The skin provides the largest interface between the human body and the external environment. Therefore, one of its most important functions is to regulate what enters the body via the skin, as well as what exits. In general, the skin is designed to let very little enter, since other tissues, such as the permeable epithelia of the gastrointestinal tract and lung, provide the primary means of regulated entry into the body. Likewise, the skin must prevent excessive loss of water and other bodily constituents.

The skin’s remarkable barrier properties are due in large part to the stratum corneum, which represents the thin outer layer of the epidermis. In contrast to other tissues in the body, the stratum corneum consists of corneocytes (composed primarily of aggregated keratin filaments encased in a cornified envelope) that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers. These structured lipids prevent excessive loss of water from the body and likewise block entry of most topically applied drugs, other than those that are lipid-soluble and of low molecular weight. This poses a significant challenge to administering medications via the skin either for local cutaneous effects or as systemic therapy following their entry into superficial dermal capillaries.

### Table 124.1 Features of the stratum corneum

- Primary barrier to drug absorption into skin
- Two-compartment organization: “bricks and mortar”
- Microheterogeneity within extracellular spaces: “There’s more to the mortar than lipid”
- Persistent metabolic activity: dynamic changes in cytosol, cornified envelope, and interstices from inner to outer stratum corneum
- Homeostatic links to the nucleated cell layers: barrier function regulates epidermal DNA and lipid synthesis
- Pathophysiologic links to deeper skin layers: barrier abrogation and/or epidermal injury initiates epidermal hyperplasia and inflammation
- Stratum corneum as a biosensor: changes in external humidity alone regulate proteolysis of filaggrin, epidermal DNA/lipid synthesis, and initiation of inflammation

**Fig. 124.1** Two-compartment “bricks and mortar” system and “pore” pathway. A. The stratum corneum is a unique two-compartment system, analogous to a brick wall. Whereas lipids are sequestered extracelularly within the stratum corneum, the corneocyte is lipid-depleted but protein-enriched. B. The degradation of cornodesmosomes results in discontinuous lacunar domains, which represent the likely aqueous “pore” pathway. These lacunae can enlarge and extend, forming a continuous but collapsible network under certain conditions, e.g. occlusion, prolonged hydration, sonophoresis.