may partially relate to skin thickness and the number of cell layers in the SC. Body areas with the lowest topical absorption rates include the palms and soles (plantar foot arch < lateral ankle) [27]. Absorption of ^{14}C hydrocortisone from the back was 1.7 times greater than the ventral forearm [27].

Rougier et al. [28] assessed the *in vivo* penetration of benzoic acid, benzoic acid sodium salt, caffeine, and acetylsalicylic acid in male volunteers and found this general order of skin permeability: forehead > postauricular > abdomen > arm. Roberts et al. [29] assessed cumulative urinary salicylate recovery after topical application of methyl salicylate to different skin sites and found the skin permeability coefficient and percentage of salicylate absorption to be in the rank order of abdomen > forearm > instep > heel > plantar.

Changing the formulation or type of application adds complexity. Maximal plasma drug concentration from transdermal drug patches vary not only with skin sites of application but also with drug physicochemical characteristics (MW, lipophilicity, partition coefficient, etc.) and other interindividual differences [20]. The interested reader is referred to empiric predictive models developed by Farahmand and Maibach [20].

21.2.6 Population Variability Factors Affecting Topical Absorption

21.2.6.1 Ethnicity/Pluralistic Societies

Although the skin is approximately equally thick in persons of different pluralistic societies, the SC in blacks has more cell layers and a higher lipid content than in whites [30]. These differences may lead to absorption differences. In addition, blacks and Hispanics have stronger irritant reactions than whites to sodium lauryl sulfate [31, 32], a surface active agent often found in nonmedicated and medicated shampoos. (Note that experimental data in comparing blacks and Hispanic skin are limited, and there are conflicting data. The interested reader can obtain more information from two editions of a textbook detailing these points by Berardesca et al. (See Further Reading section for details.) Skin irritation may lead to inflammation and enhanced absorption of topical agents.

21.2.6.2 Age

Age can significantly affect topical absorption. Aged skin is drier with less skin surface lipids [33]. It is also thinner and more friable—skin aging is associated with progressive dermal atrophy, including atrophy of the skin's capillary network, resulting in a gradual reduction of blood supply to the skin [33]. All of these changes may potentially affect topical absorption. Overall, it paradoxically appears that the *permeability barrier function* of the skin is increased as we age. In particular, percutaneous absorption of less lipophilic substances (e.g. hydrocortisone, benzoic acid, acetylsalicylic acid, caffeine) are reduced, while more lipophilic substances (e.g. testosterone, estradiol) are not [33]. However, increased friability may result in broken skin, resulting in the loss of permeability barrier function and increased percutaneous absorption.

At the other end of the age spectrum i.e. infants and children, topical absorption may be increased. In the preterm baby, the permeability barrier function of the skin is not yet intact. Prenatal skin undergoes developmental stages in utero (including permeability barrier development e.g. proteolipid layer and pilosebaceous units), but some functions are not fully developed even in the neonate [34]. Importantly, the acid mantle is developed in the first 4 weeks after birth, and skin surface pH of both term newborns and premature neonates is less acidic than that of children and adults [35]. Newborn skin has higher permeability to topical agents. Pediatric skin is thinner, potentially allowing for an increase in the rate and amount of drug absorbed. In fact, pediatric and in particular neonatal and infant skins have skin surface conditions different from adult skin surface conditions, which may enhance absorption [36]. However, the dynamic nature of pediatric and especially neonatal skin and their respective skin barrier functions must be appreciated [37, 38] and taken into consideration when assessing percutaneous absorption or toxicity studies.

Skin hydration naturally differs with age. Although at birth the skin surface is rougher and drier compared with older children, within the first 30 days the skin smoothens and skin hydration