LETTERS TO THE EDITORS

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Linkage of Physico-Chemical Processes in Biological Systems

In a previous communication[1] Prof. F. G. Donnan —to whose kindness I am much indebted—has developed further an idea arising out of work in this laboratory[2], concerning the cellular accumulation of potassium ions in association with an intracellular chemical reaction. In this process an external diffusible anion, after passing through the membrane into the cell, is converted into an indiffusible anion or anion complex (using the term 'indiffusible' with respect to the membrane). The case chosen by Prof. Donnan was the simplest, in order to illustrate the principles involved. An important biological limitation of this simplest system would be that equilibrium can occur in this case only with a pressure difference if the potassium is accumulated. On discussing this matter with Prof. Donnan, it seemed to us of interest to present the condition when this limitation disappears, and in terms of the symbols of his letter.

We need consider only the final equilibrium state, or :

$$\text{(I)}\quad \begin{matrix} Y^- \\ \Sigma A^- \\ K^+ \end{matrix} \;\vdots\; \begin{matrix} N^+ \\ \Sigma A^- \\ K^+ \end{matrix} \quad \text{(II)}$$
$$M$$

in which (I) represents the interior of the cell, (II) the fluid environment, M the semipermeable membrane, K^+ the potassium ion, N^+ an indiffusible cation (which may be taken as sodium ion) and ΣA^- various diffusible anions, of which one type combines with an indiffusible neutral substance X within the cell to form the indiffusible anion complex Y^-. For simplicity, as before, in order to illustrate the ideas involved, the applicability of the laws of very dilute solution may be assumed, and also that the ions A^- and Y^- are univalent. We have then the following relations (where C denotes molar concentrations, and accented letters refer to II) :

$$C_K = \Sigma C_A + C_Y \quad (1)$$
$$C_K \Sigma C_A = C'_K \Sigma C'_A \quad (2)$$
$$C'_K + C'_N = \Sigma C'_A \quad (3)$$

from which :

$$2C_K = C_Y + \sqrt{C^2_Y + 4\,(C'_K)^2 + (C'_K C'_N)} \quad (4)$$

and

$$2\,\Sigma C_A = -C_Y + \sqrt{C^2_Y + 4\{(\Sigma C'_A)^2 - C'_N \Sigma C'_A\}} \quad (5)$$

whence $C_K > C'_K$ and $\Sigma C_A < \Sigma C'_A$, when C_Y and C'_N have real positive values. Equation (4) gives the quantitative expression for the accumulation of potassium ions in the cell against a gradient. Simple relations can be deduced for the special conditions when the hydrostatic pressures within and without are the same. Thus

$$P_I - P_{II} = RT\,\{C_K + \Sigma C_A + C_Y - (C'_K + \Sigma C'_A + C'_N)\}$$
$$= 2RT\,\{C_K - (C'_K + C'_N)\} \quad (6)$$

or
$$= 2RT\,(\Sigma C_A + C_Y - \Sigma C'_A) \quad (7)$$

whence, if $P_I = P_{II}$,

$$C_K = C'_K + C'_N \quad (8)$$

and
$$\Sigma C_A = \Sigma C'_A - C_Y \quad (9)$$

These equations show that at equilibrium an *equality* of hydrostatic pressures could occur *together* with potassium 'accumulation' when *both* C'_N and C_Y, that is, the concentrations of the indiffusible cation without and the indiffusible anion within, have positive real values.

The membrane system so described is simpler than that existing between plasma and tissue cells, but indicates certain important relations which have been experimentally verified[2]. For C'_N we may read the sodium concentration of the plasma, and for Y^- a system similar to phosphate esters. The full membrane system for muscle has been treated elsewhere[2], as also the relations controlling the volume changes.

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[1] Donnan, F. G., Nature, 148, 723 (1941).
[2] Boyle, P. J., and Conway, E. J., *J. Physiol.*, 100, 1 (1941).

The biological condition, referred to by Prof. Conway, means that he is considering the case of a cell where the semipermeable cell-membrane does not act like an *elastic envelope*, the distension of which, when the cell volume increases, produces an increase of hydrostatic pressure inside the cell, but like an *inelastic surface-layer*, the superficial area of which can vary with variation of the cell volume without affecting the internal hydrostatic pressure, the latter remaining sensibly equal to the hydrostatic pressure in the fluid environment. Prof. Conway has made this point quite clear in the investigation published in the *Journal of Physiology*, to which he refers. In this publication Prof. Conway has deduced a remarkable cell-volume relation, which he has experimentally verified in the much more complicated case of the muscle fibre - plasma equilibrium. I hope Prof. Conway will not consider it an intrusion if I indicate briefly how his reasoning can be easily applied to the simpler case considered in his communication (the symbolism and equations of which I shall use).

From the equations relating to electrical neutrality in (I) and (II), and the equation of membrane equilibrium, we have

$$C_K(C_K - C_Y) = C'_K(C'_K + C'_N).$$

Combining this result with Prof. Conway's equation $C_K = C'_K + C'_N$ (which results from the equality of hydrostatic pressures), we obtain at once

$$C_K = C'_K + C_Y.$$

Hence $C_Y = C'_N$. This means that the condition of equality of pressures *alone* gives the relation $C_K = C'_K + C'_N$, while this condition *plus* the three other conditions (electrical neutrality in both phases and the ionic membrane equilibrium) yields the relation $C_K = C'_K + C_Y$. Thus we cannot have equilibrium with *both* these two relations unless the (internal) C_Y equals the (external) C'_N. Now C_Y may be put equal to $[X]/V$, where V is the cell volume, and $[X]$ is the original mass of X in the cell (X denoting the neutral indiffusible substance inside the cell, from which Y^- is produced). From this it follows that C'_N *determines the cell volume*, when the experimental conditions are such that $[X]$ is sensibly constant.

In conclusion, I am much obliged to Prof. Conway for his elucidation of the biological condition, and wish to thank him for his very courteous reference to my humble effort.

F. G. Donnan.
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