GENERAL CONSIDERATION

Skin is a vitally important organ, has a complicated structure, and serves many functions (Pinkus, 1977; Mehregan and Pinkus, 1966; Griffiths and Dutz, 1975). Definition of a normal skin is still an abstract. Topography and differences of different classes of animals, their habitat, age, sex and genetic constitution, introduce wide variations in skin structure. Because of the heterogeniety in the structure and functional differences of various layers constituting the skin, major lacunae still exist in the field of dermatology. Inadequate knowledge of normal development, structure and function of skin still exists. In the current study, investigations were carried out on epidermal layer of the skin, as it forms a first line defense of the body against the physical / environmental factors and also helps in thermoregulation of the animal with respect to its surrounding.

The structure, the biochemistry of lipids and enzymes of epidermis (an ectodermal derivative), play a very significant role in the formation of an effective barrier against transepidermal water loss (TEWL), and also for topical penetration of any substance / microorganisms through the skin. Because, the lipids envelope the cells from all the sides and fill the intercellular spaces, they are able to impede both intercellular and transcellular diffusion. This study was undertaken with an intention to investigate the effect of various experimental conditions on the lamellar body secretion, and the intercellular mortar lipids which contribute mainly to the barrier properties of the epidermis, using light and electron microscopy.

In psoriasis - a pathological human skin disease, most of the lamellar bodies show an abnormal configuration in their structure. As a result, even the intercellular lipid bilayers of the corneocytes, are not present as broad sheets, but instead show a whorl-like arrangement and breaks at many intervals (Chapter 1). Fatty acids, especially the essential fatty acids like linoleic acid is known to cause disruption of disc like structures of the lamellar bodies (LBs) in essential fatty acid deficiency conditions (Wertz et al., 1983; Hou et al., 1989). The 'dry' non-eczematous skin of patients with atopic dermatitis too show a defect in the maturation of LBs (Werner et al., 1987). These evidences support the current observations, wherein one could propose that the abnormality in the structure of lipid lamellae in LB of psoriatic epidermis could be due to an anomaly in the biochemistry of lipids, or in the enzymes associated with LB, or due to insufficiency of time for the transition of cells, as a result of a very short basal cell cycle.

Histochemical studies also support this view, since an increase for phospholipid staining was seen in psoriatic plaque epidermis. All the above factors, and probably a defect in the enzymes associated with the formation of broad sheets in the stratum corneum (SC) intercellular domain, could lead to an abnormal lipid bilayered arrangement, accumulation of bilayers and their retention in the outer SC. This together with increased number of desmosomes could explain an abnormal cohesion and adhesion of scales in this pathological state.

Alteration of LB secreted material and related changes in barrier properties is also evident from observations made after various topical treatments on skin. In the current experiments, it was seen that Brij 99, a non-ionic surfactant, which is used in the preparation of liquid crystalline creams (used as a transdermal drug delivery tool) (Junginger et al., 1987), causes domain separation in the SC bilayers. Bilayers are interspersed with non-lamellated lipid material and with lacunae (Chapter 4). These alterations could give a clue to the path of permeation (ingress) in the epidermis, the effect this vehicle has on the lamellar lipids, how modification in the organization of SC lipids could help in effective permeation and probably give a clue as to how 'reservoirs' could be created in SC interstices for drugs to act and for the formation of prodrugs, with minimum side effects.

Another experiment, with topical application of glycerol on 'dry and scaly' skin of pigeon apteria as a model (Lachyanker, 1987), showed that this humectant, used as a skin conditioner in cosmetic industry (Bisett and McBride, 1984), leads to a comparative increase in the number of LBs which coalesce to form neutral lipid droplets and are retained in the corneocytes. This could possibly suggest a lipid inducers role for glycerol, thus reducing TEWL (Chapter 3). Modification in the number of LBs, their secretion and arrangement in the SC interstices, thus plays a significant role in maintaining TEWL.

Various studies have been carried out in similar context on cetaceans (Elias et al., 1984; Menon et al., 1986), on pigeon skin (Menon et al., 1986), on zebra finches (xeric species) (Elias et al., 1987) and also to some extent on squamate reptiles (Landmann et al., 1981).

Accordingly with different climatic conditions the animal has to adapt itself in such a way, that least TEWL occurs, thus making survival easier/ possible in their ecological niche.

In this study, the permeability barrier mechanism in buffalo - an animal living in tropical habitat, is seen to be sub-optimal. This corresponds with the animals habit of wallowing in water for prolonged periods of time as a means of behavioural thermoregulation (Chapter 6). The paucity of keratohyalin granules in buffalo epidermis may be related to their habit of soaking in water, which alleviates the need for water holding properties of SC. Moreover, permeability studies using $LaNO_3$ (lanthanum nitrate) as a tracer (Weihe et al., 1977) showed an outward flux of this heavy metal even in the SC interstices. This can be correlated with high TEWL values in buffalo epidermis (Chapter 6). Furthermore, the lamellar contents seem to occupy a very small surface area in the SC interstices, together with a decreased staining for neutral lipids in SC, which indicate that, a possible alteration in the processing of the secreted lamellar contents could lead to an increase in the water loss through the epidermis. Water permeability is knwon to increase when integument is hydrated. Thus, permeability may be higher when skin is in contact with water than when it is exposed to air (Tercafs and Schoffeniels, 1965; Stokes, 1981). Thus behavioural thermoregulation in buffalo seems to be an excellent adaptive strategy for adaptation in the tropical habitat.

The barrier forming lipids of SC are also known to have water holding properties. Permeation of any substance through the skin, thus has to overcome this lipid barrier. In vitro permeation of water was porformed by using tritiated water, since β emitters are known to pass through the skin barrier (Schaefer et al., 1982) (Chapter 5). Heat split epidermal sheets were taken after different treatments and mounted on a permeability cell. Solvent treated skin showed a 40-50% increase in water permeation in both rat and pigeon epidermis. After topical application of glycerine, beewax and Brij 99 on the rat pup skin, the epidermis showed a change in the permeation pattern. The water permeation was seen to be very less compared to normal and solvent treated skin. The skin of dorsal and ventral skin of lizards showed negligible water permeation compared to rat and pigeon epidermis. This data is supported by the findings of Landmann et al. (1981), where it has been studied that permeation experiments with $LaNO_3$ as a tracer in squamate reptiles indicated, a strong barrier properties of the lipid lamellar sheets in the mesos layer to transcutaneous water flux. Thus, the above results using tritiated water further emphasizes the importance of epidermal lipids in water permeation. It also gives a comparative account of water permeation after various treatments and also in different classes of animals.

Apart from looking at the epidermal barrier, histochemical observations were carried out on the parakeratotic regions of tail skin and the psoriatic lesions. Rat tail skin has since long been proposed as an animal model to study psoriasis (Bladon et al., 1986; Wrench and Britten, 1975; Spearman and Hardy, 1977). Since lipids, calcium and nucleic acid distribution can give a preliminary insight into the basic similarities, if any, in rat tail skin and psoriatic epidermis, light microscopic studies were carried out to look into the same. The present study revealed that the tail skin hardly resembles the parakeratosis in psoriatic lesions with respect to the distribution pattern of lipids, nucleic acids and calcium, probably because parakeratosis is not a pathological condition in rat tail skin. For further evidence, biochemical studies are still needed to be done.

In conclusion, this current investigation gives a broader view of the role of LBs in adaptation of an animal to its habitat, in skin disorders, like psoriasis and also during vehicular permeation due to treatments with glycerol and Brij 99. Development of appropriate animal models for different skin problems like rat tail skin and pigeon apteria. The perturbation of barrier with vehicles to have effective transcutaneous absorption, would help in developing new absorption promoters for transdermal drug delivery.