in composition presumably reflects ongoing metabolic activity, further dispelling the notion of the stratum corneum as an inert tissue (20; see Table 1). Despite the paucity of phospholipids, glycosphinogolipids, and cholesterol sulfate, these constituents apparently can arrange themselves into membrane bilayers, possibly by exploiting the amphipathic properties of sphingolipids (25,29–31), which apparently are capable of extensive hydrogen bonding. Yet, the hydrophobic, long-chain bases (31,32), the long-chain, fully saturated fatty acids (28,29,31,31; Table 4), and the enrichment of sphingolipids in linoleic acid (31,33–35), all make sphingolipids particularly good candidates for epidermal water-proofing (Table 5). Hence, sphingolipids are bipolar, possessing both a relatively hydrophilic terminus, capable of intermolecular bonding that can form ordered membrane structures, and highly hydrophobic moieties that could be highly water-repellent. Still unresolved is the fate of these lamellations during the first stages of shedding: Is membrane bilayer break-up a prerequisite for shedding? Do further changes in composition or the physicochemical properties of these bilayers lead to desquamation?

IV. LIPID BIOSYNTHETIC GRADIENTS IN THE EPIDERMIS

Certain striking features of the modulations that occur in lipid composition during epidermal differentiation suggest that the nonpolar mixture that ultimately resides in the stratum corneum is important for barrier function. Yet, a lipid analytic approach provides only indirect evidence about the function of stratum corneum lipids; furthermore, it can not define the role, if any, of neutral lipids, particularly free fatty acids, free sterols, and the smaller quantities of alkanes, sterol esters, triglycerides, and cholesterol sulfate in barrier function.

In the early 1980s, we noted that the skin of both rodents and primates synthesized abundant cholesterol and other nonsaponifiable lipids (36,37). In fact, the synthetic activity of the skin rivalled that of the liver and gastrointestinal tract, the two major putative sites of sterologenesis (38). Moreover, in contrast with hepatic and gastrointestinal synthesis, cutaneous sterologenesis was not influenced by circulating sterol levels (38), suggesting an unusual degree of independence from systemic regulation. To determine whether or not barrier function can influence epidermal lipid synthesis, we have employed a functional, rather than a purely analytical, approach. The basic strategy is first, to perturb epidermal barrier function, typically with an organic solvent such as acetone