Finally, important progress has been made in characterizing a follicular pathway for penetration of solutes through the SC. The human in vivo study of caffeine absorption by Otberg and coworkers at Charité Hospital in Berlin stands out (94). They used a follicular blocking technique to demonstrate that a substantial fraction of caffeine dermal uptake was due to hair follicles. The difference at short exposure times (<30 min) was remarkable. This research group has published widely in this area for more than a decade, including two recent reviews (94–97). A significant build on the follicular blocking approach was published by Mohd and coworkers in Malaysia and Japan (98). These workers employed a blocking technique on pig ear skin in vitro and obtained evidence to support a strong dependence of follicular delivery on lipophilicity, with the more hydrophilic permeants showing larger follicular contributions.

Theoretical models: There is a wide array of modeling approaches to parameterize SC complexity, ranging from sophisticated QSPR methods (99–103) to highly detailed microstructural models (104–109). Intermediate in complexity but perhaps more accessible to many researchers are pharmacokinetic models (110), analytical (111–115), or finite difference (116–120) approximations to simplified SC structures and finite difference approximations to rectangular brick-and-mortar models (27, 121–128). The various classes of models have been further developed to include tissue binding effects (106, 112, 119, 120, 129, 130), follicular delivery (123, 128, 131), and the impact of multicomponent vehicles (101, 120, 132). Reviews of the field have appeared periodically (133–135).

Of particular interest to our research group is the ongoing discussion regarding transport mechanism(s) for hydrophilic permeants and the impact of SC lipid anisotropy on penetration pathways. The essence of the debate is whether a combination of barely permeable corneocytes plus fairly permeable, isotropic SC lipids, or fairly permeable corneocytes plus strongly anisotropic SC lipids better represents the SC diffusion barrier. A readable discussion from several years back can be found in (136). This debate has sparked a great deal of interest from my colleague Prof. Johannes Nitsche at the University of Buffalo, as well as collaborators Prof. Ludwig Nitsche at the University of Illinois at Chicago and Profs. Arne Naegel and Gabriel Wittum at the University of Frankfurt (104, 105, 107). The recent experimental work from Kodiweera et al. (90, 91) combined with Barbero and Frasch's latest finite element analysis (123) seemed to have tipped the balance in favor of the anisotropic lipid position. Prof. Nitsche (J. M.) has also done his homework in studying the related problem in phospholipid membranes (137–140), for which anisotropy is more easily demonstrated. I am honored to be a part of this research.

I offer my apologies to those whose contributions have been omitted as I try to summarize the last 16 years of research into stratum corneum heterogeneity.

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