Cohen and co-workers (12,13) have used regular solution theory and a more exact form of Eq. 6 (14) to explain how structurally similar molecules could be either depressors (anesthetics) or stimulants (convulsants) of the nervous system. Their explanation of this difference was based on an extension of the concept of Mullins (15) that linked the biological properties of a chemical with its biophase of action. Thus, drug specificity is a consequence of its preferential solubility in a subregion of the membrane exhibiting a bulk solubility parameter similar to that of the drug. In this case, low δ drugs cause excitation, whereas high δ drugs cause depression.

Martin and co-workers (16) examined the effect of solvent polarity and its ability to solvate theophylline on the in vivo absorption of theophylline from mixtures of polyethylene glycol 400 and water into the rat intestinal membrane. Their results were qualitatively similar to those observed for salicylic acid in a model system (8). The closer the δ value of the polyethylene glycol 400–water mixture was to the δ value of theophylline the slower the rate of disappearance of theophylline from the solvent mixture into the rat intestine. The authors also used Eq. 6 to calculate a δ value for the intestinal membrane of 12.6 $(cal/cm^3)^{1/2}$ from their data.

Finally, Bustamante and Selles (17) have shown that the binding of drugs to plasma protein can be analyzed by Eq. 11 in which δ_E and δ_D are the solubility parameters for albumin (or the drug-binding site in albumin) and drug, respectively, where the activity coefficient (α) is the ratio of maximum binding (B_D^M), to the real binding (B_D) by analogy to the ideal and actual solubility from the Hildebrand equation. Data for the binding of sulfonamides, penicillins, phenothiazines, and barbituric acids to human serum albumin were found to fit Eq. 11, which describes a saturation-type process, better than an Eq. like 6, which describes a distribution-type process. It was also observed that maximum binding to serum albumin occurred when the solubility parameters of the drugs were similar to that of the plasma protein. For the sulfonamides, δ_E was calculated to be 12.33 $(cal/cm^3)^{1/2}$ which closely corresponds to the average solubility parameter of the seven-amino acids sequence in human serum albumin thought to be the primary binding site for sulfonamides.

$$\log \alpha = \log(B_D^M/B_D) = V_D\phi_E^2/2.3\,RT(\delta_E - \delta_D)^2 \qquad [11]$$

III. APPLICATION OF REGULAR SOLUTION THEORY TO PERCUTANEOUS ABSORPTION PROCESSES

Two groups initiated the application of regular solution theory to the partitioning process in percutaneous absorption. In 1984 Cohen