Also, note the following: (1) there may be residual drug remaining on and in the skin even if the dose is wiped off, i.e. treatment duration may be unknowingly extended; (2) repeated exposure over time may lead to chronic toxicity manifestations, such as corticosteroid-induced skin atrophy; (3) inadvertent chemical/drug exposure may occur via transfer from one person to another, e.g. a mother wearing sunscreen and holding her infant with bare arms. (This is discussed further in Section 2.14.)

21.2.4 What Roles do Skin Appendages (Hair Follicles, Sebaceous Glands, and Apocrine and Eccrine Sweat Glands) Have in Topical Drug Absorption?

The answer to the question of whether skin appendages have a role in topical drug absorption is yes, although much of the specifics is unknown. Skin appendages, which originate in the dermis, are subanatomical pathways whereby drugs and chemicals can be transported through the skin. Diffusion of chemicals through skin appendages is termed "shunt diffusion." Hair follicles can contribute to the total skin surface area for drug absorption and have also been shown to be reservoirs for drugs or chemicals.

The SC has a reservoir function for topically applied substances [24–26]. SC concentration of a chemical ultraviolet (UV) filter increased with increasing amounts of UV filter applied *in vivo* to human skin (flexor forearms of four females and one male); however, there was a saturation point where additional increased amounts did not further increase SC concentration, but were recovered as excess [24]. This indicated a storage function for SC which is saturable.

Using nanoparticle distribution studies, Ladermann et al. [25] demonstrated a 10 times longer reservoir storage duration within hair follicles than within the SC, with nanoparticles penetrating deeply into the infundibulum versus nanoparticle storage on the skin surface and in intercellular spaces around the corneocytes in the upper two cell layers of the SC. Nanoparticles were stored for 24 hours in SC versus at least 10 days in hair follicles. However, the amount of nanoparticles in SC were eight times higher than the concentration in hair follicles [25].

Using red marker dye to visualize lateral spread *in vivo* in humans (seven females, five males), Jacobi et al. observed that hair follicles retained dye 1 hour and 24 hours after application, even when the skin had been washed or had been in contact with clothing [26]. Lateral spread is discussed in Section 2.19.

Skin appendages are especially important for the penetration and skin storage of larger molecules (e.g. proteins), as discussed in Section 2.9. Little data exist regarding transport through the eccrine, apocrine, and sebaceous glands.

21.2.5 How Do the Skin Sites of Application Affect Absorption?

There is marked regional variability in absorption: absorption rates vary at different anatomical skin sites [20, 27–29]. In general, faster/greater absorption occurs if hair follicles are present in large numbers and somewhat slower if the SC is thick [27].

More specifically, the scrotum has the highest rate of topical absorption due to having both a very thin SC and a rich blood supply. Feldmann and Maibach [27] assessed the percutaneous absorption of hydrocortisone from various skin sites by analyzing urinary excretion of ^{14}C hydrocortisone applied to the forearm (ventral and dorsal), foot arch (plantar), ankle (lateral), palm, back, scalp, axilla, forehead, jaw angle, and scrotum [27]. They found a significantly faster excretion rate and a 42 times greater percentage of the dose excreted in the urine for the dose applied to the scrotum compared to the ventral forearm [27]. Farahmond reported that the scrotum had a fivefold greater permeability to transdermal testosterone than other skin sites [20].

Feldmann and Maibach found the next highest body areas for ^{14}C hydrocortisone absorption were the jaw angle (13 times greater than ventral forearm), the forehead (6 times greater than ventral forearm), axilla, and scalp (3.6 and 3.5 times greater, respectively) [27]. These regional differences