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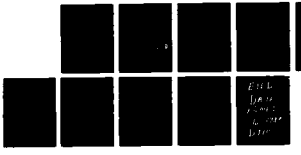

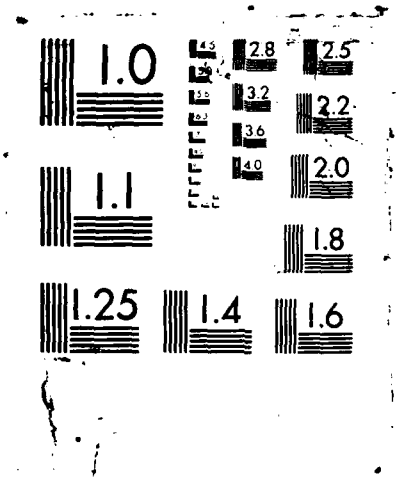
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Examination of Iotophoretic Transport of Ionic Drugs across Skin

By

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Potential induced transport of ionic drugs across skin is discussed.

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EXAMINATION OF IONTOPHORETIC TRANSPORT OF IONIC DRUGS ACROSS SKIN

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The purpose of this paper is to describe the systematic development of a new four-electrode system for studying iontophoresis of single charged drugs across the skin. It is also a critical examination of an equation which we have derived and which describes fundamentally flux enhancement across an artificial membrane or skin:

$$E = \frac{Y}{Y_o} = \frac{-ZF\Delta\Phi}{RT\left[\exp\frac{-ZF\Delta\Phi}{RT} - 1\right]} \qquad \text{Equ. 1}$$

E is the flux enhancement ratio, Y is the flux of a drug with an electric field, Y_o is the flux for the drug with no electric field across the same membrane, $\Delta\Phi$ is the potential drop across the membrane, Z is the molecular charge, D is the diffusivity, F is the Faraday constant, RT has the usual meaning.

The experimental results in Table 1 show that for the two-electrode system with a donor and a receiver compartment the flux enhancement ratio E with the benzoate ion and tetraethylammonium ion is within a factor of two to four of the theoretical predictions (assuming $\Delta\Phi$ = 10 volts) in several instances. The principal difficulty with the two-electrode system is that there is no easy way to know what the actual $\Delta\Phi$ is across the membrane. There may be significant electrical resistances at the electrode/solution interfaces and across the bulk solution between the electrodes and the membrane surface and there are no simple methods for estimating these. The two-electrode system, therefore, cannot be employed in the rigorous study of equation 1.

The developed four electrode system for a two chamber diffusion cell (see Fig. 1) allows for the first time ever to determine and control the actual potential drop on a membrane surface in a defined manner. The new two chamber diffusion cell consists of four sections, two each for the donor and two each for the receiver compartment. A ring shaped platinum wire serves as the

counter electrode in the diffusion cell. The Luggin capillary serves as a reference electrode and consists of a long thin capillary and is filled with KCl solution. The KCl solution conducts the potential from the tip of the Luggin capillary across the stop cock into a reservoir of KCl solution. A calomel electrode measures the potential and indicates it to a potentiostat. Two working compartments (6 ml volume) with their Luggin capillaries are mounted together with the membrane in between. A block diagram of the electronic circuit for the four-electrode diffusion cell is shown in Fig. 2. A pulse generator (G) supplies voltage vs. ground to the working electrode CE1. The same voltage of the opposite sign appears at the contact to the reference electrode RE1, while the contact to the reference electrode RE2 is always held at virtual ground. Only negligible current can flow through the reference electrodes. The potential drop between the tips of Luggin capillaries is then controlled in a defined way. The current flowing through the membrane is supplied by the outputs of the operational amplifier OA1 and OA3 with the platinum wires of the counter electrodes CE1 and CE2.

Fig. 3 and 4 depict flux enhancement ratios for tetraethylammonium bromide with the four-electrode system by using a cellulose acetate membrane and hairless mouse skin, respectively. As can be seen, low applied voltages between 0 and 250 millivolts the agreement between experimental and theoretical predicted flux enhancement is excellent.

At higher voltages, the experimental flux enhancement rises faster than the theoretical predictions. An explanation for this is believed to be that the applied electric field causes changes in skin properties which allows faster diffusion of molecules through the skin. These results demonstrating the quantitative applicability of equation 1 are believed to be the first of their kind.

TABLE 1

Membrane: Cellulose Acetate (25 μm)

Temperature: 37°C

Drugs	Electrolyte Solution	Voltage (V)	pH (donor initial)	P (cm/sec)	$E_{experimental}$	$E_{theoretical}$
Benzoic Acid	Saline	0	2.88	3.13×10^{-6}		
Benzoic Acid	Saline	2.5	2.88	3.80×10^{-6}	1.2	
Benzoic Acid	Saline	5.0	2.88	6.68×10^{-6}	2.13	
Benzoic Acid	Saline	7.5	2.88	8.47×10^{-6}	2.7	
Benzoic Acid	Saline	10.0	2.88	13.43×10^{-6}	4.29	
Benzoic Acid	PBS (2.0)	0	2.00	3.06×10^{-6}		
Benzoic Acid	PBS (4.0)	0	3.41	2.75×10^{-6}		
Benzoic Acid	PBS (6.0)	0	4.89	1.34×10^{-6}		
Sodium Benzoate	Saline	0	6.33	4.22×10^{-7}		
Sodium Benzoate	Saline	10.0	6.33	3.39×10^{-5}	80.3	400
Sodium Benzoate	Water	0	6.51	6.44×10^{-7}		
Sodium Benzoate	Water	10.0	6.51	1.67×10^{-6}	2.59	400
Sodium Benzoate	PBS (6.0)	0	6.00	1.99×10^{-7}		
Sodium Benzoate	PBS (6.0)	10.0	6.00	5.77×10^{-5}	289	400
Sodium Benzoate	PBS (8.0)	0	8.00	1.03×10^{-6}		
Sodium Benzoate	PBS (8.0)	10.0	8.00	4.33×10^{-5}	42	400
*TAB	PBS (6.0)	0	6.00	1.20×10^{-6}		
*TAB	PBS (6.0)	10.0	6.00	1.52×10^{-4}	126	400

*Tetraethylammonium bromide

FOUR ELECTRODE DIFFUSION HALF CELL FOR IONTOPHORESIS

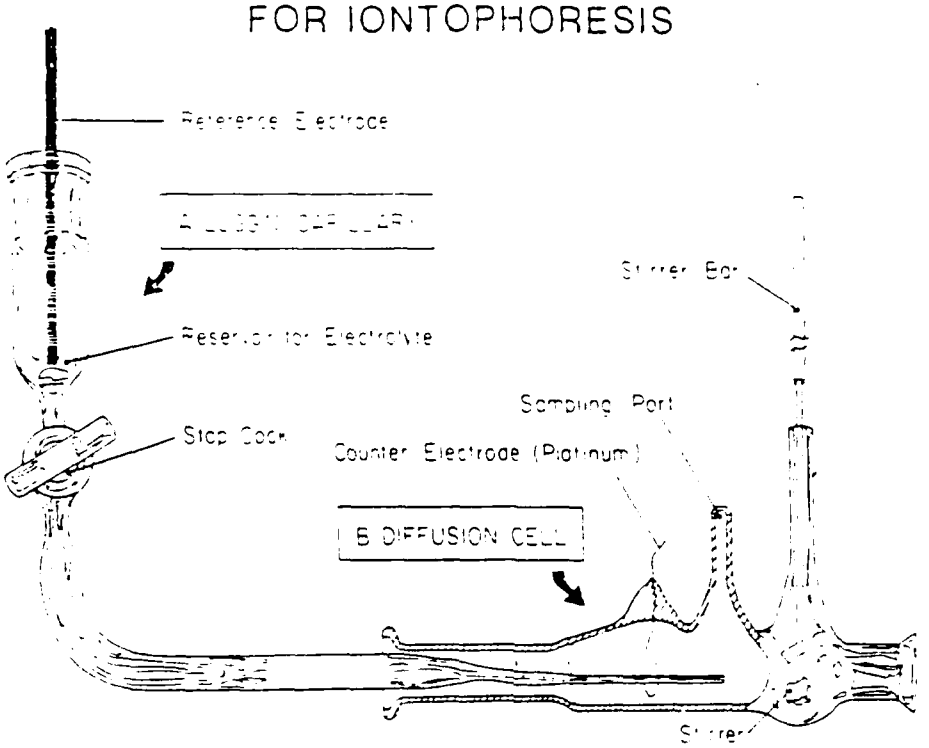

Fig. 1

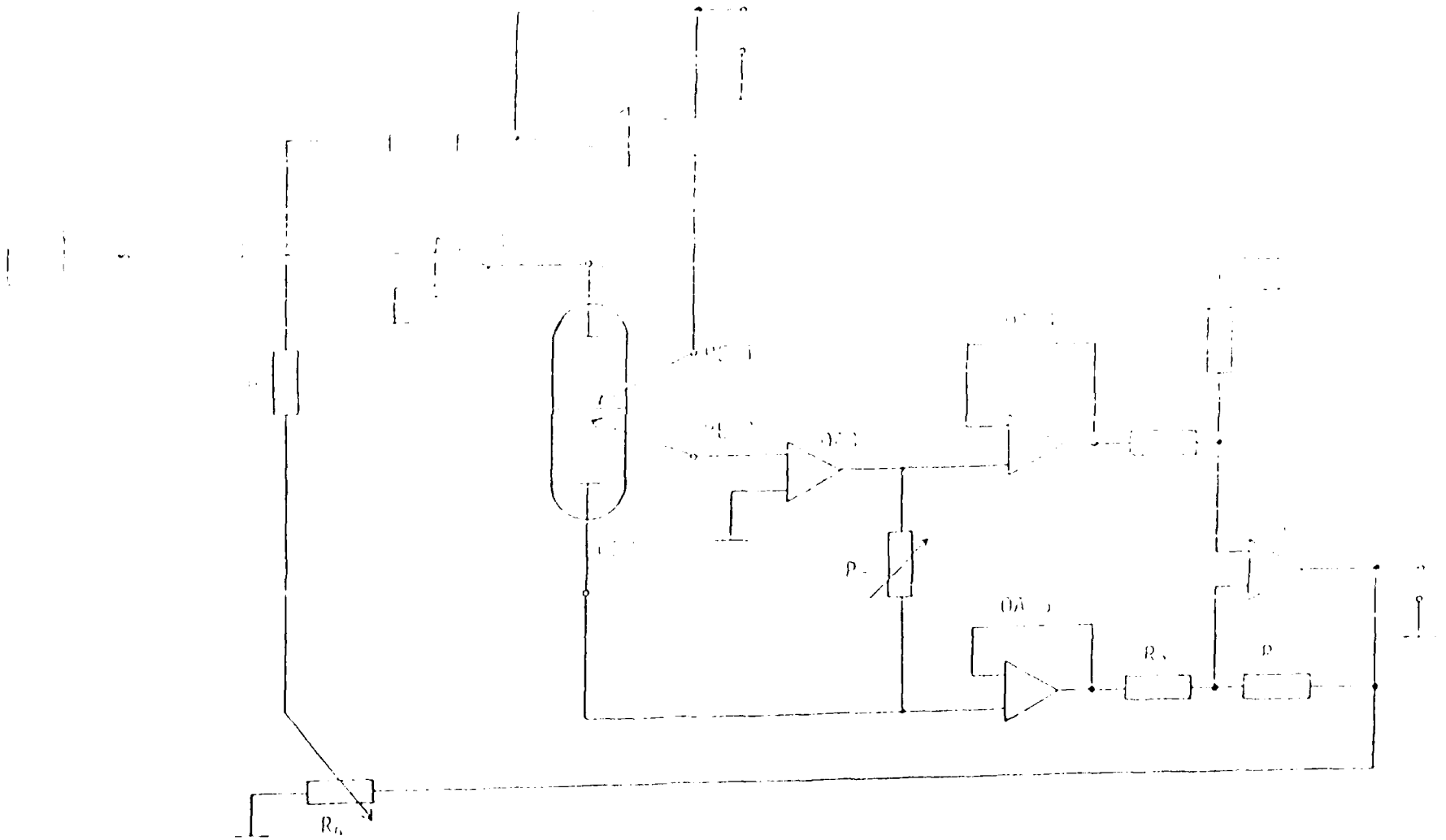

Fig. 2 : Block diagram of the electronic circuit. G, Pulse generator; X and Y, inputs of recorder; RE 1 and RE 2, reference electrodes; CE 1 and CE 2, counter electrodes; CE1 and CE2, counter electrodes;

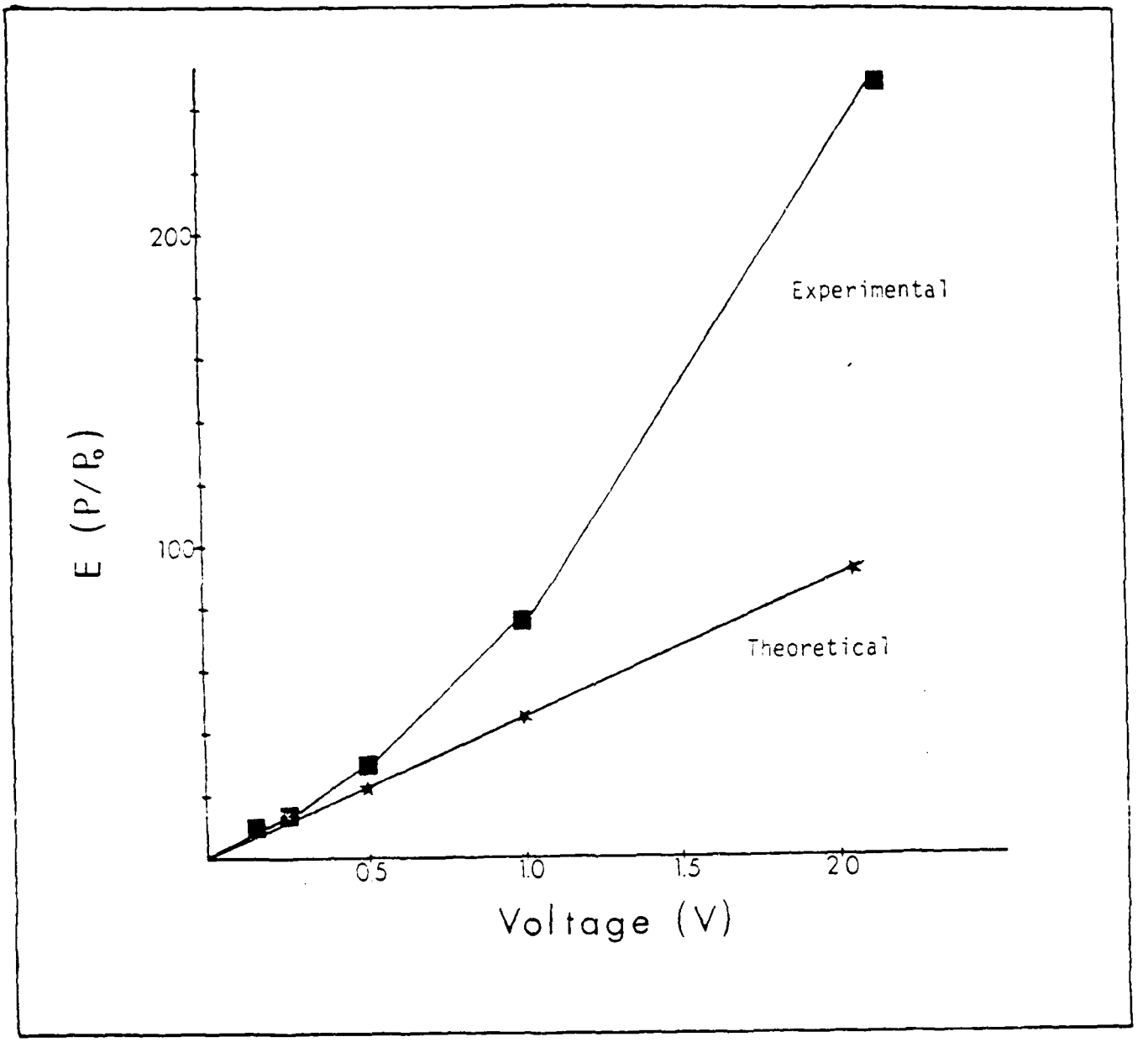

Fig. 3 : Iontophoresis of tetraethylammonium bromide

Membrane : Cellulose acetate (25 μm)

Medium : pH 6.0 isotonic buffer

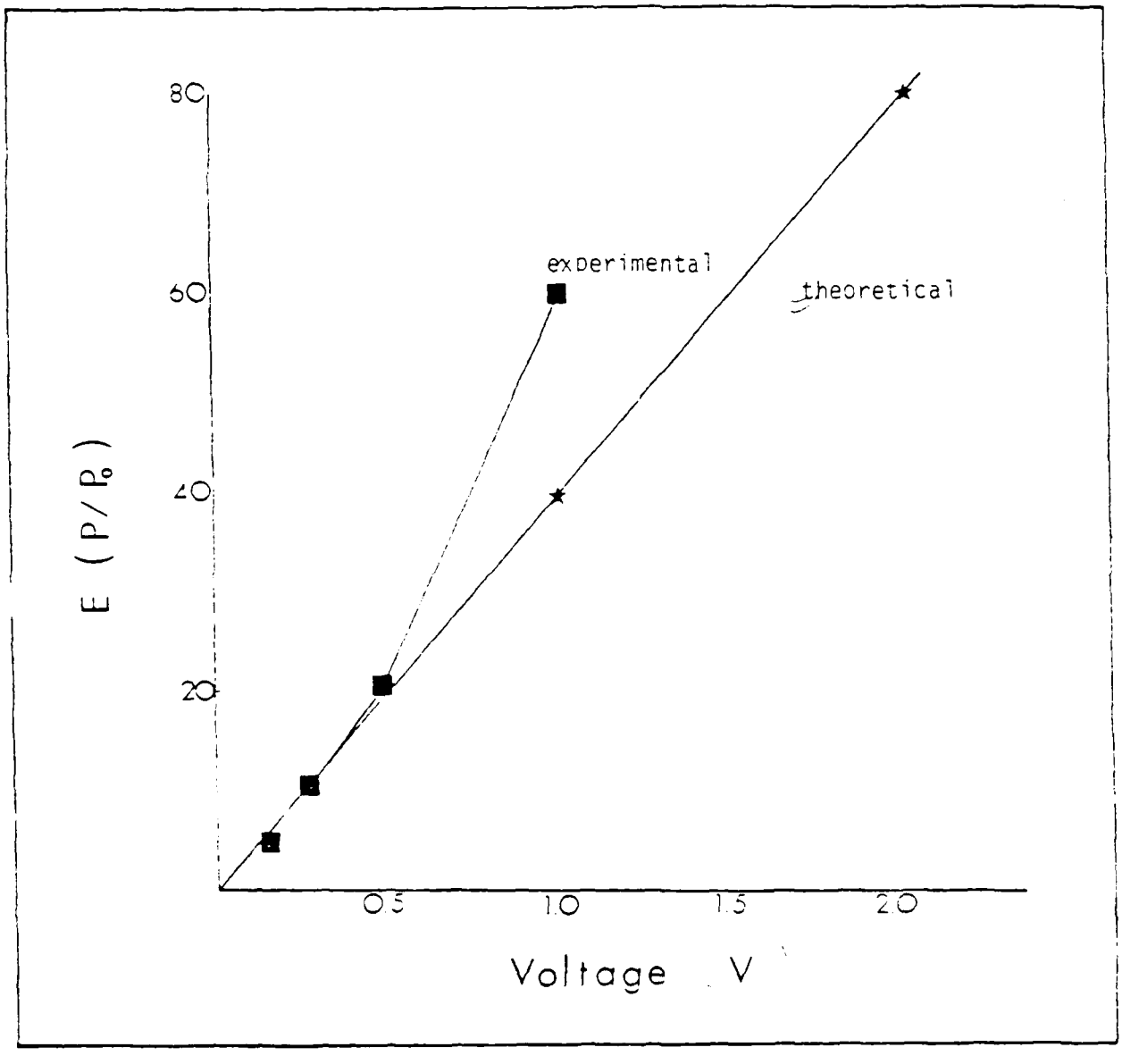

Fig. 4 : Iontophoresis of tetraethylammonium bromide

Membrane : Hairless mouse skin

Medium : pH 6.0 isotonic buffer

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