on the basis of macroscopic observations unless the underlying transport properties are known. Thus, the tortuous pathway formulation of SC permeability leads to predicted permeation profiles similar to those of Potts and Guy (12). More complex behavior is possible if the corneocytes are considered to be permeable (28, 29); however, the full implications of this approach with regard to the time course of permeation have yet to be explored.

10.1 WHAT IS MEANT BY SKIN HETEROGENEITY?

For the purposes of discussion, three levels of heterogeneity in the skin may be distinguished: (1) multiple pathways and barriers for transport through full-thickness skin; (2) the biphasic "brick-and-mortar" structure of the SC; and (3) the variation of SC properties with depth. Much has been learned about the first two levels, as summarized in the preceding paragraph, although complete descriptions of neither are available. Both are considered central to a discussion of barrier function. The impact of the third level, asymmetry of the SC, is less certain. This is an area where effective approximations to the complex structure and composition gradients are essential for predictive transport models because the microscopic transport properties of individual SC layers are not experimentally accessible. Thus, despite the eloquent arguments of Elias (30) and others regarding the biological complexity of the SC barrier, there is still merit to simpler models. This chapter will present a physical chemistry perspective on the factors that must be included in order to make a generally useful description of transport across the SC. The impact of lower skin layers and the cutaneous circulation, although important to a general picture of skin absorption, is not considered here.

10.2 THE ROLE OF APPENDAGES AND THE SKIN'S POLAR PATHWAY

The importance of skin appendages—hair follicles and sweat ducts—to the transport of ions and highly polar molecules across skin is easily established. Examples include the perifollicular wheal and flare response induced by topical application of histamine ($K_{oct} = 0.20$) (31), punctuate patterns of dyes administered to skin via iontophoresis (32, 33), and localized electric fields observed indirectly at the skin surface during passage of mild electric currents (34–36). Peck and coworkers distinguished permeants penetrating via this "polar pathway," which most likely includes microscopic defects in the SC lipid lamellar structure, by their low permeabilities and low activation energies for diffusion relative to lipophilic permeants (17, 18). Appendageal contributions to the transport of lipophilic compounds across the SC are less obvious, but still demonstrable on the basis of transient diffusion analyses (37). Figure 10.1 shows data obtained recently in our laboratory supporting the need for a two-pathway diffusion model to explain transient diffusion profiles for permeants spanning a wide range of lipophilicity. The data were obtained using small doses of radiolabeled compounds applied to split-thickness (250 to 300 μm), cadaveric human skin mounted in Franz diffusion cells and tested according to previously described methods (37, 38). In each case a homogeneous membrane model (37) failed to describe the early stage of the absorption process, which was much more rapid than can be accounted for by diffusion through a slab. In most cases (but not for the flavonoid, kaempferol), permeation after several hours was well described by the single-pathway model. The second pathway having the shorter lag time, but clearly a limited capacity, is most likely related to either skin appendages or to microscopic defects in the SC lipid lamellae. These observations are consistent with the predictions of Scheuplein more than three decades earlier (39) and also with earlier results obtained by one of the authors using aqueous ibuprofen solutions applied to split-thickness skin (40). They may be important for understanding how nicotinate esters cause flushing within minutes of application to skin in vivo (41). It may be concluded that shunt pathways are important for most compounds during the initial transient phase of absorption and at all times for very hydrophilic compounds or for high-molecular-weight species (17) that cannot otherwise penetrate the skin (37, 42).