exceed about 10^4 before the corneocytes may be considered to be effectively impermeable. A detailed analysis allowing for anisotropic transport properties in the lipid phase and in which corneocyte permeability was carefully estimated from partition data (54–56) and hindered diffusion theory (29) suggests that the contribution of corneocytes to transport across the SC is significant for many permeants, although it cannot be estimated from a single parameter ratio, as in Heisig's analysis.

10.4 THE INFLUENCE OF ASYMMETRY ON SC TRANSPORT

The location of the transport barrier in skin was debated until the early 1960s due to the propensity of the tissue to be disrupted (thereby resulting in a "basket-weave" appearance) in routine histological preparations (30). Development of the alkaline swelling technique in Kligman's laboratory (58) was a key step that allowed visualization of the highly organized, compact structure of intact SC. This was complemented by outstanding transport work, much of which was conducted by Scheuplein and Blank (7, 39, 59–63), that established beyond a doubt that the SC was the primary diffusion barrier to water and most other permeants. It was also clear by the mid-1960s that the SC barrier extended across the tissue rather than residing in a thin layer at the base of the SC, as had originally been thought (60). Scheuplein and Blank provide a fascinating summary of these developments in their 1971 review (7).

Scheuplein had several lines of evidence available to support the uniformity of the SC transport barrier. Electron microscopy showed a dense, compact structure (64, 65), although the staining techniques to bring out the intercellular lipids had not yet been developed. Light microscopy using the alkaline swelling technique (58, 66) showed the SC to have a remarkably uniform appearance from top to bottom. An example micrograph from our laboratory is shown in Figure 10.2. Studies in which water transport was measured across sequentially tape-stripped skin suggested a uniform

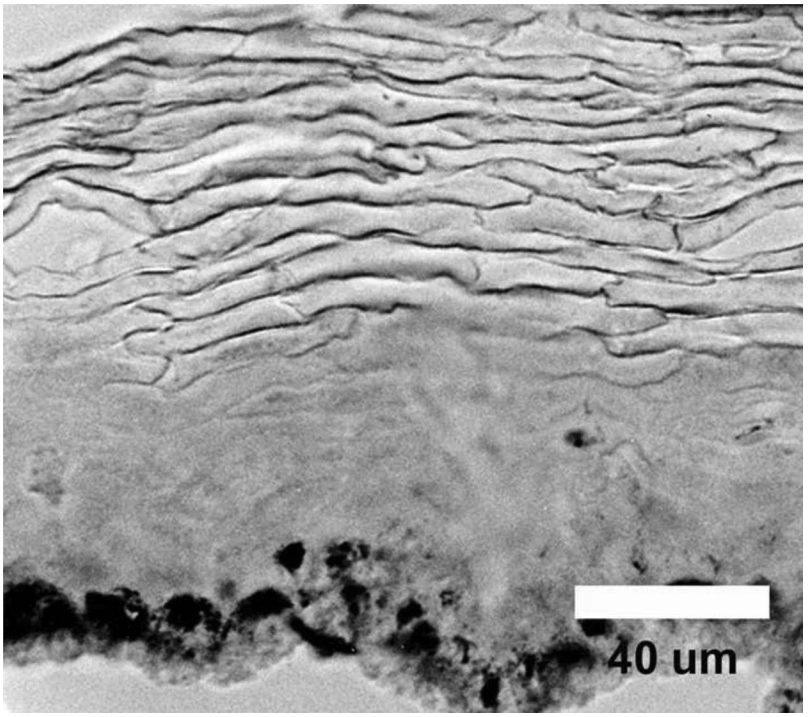

FIGURE 10.2 Brightfield image of alkaline-swollen human SC stained with methylene blue, illustrating partially ordered stacking of corneocytes. (From Reference 26.)