion would exchange across the membrane without significant movement of water. In a counter current system, the result would be a sulfuric acid solution of the higher (useful) concentration, c_1, and a waste solution of sodium sulfate of the lower concentration, c_2.
>
> "Nonelectrolytes of medium and even of low molecular weight might be separated from electrolytes by the simultaneous use of both electropositive and electronegative membranes; or electrodialysis might be used for the same purpose in a three-cell outfit with a greatly accelerated speed. Also, the separation of bivalent and monovalent ions of the same sign of charge seems to be a problem of some interest."

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The current status of the use of permselective membranes in industrial operations, particularly in electrodialysis, has been reviewed repeatedly [153, 186, 187]. The most recent literature on this topic is collected annually by R. Kunin in his progress reports on ion exchange, which have been published for many years [188].

SOME SPECIAL CROSS-MEMBRANE TRANSPORT PROCESSES AND SOME MEMBRANE TRANSPORT MODEL STUDIES OF PARTICULAR BIOPHYSICAL INTEREST

The more conventional applications of the electrochemistry of porous ionic membranes to biophysical, especially bioelectrical problems has been reviewed repeatedly by some of the previously mentioned leaders in this field [21, 105, 106, 115, 123] and will not be resurveyed here. This section is devoted to the discussion of a variety of less-known and commonly neglected transport processes across ionic membranes which are of undoubted biophysical interest. Some of them occur across single membranes. Others arise across composite membranes; these latter effects were studied in model systems into which two different types of membranes are incorporated.† Much of the material presented below represents work carried out in the laboratory of the author, who for many years has been intensely interested in these much-neglected transport effects.

The Relative Rates at which Several Co-Existing Species of Critical Ions Move across Permselective Membranes, and the Overshooting Effect

The mechanism of the differential uptake by living cells of various species of ions of the same charge from the surrounding milieu has remained for a long time one of the major open problems of physical biochemistry. André and Demoussy [190], according to Brooks [191], first realized that the preferential uptake of certain ions (for instance, of K^+ over N_a^+ or of I^- over Cl^-) by metabolizing cells must be connected with a state of nonequilibrium, quite commonly believed to be a steady drift toward a Gibbs-Donnan membrane equilibrium. In this state of nonequilibrium, maintained by the continuous production of some electrolytic metabolites such as carbonic acid, the faster-permeating ions are present in the cell at a relatively higher concentration than the more slowly penetrating ones.

Brooks [191] has stressed the fact that numerous mechanisms could explain differential rates of permeation of ions of the same

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† That composite membranes of various types are likely to be of biological significance was clearly stated by Pfeffer [189] in 1890. Since then, this idea has been rediscovered and restated many times in the literature.

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charge. He suggested that differences in the diffusion velocities of the various ions in water might be the determining factor. These differences, however, are much too small to account for the observed effects, and it seemed highly desirable to investigate in experiments with artificial membranes whether greatly differing rates of permeation of the various common univalent cations and anions across porous membranes of high ionic selectivity do occur. This prompted Neihof and Sollner [192] to show how the above-outlined theory of the origin of bi-ionic and polyionic potentials across permselective membranes readily leads to the prediction, on the basis of potentiometric data, of the existence and the magnitude of such differential rates of ion permeation across permselective membranes.

The simplest case along these lines is the ratio of the rates of exchange across a membrane of two species of critical ions which coexist at the same activity in Solution 1, for any other ions of the same charge in Solution 2:

Solution 1	$\longleftarrow\!\oplus\!\longrightarrow$	Solution 2
$a_1A^+L^-$	Cation-selective	
$a_1B^+L^-$	permselective	$a_nX^+L^-$
	membrane	

where a_1 and a_n are activities, A^+, B^+, and X^+ the exchangeable, "critical" cations, and L^- the nonexchanging anions.

The ratio $\tau^0_{A^+}/\tau^0_{B^+}$ obtained from the measurement of the bi-ionic potential $E_{\mathrm{BIP}_{A^+/B^+}}$ represents, as indicated before, the ratio of the intrinsic competitive permeabilities across a given membrane of any two ions A^+ and B^+. Accordingly, we postulated that the ratio of the rate of exchange of A^+ for X^+ ions and of B^+ for X^+ ions, that is, the ratio of the fluxes of these ions, $\varphi_{A^+}/\varphi_{B^+}$, should be the same as the ratio $\tau^0_{A^+}/\tau^0_{B^+}$ calculated from the bi-ionic potential in the system $A^+L^-\ |\longleftarrow\!\oplus\!\longrightarrow|\ B^+L^-$, independent of the nature or concentration of the X^+ ions [192]:

$$\frac{\varphi_{A^+}}{\varphi_{B^+}} = \frac{\tau^0_{A^+}}{\tau^0_{B^+}} \tag{19}$$

In expanding this line of reasoning to the more general case, that the two ions A^+ and B^+ are present in Solution 1 at different activities, we assume (as in the case of the two-ionic and polyionic potentials) that the tendencies of the two species of ions to penetrate across the membrane are proportional to the ratio of their activities in Solution 1 [192]. Accordingly, the ratio of the rates of simultaneous exchange of A^+ and B^+ across the same membrane when these two ionic species are present in Solution 1 at the different activities, $a_{A^+(1)}$ and $a_{B^+(1)}$ may be written as:

$$\frac{\varphi_{A^+}}{\varphi_{B^+}} = \frac{\tau^0_{A^+}\, a_{A^+(1)}}{\tau^0_{B^+}\, a_{B^+(1)}} \tag{20}$$

independent of the nature and activity of the X^- ions. In systems with more than two exchangeable ions in Solution 1, analogous equations may be written for each pair, such as:

$$\frac{\varphi_{A^+}}{\varphi_{C^+}} = \frac{\tau^0_{A^+}\, a_{A^+(1)}}{\tau^0_{C^+}\, a_{C^+(1)}}, \text{ etc.} \tag{20a}$$

In testing these equations, the bi-ionic potentials across a given membrane with several pairs of ions were determined and the corresponding ratios, $\tau^0_{A^+}/\tau^0_{B^+}$, $\tau^0_{B^+}/\tau^0_{C^+}$, etc., computed. The initial rates of exchange, φ_{A^+}, φ_{B^+}, φ_{C^+}, etc., of two or more species of ions of known activities in Solution 1 of a polyionic system (with the same membrane), against X^+, Y^+, etc., ions of Solution 2, were determined from the initial slopes, that is, the slopes at zero time, of the curves in which the quantities of exchanged A^+, B^+, etc., ions are plotted against time. The ratios of each two of these initial flux rates $(\varphi_{A^+}/\varphi_{B^+})_{exp}$, $(\varphi_{B^+}/\varphi_{C^+})_{exp}$, etc., were computed and compared with the ratios of the rates calculated from Eqs. (20) and (20a), $(\varphi_{A^+}/\varphi_{B^+})_{calc}$, $(\varphi_{B^+}/\varphi_{C^+})_{calc}$, etc. Representative data are shown in Table 9.

Two important facts are evident in Table 9. First, the ratios of the rates of the simultaneous exchange of ions of the same charge coexisting in solution across ion-selective membranes may be far higher than would be predicted from the differences in their diffusion velocities in water, and second, these ratios of these rates, in systems with permselective membranes, can be predicted with a fair degree of accuracy on the basis of BIP determinations in appropriate bi-ionic reference cells [192].

In a strictly analogous manner, the relative rates of the simultaneous electromigration across permselective membranes of several species of critical ions coexisting in solution can be predicted on the basis of the corresponding bi-ionic potentials across the same membrane [193], provided that the aforementioned electro-osmotic effect is disregarded, as well as membrane polarization, which at higher current densities complicates the situation. If this can be done, Eqs. (19)-(20a) should be valid also for the ratios of the rates of cross-membrane movement of A^+, B^+, C^+, etc., under the influence of an applied EMF. Experimental tests have confirmed the theoretical predictions with the expected moderate degree of accuracy [193].

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Table 9. A Comparison of the Calculated and Experimental Ratios of the Fluxes of Two and Three Species of Coexisting Critical Ions from Solution 1 into Solution 2 Across Three Representative Permselective Collodion Matrix Membranes (t = 25.0°C)

Solution 1	Membrane	Solution 2	$\varphi_{K^+}/\varphi_{Li^+}$ Calc.	$\varphi_{K^+}/\varphi_{Li^+}$ Exptl.
0.1 M KCl 0.1 M LiCl	PSSA-collodion ($\rho^* = 220\ \Omega\ cm^2$)	0.2 M NH_4Cl	6.3	6.6
0.3 M KCl 0.3 M LiCl		0.05 M NH_4Cl	6.3	6.2
0.02 M KCl 0.2 M LiCl		0.2 M NH_4Cl	0.63	0.65
0.2 M KCl 0.05 M LiCl		0.2 M NH_4Cl	25	28

Solution 1	Membrane	Solution 2	$\varphi_{SCN^-}/\varphi_{Cl^-}$ Calc.	$\varphi_{SCN^-}/\varphi_{Cl^-}$ Exptl.	$\varphi_{SCN^-}/\varphi_{Ac^-}$ Calc.	$\varphi_{SCN^-}/\varphi_{Ac^-}$ Exptl.	$\varphi_{Cl^-}/\varphi_{Ac^-}$ Calc.	$\varphi_{Cl^-}/\varphi_{Ac^-}$ Exptl.
0.05 M KSCN 0.05 M KCl 0.05 M KAc	PVMP-collodion ($\rho^* = 115\ \Omega\ cm^2$)	0.15 M KNO_3	6.0	4.8	39.0	42.0	7.3	8.9
0.05 M KSCN 0.05 M KCl 0.05 M KAc	Protamine collodion ($\rho^* = 150\ \Omega\ cm^2$)	0.15 M KNO_3	3.1	2.7	13.5	14.9	4.8	5.5

Solution 1	Membrane	Solution 2	$\varphi_{SCN^-}/\varphi_{I^-}$ Calc.	$\varphi_{SCN^-}/\varphi_{I^-}$ Exptl.	$\varphi_{SCN^-}/\varphi_{Cl^-}$ Calc.	$\varphi_{SCN^-}/\varphi_{Cl^-}$ Exptl.	$\varphi_{I^-}/\varphi_{Cl^-}$ Calc.	$\varphi_{I^-}/\varphi_{Cl^-}$ Exptl.
0.05 M KSCN 0.05 M KI 0.05 M KCl	PVMP-collodion ($\rho^* = 115\ \Omega\ cm^2$)	0.15 M KNO_3	1.98	1.80	6.0	4.6	2.9	2.6
0.05 M KSCN 0.05 M KI 0.05 M KCl	Protamine collodion ($\rho^* = 150\ \Omega\ cm^2$)	0.15 M KNO_3	1.86	1.78	3.1	2.7	1.63	1.52

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The consideration of the differential rates at which several species of coexisting critical ions exchange in polyionic systems across permselective membranes as these systems drift toward the Donnan equilibrium, and of the ultimately reached Donnan equilibria, leads to the prediction of an "overshooting" and "undershooting" effect [194] which may be of some specific biophysical interest.

The differential uptake by living cells of various species of ions of the same charge from the surrounding milieu was commonly believed to be connected with conditions amounting to a steady state in the drift of the cells toward the Donnan equilibrium. According to this view, the faster penetrating ions may be present in the cell at a relatively higher concentration than the more slowly penetrating ions, but these concentrations would always be lower than those corresponding to the Donnan equilibrium. It is commonly believed that this exhausts the range of usefulness of the Gibbs-Donnan principle in the consideration of the stated problem. However, this is not the case. The theory of membrane equilibria, when applied to this problem in a suitable manner, leads for certain systems to the conclusion that ionic concentrations may be reached temporarily which may be far above those described by the Donnan equilibrium which the system would ultimately reach [194].

Consider, for example, the following system:

Solution 1	⟵⊕⟶	Solution 2
A^+L^- 0.01 M	Cation-selective	
B^+L^- 0.01 M	permselective	C^+L^- 0.3 M
C^+L^- 0.01 M	membrane	

where A^+, B^+, and C^+ represent the exchangeable cations, and L^- the nonexchanging anions. The volume of Solution 1 is so much larger than that of Solution 2 that the composition of the former is not altered measurably by the exchange of ions across the membrane. Whatever these rates or their ratios may be, the system will reach in course of time the state of membrane equilibrium for which Donnan's above-derived Eq. (8) holds true:

$$\frac{[A^+]_1}{[A^+]_2} = \frac{[B^+]_1}{[B^+]_2} = \frac{[C^+]_1}{[C^+]_2} \tag{21}$$

Though the Donnan principle is not concerned with the way in which a system may reach the equilibrium state, it can be utilized in the consideration of the dynamics of the processes by which our system degrades toward equilibrium.

Suppose one species of ions, A^+, in Solution 1 exchanges across the membrane at a rate which is exceedingly high compared with

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the rates of exchange of B^+ against C^+ or A^+. After some time a partial membrane equilibrium with respect to A^+ and C^+ ions will be reached, or virtually reached, before a significant quantity of B^+ ions has penetrated across the membrane. While this state of partial equilibrium prevails (in which the B^+ ions do not participate), the concentration both of A^+ and C^+ ions in Solution 2 will be 0.15 N, according to Eq.(21). During a further, very prolonged period the B^+ ions will exchange across the membrane until our system reaches the state of the true, final membrane equilibrium in which, according to Eq.(21), A^+, B^+, and C^+ will be present in Solution 2 at the same concentration, 0.1 M. Thus, the A^+ ions temporarily reach in Solution 2 a concentration in excess of that existing in the final, true equilibrium state.

It can be demonstrated in an analogous manner that under suitable conditions the converse effect must arise, namely, a transitory depletion of the concentration of some ionic species in Solution 2.

The extent to which these overshooting and depletion effects are realized in model systems depends on the relative rates of exchange across the membrane of the ions under consideration [194].

Figure 6a shows an example of the overshooting effect (magnesium salts being used to minimize cation leakage); Fig. 6b presents an instance of the depletion effect. The experimental points pertaining to the ions that show the overshooting and the depletion effects are connected by a heavy solid line; the corresponding partial and final equilibrium concentrations are indicated by dotted lines.

With permselective collodion matrix membranes giving convenient exchange rates, and various pairs of common ions, overshooting and depletion effects of 50-85% of those calculated for the partial equilibrium were regularly observed. The percentagewise overshooting of the equilibrium concentration in some systems with low relative concentrations of the overshooting ions reached several hundred per cent, as seen in Fig. 6a. The possible biophysical significance of this effect has been pointed out [195].

Ion Movement across Ionic Membranes as a "Carrier" Process

We will now turn our attention to one particular aspect of the ion movement across ionic membranes, most clearly seen in permselective membranes of high ionic selectivity, namely, the fact that the movement of ions across ionic membranes can properly be considered as a carrier process [15].

While the idea of carrier transport has been discussed extensively in the biological literature, this concept has attracted only scant attention in physicochemical membrane investigations. Carriers and carrier processes in living systems [196] are now commonly postulated whenever a membrane transport is unusually fast, selective, or specific beyond the expectation based on the classical criteria

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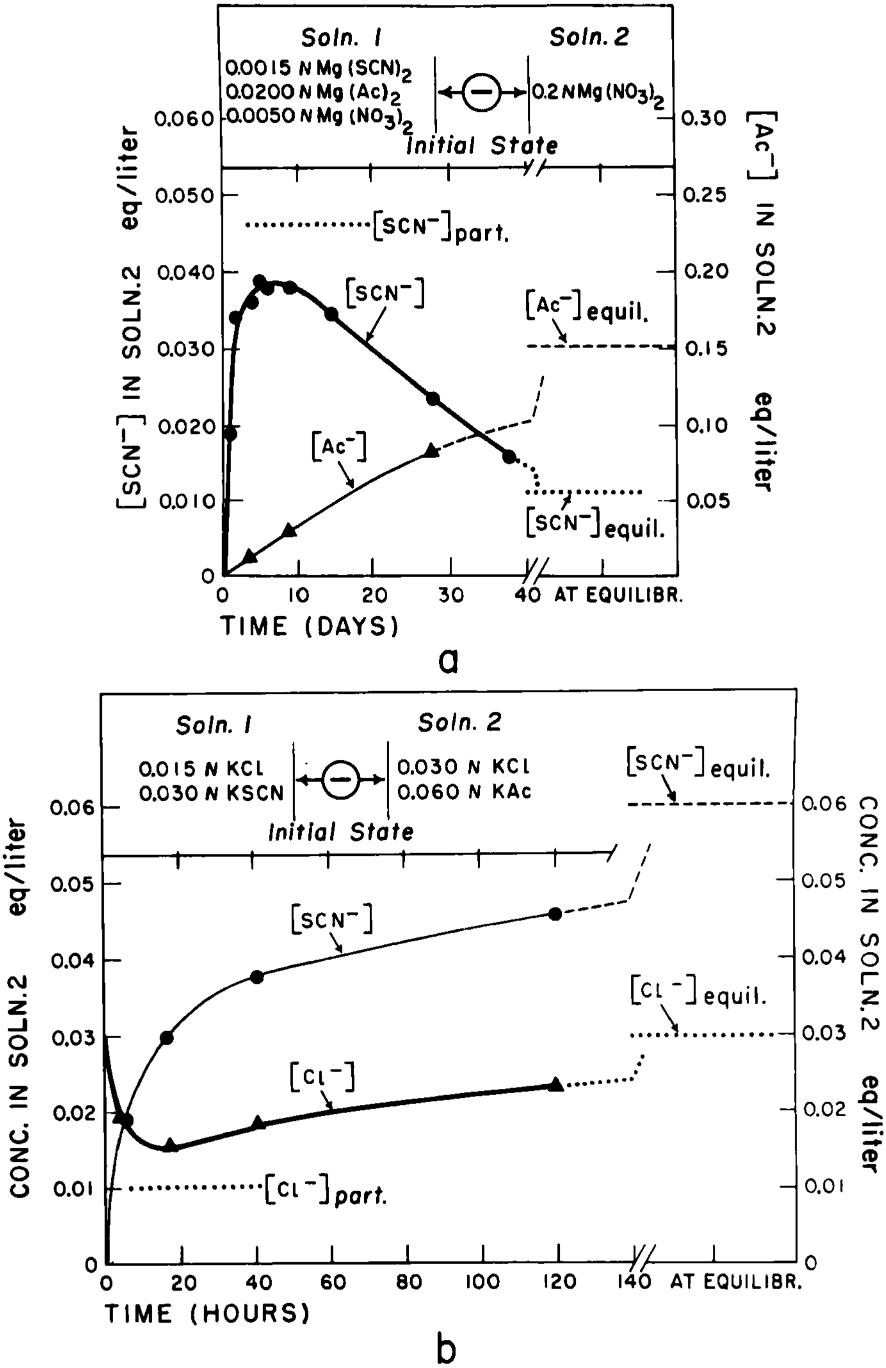

Fig. 6. Time-concentration relationships in two representative polyionic systems with permselective membranes. (a) An example of the overshooting effect, (b) an example of the depletion effect.

of lipoid solubility, molecular size, and electric charge. The obvious and currently much-favored assumption is that transmembrane passage involves a temporary binding of the transported material to some component of the membrane, the "carrier," and the passage of this complex across the membrane by diffusion (or convection). The chemical nature of these hypothetical carriers in biological systems is still unknown. Carrier transport is generally assumed to exist if the rate of transmembrane transport of the molecular species under consideration, when above a certain concentration in solution, is independent of this concentration. In this case all the sites on the "carrier" are assumed to be occupied by the carried molecular species, and one speaks of "saturation kinetics."

In the course of our recent studies on "liquid ion exchanger membranes" [14, 15, 17, 19], we were dealing with an ion transport mechanism whose carrier nature is obvious and clear beyond any doubt. In this case, the carriers are well-defined substances of known chemical constitution which react in a known manner with the carried materials, their counterions, with which they form virtually undissociated complexes. Of necessity, these carrier-type membranes show all the effects which commonly are taken as proof of the existence of a carrier mechanism, particularly saturation kinetics, and further, competition, specificity, and susceptibility to poisoning. These results obtained with liquid ion exchanger membranes prompted us recently [15] to elaborate on the idea that the fixed charged groups in porous ion exchange membranes act as carriers, a concept touched upon repeatedly in the literature [196, 197].

For the sake of simplicity we shall discuss here only, in an explicit manner, the carrier-process nature of the ion transport across permselective membranes of high ionic selectivity; the extension of the following considerations to leaky membranes is obvious. In the permselective membranes the fixed charged wall groups are the necessary prerequisite for the presence of their counterions in the pores; these ionic wall groups therefore must be considered as carriers for the movable, critical ions. As pointed out in preceding sections, the rates of movement of critical ions across these membranes, either by diffusion or by electromigration (and therefore the conductance of the membranes), depend entirely upon the quantity of dissociable wall groups within a membrane (as determined, e.g., with our collodion matrix membranes by their loading with polyelectrolyte), as is evident from Table 2.

A satisfactory physical picture which clearly brings out the carrier-type movement of the counterions of fixed wall charges was developed in a different context more than 30 years ago by Jenny [198]. Jenny's concept is sketched schematically in Fig. 7, which represents a pore of a permselective membrane. The minus signs in this figure indicate the fixed wall charges, say, carboxyl or sulfonic acid groups, which are fixed immovably to the pore walls (indicated by striation). The plus signs are the movable counterions.

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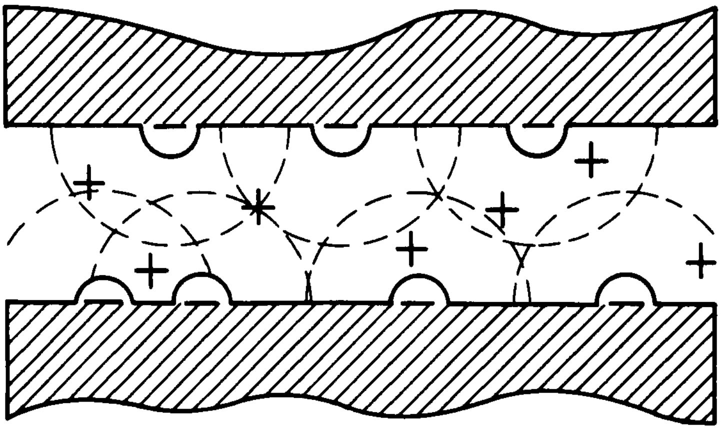

Fig. 7. A pore with rigidly fixed anionic wall charges and positive counterions; the "oscillation cells" of the latter are indicated by broken line half circles.

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According to Jenny, the cations in Fig. 7 move freely by thermal motion in their "oscillation cells," which in the figure are indicated by broken-line half circles. If the "oscillation cells" of the critical ions overlap, these ions readily exchange into an adjacent "oscillation cell" and ultimately may move across the membrane. In a concentration cell, for example, during the potential measurement when current (ions) moves through the pore, the driving force is the difference in the concentrations of the counterions in the two solutions separated by the membrane. In the exchange of different species of cations across the membrane, this process represents an interexchange of the counterions of the fixed wall groups. In cross-membrane electromigration of the critical ions, the applied EMF superimposes a unidirectional pull on the thermal motion of these ions. The close relationship of these processes of interfacial migration and surface conduction was pointed out by Jenny and Overstreet [198].

The experimental facts bear out the view that the transport of counterions across ionic membranes is a carrier process. The main criterion of carrier transport, saturation kinetics, seems adequately fulfilled with the permselective membranes, most pronouncedly with membranes of relatively high resistance in systems with dilute solutions. We recall the aforementioned observation that the resistance of a membrane of 80 Ω cm^2 standard resistance, ρ^*, changed only by a factor of 2 when the solution concentration changed from 0.01 N to 1.0 N [147]. Further evidence is presented in Fig. 5, particularly by the membranes of highest resistance shown in this figure [171]. The cause of the observed deviations, the presence of some "nonexchange electrolyte" in the membranes at higher concentrations, is clearly understood. The other conventional criteria of carrier transport are also satisfied with the permselective membranes. Competition between two or more species of coexisting species of critical ions arises, as discussed before in detail, and its corollary, the competitive ionic specificity of the transmembrane movement of ions also arises. Susceptibility of the membranes to poisoning manifests itself in the case of extremely strongly absorbed ions which form essentially undissociated compounds with the ionic membrane groups, thus destroying the functional availability of the latter.

It can be readily foreseen how ion exchange membranes (especially the liquid ion exchanger membranes) could lend themselves to model studies which would be helpful in clarifying transport mechanisms across living membranes with which the carriers, at present, are still only hypothetical entities.

Anomalous Osmosis

The phenomenon now known as "anomalous osmosis" was first described by Dutrochet in 1835 [199] and later by Graham in 1854 [200]. These investigators observed that seemingly rather erratic osmotic phenomena arise in many instances when membranes of the dialyzing type separate an electrolyte solution and pure water, or two electrolyte solutions of different concentrations. The rate of "osmotic" movement of liquid across membranes, particularly at low electrolyte concentrations, may be far greater than that caused by nonelectrolytes of equal concentration; this effect is called "anomalous positive osmosis." Or, in some instances, the flow of solvent is in the direction opposite to that expected on the basis of the concentration difference; in this case one speaks of "anomalous negative osmosis" or "negative osmosis".

Anomalous osmotic effects are never observed with strictly semipermeable membranes, impervious to the electrolytic solute under consideration. Anomalous osmosis is a dynamic, transient phenomenon. After a sufficiently long time the electrolyte concentrations on both sides of the membrane are the same and hydrostatic heads that have developed intermediately have disappeared. Anomalous osmosis has attracted the curiosity of physical chemists [57-64] for many years, since it seemed to be incompatible with the classical Pfeffer-van't Hoff-Arrhenius concept of osmotic phenomena.

The technique of studying anomalous osmosis, as used, for instance, by Loeb [39-43], is essentially as follows [100, 101, 135, 149]. A collodion bag is tied to a glass ring that is fitted to a rubber stopper carrying a capillary manometer tube. The membrane is filled in succession with solutions of graded concentrations of different electrolytes and with solutions of a reference nonelectrolyte such

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as sucrose, and is suspended in a large beaker filled with water. With each solution the rise of the meniscus in the manometer after a stated time is determined repeatedly. If these data are plotted in pressure/concentration diagrams, the solutions of electrolytes yield curves that have a characteristic N shape, while the solutions of nonelectrolytes give pressure rises that are strictly proportional to the concentration of the solute. Pressure rises which deviate significantly from those obtained with the nonelectrolytic reference substance of the same concentration are commonly considered to be due to anomalous osmosis. Some results of studies on anomalous positive osmosis with membranes of about equal porosity are summarized in Fig. 8. The abscissas give the concentration of the solutions inside the membranes which are immersed in a large volume of distilled water. The ordinates represent the pressure rise in millimeters of water after 20 min.

We focus our attention first on a comparison of the shapes of the curves obtained with solutions of electrolytes which yield maxima,

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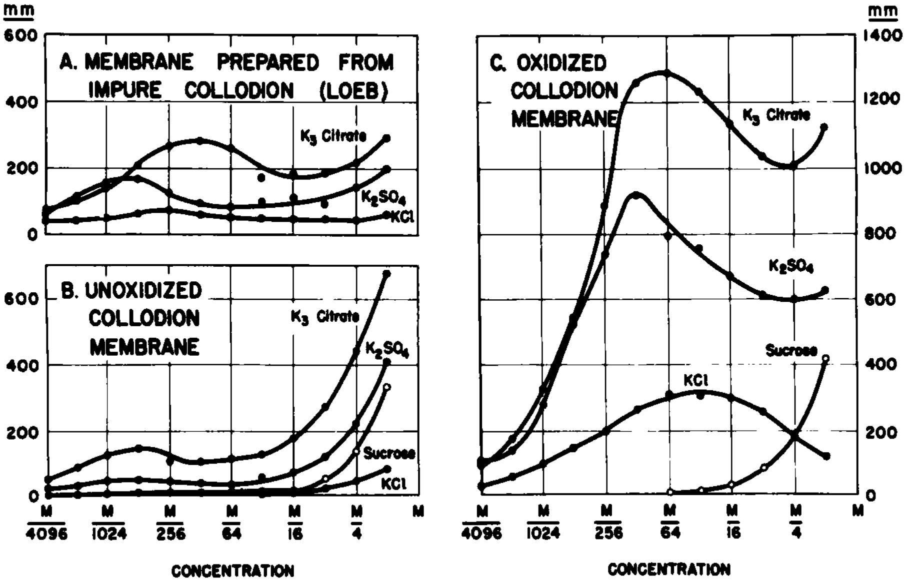

Fig. 8. Anomalous osmosis across various collodion membranes of about equal porosity; pressure rises in millimeters of water after 20 min. A) Data by Loeb obtained with a membrane of medium electrochemical activity, B) the behaviour of a membrane of low electrochemical activity (see text), C) the behaviour of the same membrane specimen as in B) after activation by oxidation.

with the contrasting shapes of the curves obtained with the nonelectrolyte sucrose. The maxima obtained with electrolyte solution are in many instances of considerable height at fairly low concentrations, while sucrose at the same low concentrations gives only minimal, barely detectable osmotic effects.

In the attempt to understand his observations of this type, Graham [200] had already suggested that anomalous osmosis is some kind of electro-osmotic effect. This idea was experimentally verified by later investigators, particularly Bartell et al. [57] and Loeb [39-44], who demonstrated that anomalous osmosis is essentially a spontaneous electro-osmosis that occurs when an electrolyte diffuses across a charged membrane. The driving energy of the process is obviously derived from the diffusion of the electrolyte across the membrane.

According to Loeb's observations, the extent of anomalous osmosis is approximately proportional to the product of the concentration potential measured across the membrane and the electrokinetic potential of the latter. Since both of these effects depend on the charge density on the pore walls, the extent of anomalous osmosis is a particularly sensitive indicator of the electrochemical activity of membranes of high porosity. This is borne out by Fig. 8, which compares the magnitudes of the anomalous osmotic effects obtained with membranes of about the same porosity. Figure 8A shows data by Loeb, who used a membrane prepared from an impure collodion preparation containing a significant quantity of dissociable groups; Fig. 8B gives data by Sollner and Abrams [135] obtained with a membrane prepared from pure commercial collodion, which is nearly devoid of dissociable groups; and Fig. 8C shows the behavior of the same membrane after oxidation, whereby a considerable number of dissociable groups were created at the walls of its pores without a significant change in membrane porosity [152].

We cannot go into the theory of anomalous osmosis here. In 1930 the author tried to explain this effect by reference to the heteroporosity of membranes, which were considered as mosaics of pores of different characteristics [60, 61]. Pores of the same charge density but different width, as well as pores of the same width but different charge density, yield in concentration cells different pore potentials. The latter, short-circuited by the two solutions, give rise to local electrical circuits through the pore system of the membrane, in a manner somewhat similar to the local electric circuits which are commonly considered as the main cause of metallic corrosion. That membranes of different porosities, when studied in two-membrane models, can bring about an electro-osmotic water movement was demonstrated by Sollner and Grollman [62, 64] and Carr and Sollner [201]. Sollner's theory, which had been accepted rather generally for many years, has been challenged by Schlögl [202] with the very ingenious idea that the membrane may be considered as a porous

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polyion which in the electric field of the diffusing electrolyte moves with respect to the water in its pores; experiments to prove this concept have not yet been reported. It is entirely possible that both these proposed mechanims contribute to the effect of anomalous osmosis. More recently, Kobatake and Fujita [203, 204] and Kedem and Katchalsky [205] have started to discuss the mechanisms of anomalous osmosis. For the time being, one must conclude that the mechanism of this effect is still an open question.

Whatever the ultimate outcome of these theoretical discussions will be, there was a lack of information on several basic factual aspects of the effect of anomalous osmosis which needed clarification before its potential biophysical significance could be evaluated in a meaningful manner. Grim and Sollner [206, 207] undertook to clarify the question of whether anomalous osmosis can occur to a significant extent under conditions which are at least superficially similar to those frequently existing in vivo. The published data referred almost exclusively to the rates of pressure rise in systems in which a membrane separates the solution of an electrolyte from distilled water, or from an extremely dilute solution of the same electrolyte—situations which are not likely to be similar to anything found in mammalian physiology. Virtually no data were available on systems in which a membrane separates solutions of different composition both of which are at physiologically significant concentrations. In addition, the data referred to pressure rises, in some instances of considerable magnitude (see Fig. 8), whereas, in all probability, volumes transported against small pressures are of greater physiological interest.

The first problem was to find a method which permits a clear distinction between the contribution of normal osmosis and the contribution of anomalous osmosis toward the gross observed effects. The customary assumption, that the extent of normal osmosis across the given membrane at a given concentration difference can be determined with solutions of the same concentration of some arbitrarily chosen nonelectrolyte, is obviously rather crude, since nonelectrolytes of different molecular size differ greatly in their osmotic efficacy [206]. This problem can be solved by using each electrolyte as its own reference substance in conjunction with membranes which can be brought in a reversible manner and without changes in their geometrical structure into a charged state, positive or negative as the case may be, and into the uncharged, isoelectric state [206]. With the membrane in the charged state, anomalous osmosis can occur; the observed, gross osmotic effect is composed of a normal and an abnormal component. With the membrane in the isoelectric state, anomalous osmosis does not occur; here, the total observed osmotic effect is due to normal osmosis. Thus, the difference in the effects with the membrane in the charged state and in the isoelectric state is a measure of the true anomalous osmosis.

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Grim and Sollner used the amphoteric, nonswelling oxyhemoglobin-collodion matrix membranes prepared by the adsorption of hemoglobin on membranes of suitably high porosity [206]. The isoelectric point of these membranes, at which they do not show any net charge, is near pH 6.75. These membranes can be readily charged positively or negatively by adjusting the pH of the experimental solutions; pH 4.0 and pH 10.0 were chosen in our work.

In our experiments, unless stated otherwise, the outside solution (very large in volume) was half the concentration of the inside solution. The rates of liquid movement across the membrane against a negligible small pressure, under quasi-stationary state conditions, were determined in 5-minute experimental periods. Some typical results obtained with single solute systems are shown in Fig. 9. The osmolar concentrations given in this figure and in Fig. 10 refer to the inside solutions, which had twice the concentration of the outside solutions.

Figure 9 demonstrates how the outlined method permits the separation of the anomalous osmotic effect from the over-all observed liquid movement, both in the case of anomalous positive and anomalous negative osmosis, a minus sign indicating a movement of liquid into the more dilute solution. The heavy solid-line curves give the difference, Δ, of the effects observed in the charged and in the isoelectric state and thus represent the true anomalous osmotic component of the observed effect.

Figure 10 presents the rates of liquid transport by true anomalous osmosis through an oxyhemoglobin membrane, arrived at in the

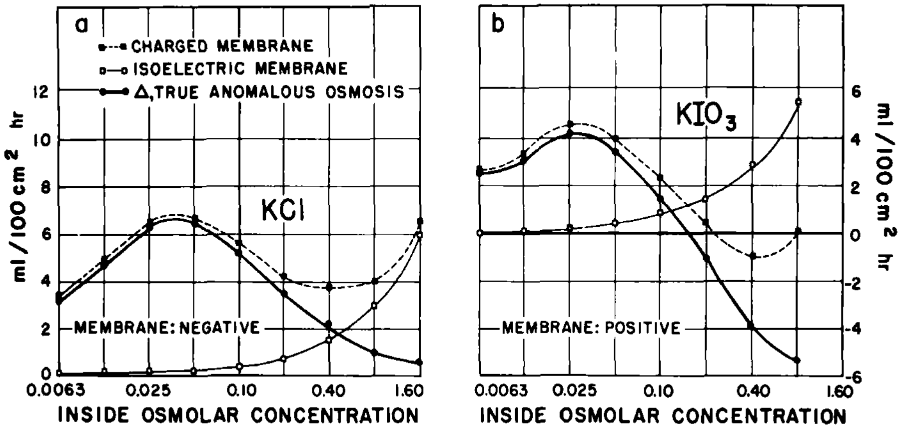

Fig. 9. The rates of transportation of liquid through an oxyhemoglobin collodion membrane in the charged state and in the isoelectric state, and the rates of true anomalous osmosis. $c_{in} : c_{out} = 2 : 1$.

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outlined manner, for several systems in which anomalous positive as well as anomalous negative osmosis occur. The data are plotted on an osmolar, not on a molar, basis; the concentration range of particular interest in mammalian physiology is indicated by crosshatching.

Figures 9 and 10 prove that, for single-solute, low-concentration-ratio systems, anomalous osmosis can occur at a rather conspicuous rate at physiological concentration levels. Thus, the question as to the feasibility of this phenomenon in mammalian organisms is answered in the affirmative.

Of greater specific interest for mammalian physiology, however, than the single-solute systems with 2:1 concentration ratios are systems containing more than one solute, particularly systems of this nature in which two solutions of identical over-all concentration (in the physiological range) are separated by the membrane.

Anomalous osmosis in systems with more than one solute has not been considered in the literature from a theoretical viewpoint [207]. Space does not permit a discussion of this rather involved matter. Suffice it to say that such systems can be considered on the same basis as single-solute systems [207]. Data of the type presented in Figs. 9 and 10 make it possible to predict semiquantitatively the

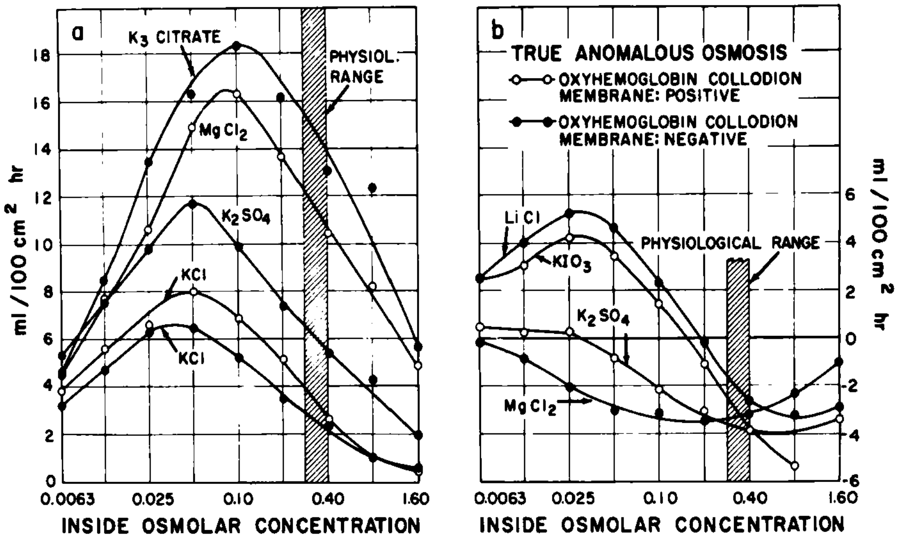

Fig. 10. The rates of transportation of liquid by true anomalous osmosis across an oxyhemoglobin collodion membrane in the charged state. $c_{in} : c_{out} = 2:1$. a) Systems in which the theory predicts anomalous positive osmosis only, b) systems in which the theory predicts anomalous positive osmosis for low concentrations and anomalous negative osmosis for higher concentrations.

extent of anomalous osmosis that can be expected in systems with two or more solutes.

The rates of true anomalous osmosis in two or more-solute systems can be determined experimentally by measuring the liquid transport rates with the membrane in the charged and in the isoelectric state, in the same manner as was done in the single-solute systems of Figs. 9 and 10.

Several experiments of this general nature with solutions of equal osmolar concentrations and the membranes in the positive state are summarized in Table 10. The results with membranes in the negative state, which are omitted from this table, are analogous. In Table 10 a movement of liquid from the outside to the inside solution is indicated by a plus sign; a movement in the opposite direction is indicated by a minus sign.

Table 10. Representative Rates of Transportation of Liquid and of True Anomalous Osmosis Across an Oxyhemoglobin Collodion Matrix Membrane in the Electropositive and in the Isoelectric State

				Rates of transport of liquid		
Inside solution		Outside solution		Membrane		True anomalous osmosis, Δ ml/100 cm^2 per hr
Solute	Concn. osmolarity	Solute	Concn. osmolarity	Charged ml/100 cm^2 per hr	Isoelectric ml/100 cm^2 per hr	
KCl	0.40	Glucose	0.40	+13.2	−7.0	+20.2
$MgCl_2$	0.20	Glucose	0.20	+70.0	+2.2	+67.8
$MgCl_2$	0.40	Glucose	0.40	+53.1	+1.7	+51.4
K_2SO_4	0.40	Glucose	0.40	−16.2	+0.8	−17.0
$MgCl_2$	0.40	KCl	0.40	+17.3	+3.4	+13.9
$MgCl_2$	0.40	KIO_3	0.40	+31.2	+1.4	+29.8
$MgCl_2$	0.40	K_2SO_4	0.40	+15.4	−1.8	+17.2
$MgCl_2$ + glucose	0.20 0.20	Glucose	0.40	+58.5	+0.2	+58.3
$MgCl_2$ + KCl	0.20 0.20	KCl	0.40	+8.7	0.0	+8.7
$MgCl_2$ + KCl	0.20 0.20	K_2SO_4 + KIO_3	0.20 0.20	+12.1	−3.7	+15.8

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Table 10 shows that true anomalous osmosis occurs at a very considerable rate in systems with more than one solute. With isoosmotic, 0.40 osmolar solutions of electrolytes, the true anomalous osmosis liquid transport rates are in the range of 8-30 ml/100 cm^2 per hr. If one of the solutes is a nonelectrolyte, these rates are about twice as high.

The potential physiological significance of the data on transport rates given in Table 10 can be seen from the fact that they are, for instance, several times as high as the highest reported rates of intestinal absorption. They are of the same order of magnitude as, and in some cases considerably higher than, the unidirectional rates of fluid movement which have been postulated as the physical basis of this process [208, 209]. However, it must be emphasized that the foregoing data do not prove in any way that anomalous osmosis actually is an important mechanism in the translocation of liquid in the mammalian organism; it only furnishes proof that such a process is a possibility from the strictly physicochemical point of view.

The Electrical and Permeability Properties of Mosaic Membranes Which Are Composed of Exclusively Anion- and Exclusively Cation-Permeable Parts

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In this and the subsequent section we deal with the use of permselective membranes in the study of complex membrane model systems which, aside from their inherent electrochemical interest, are likely to be of considerable help in the elucidation of the mechanisms of the characteristic functional behavior of biological membranes.

The heterogeneities that can be found in real membranes are by no means confined to differences in pore size, charge density, charge distribution, or a combination of these factors, which were referred to above in the discussion of a suggested mechanism of anomalous osmosis. Layered membranes and "mosaic" membranes composed of parts varying in other respects must likewise be considered.

The simplest and most precisely definable objects to start a study of mosaic membranes are mosaic membranes which are composed of strictly anion-selective and strictly cation-selective parts. A quantitative theory of the electrolyte permeability of such mosaic membranes was outlined more than 35 years ago by the author [69]. It is most easily developed by reference to a sequence of line drawings [69, 210, 211].

Figure 11a illustrates schematically a system in which a mosaic membrane separates a lower compartment (of invariable volume) from an upper compartment; the striated structure in the figure indicates the membrane. The electronegative, cation-permeable (anion-impermeable) parts of the membrane are here indicated by minus signs, and the electropositive, anion-permeable (cation-impermeable) parts by plus signs. The lower compartment is filled with 0.1 N and the upper one with 0.01 N potassium chloride solution.

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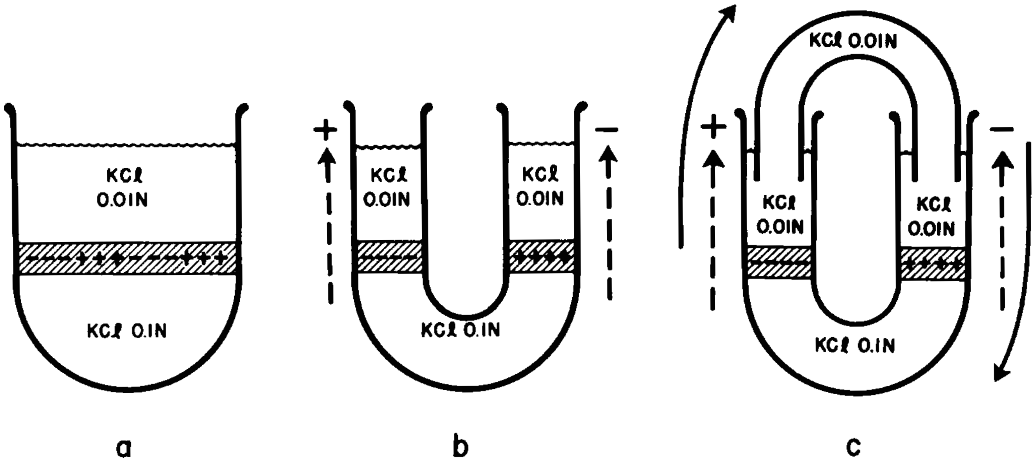

Fig. 11. Pictorial development of the theory of electrolyte permeability of mosaic membranes that are composed of ideally anion-selective and ideally cation-selective parts. (a) Mosaic membrane with adjacent cation-selective and anion-selective parts, (b) spatial and electrical separation of the cation-selective and anion-selective parts of the membranes, (c) the spatially separated cation-selective and anion-selective parts joined electrically by a bridge of solution in an all-electrolytic circuit.

Contrary to certain ideas presented in the literature [54], it was postulated [69] that such membranes permit the penetration of electrolytes from the lower compartment to the upper one. Cations move through the electronegative parts of the membrane and anions through the electropositive parts, neutralizing each other electrically. Thus, a continuous movement of the electrolyte must occur across the membrane, which does not cease until equilibrium between the two compartments is established.

In formulating this concept for a quantitative test, it is necessary to consider a system in which the cation-permeable and anion-permeable parts are separated from each other. Figure 11b shows a U-tube containing in its left arm an electronegative, cation-permeable membrane and in its right arm an electropositive, anion-permeable membrane, both of ideal ionic selectivity. The lower part of the system (having an invariable volume) is filled with 0.1 N KCl chloride solution; the two compartments above the membranes contain 0.01 N KCl. The only processes that can occur in this system consist of the establishment of static membrane concentration potentials across the two membranes and the establishment of a hydrostatic pressure in the lower compartment.

The magnitude of each of the two membrane potentials in the system of Fig. 11b is defined by the identical Eqs. (7) and (10): $E = \pm RT \ln a_1/a_2$. The direction of the two electromotive forces is shown in Fig. 11b by broken-line arrows pointing at a plus and a minus sign.

In order to reestablish in Fig. 11b the essential features of the situation represented in Fig. 11a, it is necessary to connect the two compartments containing dilute solution by a liquid conduit filled with 0.01 N potassium chloride solution, as shown in Fig. 11c. This system may be considered as a "Flüssigkeitsring," an all-electrolytic electrical circuit [212]. A (positive) current flows in a clockwise direction through the system, as is indicated by the solid arrows in Fig. 11c; the total EMF in the system is 2E, at 25.0°C 2 × 55.1 mV. The strength or the current, I, is defined by Ohm's law: $I = 2E/\rho$, where ρ is the total resistance of the system.

The current that flows in a clockwise direction in the system of Fig. 11c is transported through the negative membrane in the left arm of the system exclusively by cations that move clockwise, in the direction of the broken-line arrow; through the positive membrane in the right arm the electricity is transported exclusively by an equivalent quantity of anions that move in a counterclockwise direction, as indicated by a broken-line arrow. Thus, the number of the equivalents of electrolyte that move in a given time in the mosaic system of Fig. 11c from the concentrated to the dilute solution must be numerically identical with the number of faradays that flow in the system during the same period.

The experimental test of this theory of the electrolyte permeability of mosaic membranes consists in the study of model systems

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identical in all essential features with the all-electrolytic ring system of Fig. 11c. The obvious approach lies in some alteration in the theoretical model of Fig. 11c that will permit the accurate determination of the current that flows in the system. One way is to cut the system at some suitable point and attach to the two open ends of the interrupted circuit two symmetrical electrodes that can reversibly take the current from, and return it to, the system. The two electrodes are connected to each other by a current-measuring instrument, a coulometer or an ammeter, whereby a closed circuit is reestablished. The electrodes must be chosen so that they do not bring about any significant change in the original system that would not occur on closed circuit in their absence. They may be either specific electrodes for one of the ions in the solutions or nonspecific electrodes of the Cu | $CuSO_4$ | agar bridge type [210].

The system shown in Fig. 12a illustrates schematically an arrangement which makes use of silver-silver chloride electrodes in chloride solutions. It is a galvanic cell, which may be represented as

$$\begin{array}{cccccc} & & \leftarrow\!\oplus\!\rightarrow & \leftarrow\!\ominus\!\rightarrow & & \\ \mathrm{Ag}\,|\,\mathrm{AgCl} & |\,\mathrm{KCl}\ c_1 & |\,\mathrm{KCl}\ c_2 & |\,\mathrm{KCl}\ c_1 & |\,\mathrm{AgCl} & |\,\mathrm{Ag} \\ E_1 & E_2 & E_3 & E_4 & E_2' & E_1' \end{array}$$

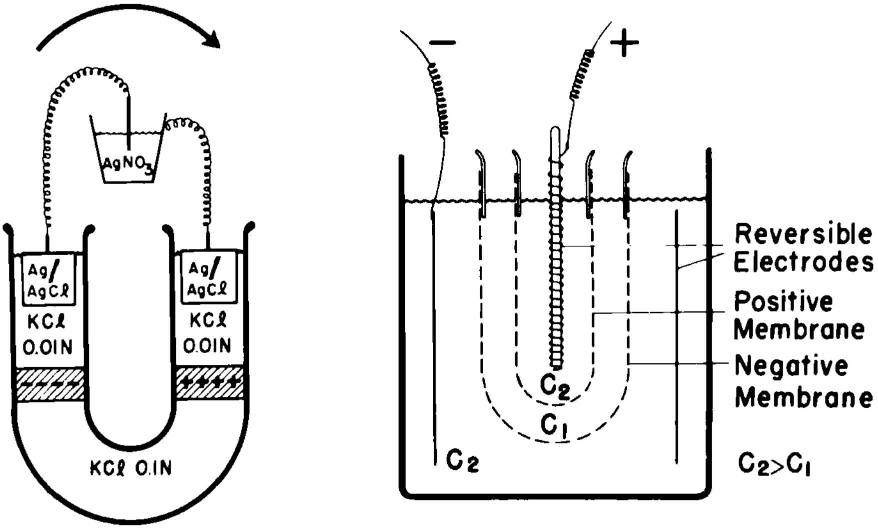

Fig. 12. Mosaic membrane models with auxiliary electrodes through which the current flows. (a) A schematic model, (b) the experimental model.

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where the negative, cation-permeable membranes and the positive, anion-permeable membranes are represented by the symbols ←⊕→ and ←⊖→. In this cell, the electromotive forces, E_1 and E_1' and E_2 and E_2', are equal and opposite in direction; they cancel and do not contribute to the effective EMF of the cell.

Another possible approach, which avoids the use of auxiliary electrodes through which the current flows, consists in determining the current by measuring, by means of probe electrodes, the potential difference across an element of the circuit of known resistance, which does not change during the experiment [212]. Figure 13a sketches such an arrangement in a highly schematic manner; the planes of the location of the probe electrodes are indicated by Y and Y′.

The essentials of the geometry of the working models are shown in the schematic Figs. 12b and 13b. The electrical identity of the systems in Figs. 12a and 12b and in Figs. 13a and 13b is evident.

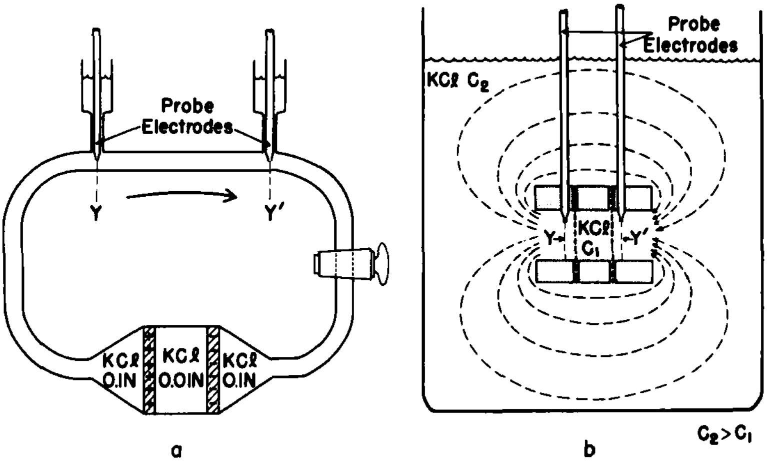

Fig. 13. All-electrolytic mosaic membrane models. (a) A schematic model, (b) the experimental model.

Table 11 summarizes some of the results obtained with model systems both with and without auxiliary electrodes through which the current flows [211, 212]. The correction for leakage of electrolyte across the membranes, due to their deviation from ideality, is noted in the sixth column of Table 11. The theoretically postulated numerical agreement of the experimental data in the last two columns of Table 11 seems most satisfactorily fulfilled, considering the experimental difficulties involved in these experiments.

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Table 11. A Comparison of the Quantities of Electrolyte and of Electricity Moved in Model Systems of Mosaic Membranes That Are Composed of Anion- and Cation-Selective Parts

Electrolyte solutions							
Electrolyte used	Concn. on closing of circuit, eq/liter	Electrodes	Volume of dilute solution, ml	Increase in concn. of dilute solution, eq/liter	Correction for leak, eq/liter	Equivalents of electrolyte moved, eq × 10^{-6}	Quantity of electricity moved, F × 10^{-6}
KCl	0.050/0.00521	Ag ∣ AgCl	70.0	0.00116	None	81.2	82.2
KCl	0.100/0.01050	Ag ∣ AgCl	65.0	0.00105	0.00008	63.1	61.8
KCl	0.050/0.001500	Cu ∣ $CuSO_4$ ∣ agar	80.0	0.000420	None	33.6	33.5
K_2SO_4	0.050/0.001681	Cu ∣ $CuSO_4$ ∣ agar	74.0	0.000417	0.000064	26.1	25.7
KCl	0.050/0.001554	None	19.00	0.001308	0.000046	24.0	24.6
LiCl	0.050/0.004898	None	19.00	0.000657	0.000009	12.3	12.2
KIO_3	0.050/0.004938	None	19.00	0.000435	0.000019	7.90	8.08

A Physicochemical Cell Model which Simultaneously Accumulates Anions and Cations against Concentration Gradients

The accumulation of electrolytes by living cells (the simultaneous accumulation of both anions and cations) up to concentrations many times greater than those in the surrounding medium is one of the central unsolved problems of physicochemical biology. Membrane equilibria across a single membrane cannot furnish an adequate explanation, as was stressed by Dean [213]. Other explanations of an electrochemical nature that have been suggested were based on the assumption of various vaguely conceived mosaic structures [214]. The indefinite nature of these ideas has precluded their use as starting point of meaningful experimental work.

The model whose theory and experimental verification will be outlined here is based on a clearly defined type of structure composed of ideally cation-selective and ideally anion-selective parts, across which, under the proper conditions, two Donnan equilibria arise, one with respect to cations and the other with respect to anions [215].

Let us assume a cation-permeable, anion-impermeable membrane that separates an "inside" solution, which is kept constant at 1 × 10^{-3} N with respect to H^+ by the continuous addition of nitric acid of high concentration (which represents the continuously developing metabolite in the living cell), and an outside solution, which is maintained at 1 × 10^{-5} N with respect to HNO_3 and 1 × 10^{-3} N with respect to NH_4Cl. The water permeability of the membrane may be assumed as negligibly small. In this system H^+ will exchange against NH_4^+ until the Donnan equilibrium of ion distribution, Eqs. (8) and (21), is reached:

$$\frac{[H^+]_{in}}{[H^+]_{out}} = \frac{[NH_4^+]_{in}}{[NH_4^+]_{out}} = \frac{10^{-3}}{10^{-5}} = \frac{100}{1} \tag{22}$$

Accordingly, the concentration of NH_4^+ ions in the inside solution under equilibrium conditions will be 1 × 10^{-1} N; the counterions of the NH_4^+ ions are the NO_3^- ions which were added continuously to the system in the form of HNO_3 while the H^+ ions exchanged across the membrane for NH_4^+ ions.

In an analogous system an exclusively anion-permeable membrane is interposed between an inside solution, the concentration of which with respect to NO_3^- is kept constant at 1 × 10^{-3} N by the addition of HNO_3, and an outside solution which, as in the preceding case, is maintained at 1 × 10^{-5} N with respect to HNO_3 and at 1 × 10^{-3} N with respect to NH_4Cl. Under equilibrium conditions we find:

$$\frac{[NO_3^-]_{in}}{[NO_3^-]_{out}} = \frac{[Cl^-]_{in}}{[Cl^-]_{out}} = \frac{10^{-3}}{10^{-5}} = \frac{100}{1} \tag{22a}$$

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In other words, the concentration of Cl^- in the inside solution will be 1 × 10^{-} N, with an equivalent amount of (nondiffusible) H^+ ions being present to establish electroneutrality.

The membrane equilibria which are reached in these two independent systems are indicated in Fig. 14, in which a cation-permeable and an anion-permeable membrane are located next to each other in the same unchanging outside solution.

If the two "inside" solutions of Fig. 14 were now connected by means of an electrolytic bridge (having, for instance, the same composition as one or the other of the inside solutions), a closed all-electrolytic circuit would be established. The system would now be composed of two concentration cells arranged in series in a closed circuit. A current would flow from one inside solution through the electrolytic bridge to the other inside solution and back through the outside solution compartment. The system would discharge spontaneously, in a manner similar to that of the previously discussed mosaic systems of Fig. 11c and 13. In the present case, however, a stationery state would be reached in which the rate of accumulation of electrolyte and the rate of discharge balance. Qualitatively, it is obvious that the lower the electrical resistance of the short-circuited system, the lower must be the degree of electrolyte accumulation which is obtained in the stationary state.

Let us now consider a system with the same two membranes as those shown in Fig. 14, in which, however, the two inside solutions are continuously mixed mechanically and thus are maintained at the

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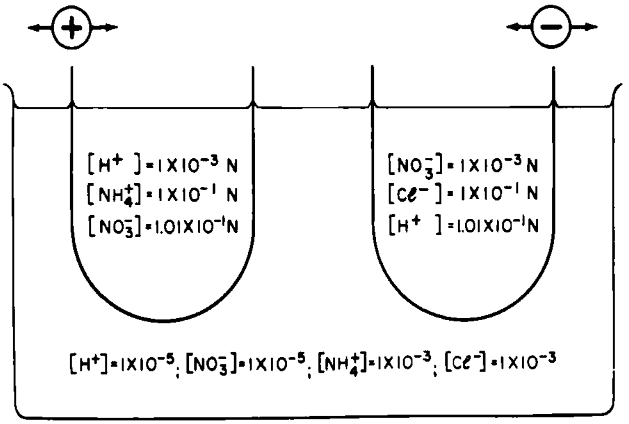

Fig. 14. The two Gibbs-Donnan membrane equilibria with the same "outside" solution across an exclusively cation-permeable membrane (left side) and across an exclusively anion-permeable membrane (right side).

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same concentration with respect to all their constituents, while at the same time no current can flow in the system, as is indicated in Fig. 15. This may be achieved, as is indicated in the figure, by means of a circulating pump that forces liquid through a tubing in a manner which prevents a direct electrical contact of the liquids inside the two membranes. In the return flow of the solution, the same result is achieved by letting the liquid drop back into the left compartment. The solution inside the two membranes is kept 1×10^{-3} N with respect to both H^+ and NO_3^- ions. The two membranes are inserted side by side in the same outside solution, which is kept continuously 1×10^{-5} N with respect to HNO_3 and 1×10^{-3} N with respect to NH_4Cl. (For the sake of simplicity we may assume here that the rates of exchange of the cations and of the anions across the two membranes are the same.)

In the system of Fig. 15, H^+ ions will continuously exchange across the cation-permeable membrane for NH_4^+ ions until the Donnan equilibrium with respect to the cations, defined by Eq. (22), is

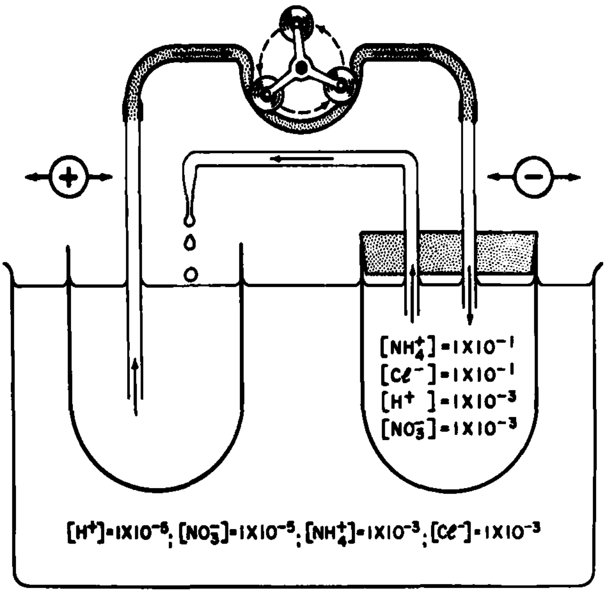

Fig. 15. The simultaneous accumulation of cations and anions against concentration gradients by the combination of an exclusively cation-permeable membrane and an exclusively anion-permeable membrane in a system in which the solutions in the two "inside" compartments are mixed mechanically but are not connected electrically by means of a conducting bridge.

reached; similarly, NO_3^- ions will exchange for Cl^- ions across the anion-permeable membrane until Eq. (22a) is satisfied. The final equilibrium state of our system is shown in Fig. 15; the NH_4^+ and the Cl^- ions are accumulated 100-fold, up to 10^{-1} N, from 10^{-3} N in the outside solution.

A limited number of experiments to test the validity of the outlined theory were performed. Dr. Rex Neihof, and Dr. Marc Lewis (unpublished), using permselective collodion matrix membranes in model systems essentially identical to that shown in Fig. 15, found electrolyte accumulations up to 35 times the outside concentration [215]. The calculated equilibrium ratio of accumulation, however, has not yet been reached in full, probably because of leakage of noncritical ions across the membranes, the influence of which increases greatly as the degree of electrolyte accumulation increases. The experimentally obtainable final state is the stationary state in which the rates of accumulation and of leakage balance. The experimental data, nevertheless, prove that the outlined theory describes a conceivable mechanism of electrolyte accumulation against concentration gradients.

From the biological point of view, the model of Fig. 15 seems somewhat unrealistic because the high resistance in the accumulating system is assumed to be located in an aqueous solution, which in Fig. 14 corresponds to the cell sap, while the high-resistance components of living cells are their membranes. Thus, a more realistic model requires that that part of the system which represents the membrane should be its high-resistance element [216]. This membrane must fulfill the conditions that it facilitates a high rate of cross-membrane transportation both of anions and of cations by some non-ionic process or processes, while the rates of cross-membrane movement of ions by ionic processes, diffusion, and electromigration are low.

Two types of membranes have been suggested which fulfill these requirements by means of entirely different mechanisms [216]. One makes use of the two facts that stirring enormously increases the rates of transportation of solutes in and across liquid phases far above those which are due to diffusion in the unstirred liquid, and that the conductance of an electrolytic solution is not affected by stirring. Thus, stirring will greatly increase the rates of the exchange of ions across aqueous membranes, and therefore also the rates of electrolyte accumulation in suitable models, while the strength of the discharging current remains unaffected by it. This combination of factors leads to conditions which approach those assumed in the model of Fig. 15. It thus facilitates, by the use of stirred membranes of suitable geometrical shape, the construction of model systems identical in all essential aspects to that of Fig. 15. Preliminary experiments have shown that the construction of effective accumulation models of this type is feasible.

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The other clearly visible possibility of an accumulation model of this general nature can be based on the use of "oil" membranes consisting of essentially nonconducting phases across which the exchange of ions occurs by nonionic processes, namely, with the ions bound to some carrier in an essentially undissociated complex [216]. The "liquid ion exchanger membranes" mentioned before [13-20] fulfill this condition in a virtually perfect manner. In some preliminary experiments to test this model (unpublished), Dr. Gerald M. Shean has obtained in some instances accumulations of more than 30% of the calculated values. However, since the liquid ion exchanger membranes were not treated in this paper, the discussion of the models based on such membranes is likewise outside its scope.

Some Additional Membrane Effects and Membrane Model Systems; Layered Membranes, Thermo-osmosis, Electro-osmosis in Mosaic Systems; Concluding Remarks

The membrane effects and models which were discussed in the preceding pages represent only a selection of the heretofore investigated cases. Many more interesting membrane effects exist, and many other types of model systems can be constructed and studied. A few examples will be sketched briefly here.

There are, first and foremost, the layered membranes, a group of composite membranes which must be sharply distinguished from the mosaic membranes discussed up to now. Whereas the parts of diverse intrinsic properties of mosaic membranes lie in juxtaposition to each other, the various component parts of different intrinsic properties of layered membranes are superimposed upon each other in the form of sheets of equal size, and united bodily in a single physical unit [217].†

The author, who has no first-hand experience with layered membranes, will not attempt to review here the literature in this field but will only mention some of the pertinent publications. Suffice it to mention the pioneering papers by Wilbrandt [87] and Meyer and Bernfeld [99], and to direct the attention of the reader to the clearly defined and by now thoroughly investigated "bipolar" membranes which consist of a highly anion- and a highly cation-selective layer superimposed on each other [218]. Membranes of this type act as rectifiers, in many ways very similar to solid-state p-n semiconductor junction diodes [218]. For this reason alone, they are of great electrophysical interest, and might turn out to be of considerable technological significance. The main biophysical importance of these bipolar membranes lies in the fact that they can be considered

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† The first to have conceived the idea of such bipolar "double membranes" was seemingly M. Cremer. (See Reference [217] p. 876.)

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as models for many living membranes which show very similar electrical responses when an outside electric field is applied. This most interesting and promising approach deserves a great deal of further investigation.

Nonisothermal membrane phenomena have been studied only in a few isolated instances. The longest-known nonisothermal membrane effect is "thermo-osmosis," the transport of liquid across membranes, ordinarily of the porosity of dialyzing membranes, which separate two solutions of identical composition but different temperature. It was studied experimentally mainly by Lippmann [219] and Aubert [220], and by Carr and Sollner [221]. No thermo-osmosis was observed with water or aqueous solutions of nonelectrolytes. With aqueous solutions of electrolytes, thermo-osmosis occurs across electrically charged membranes but not across uncharged membranes [221]. While thermo-osmotic effects are small, their reproducibility is good. The rate of thermo-osmosis is proportional to the temperature difference across the membrane. The direction of the thermo-osmotic movement depends on the sign of charge of the membrane and the nature and concentration of the electrolyte in the solution. The thermo-osmosis observed with electrolytic solutions is an electrochemical phenomenon [219-221]. The direction and rate of thermo-osmosis depend in a strikingly similar manner on those factors which determine the direction and rate of anomalous osmosis, namely, the charge of the membrane and the nature and concentration of the electrolyte solution used. This similarity is strongly suggestive evidence of a fundamental, close relationship between these two phenomena [221]. A theory of the mechanism of thermo-osmosis has been put forward recently by Kobatake and Fujita [222]. The available data indicate that thermo-osmosis, from the physiological point of view, is not, in all probability, of much interest. The temperature differences which arise even under extreme conditions in living systems are too small, as far as the available evidence indicates, to be able to produce significant thermo-osmotic effects.

In discussing the mosaic systems shown in Figs. 11-13, we were only interested in the correlation of the transmembrane movement of electrolyte and the quantities of current flowing simultaneously in these systems. With these systems the question of a concurrent water transport did not arise, since it could have caused only a negligible error. Nevertheless, the essentially electro-osmotic water transport which in such mosaic systems may accompany the flow of current is of some interest. Carr and Sollner [223] have tried to assess this effect quantitatively in model systems with auxiliary electrodes like that shown in Fig. 12b. For this purpose they used membranes somewhat less dense than those employed in the previously described mosaic systems, since membranes with wider pores yield a higher electro-osmotic water transport per faraday [224]. For instance, with membranes with a standard resistance, ρ^*, of 10 Ω cm^2, the water transports varied from about 20 moles of water/faraday with solutions of KCl to about 60 in the case of LiI as solute. In order to appraise the conceivable physiological significance of this type of water transport in micromosaic systems, one must consider the difference in the linear distances and in the corresponding resistances over which the current flows through the solutions in the macromodels and in the case of true mosaic membranes. With true mosaic membranes the sum of the local currents could easily be greater by two orders of magnitude, or more, than those measured in corresponding model systems. Accordingly, the rates of electro-osmotic transport of liquid across true mosaic membranes might be of the same order of magnitude as, or even larger than, the transport of liquid across the individual part of the membrane by normal or anomalous osmosis [223]. This conclusion, however, does not answer the question of whether or not the electro-osmotic transport of water across charge-mosaic membranes is of biological significance.

As a concluding remark to this paper, the author would like to state his considered opinion that further, more extensive and more refined work on the electrochemistry of porous ionic membranes is bound to yield results of increasing electrochemical, biophysical, and technological interest and importance. The rate of progress will largely depend on the availability of membranes with properties tailor-made, so to speak, for the various investigative purposes. The open problems include the development of relatively simple methods for the preparation of membranes, other than cellulosic membranes, whose porosities can be adjusted at will from the low porosities of dense permselective membranes up to the high porosities of dialyzing-type membranes; the creation of membranes with functional ionic groups different from the few studied thus far; methods for the preparation of membranes with which not only the gross charge density but also the microdistribution of the functional groups can be controlled down to the molecular level; the development of homeoporous membranes, a problem that is currently much investigated in the context of the problems of hyperfiltration (so-called "reverse osmosis"); and, last but not least, the development of a great variety of composite membranes, particularly layered membranes for the study and utilization of the important electrochemical properties of these involved structures. It is obvious that progress along these lines will mainly depend on the skillful and imaginative work of polymer chemists willing to join in the search for a deeper understanding of the electrochemistry of membranes.

SUMMARY

The purpose of this review paper is twofold; it presents, for readers unfamiliar with the field, the basic facts and concepts of the

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electrochemistry of porous membranes of ion exchange character ("ionic" membranes), and selectively reviews some less widely known electrochemical membrane effects and membrane model studies of biophysical significance.

The two-sided character of membranes is pointed out, e.g., their nature as restrictive barriers and as physiochemical machines, i.e., as transducers. The development of the electrochemistry of membranes out of the classical physical chemistry of electrolytic solutions under the stimulus of electrophysiological interest is outlined. This introduces the basic experimental facts and concepts of the electrochemistry of ionic membranes which have been integrated in the Teorell and Meyer-Sievers fixed charge theory of ionic membranes. The state of the art of preparing membranes of highly developed electrochemical properties is outlined, with emphasis on the preparation of "permselective" membranes which combine very high ionic selectivities, cationic or anionic as the case may be, with high transmissivities for the permeable ions. The basic electrochemical properties of the permselective membranes are reviewed: exchange capacity, water content, rate of osmotic water movement, resistance, electromotive action in concentration cells—concentration potentials, bi-ionic potentials, rates of cross-membrane exchange of two species of permeable ions, and ionic selectivity. The use of permselective membranes as membrane electrodes, in the study of membrane equilibria and in preparative and industrial operations, is briefly touched upon. The reviewed cross-membrane transport processes and membrane model systems of presumed biophysical interest include: The relative rates at which several coexisting species of critical ions move across permselective membranes, and the "overshooting effect"; the "carrier" process nature of the movement of ions across ionic membranes; anomalous osmosis; the electrical and permeability properties of mosaic membranes which are composed of exclusively anion- and exclusively cation-permeable parts; and a physicochemical cell model which simultaneously accumulates anions and cations against concentration gradients. In addition, layered membranes, thermo-osmosis, and electro-osmosis in mosaic membrane systems are briefly discussed.

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