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The "Multiple Partition Coefficient" Hypothesis in Relation to Permeability.

MATILDA MOLDENHAUER BROOKS AND S. C. BROOKS.

From the Department of Zoology, University of California.

Irwin's "multiple partition coefficient" theory[1] has been examined with reference to the adequacy of its theoretical and experimental bases. This theory proposes that the rate of diffusion of a substance from (A)/ to (C) in a system: aqueous phase (A)/ non-aqueous phase (B)/ aqueous phase (C) depends upon the partition coefficients between adjacent phases. Suppose the diffusing substance to be a dye originally dissolved in (A): with time its fugacity in (B) will approach but not exceed that in (A) (which we may assume to be kept constant). Its stoichiometric concentration in (B) will assume a value which characterizes the partition coefficient, but its fugacity from (B) will be independent of the partition coefficient. The rate of diffusion out of (B) into (C) will depend upon both its fugacity and its stoichiometric concentration in (B), and also of course in (C). The rate of diffusion across either or both phase boundaries may also be affected by local conditions at the interface peculiar to the nature of the 2 phases and the diffusing substance. For these reasons the hypothesis, insofar as it is based on partition coefficients alone, is physically unjustifiable, and we would expect it to have a very limited applicability.

The supposed experimental proof[1] of the hypothesis rests upon parallelism between the relative rates of uptake of a relatively small number of dyes into the sap of living cells of *Valonia* or *Nitella,* and their uptake by the "sap" of an artificial cell. This artificial cell consists of a horizontal glass tube bearing 3 upright arms; the horizontal tube is filled with $CHCl_3$, which separates sea water in one

[1] Irwin, M., PROC. SOC. EXP. BIOL. AND MED., 1928, **26**, 125.

end arm from natural or artificial sap in the other. Sea water, $CHCl_3$, and sap correspond to (A), (B), and (C) above, and the $CHCl_3$ is supposed to correspond to the plasma membrane of a living cell. All are stirred. Dyes are placed in the sea water and their relative rates of entry into both (B) and (C) noted.

As indicated above, the time-distribution relations of the dye in the artificial cell are not determined by partition coefficients alone. Furthermore, since partition coefficients were not determined, the artificial cell affords no evidence at all as to the part played by them. It is not therefore allowable to conclude that partition coefficients account for the general parallelism between artificial and living cells. Such parallelism is better correlated with other well-defined characteristics of the dyes used. No dye with a formula weight exceeding 456, nor any acid dye, was found in the sap of either the living or artificial cell at the time of the only recorded observation (3 hours). Among the basic dyes, the most highly ionized penetrated slowest; and all the acid dyes tested are strong acids. Formula weight, ionization, or sign of charge might account for the failure to enter the cells.

Confirmation of the above criticisms was obtained by applying similar tests to a series of redox indicators and other dyes: we used 4 indophenols, 3 indigo sulphonates, methylene blue, erythrosine, and brilliant cresyl blue. Many discrepancies between the artificial and living cells were found. In particular, all the indophenols went into the $CHCl_3$ of the artificial cell; all except one entered living *Valonia* cells, but none went into the "sap" of the artificial cell. The multiple partition coefficient hypothesis therefore, rests upon unsound theoretical and experimental bases.

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Effect of Liver Poisoning on the Action of Parathyroid Extract.

DAVID M. GREENBERG.

From the Division of Biochemistry, University of California Medical School, Berkeley.

The mechanism by which parathyroid extracts increase the level of the blood calcium is almost completely unknown. Sendroy and Hastings[1] have shown that *in vitro* such extracts have no effect on

[1] Sendroy, J., and Hastings, A. B., *J. Biol. Chem.*, 1927, **71**, 783, 797.