INTRODUCTION AND REVIEW OF LITERATURE

Psoriasis is one of the oldest of all recorded skin diseases. The first recognizable description of psoriasis was attributed to *Celsus* (25 Before Christ(B.C.) - 45 Anno Domini(A.D.) ie.years since the birth of Christ) in his "Dere medica" nearly 2000 years ago. The disease was described under the heading of impetigo (from the Latin impeto= to attack). *Galen* (133 - 200 A.D.) was credited as the first person to use the correct word "psoriasis" as it came from the Greek word "psora"; the itch. Uptill the eighteenth century, psoriasis was grouped with leprosy. *Willan* (1809)was the first to accurately describe psoriasis and its various manifestations but the author did not separate it with certainty from leprosy. This was left to *Hebra* (1841).

Since its early recognition, psoriasis has been a constant challenge to the dermatologically concerned physicians, both in regard to find its specific treatment and in regard to disclose its fundamental cause. However, the pathogenesis of this disease remained speculative and handicapped by a lack of good animal models *(Anderson, 1982)*.

Psoriasis is a common, chronic, recurrent skin disease of unknown etiology showing a wide variation in the severity. The psoriatic lesion is characterized by the presence of

North America, less common in yellow- brown people, and least common in black people(*Nall and Faber, 1977 and Rook et al., 1986*). In Egypt, the prevalence was found to be 3% as recorded by *El- Zawahry (1964)*. Also, *Abdel-Rehiem et al.(1974)* had found that the incidence of psoriasis in Assuit (upper Egypt) was 1.7% among patients with skin diseases. Recently, *Younis (1989)* had found that the incidence of psoriasis was 1.87% among patients with skin disease.

Histopathologically, psoriasis varies considerably with the stage of the lesions and usually the changes are most characteristically diagnostic only in early scaly papules and at or near the margins of advancing plaques (*Lever and Schaumburg-Lever, 1983*). The earliest pinhead-sized macules or smooth-surfaced papules show a non-specific histologic picture with a preponderance of dermal changes. At first, there is capillary dilatation and edema in the papillary dermis, with a mononuclear infiltrate surrounding the capillaries. Spongiosis develops at the lower portion of the epidermis followed by focal changes in the upper portion of the epidermis where granular cells become vacuolated and disappear, and parakeratosis forms above these focal changes. At this point, the phenomena of the "squirting papillae" occur. Neutrophils are discharged intermittently from papillary capillaries and are attracted to the parakeratotic zones. These parakeratotic

mounds with their admixture of neutrophils represent the earliest manifestation of Munro microabscesses. At this stage, characterized clinically by an early scaling papule, a histologic diagnosis of psoriasis can often be made when there is marked exudation of neutrophils which may aggregate in the spinous layer to form spongiform pustules. Mononuclear cells remain confined to the lower epidermis which, as more and more mitoses occur, become increasingly hyperplastic. The epidermal changes at first are focal but later on become confluent; leading clinically to the formation of plaques.

Again, *Lever and Schaumburg-Lever (1983). and Milne et al. (1984)* described the fully developed lesions of psoriasis as to be best seen at the margin of enlarging plaques. The histologic picture of fully developed lesions are characterized by regular elongation of the epidermal ridges with thickening in their deep portion. This is a constant feature of psoriasis; the epidermal ridges show considerable elongation and extend downwards to a uniform level, resulting in regular acanthosis; i. e., thickening of epidermal ridges. The ridges are often slender in their superficial portion but show clubbing in their deep portion, the neighbouring ridges are seen to coalesce at their bases with apparent branching. There is neither intercellular nor intracellular edema in the epidermal ridges. Also, mitoses are not limited, as in normal

skin, to the basal layer but are seen also in the two rows of cells above the basal layer. In addition, elongation and edema of the dermal papillae are noticed and the tips of papillae tend to be dilated or spatulate in shape. They also show dilated and tortuous capillaries, and a relatively mild inflammatory infiltrate consisting mainly of mononuclear cells.

Thinning of the suprapapillary portions of the stratum Malpighii, with the occasional presence of a very small spongioform pustule is not uncommon. Such a spongioform pustule is a high aid for diagnosing psoriasis and its variants. It shows aggregates of neutrophils within the interstices of a sponge like network formed by degenerated and thinned epidermal cells. The epidermis over the tips of the papillae, being reduced to 2 or 3 cells thick, is useful in clinical diagnosis as if the scale is removed by currette or finger nail, it will result in the appearance of a tiny bleeding point (Auspitz sign) due to the exposure of the dilated tortuous capillary and damaging its endothelium; causing the bleeding point. The horny layer in some instances consists of parakeratotic cells; there is abnormal keratinization of cells so that the keratin layer consists of plumps of nucleated keratinized cells instead of anuclear squames and since, in the epidermis, a direct relationship

exists between the absence of keratohyaline granules and the development of parakeratosis, there is concomitantly an absence or thinning of stratum granulosum. Parakeratotic keratin does not have the cohesive properities of normal keratin so that splits in it appear even in vivo; allowing the formation of air spaces. This phenomenon is responsible for the silvery appearance of psoriatic scales which is so noticeable in clinical examination. However, orthokeratosis (hyperkeratosis) is sometimes present in the underlying granular cells; thickening of horny layer and increasing in granular layer. In some cases, orthokeratosis may be more prevalent than parakeratosis. Orthokeratosis often appears intermingled with parakeratosis; i.e.,vertically adjoining areas of hyperkeratosis, patchy parakeratosis or, occasionally, alternating layers of orthokeratosis and parakeratosis. Munro'microabscesses, one of the diagnostic features of psoriasis, are located within the parakeratotic areas of the horny layer. They consist of accumulation of pyknotic nuclei of neutrophils that have migrated there from capillaries in the papillae through the suprapapillary epidermis. Munro' microabscesses are found in early lesions but are few in number or absent in old lesions. Also, *Saiag et al. (1985)* stated that the main feature of psoriatic plaques is keratinocyte hyperproliferation and incomplete keratinization,

and this epidermal hyperproliferation is manifested clinically by production of scales.

In active lesions of psoriasis, the rate of epidermal cell replication is markedly accelerated as shown by the higher, than normal, number of mitotic figures, and the greater number of premitotic cells labelled by tritiated thymidine *(Weinstein and Mc-Cullough, 1985)*. The authors added that epidermal cell cycle is shortened with a dramatic shortening of epidermal turnover time due to the notation that psoriatic epidermal cell is one of the most rapidly proliferating cells in the body. It had appeared likely that, in psoriatic lesions, there was a great acceleration of the transit time of cells from the basal cell layer to the uppermost row of the squamous cell layer from approximately 13 days in normal epidermis to only 2 days in the epidermis of active psoriatic lesions, and that the reproductive cell cycle was reduced from 457 hours for normal germinative cells to 37.5 hours for psoriatic germinative cells. More recently, *Staiano-Coicos et al. (1987)* have shown that the transit time of cells from the basal cell layer to the uppermost row of the squamous cell layer amounted to 5 days rather than 2 days, as originally assumed, and that the reproductive cell cycles for normal germinative cells and for psoriatic germinative cells were 200 hours and about 100 hours respectively. These figures

thus indicate that there is no 12-fold speeding-up of the cell division cycle time of germinative cells in psoriatic epidermis, as had been originally assumed, but merely a two fold speeding up. In this concept, *Cormack (1987)* stated that in cases of psoriasis, the transit time for cell displacement from the stratum germinativum to the outer surface of the skin was only approximately 1 week, while in normal skin was about 4 weeks. This is because proliferation occurs in the bottom three layers of the epidermis instead of being largely confined to the stratum germinativum. Also, the intercellular space in psoriatic epidermis remains usually wide because there is insufficient time to allow for full maturation of its keratinocytes.

The etiology of psoriasis is still disputed; many different theories have been proposed. Investigations for the etiology of psoriasis are directed along several and even different lines of research. The site of primary lesion is still unknown, whether the site of the primary event is the epidermis, the dermis, or elsewhere *(Baden, 1984 and Doherty, 1990)*

FIBROBLASTS

The interrelations between the dermal and the epidermal compartments have been judged relevant in the search for the pathomechanism of psoriasis. Fibroblasts, quantitatively the major constituent of the dermis, have therefore been studied in psoriasis (*Bos, 1988*).

Fibroblasts are derived from undifferentiated mesenchymal cells (UMC) in young embryonic tissue, or locally from the pericytes which arise from UMC in older tissues (*Badawy et al., 1986*).

By light microscope, fibroblast appears as a large, flattened and branching cell with a spindle shape in the profile view. Its cytoplasm appears abundant, clear or finely granular, basophilic with indistinct outlines. Its nucleus appears large, oval in shape, pale coloured with a distinct nucleolus and a delicate nuclear membrane. By electron microscope, the cytoplasm of fibroblast possesses well developed rough endoplasmic reticulum, a plenty of ribosomes, a well developed Golgi apparatus, and many slender rod shaped mitochondria (Badawy et al., 1986).

Fibroblasts become less active during adult life and are then often referred to as fibrocytes. Fibrocytes have little pale more acidophilic (less basophilic) cytoplasm than that of

The evidence that there is increased urinary excretion of hydroxyproline and uronic acids, a greater content of glycosaminoglycans, and less cross-linked collagen, in psoriatic patients had led to the attention of the role of fibroblast in psoriasis *(Brunish and Sorensen, 1965 and Fleischmajer and Blumenkrantz, 1970)*.

The search for the primary site of the defect in psoriasis had led to studies in which lesional and uninvolved psoriatic skin and normal human skin were transplanted onto nude (immune defective) mice, and studies for persistence of psoriatic characteristics had been done. *Briggaman and Wheeler (1980) and Fraki et al. (1983)* had transplanted lesional and uninvolved psoriatic skin and normal human skin onto nude mice. They had found that when only in the combination of psoriatic epidermis and psoriatic dermis were transplanted onto nude mice, the characteristics of psoriasis did persist. *Baden et al. (1981) and Haftek et al. (1981)* used another model to study the ability of psoriatic fibroblasts to stimulate growth of epidermal cells by comparing the capacity of murine 3T3 cells, normal fibroblasts, and psoriatic fibroblasts to act as feeder layers for cultured normal human kerationcytes. They found that there is no increase in keratinocyte growth from skin explants cultured on a feeder of normal or psoriatic dermal fibroblasts, and 3T3 cells

consistently gave shorter time to confluency than normal or psoriatic cells which were about the same.

In contrast, *Saiag et al. (1985)* had described a series of elegant studies. They had found that when full thickness psoriatic skin was grafted to the nude mouse, the epidermis from lesions (involved psoriatic skin) had maintained most of its pathological features for at least 6 weeks. So, they concluded that psoriatic fibroblasts, but not normal fibroblasts, had induced hyperproliferation of normal epidermis. This result suggested that the primary defect leading to hyperproliferation of keratinocytes in psoriasis lie within the dermis; in fact within the dermal fibroblasts. However, these results are controversial and may be artefactual as they are based on data obtained in vitro. Also, both explant and transplant experiments have the additional disadvantage that they disregard the complexity of skin and reduce it to essential cellular components such as keratinocytes and fibroblasts. In all these experiments, both epidermal and dermal constituents of the skin immune system are co-transplanted, and some of them may have had profound effects on the results obtained *(Bos, and Kapsenberg, 1986 and Bos, 1988)*

Priestley and Adams *(1983)* found that fibroblasts explanted from both uninvolved and lesional psoriatic skin had

shown a persistent hyperproliferation in-vitro effect and the proliferation rate of psoriatic fibroblasts was slightly quicker than that from control skin. Also, Priestley (1983) had found that the average rates of glycosaminoglycan secretion were higher in psoriatic skin than in control strains, with the psoriatic cells secreting appreciably more glycosaminoglycans at higher cell densities. The nature of glycosaminoglycans produced was the same in psoriatic and normal strains. However, psoriatic fibroblasts strains synthesized more collagen than the control strains. These findings confirmed that fibroblasts from psoriatic skin are hyperactive in vitro. Recently, Priestley (1987) concluded that the proliferation of psoriatic fibroblasts was more sensitive to antiinflammatory drugs as retinoids than was that of the normal cells.

LANGERHANS´CELLS

History and origin of Langerhans'cells

Paul Langerhans (1868) discovered a population of non pigmentary dendritic cells in the suprabasal regions of human epidermis, and were stained with the gold chloride technique. Because this technique also delineated neural tissue, these cells, (Langerhans'cells) were for many years erroneously thought to be related to neuroectoderm.

Later on, alternative theory suggested that Langerhans' cells (L.Cs) might be related to melanocytes, representing worn-out melanocytes, daughter cells of dividing melanocytes, or melanocytes in an arrested stage of development (*Masson, 1951 and Zelickson, 1965*).However, *Wolff and Winkelmann. (1967a)* had reported that L. Cs.and melanocytes were not related, because L. Cs.constituted a highly constant cell population of the epidermis, whereas melanocytes showed a marked variation in the density of their regional distribution. Also, the ratio of L. Cs.to melanocytes was variable; indicating the absence of a constant numerical relationship between the two cell types. These data had indicated that L. Cs.and melanocytes were independent of each other and that they represented two distinct and self-maintaining cell populations.

Ultastructural feature studies of L. Cs. did not provide support for relationship between L. Cs and either neuroectoderm or melanyocytes (*Tarnowski and Hashimoto, 1967*). The authors observed that cells with ultrastructural features identical to cutaneous L. Cs.(i. e. presence of Birbeck's granules) were characteristic of lesions of histiocytosis-X. So, they had promoted the speculation that Langerhans' cells might represent epidermal histiocytes or macrophages. Also, both the neural and melanocyte theories had been disproved by

Breathnach et al. (1968) who showed that L. Cs, but not melanocytes or other neural cells, were consistently presented in mouse skin which had been, experimentally deprived of its neural crest component.

Rowden et al. (1979) and *Klareskog. (1979).* had postulated that the distribution of Langerhans cells in mesodermal tissues; e. g., lymph nodes and thymus had indicated that L. Cs.were probably of mesenchymal origin.

In the same context, immunofluorescence techniques have established that the surface marker characteristics of Langerhans cells were identical to those of monocyte-macrophage series *(Stingle et al., 1978; Klareskog, 1979a and Rowden et al, 1979a).*

Katz et al. (1979) had indicated that epidermalL.Cs.were derived from, and continually repopulated by a mobile pool of precursor cells originating in the bone marrow. The most likely precursor cell was the monocyte; as L. Cs. exhibited similar, if not identical, surface marker characteristics to cells of the monocyte-macrophage series. In this concept,*Bergstresser et al. (1980)* and *Stingle et al. (1980)* found that both L. Cs.and macrophages bore surface receptors for the Fc portion of immunoglobulin molecules (Fc-IgG) and for the third component of complement (C3 component).Also, both expressed on their cell surfaces the immune associated

(Ia) antigen which could be encoded for by the major histocompatibility complex.

Volc-Platzer et al. (1984) had found that allogeneic L. Cs. had also been detected in the epidermis of a human recipient of a bone marrow graft. More recently, *Katz (1985)* by using mouse bone marrow chimerization techniques established that allogeneic donor L. Cs.first became detectable in the skin of recipients 13 days after chimerization, and that after 85 days up to 80% of L. Cs.were derived from the bone marrow of the donor animal, and the relatively slow replacement of recipient by donor cells might reflect the longivity of resident epidermal L. Cs. Also, *Stingle et al. (1987)* had established that epidermal L.Cs.were derived from & continually repopulated by, a mobile pool of precursor cells originating in the bone marrow. In addition, L. Cs.probably had a limited capacity to undergo proliferation within the epidermis.

Identification of Langerhans'cells

Langerhans' cells could be identified at the light microscopic level by a wide range of techniques, including binding of various metal ions (Staining techniques), reactivity for enzymes (Histochemical techniques) and demonstration of cell surface antigen (Immuno-histochemical techniques).

I- Staining techniques

Exposure to osmium-Zinc-iodide had permitted staining of L.Cs. While retaining subcellular morphology, however, its specificity for L. Cs.was not absolute, as it also stained melanocytes and keratinocytes *(Breathnach and Goodwin, 1965)*. Also, L. Cs.were unique among epidermal cells in their affinity for metal ions and they could be identified in sections impregnated with gold chloride. The affinity of these cells for acid solutions of gold chloride made it possible for Langerhans to describe them one hundred years ago. However, it is important to stress that gold chloride impregnation is specific for L. Cs, only if one limits his observation to the epidermis as gold deposits can be found in cytoplasm of both dermal fibroblasts and dermal mast cells *(Zelickson, 1979)*.

II- Histochemical techniques

L. Cs.contain various hydrolytic enzymes which can be demonstrated by histochemical techniques, since these procedures revealed only weak or no reactions with other epidermal cells. So, they permit selective visualization of L. Cs.not only in frozen skin sections, but also in epidermal sheet preparations. These techniques included

Adenosine triphosphatase (ATPase) activity

The demonstration of Langerhans'cells plasma membrane-bound, formalin- resistant, and sulfhydryl-

dependent 5 adenosine triphosphatase (ATPase) activity considered it as a Langerhans'cell-specific property among human, guinea pig, and rat epidermal cells and this is a highly reliable and widely used procedure for the identification of epidermal L. Cs.(*Wolff and Winkelmann, 1967a; Wolff, 1972 and Berman and Francies, 1979*). Also, the latter investigators confirmed the observations of both **nonspecific esterase and alkaline phosphatase** activity in Langerhans'cells.

Aminopeptidase activity could be demonstrated in L. Cs. and if serial sections were treated alternatively with aminopeptidase and ATPase methods, it could be demonstrated that aminopeptidase and ATPase positive cells were identical. In addition, if the aminopeptidase and DOPA reactions were performed on the same section, DOPA-positive melanin was not found in aminopeptidase positive cells (*Berman and Francies, 1979*) . However, many investigators have stated that among all histoenzymologic methods, the method for ATPase had been proved to be most helpful for studies of Langerhans cells, and that ATPase enzymatic activity had not been revealed within the other epidermal cells. This specificity of the ATPase method had formed a basis for the study of the variations of L. Cs.density in many skin diseases (*Morhenn et al., 1982; Baker and Habowsky, 1983; Chene and Silvers, 1983; Haftek et*

al., 1983; Chene et al., 1985; Gommans et al, 1985; Hanau et al., 1985; Hanau et al., 1986; Halliday et al, 1986 and Kobayashi et al., 1987). Moreover, the authors had added that the labelling of L. Cs.through the detection of their membranous ATPase activity constituted one of the best available techniques for their visualization. Also, the presence of this ATPase activity appeared to be a prerequisite for the induction of contact sensitivity, since in the absence of such activity the epicutaneous application of a hapten induced a state of immunological tolerance. Moreover, the formation of Langerhans granules seemed to be linked up with the membranous ATPase activity of epidermal Langerhans'cells.

III-Immunohistochemistry

L. Cs.differ from normal melanocytes and keratinocytes in that they possess surface antigens and receptors that are known to be involved in immune reactions in vivo. Stingle et al. *(1977)* observed that L. Cs.but not other epidermal cells expressed receptor sites for the Fc portion of the IgG molecule (Fc- IgG receptors) and the third component of complement but lacked classical T-and B-cell markers. More recently, it has been found that OK T-6 one of a number of monoclonal antibodies, selectively binds to humman epidermal Langerhans' cells and of greater interest is the absence of binding of this antibody to circulating blood leukocytes

(Fithian et al., 1981; Murphy et al., 1981; Morhenn, 1983 and Carolyn; et al.,1986). Also, Langerhans' cells are the only cells in normal epidermis which express Ia (immune response-associated) or class II major histocompatibility complex (M. H. C) antigens (HLA-DR) as has been proved by *Morhenn et al. (1982); Haftek et al. (1983)* and Liu et al.(1986).The latter authors proved that OK T-6 was not superior to HLA-DR or ATPase as a marker for Langerhans' cells in normal human epidermis.

Distribution of L. Cs

Langerhans' cells appeared to be restricted to mammals and they were found within stratified squamous epithelia, including those of the epidermis. Within the skin, in addition to the epidermis, L. Cs were present within epithelia of skin appendages including the external root sheath of hair follicles and ducts of sweat glands *(Zelickson, 1965).* Also, L. Cs.were present in oral cavity, oesophagus, nasopharynx, conjunctiva and female genitourinary tract *(Silberberg, 1977 and Brukhardt, 1979).* However, it became apparent that L. Cs.were found, though in smaller numbers, within tissues of mesodermal origin including the thymus *(Hoshino et al.,1970),* lymph nodes *(Toews et al., 1980) and* the lymphatic vessels draining the skin, and in normal 'skin capillaries *(Jinbow et al., 1982 and Wolff and stingle, 1983).*

Number of L. Cs

Although numerous studies of L. Cs.had been performed, a little amount of data was available regarding their quantitative distribution. *Wolff and Winkelmann (1967)* in their study on guinea-pig epidermis had observed no variations of L. Cs.densities in different anatomical regions (ear, lower back, and abdomen).

However, more recent studies revealed regional differences in epidermal L. Cs.densities of various rodent species. *Bergstresser et al. (1980)*; *Streilein et al. (1980)* and *Toews et al. (1980)* found variations in the regional densities of rodent epidermal L. Cs .as detected by ATPase activity, as they found significantly lower densities within the hamster cheek pouch when compared to those of specimens from the ear, back, foot pad and buccal mucosa, and that the density of epidermal L. Cs.of the cornea (of the hamster, mouse and guinea-pig) and of the tail of the mouse were also found to be less than within the other aforementioned anatomical sites. *Berman et al. (1983a)* determined the densities of human epidermal L. Cs. within eight anatomical regions using OKT-6 monoclonal antibody. They found that the regional mean densities of epidermal L. Cs.per mm^2 were; head and neck, 489±27; chest, 466 ±22; back,466±11; upper extremities, 458±25; lower extremities, 431±30; buttocks,

411±11; genitalia, 298±45 and soles 58±12. They found that there was no statistically significant differences among any of these L. Cs.densities except for that of the soles which was lower than those of all other regions ($p < 0.001$).

In this concept, *Czernielewski et al. (1985)* found that the mean number of epidermal L.Cs.in control subjects using the three staining procedures, ATPase, OKT-6 and anti HLA-DR monoclonal antibodies, varied between 888-987 cells per mm^2. However, *Chen et al. (1985)* stated that there was regional difference in epidermal L.Cs densities as they indicated that the skin obtained from the face and neck contained the highest density of Langerhans' cells ($976^{+}_{-}30$ $/mm^2$) while that in trunk, scalp and arm or leg skin appeared to have lower densities. The densities of L.Cs.were $740^{+}_{-}28/mm^2$ in trunk skin, $693^{+}_{-}69/mm^2$ in the scalp and $640^{+}_{-}40/mm^2$ in the arm or leg skin. Also, buccal mucosa had significantly fewer L.Cs. ($567^{+}_{-}42/mm^2$) than trunk skin, and sacrococcygeal skin and palm and sole skin exhibited the smallest number of these cells ($267^{+}_{-}56/mm^2$ and $189^{+}_{-}19/mm^2$ respectively). In the same connection, no L.Cs were observed in the center of corneal specimens. The authors utilized in their investigation both OK T-6 and ATPase techniques, and they found that there was scarcely any difference between the results of the two procedures. Also, they attributed the difference between their results and the

results obtained by *Berman et al. (1983a)* to the difference in age; as Berman and his coworkers utilized patients of older ages.

Recently, *Breathnach (1988)* concluded that in man, there was some regional variation in the number of L.Cs.per unit area of the skin; the range being 460 to 1,000/mm^2 of body surface, and an average adult man has a total number of about $2x10^9$ L.Cs.in his skin.

Shape of Langerhans' cells

L.Cs.appeared as dendritic cells in ethylenediamine tetraacetic acid (E.D.T.A) separated epidermal sheets stained by ATPse or by anti HLA-DR or OK T-6. *(Halliday et al., 1986)*.

In cryostat vertical section of skin, L.Cs. image may vary with the plane of sectioning. L.C.may appear as a cell body having many branches, dendritic cell, or may appear as polygonal to oval or circular cell body, or it may appear as dendritic fragments resembling oblique sectioned parts of a cell body *(De Jong et al., 1986)*.

Effect of age on L.Cs density

*Gilchrest et al. (1982) and Thiers et al. (1984)*found that L.Cs.were significantly more numerous in young adult than in old adult skin. Also, they reported that the number of L.Cs. was significantly decreased in older individuals. However, *Gommans et al. (1987)* found that there was no age

difference in density of epidermal L.Cs.

Carolyn et al. (1986) found that L.Cs could be identified in human skin by 10 weeks estimated gestational age, migrated into epidermis during the first trimester and resembled the adult phenotype by the second trimester; long before the immune system was fully activated.

Effect of sex on the density of L.Cs

Berman et al. (1983a) Chen et al. (1985) and Gommans et al. (1987) reported that there was no significant sex difference in L.Cs. density. For example, the mean number of cells in female trunk skin was $743^{+}_{-}30/mm^2$ and in male trunk skin was $739^{+}_{-}38/mm^2$. In contrast, *Koyama et al. (1987)* found that epidermal L.Cs. density depended on sex as they found that the density of L.Cs. of hind limb epidermis in male mice ($823^{+}_{-}20/mm^2$) was significantly ($P<0.001$) less than that in female ($1363^{+}_{-}52/mm^2$). Also, the density of L.Cs.in the ears of male mice ($465^{+}_{-}24/mm^2$) was also significantly ($P<0.001$) less than that in females ($542^{+}_{-}17/mm^2$). They also, found that experimental ovariectomy failed to bring about any change in L.Cs. density of hind limb epidermis in female,and the L.Cs density in male mice increased significantly at 4 weeks following orchidectomy. So, they concluded that the reduction in L.Cs. density in males might possibly be caused by ,the testis

Function of L.Cs

Although L.Cs were originally discovered more than one century ago, only in the past few years some progress had been made in understanding their functional capacities. It is conceivable that L.Cs.play a vital role in a variety of physiologic and pathologic processes of the skin *(Stone, 1985)*.

Immunologic function

The only functional capacity of L.Cs.for which experimental proof is currently available is the immunologic function of this cell type. Their immunologic function was observed by *Silberberg (1976) and Stingle et al. (1980)*. They observed that in humans and guinea pigs actively or passively sensitized to dinitrochlorobenzene (DNCB), which is a contact allergen, a close apposition of L.Cs. to lymphocytes occured only a few hours after antigenic challenge. It was observed that L.Cs. appeared damaged and reduced in number at the peak of the response. These phenomena were observed only in allergic contact dermatitis, but not in primary contact dermatitis. So, *Silberberg (1976)*, *Stingle et al. (1980) and Steigleder (1981)* suggested that L.Cs. served as an important induction and target structures in cutaneous delayed-type hypersensitivity reactions. Also, they observed that, in passively sensitized guinea pigs to DNCB, L.Cs. were

identified in dermal lymphatics and increased in number in the dermis after challenge with the contact allergen. From their observations, they concluded that L.Cs. picked up antigen in skin and from there they moved to the draining lymph nodes, where they presented the antigen to immunologically relevant cells (T-lymphocytes) both in skin and lymph nodes.

Experimental evidence for an immunologic role of L.Cs. was obtained when it was found that in all species so far investigated (man, guinea pig and mouse) L.Cs.were the only epidermal cells that possessed surface characteristics of immunocompetent cells. The demonstration that L.Cs.expressed Fc-IgG receptors, complement receptors and that they synthesized and expressed Ia antigen had suggested immunologic functions similar to Ia positive macrophages. Unlike T-lymphocytes, L.Cs.did not form rosettes with sheep RBCs; i.e., lacked erythrocyte (E) receptors, and unlike B lymphocytes, they did not bear surface immunoglobulins. Thus, the surface marker characteristics of L.Cs.were similar, if not identical, to those on the cells of the monocyte-macrophage series *(Streilein, 1980 and Streilein and Bergstresser, 1983)*.

Katz et al. (1985) also stated that considering the fact that L.Cs. are located in the most peripheral tissue of the organism; i.e., the epidermis, it seemed conceivable that they

played a functional role in the induction of the afferent limb of the immune response in a manner similar to that of Ia bearing macrophages.

The immunologic functions of L.Cs include

A- antigen presentation function : One of the immunologic functions of L.Cs.is that of their antigen presentation. *Friedmann (1981) and Stingle et al. (1983)* investigated the antigen-presenting capacity of L.Cs.in the mouse by using an in vitro system; that had previously been used successfully for the elucidation of macrophage antigen-presenting function. The investigators found that epidermal cell suspensions pulsed with soluble protein antigens or modified with simple chemical haptens (compound of low molecular weight that can elicit antibody formation by combining with a carrier protein) could stimulate a vigorous antigen specific proliferation of immune T-cells. However, they observed that the pretreatment of the epidermal cells with anti-Ia serum and complement, but not with normal serum and complement, had led to total abrogation of antigen presentation function. Since L.Cs.were the only epidermal cells that expressed Ia antigens, these experiments might provide an evidence that epidermal cell induced antigen specific T-cell stimulation was critically dependent on the presence of L.Cs. The authors, therefore, concluded that L.Cs, but not other epidermal cells, proved to be as potent

stimulators of antigen-specific T-cell proliferation as were macrophages. Similar results were obtained in humans, and the antigen presenting capacity of L.Cs.had subsequently been confirmed in humans by *Czernielewski et al. (1983), Bjercke et al (1984) and Streilein and Bergstresser (1984)*. In agreement with the reports of those authors, *Katz et al. (1985)* concluded that L.Cs.were effective antigen-presenting cells, and that epidermal L.Cs.were the only cells (within normal epidermis) which synthesized and expressed Ia antigens. So, such cells were critical for these antigen presentation functions. Also, *Bjercke et al. (1985)* reported that L.Cs.were more efficient antigen-presenting cells (APC) than blood-derived dendritic cells from the same donor, and that Langerhans'dendritic cells expressed 50-100 times more HLA-DR molecules than monocytes and blood derived dendritic cells.

Recently, *Ashworth et al. (1988); Breathnach (1988) and Baker et al. (1988)* established the antigen presenting functions of L.Cs. in humans

B- L.Cs stimulate allogeneic and syngeneic T-cell activation

Braathen and Thorsby (1980) and Aberer (1981) revealed that, in both guinea pig and humans, L.Cs.were the only epidermal cells capable of acting as stimulators in the mixed leukocyte reaction; this reaction occurred when there were disparities in the Ia antigen compositions of the two involved

cells; i.e., when lymphoid cells from histocompatible animals were mixed together. In this reaction, called allogeneic reaction,L.Cs. had proved to be the only epidermal cells capable of substantially stimulating allogeneic T-cell activation. In addition, they reported that L.Cs. were able to present T-dependent antigens to lymphocytes. This interaction is dependent upon the identity of Ia antigens of the two cell types; i.e., syngeneic reaction. The phenomenon of T-cell activation by syngeneic non-T-cells is termed syngeneic mixed leukocyte reaction or syngeneic epidermal cell lymphocyte reaction.

Also, *Czernielewski etal.(1983)*concluded that L.Cs.are required as critical stimulator cells in the allogeneic and syngeneic epidermal cell lymphocyte reaction, where the proliferative response to epidermal cells of a T-cell subset was assessed by analogy to the T-cell response in the mixed leukocyte reaction towards certain leukocytes bearing defined immunogenetic specificities; e.g., Ia antigen. In addition, *Katz et al. (1985)* concluded that the in-vitro data had strongly suggested that L.Cs were the most peripheral outpost of the immune apparatus and played a decisive role in the afferent limb of the immune response. It had appeared likely that cutaneously applied antigen was taken up by a variety of cells, including keratinocytes, but that only L.Cs. had the

capacity of processing the antigen and, more importantly, of presenting immunologically relevant determinants to the T-lymphocytes; an event that triggered a strong sensitizing signal to the immune apparatus.

C- L.Cs and Cytotoxic reactions

L.Cs. fulfilled a critical accessory cell function in the epidermal cell-induced generation of cytotoxic T-lymphocytes *(Pehamberger et al., 1983)*. In this context, *Streilein and Bergstresser (1984)* stated that it was even conceivable that antigen-modified L.Cs. represented preferential target structures in hapten and virus-specific cytotoxic T-cell reactions affecting the skin. They also reported that L.Cs. induced the maturation of T-lymphocytes into cytotoxic T-lymphocytes. However, a cytotoxic potential of L.Cs. perse had so far not been demonstrated. *Baker et al. (1985)* added that it was also conceivable that L.Cs. accounted for the effective immunogenic presentation of viral and tumour-associated antigens and, thus, L.Cs. might play a crucial role both in the prevention of devastating of viruses infecting the skin, and also in the elimination of neoplastic epidermal cell clones.

D-L.Cs and delayed hypersensitivity

The finding that hapten-modified L.Cs. but not hapten modified keratinocytes had stimulated activation of

hapten-sensitized T-lymphocytes strongly suggested that L.Cs played an important role in the inductive phase of contact hypersensitivity. Also, another body of evidence pointing to an important role for L.Cs.in contact hypersensitivity stems had been obtained from the observation that skin relatively deficient in L.Cs (such as mouse tail epidermis) was resistant to sensitization to DNCB *(Toews et al., 1980)*. Also, *Bergstresser and Streilein (1983), Baker et al. (1985), Breathnach and Katz (1985), Krueger and Eman (1986) and Cormack (1987)* had established that L.Cs.were the antigen presenting cells that promoted cutaneous delayed hypersensitivity reactions; i.e., contact allergic dermatitis.

E- L.Cs and graft rejection

The allogeneic epidermal cell lymphocyte reaction implied the role of L.Cs.in allograft rejection or the graft-versus-host reaction *(Chen and Silvers, 1983 and Koyama et al., 1987)*.

II L.Cs and Keratinization

Breathnach and Wyllie (1965), Hashimoto et al. (1966), Prunieras (1969) and Hutchens et al. (1971) had speculated that L.Cs. might be concerned in the keratinization process in normal epidermis. Such a speculation had been supported both by ontogenetic observations and by morphological studies; as the authors had reported that L.Cs.were limited to the

keratinized areas in the oral epithelium of rehesus monkeys, and they were able to show a selective localization of L.Cs. in the orthokeratinizing region of adult mouse tail epidermis. Also, Potten and Allen (1976) had reported that L.Cs.might well be necessary in the maintenance of a physiological equilibrium between differentiation and mitotic activity of the keratinocytes. They had put an evidence for such a regulatory function that the L.Cs.population were present in decreased number in diseases characterized by increased mitotic activity and parakeratosis, and the reverse was true as L.Cs.were increased in diseases in which mitotic activity was limted, and the epidermis showed reduced thickness. In this context, *Schweizer and Marks* (1977) found that L.Cs.and granular cell layer, which was known to be involved in the process of orthokeratinization, both had appeared at the same time when keratinization commenced in the human foetal epidermis. Also, they noted that in adult mouse tail epidermis the parakeratotic scale regions lacked both L.Cs.and granular cell layer, and the treatment of the adult mouse tail skin with topical vitamin- A acid over a period of 2 weeks resulted in the conversion of the parakeratotic scale regions to orthokeratosis. This conversion was accompanied by the appearance of both L.Cs.and granular cell layer. So, they suggested that there was functional relationship between L.Cs,

epithelium under observation. So, the author's hypothesis that L.Cs. might be involved in the growth control of keratinocytes indicated that a high frequency of L.Cs. implied a low proliferative rate in a given epithelial tissue

Though these observations had provided an important evidence of an association between L.Cs.and keratinization, *Ford (1983)* suggested that L.Cs.had no primary role in the process of keratinization. This was indicated by experiments in which the outer layers of the epidermis were removed by cellophane tape stripping as was described previously by *Lessard et al. (1968)*. *Ford (1983)* found that the squamous cells had regenerated and keratinized several days before the L.Cs reappeared; which required about 1-2 weeks to repopulate in the epidermis. Also, his finding that the L.Cs.number and morphology were normal in autosomal dominant ichthyosis vulgaris was also against the hypothesis that L.Cs were involved in the process of keratinization, although the functional capabilities of L.Cs. in this condition remained undetermined. Again, *Ford (1983)* explained the apparent association, which had been suggested by *Schweizer and Marks (1977)*, between L.Cs. the granular layer, and keratinization to be of a secondary nature; the L.Cs.in some way being attracted to areas of orthokeratinization, where their immunological activities would complement the physical and

protective properties of the keratinized epidermis. However, *Breathnach (1988)* concluded that the suggestion that L.Cs. might in some way control the growth and differentiation of a pool of neighbouring keratinocytes in an "epidermal proliferative unit" had not been entirely refuted.

Effect of Physiochemical agents on L.Cs.

Breathnach (1988) stated that therapies which were widely used in dermatology, including U.V.B., P.U.V.A. and topical steroid treatment, might exert their effect in part as a result of their effects on L.Cs.

Ultraviolet irradiation (U.V.B) caused a dose-dependent decrease in L.Cs. membrane markers defined by ATPase activity and monoclonal antibodies and this was associated with a decrease in epidermal antigen-presenting capacity secondary to impaired L.Cs. function. The irradiated, L.Cs.depleted, skin was incapable of initiating a delayed hypersinsitivity response to D.N.C.B. *(Aberer et al., 1981; Moss et al., 1981; Nordlund and Ackles, 1981; Gilchrest et al., 1982; Bergstresser et al., 1983; Kripke et al., 1983; Wolff and Stingle, 1983; Breathnach and Katz, 1985; Koulu et al., 1985 and Cole, 1986)*. In this context, *Cole et al. (1987)* reported that UVB irradiation depleted L.Cs.of their surface markers but did not induce a significant destruction of L.Cs population itself as they demonstrated that exposure of

epidermal cells to 10 to 20 mj/cm^2. UVB had led to an abrogation of the L.Cs-induced antigen-specific and allogeneic T-cell activation without producing lethal cell damage to the majority of the residual cells.

By using topical 8-methoxypsoralen plus ultraviolet A(P.U.V.A.) three times per week for a total of three weeks, the number of L.Cs had decreased by aproximately 50 percent after 1 week of PUVA and 64 percent after 3 weeks. However, 3 weeks after stopping PUVA, they were reduced to 12 percent of the original density, and two weeks later their number had returned to normal. Also, throughout the course of PUVA treatment, L.Cs numbers remain low and by electron microscopy it was confirmed that L.Cs. had disappeared and not simply lost ATPase activity (*Bridges and Strauss, 1980; Strauss et al., 1980; Kripke, 1981; Friedmann et al., 1982; Ref.1982; Aberer et al., 1986 and Koulu and Jansen, 1988*).

Localized gamma radiation caused a dose-related reversible decrease in the number of ATPase positive Langerhans'cells. Also, the lethal whole body X-irradiation of mice resulted in a dose and time-dependent decrease in the number, and alloantigen-and antigen-presenting capacity of L.Cs. Thus, X-irradiation of the skin may affect inflammatory and neoplastic processes not only by its antimitotic activity, but also by a direct action on the skin immune system of L.Cs

(Breathnach and Katz, 1985a).

Glucocorticoids are the agents most commonly used for the treatment of skin diseases. Several workers, therefore, investigated the effect of these agents on L.Cs. Studies in rodents and humans had shown that topical corticosteroids caused a dose-related reversible decrease in L.Cs.surface markers (including membrane ATPase, Fc-IgG and C_3 receptors, Ia/HLA-DR antigen and T-6 antigen) and that topical steroids, applied twice daily to human forearm skin for 7 days significantly decreased not only the number of HLA-DR and OK T-6 positive L.Cs, but also the Langerhans'cell-dependent capacity of epidermal cells to present antigen to lymphocytes. Also, glucocorticoids caused a significant reduction in ATPase positive L.Cs.when administered topically but not systemically because the systemically administered drugs, although given in a high concentration, might not have penetrated the epidermis in sufficient concentration to disrupt the L.Cs.membrane *(Nordlund and Ackles, 1981; Belsito et al., 1982; Berman et al., 1983; Aberer et al., 1984; Braathen and Hirschberg, 1984; Aberer et al., 1986; Halliday et al., 1986a; Pakes et al., 1986; Rhodes et al., 1986 and Ashworth et al., 1988).*

The fact that depletion of HLA-DR+ve Langerhans'cells following steroid therapy, UVB and PUVA was reversed with time, even when human skin was transplanted onto athymic(nude)

mice, a system devoid of circulating precursors for human L.Cs, suggested that these agents had induced modulation of L.Cs.markers rather than bringing about cell death *(Breathnach, 1988)*.

The systemic administration of aromatic retinoids had stimulated Langerhans' cells so that the number of OKT-6, HLA-DR and ATPase positive L.Cs. might increase after 1-3 weeks of therapy *(Tsambaos and Orfanos, 1981; Van Der Schroeff et al., 1982; Haftek et al., 1983 and Kanerva et al., 1986)*.

Langerhans'cells and Psoriasis

Quantitative studies of L.Cs. in a variety of diseases have abounded recently with many authors attempting to correlate an increase in or paucity of L.Cs with the pathogenesis of the disease *(Stone, 1985)*.

Since it became evident that L.Cs.might play an important role in immunological reactions of the skin and possibly also in the regulation of epidermal proliferation, it was evident, in view of these properties, that L.Cs.could have a certain role in the pathogenesis of psoriasis. Notably, changes in the frequency and distribution of L.C.in psoriasis have been studied *(Stone, 1985)*. In this concept, *Mier et al. (1980)* had attributed the increased proliferation of epidermis, which was the characteristic feature of psoriatic lesion, to L.Cs. They had extracted their results depending on

previous theories which had proved that L.Cs. have been conjectured to participate in the regulation of epidermal keratinization. They also had implicated that the primary expression of the psoriatic gene was in the monoblast; this was perpetuated in the promonocyte, the monocyte, the macrophage, and finally the L.Cs. The precise nature of this defect, although of course unknown, was manifested as a reduced intracellular cyclic A.M.P level. Cyclic AMP-mediated function, which at the L.Cs.stage included the promotion of differentiation in the surrounding keratinocytes, will be altered. So, the formation of an intact orthokeratotic horny layer would cease, and a clinical lesion would appear. However, from the Mier's point of view, the two axioms on which most biochemical theories did rest were abolished. First, if the defect was expressed in the bone marrow rather than the keratinocyte, psoriasis must be regarded as a systemic rather than a localized disorder; a concept advocated by *Mali (1979)* who had described the disease as a destabilisation of the epidermis. Secondly, if the primary change in the skin lesion was an impaired differentiation, one must interpret the tendency to increased proliferation as a result of the larger germinative cell population. The fact that the cause of psoriasis was a defect in the monocyte-macrophage-L.Cs.line was compatible with data that

had been proved by *Chapman et al. (1979)* and *Shuster et al. (1980)*. They found that, in psoriatic lesion, there was lack of inducibility of aryl hydrocarbon hydroxylase (A.H.H) and, that there was unique defect of A.H.H enzyme activity. This enzyme initiated the chemical degradation of many xenobiotics and since L.Cs specifically took up such enzyme and that the epidermal A.H.H was in fact located in L.Cs, it was not possible to exclude the role of L.Cs.in psoriasis and, consequently, the arm of coincidence upon which Mier's hypothesis had rested .

Also, the available data had suggested that in patients with psoriasis, a disease characterized by epidermal hyperproliferation, there was an aberration in the body's immunoregulatory mechanism as raised serum level of Ig-A, Ig-E and Ig-G and of anti Ig-G factors *(Cormane, 1981; Cram, 1981 and Krueger, 1981)*. Also, in psoriatic patients there was a number of abnormalities of the immune system, as monocyte showed an increased locomotion and thymus derived lymphocyte (T-lymphocyte) obtained from psoriatic patients showed functional defect *(Bjerke, 1982; Bos et al., 1983; Baker et al., 1984; Kaudewitz et al., 1984; Tagami et al., 1987 and Ramirez-Bosca et al., 1988)*. Accordingly, such aberrations in the body's immunoregulatory mechanism and the body's immune system in psoriatic patients had encouraged many investigators

to study L.Cs. their distribution, and their number in psoriatic patients as it had been known that L.Cs. played a major role in skin immune reactions *(Stone, 1985)*.

Distribution of L.Cs in psoriatic patients

The distribution of L.Cs in psoriatic skin, differed from that of normal skin. While in normal skin L.Cs were located in the suprabasal position of the epidermis, they were never seen in the stratum corneum nor in the dermis. However, they could be found in skin appendages including external root sheath of hair follicle, ducts of sweat glands .In psoriatic skin, the distribution of L.Cs was disturbed *(Stone, 1985)*. In this concept, *Morhenn et al. (1982)* found that the distribution of L.Cs in the epidermis was altered as they found that large segments of the epidermis were totally devoid of L.Cs. Also, there was abnormal clumping of L.Cs.in the epidermis as there were groups of ATPase positive cells. Presumably L.Cs. seen at any level of the psoriatic epidermis and frequently cells were clustered at the tip of the dermal papillae. They concluded that clustering of L.Cs.in the epidermis might reflect migration of L.Cs.to areas of increased mitotic activity. Also, many investigators found that, in involved psoriatic skin, the distribution of L.Cs.(as demonstrated by using both 2 monoclonal antibodies (MCAB) ; an anti-HLA-DR and OK T-6 MCAB and ATPase methods) was disturbed

(*Haftek et al., 1983; Bos et al., 1983; Bos and Krieg 1985; Poulter et al., 1986; and Baker et al., 1988*). They found that in large areas of the epidermis no cells were seen and cells were aggregated in clusters, mostly above the elongated dermal papillae, in the dermal papillae themselves, and predominantly distributed around hair follicle orifices. More recently, *Bieber and Braun-Falco (1989)* found that the distribution of L.Cs. in the epidermis of chronic psoriatic skin was disturbed. They found that in some areas, L.Cs.were completely absent, though their distribution in appendages seemed to be conserved, and L.Cs. were grouped near the upper papillary dermis.

The distribution of L.Cs.in the dermis of psoriatic skin :*Morhenn et al. (1982)* found that the presence of L.Cs. in the dermis of psoriatic skin was not a constant finding. They found that, in only 2 out of 7 patients studied,a pronounced accumulation of L.Cs.in the dermis was demonstrated. However, *Haftek et al. (1983)* found that there were no L.Cs.in the dermis The presence of clumps of L.Cs.in the dermis and in papillary dermis was found to be characteristic of, although not entirely specific for, psoriasis (*Bos et al., 1983 ; Bos and Krieg 1985; Bos et al., 1986; Gottlieb et al., 1986; Kanerva et al., 1986; and Poulter et al., 1986*). More recently, *Bos (1988) and Bieber and Braun-Falco (1989)* found

that L.Cs.were grouped in the outer part of the dermis and in the dermal papillae of chronic psoriatic skin.

The number of L.Cs in psoriatic skin

It was still a point of controversy whether the number of L.Cs.in psoriatic skin decreased or increased *(Rook et al., 1986)*. Also, the reports regarding the density of L.Cs.in psoriatic lesion were extremely conflicting *(Gommans et al., 1987)*.

A decreased number of L.Cs./$mm^2$of epidermal surface as demonstrated by ATPase staining and by monoclonal antibodies had been recorded in psoriatic skin compared to that of normal skin *(Morhenn et al., 1982; Bos et al., 1983; Haftek et al., 1983 ; Bos and Krieg, 1985 ; Narayanan and Girdhar, 1985 ; Kanerva et al., 1986 ; Poulter et al., 1986; Oxholm et al., 1987; Torinuki et al., 1987; Baker et al., 1988; Bos, 1988;* Biber et al.,1988 *and Bieber and Braun-Falco, 1989)*. Also, *Ashworth and Mackie (1985 and 1986)* had found that the number of epidermal L.Cs. was decreased in psoriatic skin when expressed as the number of L.Cs.overlying 200 basal cells when compared to that ratio of normal skin.

On the contrary, *Swain et al. (1985)* had found that in psoriatic epidermis the number of HLA-DR+ve L.Cs per 100 high power field were significantly increased. In addition, *Willemze et al. (1985)* found that the number of OK T-6

positive epidermal L.Cs per 200 basal cells of epidermis increased in psoriatic skin when compared to that ratio of normal skin. Also, in the active edge of psoriatic plaques, the absolute number of L.Cs.per linear mm of surface epidermis was increased compared to adjacent uninvolved skin and to normal skin *(Ashworth and Mackie 1985; Ashworth and Mackie, 1986; Valdimarsson et al ., 1986 and Fry, 1988.*

On the other hand, *Czernielewski et al. (1985)* had found that the number of L.Cs.per mm^2 of epidermal section surface (measured by ocular square grid) as was demonstrated by using ATPase, OK T-6 and anti HLA-DR monoclonal antibodies of psoriatic lesions was similar to that observed in skin of normal appearance as well as in skin from control subjects. In accordance with this finding,the authors added that,the percentage of OK T-6 positive L.Cs in lesional and uninvolved epidermis of patients with untreated psoriasis did not differ significantly from control values *(Gommans et al., 1987).* Likewise, *Ramirez-Bosca et al.(1988)* found that there was no significant decrease in the number of epidermal L.Cs. in vertical skin sections obtained from psoriatic patients.

In this context, *Bieber et al. (1988)* proposed that the number of L.Cs. varied considerably and that the results were sometimes contradictory according to the method of enumeration used. The authors quantified L.Cs. in cryosections of normal

human skin and psoriatic skin using different methods. They found that there was no significant difference between psoriatic and normal skin when L.Cs. density in the epidermis was calculated as the number of L.Cs./ 20 high power fields (x40 obective) or as the number of L.Cs./mm length of epidermal surface, measured by morphometry. However, there was significant decrease in the number of L.Cs. in psoriatic skin than in normal skin when expressed as the number of L.Cs./mm length of basement membrane, measured by morphometry, or as L.Cs. overlying 200 basal cells, or as the number of L.Cs./mm^2 epidermal section surface counted with an ocular square grid.

Role of heredity in psoriasis

The genetic basis of psoriasis was indisputable and rested on the evidence of population surveys, twin studies and pedigrees analysis *(Rook et al., 1986)*.

Family incidence

Familial incidence of psoriasis had been reported by many authors and the percentage given by different authors varied as widely as from only 4% to 91%. *Schamberg (1924)* reported a family occurrence of 13% of his psoriatic patients. *Lerner (1940)* also had observed that about 42% of 1972 patients had a positive family history for psoriasis. *Ashner et al. (1957)* found that among 239 patients with psoriasis,

17.9% were familial. *Baker (1966)* also found that siblings of psoriatic patients were more frequently affected when one parent was affected (the ratio of affected to normal siblings was 1:8) than when neither parent was affected (the ratio decreased to 1:12). *Faber et al. (1974)* stated that 36% of 2144 psoriatics surveyed had a positive family history. *Nall and Faber (1977)* had reported 8-12% of both Hong kong and Sirilank series which showed a lower familial frequencies than others from the same study as Denmark, 54%; United states, 40%; and Kuwait, 26%. *Adam (1980)* reported a familial occurrence of 13% of 203 psoriatic patients. Likewise, the familial frequency recorded by *Benacerraf (1981)* was 12% of 3500 psoriatic patients. *Liu and Rui (1982)* also had observed that about 24% of 336 patients gave a family history for psoriasis, and *Brandrup et al. (1982)* found that among 406 patients with psoriasis, 49% were familial. So, from this high occurrence of family cases, the authors had concluded that genetic factors might play a role in the pathogenesis of psoriasis *(Henry et al., 1985)*.

Recently, *Kennedy (1988)* stated that a genetic transmission of the tendency to have psoriasis had existed.

Twin studies

Twin studies also had confirmed the role of inheritance of psoriasis without illuminating the mechanism. *Faber et al.*

(1974) found that in 80 monozygotic twin pairs, about 70% were concordant for psoriasis, where as of 60 dizygotic pairs only 23% were concordant. Furthermore, they found that psoriasis in concordant monozygotic twin pairs tended to be similar with respect to age onset, distribution pattern, severity and course. These similarities were not seen in concordant dizygotic twin pairs. This striking difference in the rate of concordance for psoriasis between monozygotic and dizygotic twin pairs had indicated an inheritable contribution to the etiology of psoriasis. Moreover, *Brandrup et al. (1978)* and *Brandrup and Green (1982)* also found from the study of Danish twin register that there was higher concordance rate of psoriasis in monozygotic than dizygotic twin pairs, and this twin studies provided a possible evidence that psoriasis was heriditary.

Mode of inheritance

The mode of inheritance of psoriasis was still controversial and the opinions regarding the mode of inheritance of psoriasis vary widely. There were 3 theories regarding the mode of inheritance; some had suggested that psoriasis was a monogenic disease caused by dominant genes, others had supported recessivity as a mode, and still others supported multifactorial mode of inheritance *(Henry et al., 1985)*.

Romanus (1945) had concluded from a long-term study of 768 patients that psoriasis was inherited as a dominant trait with "manifestation probability" (penetrance)of about 18%. *Hoede (1957)* found also that the frequency of psoriasis among siblings of probands was 4.5% in families with unaffected parents and 11% when one of the parents had psoriasis. From this result, the author concluded that the distribution of psoriasis in these families was by an autosomal dominant inheritance. This mode of inheritance had been supported by a number of investigators *(Abele et al., 1963; Kimberling and Dobson, 1973; Marcusson et al., 1979; Cutler et al., 1980, and Dobson, 1981).* In this concept, *Burch and Rowell (1981) and Philip et al. (1981)* had supported an autosomal dominant mode of inheritance.

In contrast, *Steinberg et al.* (1951) disagreed with the autosomal dominant as a mode of inheritance in psoriasis. They concluded, from analysis of the families of 464 patients with psoriasis, that there was no evidence for sex limited or sex linked mode of inheritance, and they had selected recessive gene as a mode of inheritance. In this concept, *Aschner et al. (1957), Ward and Stephens (1961)* and *Lomholt (1963)* suggested that the mode of inheritance of psoriasis was by recessive gene.

In the same context, *Hellgren (1967)* had excluded simple monogenic types of inheritance in psoriasis and from their data they selected multifactorial inheritance. *Falconer (1970)* and *Edward (1971)* had advocated multifactorial as a mode of inheritance of psoriasis. *Watson et al.(1972)* had stated that psoriasis was inherited as a multifactorial trait, and that genetic factors played a relatively important role in the etiology of psoriasis. They added that in multifactorial inheritance, the heritable components were alleles at an unspecific numbers of different loci, each contributing a small effect, and interacted with environmental variation to bring about the character or trait. Also,they concluded that psoriasis was inherited by multifactorial inheritance which dictated that multiple heritable and enviromental factors were necessary for the manifestation of the trait and by this conclusion, the authors explained the role of predisposing factors to induce psoriasis. Likewise, many authors had agreed with multifactorial inheritance for psoriasis *(Ananthakrishnan et al., 1973; Moll and Wright, 1973; Faber et al., 1974; Karvonen, 1976; Moller and Vinje, 1979; Morel et al., 1980; Moller and Vinje, 1980; Tillikainen et al., 1980; Dobson, 1981; Moller et al., 1981; Mordovtseve et al., 1981; Moller and Berg, 1982 and Vogel and Motalsky 1982).* They discussed

the difficulty of resolving the controversy surrounding the mode of inheritance in psoriasis and they remarked that psoriasis was not a single gene disorder but that the genesis of psoriasis might be multifactorial; involving various heritable and non heritable processes. *Pietrzyk et al. (1982)* concluded from analysis of the results of 244 families with psoriasis that multifactorial inheritance was feasible as a mode of inheritance of psoriasis. *Brandrup and Green (1982)* concluded from the finding that not all monozygotic twin pairs were concordant that environmental factors were also important and to support the theory of multifactorial inheritance of psoriasis. However, *Faber and Nall (1984)* concluded that not everyone possessing the genetic potential for psoriasis would manifest it clinically. However, certain stimuli or triggering factors could convert latent to overt psoriasis. Although the knowledge of triggering factors was incomplete, there were certain determinants that had been established. These triggering factors include:infection; which is now generally accepted that streptococcal infection is the major precipitating factor in psoriasis. There is evidence that infection precipitates psoriasis in genetically predisposed individuals and gives rise to a self perpetuating auto-immune state *(Swerlick et al., 1986)*. The other precipitating factors are certain drugs,notably lithium and Beta blockers,

non-steroidal antiinflammatory drugs such as indomethacin, and antimalarials have been reported to aggravate psoriasis. Also, the withdrawal of corticosteroids has been reported to activate pustular psoriasis. However, considering the common use of these drugs, it is possible that the aggravation of the disease may be idiosyncratic response; as it certainly does not occur in all patients with psoriasis taking the drugs. As all these drugs have different modes of action, it can be said that they are likely to be influencing the psoriatic process at different points in the complex biochemical pathways involved in the disease.Also, hypocalcemia has been reported to aggravate psoriasis, but since it is in itself an extemely rare condition, it plays little role in the etiology of the disease *(Abel et al., 1986 and Fry, 1988)*.The-stress and strain of psychological nature are regarded as factors, e.g.which produce worsening of psoriasis or act as a triggering factors. Other precipitating factors are skin trauma and cold weather *(Fry, 1988)*. *Henry et al. (1985)* concluded that difficulty in illustrating the mode of inheritance of psoriasis might be due to the fact that psoriatic diathesis might not become clinically manifested until late in life and attempts at genetic analysis of pooled clinical data had met this difficulty.

Chromosomal study

Chromosomal study of psoriatic patients showed no abnormalities in the studies of karyotypes from leukocytes and cultured fibroblast *(Hochglaube and karasek,1965)* Also,Faber and *Nall (1974), Nall* and *Faber (1977), Adam (1980), Benacerraf (1981), Brandrup et al. (1982), Brandrup and Green(1982) and Liu and Rui(1982)* found from chromosomal study of psoriatic patients that no statistically significant chromosomal aberration could be detected.

In addition, *Swanbeck et al. (1975), Mourelatos et al. (1977), Fraki et al. (1979), Faed et al. (1980) and Bredberg et al.(1983)* did not detect significant chromosomal aberration in karyotypes of psoriatic patients. Moreover, the authors had studied the different effects of certain drugs used in treatment of psoriasis as UVA and PUVA on chromosomes of healthy persons and psoriatic patients.They found that the types of aberrations that showed an increase after irradiation were chromatid breaks and rearrangements ,whereas the frequency of gaps was not significantly different (P>o.25) from that in untreated cells. Also, the authors found that the numbers of sister chromatid exchange in lymphocytes of psoriatics before and after irradiation were within the range found in normal subjects. Also, Lober et al.(1985) did not detect significant chromosomal aberration in karyotypes of

psoriatic patients. Moreover,the authors had studied the different effects of certain regimens used in treatment of psoriasis as UVA and PUVA on chromosomes of healthy persons and psoriatic patients. They found that exposure of non psoriatic lymphocytes to UVA and PUVA had increased significantly the rate of premature centromeric division (P.C.D) and major coiling generation (M.C). However, in experiments with psoriatic lymphocytes, a nuch weaker effect was found and there was moderate increase of P.C.D and M.C. after UVA and PUVA.

Moreover, Tillikainen et al. (1980) and Henry et al. (1985) found no chromosomal aberration in karyotypes of psoriatic patients though the authors found that there was disequilibrium between HLA types and psoriasis and there was prevalence of histocompatibility antigen HLA-CW6 and excess of several HLA-B locus genes in psoriatic patiensts.The authors added that psoriasis appeared to be the first disease more closely associated with C-locus and suggested that CW is perhaps a genetic marker for the gene determining susceptibility of the patients. Also *Bianch and Iracie (1989), Wyatt et al. (1989), Elder et al. (1990) and Takahashi et al. (1990)* had found that there was an increase ofHLA-B 17, CW6 in the psoriatic patients.