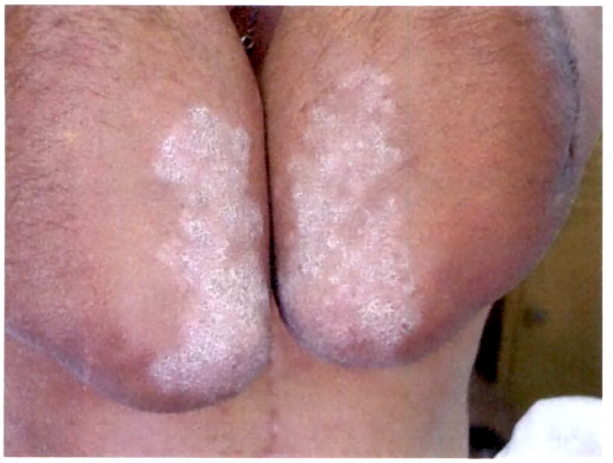
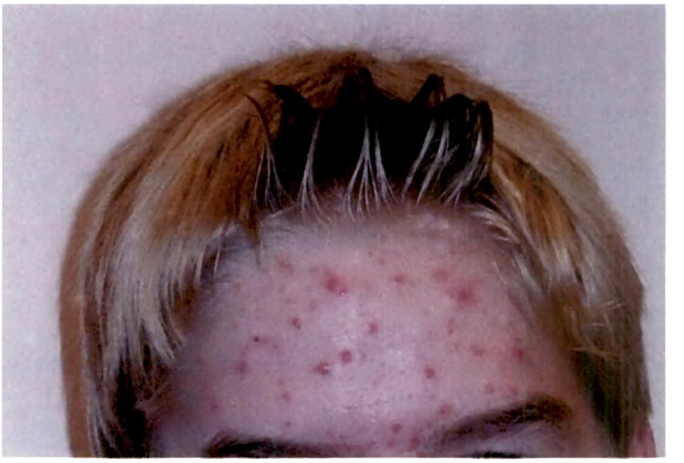
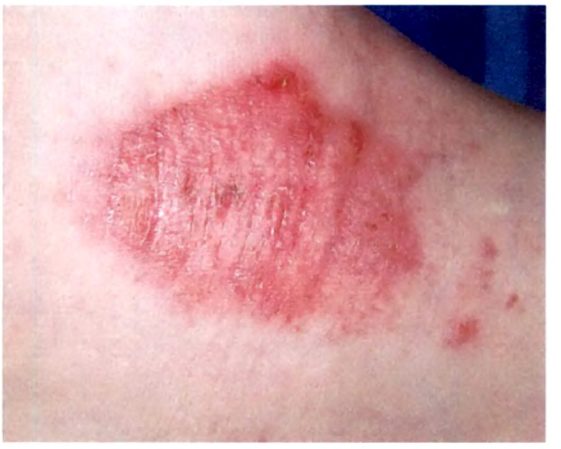
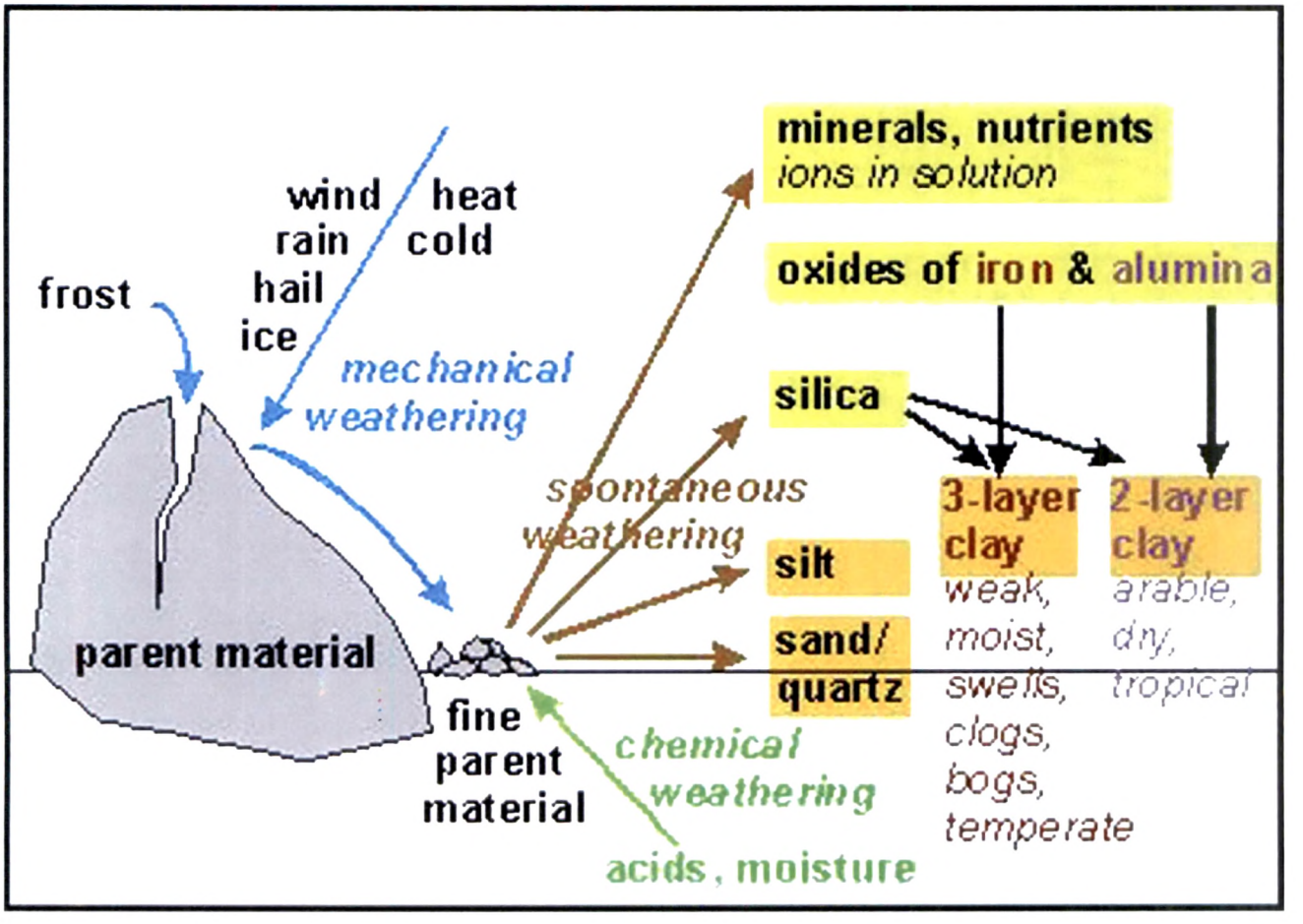
CHAPTER -1

INTRODUCTION








wind
rain
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mechanical weathering
parent material
fine parent material
chemical weathering
acids, moisture
spontaneous weathering
minerals, nutrients
ions in solution
oxides of iron & alumina
silica
silt
sand/ quartz
3-layer clay
weak, moist, swells, clogs, bogs, temperate
2-layer clay
arable, dry, tropical

1.0 Introduction

Mud has been associated with human beings right from the origin of life. Presence of mud goes synonymously with the presence of life. Scientists have been painstakingly analyzing soil samples from the Moon and the Mars, searching for traces of origin of life. Our Indian Vedic literature has professed that man is born from mud and disintegrates into mud after death (*Panchmahabhut).* In Islamic and English culture, dead bodies are buried in mud and if the grave is dug after a year then , only remnants of skeleton is obtained from it , meaning to say that flesh, skin, organs all disintegrate and merge into mud . Thus it implies that our body is made up of constituents of mud which on decaying become a part of it.

Except for the physical association, human beings have emotional attachment too. It is for the emotional attraction to the motherland, that many wars have been fought for it, to protect its sanctity. After returning from the World Religion Conference, in America, Swami Vivekanand first kissed the soil of the airport as an expression of gratitiude to the motherland. Thus soil or land plays an important emotional role in life of human beings.

From time immemorial, mud (wet soil) has been used for mankind in different forms. It may be in the form of pottery, houses, toys, or furnaces .Whatever may be the form , man has benefitted from it either physically for e.g increasing oxygen content of water stored in earthern pots, emotionally (feeling of calmness on sleeping on mud floor), and irradiationally (protection from harmful radiation, during bomb blast in Hiroshima and Nagasaki). A recent report on Bhopal Gas Tragedy stated people in closed mud huts were not affected by the gas.

Use of mud therapeutically, has also been a tradition not only in India but in Germany, Italy and Russia too. Gandhiji popularized the use of mud as a therapy in India. During his stay in Oorlikanchan and Vardha ashram with Vinoba Bhave in Maharashtra, he professed the use of mud for constipation, for reducing fever and for rupture of boils on skin. Rajput Queens of Rajasthan used to apply 'multani mitti'

for skin beutification. Geophagy (purposeful eating of soil) in children is very common and a US Patent has been permitted for a formulation to remove toxins from the body (US Patent 2009).

Thus mud has been a part and parcel of human life and we are highly obliged by its existence, otherwise where would the crops grow and how would we exist!

Mud has been used to treat skin disorders like psoriasis, eczema and acne, also since olden times (the details of which is given in the foregoing text), and it is our humble effort to investigate upon four samples of muds of India which have not been explored scientifically, and to prepare user friendly formulations from it.

1.1 Human Skin

As in other mammals, human skin consists of a stratified, cellular epidermis and an underlying dermis, connective tissue. The dermo-epidermal junction is undulating in section; ridges of the epidermis, project into the dermis. The junction provides mechanical support for the epidermis and acts as a partial barrier against exchange of cells and large molecules. Below the dermis is a fatty layer, the panniculus adiposus, usually designated as" subcutaneous". In most mammals this is separated from the rest of the body by a flat sheet of striated muscle, the panniculus ornosus, but the layer is vestigial in humans.

There are two main kinds of human skin. Glabrous skin (non-hairy skin), found on the palms and soles, is grooved on its surface by continouously alternating ridges and sulci, in individually unique configurations known as dermatoglyphics. It is characterized by a thick epidermis divided into several well-marked layers, including a compact stratum corneum, by the presence of encapsulated sense organs within the dermis, and by a lack of hair follicles and sebaceous glands. Hair bearing skin on the other hand, has both hair follicles and sebaceous glands but lacks encapsulated sense organs.

The superficial epidermis is a stratified epithelium largely composed of keratinocytes which are formed by division of cells in the basal layer, and give rise to several distinguishable layers as they move outwards and progressively differentiate. Within the epidermis, there are several other cell populations namely melanocytes, which donate pigment to the keratinocytes, Langerhans' cells, which have immunological function and Merkel cells.

The basis of the dermis has supporting matrix or ground substance in which polysaccharides and proteins are linked to produce macromolecules with a remarkable capacity for holding water in their domain. Within and associated with this matrix are two kinds of protein fibres: collagen, which has great tensile strength and forms the major constituent of the dermis, and elastin which makes up only a small proportion of the bulk. The cellular constituents of the dermis include fibroblasts, mast cells and histiocytes .The dermis has a very rich blood supply, although no vessels pass the dermo-epidermal junction.

The motor innervations of the skin is autonomic, and includes a cholinergic component to the eccrine sweat glands and adrenergic components to both the eccrine and apocrine glands, to the smooth muscle and the arterioles and to the errector pili muscle. The sensory nerve endings are of several kinds: some are free, some terminate in hair follicles and others have expanded tips. Only in glabrous skin are some encapsulated (Eady RAJ 2004).

A schematic diagram of human skin describing its different layers and cellular components is given in figure no. 01.

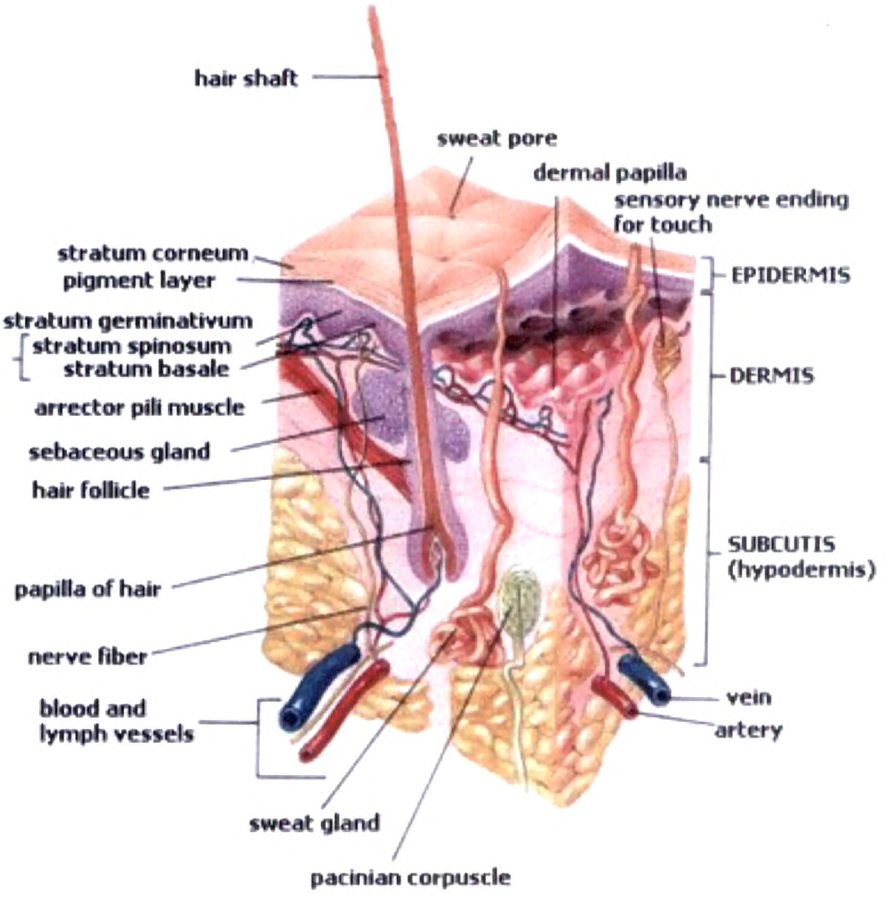


Fig no.: 01 Human skin (www.makehumans.com/skin)

1.1a Epidermis

The normal epidermis is a terminally differentiated, stratified and squamous epithelium. The major cell, making up 95% of the total is the keratinocyte, which moves progressively from attachment to the epidermal basement membrane towards the skin surface, forming several well-defined layers during its transit. Thus, on simple morphological grounds, the epidermis can be divided into four distinct layers: stratum basale or stratum germinativum, stratum spinosum, stratum

granulosum and stratum corneum. The term Malphighian layer includes both the basal and spinous cells. Other cells resident with the epidermis include melanocytes, Langerhans' cells and Merkel cells.

The stratum basale is a continuous layer that is generally described as only one cell thick, but may be two to three cells thick in glabrous skin and hyperproliferative epidermis. The basal cells are small and cuboidal (10-14nm) and have large, dark-staining nuclei, dense cytoplasm containing many ribosomes and dense tonofilament bundles. Immediately above the basal cell layer, the epibasal keratinocytes enlarge to form the spinous/prickle cell layer or stratum spinosum distinguished by numerous desmosomal connection plaques, which interact between adjacent keratinocytes forming a stabilizing network of surface interconnections. Desmosome are symmetrical, laminated structures formed in apposed plasma membranes with linear intercellular and intracellular components. Cytoskeletal tonofilaments (keratin intermediate filaments) seem to attach close to desmosomes, providing stability across the cell layers.

The stratum spinosum is succeeded by the stratum granulosum or granular layer because of the intracellular granules of keratohyalin. At high magnification, the dense mass of keratohyalin granules from human epidermis has a particulate substructure, with particles of irregular shape on average 2 nm length and occurring randomly in rows or lattices. The cytoplasm of cells of the upper, spinous layer and granular cell layer also contains smaller lamellated granules averaging 100-300nm size, which are known as lamellar granules or bodies, membrane –coating granules or Odland bodies These are numerous within the uppermost cells of the spinous layer and migrate towards the periphery of the cells as they enter the granular cell layer. They discharge their lipid components into the intercellular space, playing important roles in barrier function and intercellular cohesion within the stratum corneum.

The outermost layer of epidermis is the stratum corneum where cells (now corneocytes) have lost nuclei and cytoplasmic organelles. The cells become flattened and the keratin filaments align into disulphide cross-linked macrofibres, under the

influence of filaggrin, the protein component of the keratohyalin granule, responsible for keratin filament aggregation (Lynley AM 1983). Filaggrin influences the skin barrier function and plays a important role in atopic dermatitis. The corneocyte has a highly insoluble cornified envelope within the plasma membrane, formed by cross-linking of the soluble protein precursor, involucrin (Rice RH 1977) following the action of a specific epidermal transglutaminase also synthesized in the high stratum spinosum (Boxman MM 1978). The process of desquamation involves degradation of the lamellated lipid in the intercellular spaces and loss of the residual intercellular desmosomal interconnections. **There is excessive desquamation of stratum corneum in psoriasis.** In palmoplantar skin there is an additional zone, also electronlucent, the stratum lucidum between the granulosum and corneum. These cells are still nucleated, and may be referred to as 'transitional 'cells.

The process of terminal differentiation, which is commonly termed keratinization, therefore includes changes in keratins, envelope proteins, plasma-membrane glycol-proteins, intercellular lipids, desmosomes and other intercellular adhesion proteins. Specific factors regulate these processes. Thus, keratinization is not a simple change in keratin expression, but the formation of the corneocyte.

Regulation of epidermopoeiesis

Psoriasis, eczema and acne are diseases of epidermis and so study of epidermopoeiesis becomes very important. Several factors influence generation and growth of epidermal cells which are explained in detail below.

Growth factors

As epidermal thickness and the population size appears to remain constant, the rate of cell production in the germinative compartment must be balanced by the rate of cell loss at the surface of the stratum corneum. In case of psoriasis epidermal thickness increases due to uncontrolled proliferation of cells. The control mechanism of this epidermopoeisis consists of a balance of stimulatory and inhibitory signals. Diffusible factors known as cytokines (small peptides originally described as macrophage monocyte products that mediated inflammatory or

immunological reactions) or growth factors (mediating the growth of different cell types) have been identified. They are produced by keratinocytes in vitro and can be found in physiological amounts in normal humanskin. Each cytokine exerts different effects on multiple cellular targets, so the net effect in a complex tissue such as skin depends on complex balances or cascades of cytokines. It is well established that cytokines play an important role in the pathogenesis of psoriasis, eczema and acne.

Growth stimulatory signals (Mckay IA 1993)

More than 90% of autocrine growth of keratinocytes is mediated through the EGFr (epidermal growth factor receptors) but other cytokines synthesized by keratinocytes including interleukin 1 (IL1) interleukin 6 and granulocyte- macrophage colony stimulating factor (GM-CSF) can also stimulate growth (KupperTS 1988). All these components are overexpressed in psoriasis, (Nanney LB 1990), eczema (Leung DYM 2004) and acne (Jeremy AH 2003). Paracrine factors may be produced by dermal fibroblasts and microvascular endothelial cells. Some members of the fibroblasts growth factor (FGF) family stimulate keratinocyte growth, including acidic and basic cells. Keratinocyte growth factor (KGF: FGF7), in particular has a specificity for keratinocytes and is induced in dermal fibroblasts within 24h of wounding (MCkay IA 1991). Factors induced by leukocytes and macrophages-platelet-involved growth factor (PDGF), (Raines EW 1986) TGF-α, IL-1β,Tumor necrosis factor (TNF)-induce the KGF gene and thus induce this rapid response.

Growth inhibitors for keratinocytes:

It has long been suggested that epidermal growth is under the influence of a negative-feedback mechanism,. Bullowgh and colleagues proposed the existence of growth inhibitors or chalons produced by suprabasal cells, which slow basal mitosis (Bullowgh WS 1967, Elgie K 1986). Recent studies have purified a number of defined growth inhibitory substances, which are produced in skin and may have contributed to activities within the previous crude biological extracts. It is likely, that further

cytokines with growth inhibitory activity towards keratinocytes remain to be found, some of which may be site or cell specific.

Transforming growth factor –β (TGF-β) comprises a family closely related to, two – chain polypeptides present in normal cells and malignant cell line (Derynck R1985). TGF-β1 stimulates fibroblast growth and increases fibrosis but inhibits growth of keratinocytes (Shipley FD 1986). TGF-βreceptors are ubiquitous, and are likely to be important regulatory molecules in inflammation and repair and epithelial mesenchymal interactions.

Interferons –α and –γ (IFN-α and IFN-γ) have cytostatic effects on keratinocytes both in vivo following systemic administration, and in vitro (Symington FW 1989). Following stimulation with IFN-γ, keratinocytes express class II antigens, predominantly human leukocyte antigen (HLA)- DR, in a dose-dependent manner but higher doses are cytotoxic to keratinocytes.

TNF-α, a macrophage cytokine, induces neutrophil activation (Beutler BA 1985) endothelial activation, fibroblast stimulation, endotoxic shock and acute phase protein release, but is also secreted by keratinocytes, especially after ultraviolet radiation. TNF is reversibly cytostatic to keratinocytes, but stimulates fibroblast proliferation and cytokine production.

Regulation of epidermopoiesis: signal transduction and growth control

The ability to respond to external signals allows cells to adapt to a changing environment (like cold, exposure to chemicals etc) by changes in the rate and spectrum of gene expression.

Signal transduction reflects the mechanism by which signals from outside a cell, such as **hormones,** combine with cell receptors to act intracellularly via serine-threonine or tyrosine kinases. Protein phosphorylation transmits this information to the nuclear transcriptional machinery. A number of signal transduction pathways have been postulated to be important in the regulation of growth and differentiation in

the skin, involving growth factors, hormones, cell – surface receptors, second messengers and their control.

Many extracellular signals degrade inositol phospholipids (PI) in the cell membranes. Diacyl glycerol, a metabolite of PI, activates protein kinase C. Inositol triphosphate (IP3), another metabolite of PI, mobilizes intracellular calcium, which combines with calmodulin to activate calcium and calmodulin-dependent protein kinase.It should be noted that defective calcium-mediated cell signaling was observed in cultured psoriatic keratinocytes (Karvonen SL 2000, Korkiamaki T 2005).

Selective cell death is a way of eliminating unwanted cells during normal differentiation, or when cells are damaged (Arends MJ, 1991). There are two pathways: necrosis, when cells are passively damaged with membrane damage, cell swelling and rupture; and apoptosis, an active process. Apoptosis or programmed cell death is characterized by nuclear fragmentation, and shrinkage of the cells into small fragments, phagocytosed by surrounding cells.

In summary, there is evidence for the local existence of both stimulators of epidermal proliferation and inhibitors (or Chalones). On the one hand, polypeptide growth factors have been sequenced and their receptors have been identified at the cell surface, and the keratinocyte appears to produce and respond to numerous growth factors. Inhibitory substances are also synthesized in skin, and their nature has been in part determined, although the balance between these opposing forces is not clear. Intracelllular pathways of signal transduction, following binding to cell surface receptors of specific ligands, require action on second messengers of PKC and inositol phosphate pathways. Factors that modulate the rate of epidermal cell production may not affect the rate of desquamation in the short term, and vice versa. It is only in the longer term that these two aspects of epidermal activity – production and cell loss- appear to be closely linked.

Cell proliferation in Normal epidermis

Gerald D. Weinstein et al (1984) developed a quantitative interrelationship among the 3 major cellular compartments of the epidermis –the proliferative, the viable differentiated (stratum malpighii), and the stratum corneum. To assure a kinetic and physiologic homeostasis in the epidermis, the rate of birth / entry, transit, and / or loss of keratinocytes in each of these compartments must be approximately the same.

They found out that the turnover or renewal time of normal epidermis in its entirety can be viewed as the sum of the turnover (transit, cell cycle) times for each of the separate compartments.The mean epidermal turnover time is thus 39 days, consisting of 13 days for the proliferative compartment, 12 days for the differentiated compartment, and 14 days for the stratum corneum. However, this changes in case of disease conditions. For e.g., in psoriasis, excessive cell proliferation i.e germinative cell cycle 36 h is 8 times shorter than the normal epidermal proliferative compartment cell cycle i.e. 312 h (13 days).

1.1b Dermis

The dermis, which is bounded externally by its junction with the epidermis and internally by subcutaneous fat, contributes 15-20% of the total weight of the human body. It varies in thickness from about 5mm on the back and thighs to 1mm on the eyelids. It is tough and resilient, providing nutriment to the epidermis and cutaneous appendages and cushioning the body against mechanical injury.

It largely consists of a supporting matrix or ground substance, in which, polysaccharides and protein coexist and interact to produce hygroscopic proteoglycan (PG) macromolecules, which strongly attract and retain water. Running through and attached to this matrix are several kinds of protein fibre, such as interstitial collagen, with great tensile strength, elastin, with considerable elasticity, and various other microfibrillar components such as fibrillin (tupesI and II) microfibril-associated glycoprotein (MAGP), microfibril –associated fibrillar protein

(MAFP), collagen VI and lysyl oxidase. Collagen represents 75% of the dry weight and 18-30% of the volume of dermis, of which morethan 70% is type I collagen and 15% type III collagen.

The underlying nine-tenths is called the reticular dermis:; it blends with the subcutaneous fat. In regions such as the nipple, penis, scrotum or perineum, there are also stress-orientated smooth muscle fibres in the reticular dermis.

Elastin fibres also form an extensive network, which intermeshes with collagen fibres.

The predominant dermal cellular elements are fibroblasts which secrete the ECM(Extracellular matrix) proteins. Others include mast cells, histiocytes, macrophages, lymphocytes and other leukocytes, and melanocytes. The dermis also contains capillaries, arterioles, venules and lymphatics, as well as peripheral, sensory and motor nerve endings.

The dermo-epidermal junction

The dermo-epidermal junction is one of the largest epithelial –mesenchymal junctions in the body. It forms an extensive interface between the dermis and epidermis, and is continuous with the junction between dermis and epidermal appendages. By virtue of its anatomical location and highly complex composition, the dermo-epidermal junction and its major constituent, the basement membrane, have a key role in a wide range of epithelial –mesenchymal interactions including epidermal cell anchorage, adhesion, migration and differentiation. It is also involved in signalling between the extracellular matrix and basal cells, and serves as a barrier and filter.

Nerves and sense organs

The skin may be innervated with around one million afferent nerve fibres (Allenby CF 1970). Groups of myelinataed fibres fan out in a horizontal plane to form a branching network from which fibres ascend, usually accompanying blood vessels, to form a

web of interlacing nerves in the superficial dermis. Most end in the dermis; some penetrate the basement, but do not travel far into the epidermis.

Blood vessels: (Montagna W1961, Moretti G 1968, Ryan TJ 1983)

The arteries entering the skin form a deep plexus – the 'fascial' network. From this region vessels rise to the border between the subcutaneous adipose tissue and the corium, and these form a cutaneous network. This gives branches to the various cutaneous appendages, and provides ascending arterioles to supply a subpapillary plexus, which itself forms capillary loops in the papillary layer between the ridges of the dermo-epidermal frontier. From these capillaries the blood is drained by venules which descend to intermediate plexuses (Braverman IM1982, Yen A 1976). The vasculature is more elaborate than would be necessary solely for nutrition of the skin and temperature control is an important function. It is believed that the amount of blood flowing through the superficial layers of the dermis can be controlled by arteriovenous anastomoses, which act as shunts to short circuit the flow. However, although anastomoses occur in some acral sites, such as the fingertips, they have not been found to be regular components of the microvasculature elsewhere.

The microvasulature is a rich source of enzymes that may be involved in intracellular processes such as endocytosis and vesicular transport.

1.1c Cutaneous Biochemistry

Skin is a unique organ specialized to be a flexible, resilient, self-renewing barrier to water loss and penetration by outside physical, chemical, and biologic insult. The skin is composed of two layers: (1) an epidermal cell population, whose metabolism is primarily involved in continual renewal and in the production of stratum, corneum, proteins (keratins) and lipids; and (2) dermis, whose cell products of collagen, elastin, and ground substances form the superstructure needed to support the epidermis and other skin structures. **The metabolic pathways appear to be geared toward energy production with a shift in dependency from the efficient Krebs cycle to the glycolytic pathway. It is possible that this is due to the energy costs of a constantly**

renewing system and to the relatively low oxygen tensions of the epidermis (Thomas FA 1984). Alternatively, the abundant lactate produced may be "useful" to the skin as a suitable ionic environment for the keratin proteins in the stratum corneum or as a feedback circuit linking the skin to total body metabolism (Meir PD 1976).

Mechanism of Hormone action

One mechanism whereby the cell surface communicates with the nucleus might be through the microtubule-microfilament network. This network, made up in part of tubulin and actin proteins, may be important in cellular motility, phagocytosis, exocytosis, and normal cellular morphology. This "cytoskeletal system" has been shown to be abnormal in proliferative tissues such as psoriasis and neoplasia (Puck TT 1977, Voorhees JJ 1981).

Cyclic nucleotide system

Cyclic nucleotide system is a cell surface receptor model of hormone action. A lipid soluble adenylate cyclase guanosine triphosphate (GTP) binding protein complex within the membrane is activated, and adenosine triphosphate (ATP) is then converted to cAMP inside the cell. Before this" second messenger" is hydrolyzed by cyclic nucleotide phosphodiesterase (cPDE) activity, it may bind to cAMP dependent protein kinase, which in turn catalyzes the phosphorylation of certain proteins such as phosphorylase B-kinase or glycogen synthase.

Cyclic nucleotides have been shown to be the molecular mediators of a wide variety of important functions. These include many hormone actions (such as melanocyte – stimulating hormone), neuronal function in muscular contraction, secretion in phagocytosis and many immune mechanisms (Larner I 1976). For example, in addition to the IgE receptors, mast cells appear to have beta receptors and H_2 receptors that modulate the secretion of histamine granules in urticaria (Lewis RA 1981, Monroe EW 1977). Genetic defects in the cyclic nucleotide system have been

implicated in the pathophysiology of a number of disorders, including psoriasis and atopic dermatitis (Parker C 1977, Voorhees JJ 1981).

Arachidonic acid and prostaglandin metabolism

Another perturbation of the cell surface that may have important cellular modulating effects is the release of arachidonic acid from cell membrane phospholipids such as phosphatidylcholine (lecithin) (Penneys NS 1980). Arachidonic acid release appears to be the rate-limiting step in the formation of prostaglandins. This step is catalyzed by an enzyme known as phospholipase A2 which can be triggered by thermal, mechanical, electromagnetic, chemical, pharmacologic, or immunologic stimuli ((Penneys NS 1980, Kuehl FA Jr. 1980). Once released, arachidonic acid is metabolized either by the cyclo-oxygenase pathway to prostaglandins (mainly PGE2 and PGD2 in the skin) or via the lipoxygenase pathway to 12-L-Hydroxy-5, 8, 10, 14 eicosatetraenoic acid (12-HETE) in the epidermis. In tissues such as the dermal mast cell or recruited inflammatory cells, unique fatty acids with double bonds known as leukotrienes are also formed.The cyclo-oxygenase products of the arachidonic acid cascade have multiple effects in the skin .They probably mediate the first 24 hours of sunburn erythema (Greeves MW 1980). They are likely to be important in a wide variety of circumstances that result in inflammation or cutaneous vasodilatation (Zurier RB 1981). Prostaglandins E2 and D2 can stimulate adenylate cyclase, raising cAMP levels and thus modulating cell function. Prostaglandin F2α has vasoconstricting and other opposing effects to prostaglandin E2. It has been postulated that a balance between these two prostaglandins may also be important in normal epidermal metabolism. The concentrations of the vasodilating prostacyclin (PGI2) and the potent vasoconstricting thromboxanes are very low or absent in the epidermis. However, these arachidonic acid products may be synthesized in vascular endothelial cells and by platelets and thus be important in regulating cutaneous blood flow and blood clotting in the dermis (Moncada S 1979).

However, in some forms of cutaneous injury, arachidonic acid appears to be shunted through the lipoxygenase pathway. **For example, in psoriasis, lesional skin contains a 26-fold increase in the content of free arachidonic acid and an 82-fold increase in HETE levels compared with uninvolved epidermis (Hammarstrom S 1975). This , in conjunction with a less than two-fold increase in prostaglandins E2 and F2α in lesional skin , has suggested the existence of an endogenous cyclo-oxygenase inhibitor in psoriasis (Penneys NS 1980).** An inhibitor substance has been removed from the vasoconstricted Woronoff ring seen surrounding plaques of psoriasis treated with ultraviolet light. This inhibitor can also be found in other inflammatory proliferative conditions such as contact dermatitis, but not in noninflammatory proliferative conditions (Penneys NS 1980). For every molecule of arachidonic acid that is formed from cell membrane phospholipid, one molecule of lysolecithin is produced. Since lysolecithin is a potent stimulator of guanylate cyclase and is an inhibitor of prostaglandin biosynthesis, it has been proposed as a possible candidate for this endogenous inhibitor of prostaglandin cyclo-oxygenase (Voorhees J.J 1981). The products of the lipoxygenase pathway may be important in abnormal inflammatory reactions. In epidermis, the major product of the lipoxygenase pathway 12-HETE, has been shown to be highly chemotactic, both in vitro and in vivo. **As HETE and arachidonic acid are both markedly elevated in psoriatic lesions, they may be important in the formation of the psoriatic pustule.** HETE and related fatty acids have also been shown to stimulate guanylate cyclase (Cantiere JS 1980). **Thus, the high HETE content could explain the finding of constant increased cGMP in psoriatic lesions.**

Polyamine biosynthesis

Another metabolic pathway that seems critically linked to proliferation of many mammalian cells, including epidermis, is polyamine biosynthesis. Polyamines are strongly basic substances derived from the amino acid ornithine. Ornithine decarboxylase (ODC) is the rate –limiting enzyme in the synthesis of the polyamines putrescine and spermidine.

Polyamine biosynthesis is frequently elevated in proliferating tissue. Ornithine decarboxylase can be artificially stimulated in epidermis by a wide variety of processes or agents known to induce mitotic activity, including physical trauma; proteolytic enzyme digestion; hormonal stimulation with estrogen, epidermal growth factor, or beta adrenergic agonists; mitogenic lecithins; and ultraviolet light. **By contrast, ODC production can be inhibited by protein deprivation, glucocorticoids, vitamin A or other retinoids, and prostaglandin synthesis inhibitors such as indomethacin (Buxamn MM 1981, Duell EA 1982).** Once putrescine is formed, the enzyme S-adenosyl methionine decarboxylase and spermidine or spermine synthase complete the production of these very basic substances, which easily and readily complex with nucleic acids.

There appears to be a fairly consistent polyamine spike at the G_1-S boundary of the cell cycle in many proliferating systems. **For instance, ODC activity is elevated in psoriatic lesions as compared with activity in normal skin. This activity decreases toward normal in steroid or anthralin- treated skin. In the treatment of psoriasis with glucocortisoids, anthralin, or systemic retinoids, the activity of ornithine decarboxylase is decreased in association with improvement of the skin condition (Proctor M 1979, Russell DH 1978).**

Proteinase-peptide metabolic regulation

Another critical pathway that illustrates the complexities of metabolic regulation is the peptide hormone-proteinase system (Keil B 1979). This system provides the means for modulating a wide variety of peptide hormone actions, inflammatory immune reactions (complement, kinins), the intrinsic blood clotting system, and the metabolism and transport of proteins such as collagen and elastin (Reich E 1975).

Lazarus and associates (1977) have shown that psoriatic plaques, compared with normal skin, contain increased amounts of a complement-dependent chemotactic factor that is inhibited by diisopropyl fluorophosphates (a known serine proteinase inhibitor).

Keratinization

The major product of the epidermis is the stratum corneum, made up of phospholipid cell membranes and fibrous proteins called keratins. **Alteration of the normal pathway of keratinization results in a wide variety of disease states, ranging from microcomedo formation in acne to various forms of ichthyosis.**

Presumably, certain cellular events, mediated by pathways previously discussed, trigger the cessation of DNA synthesis and the production of keratin messenger RNA (Gibbs and Freedberg, 1980), which finally results in the assembly of keratin fibrous proteins. These proteins form the tonofibrils in the basal layer of the epidermis and show a characteristic alpha-helical pattern on x-ray diffraction. As the keratinocytes ascend to the stratum corneum, these tonofibrils coalesce into tonofilament. These filamentous proteins are cross-linked by the enzyme epidermal transglutaminase and are closely associated with the keratohyaline proteins. This results in a highly insoluble stratum corneum-protein complex. **It is of interest that the hyper and parakeratotic epidermis found in ichthyosis vulgaris, psoriasis, and squamous cell carcinoma is negative histochemically for transglutaminase activity, suggesting the importance of this activity in normal terminal differentiation (Buxman MM 1981).**

Vitamin A and the related family of retinoids have been shown to be important modulators of epidermal keratinization (Orfanos CE 1980) and so it is used in the treatment of acne. The aromatic retinoid Ro 10-9359 has been useful in the most severe forms of psoriasis, particularly in combination with phototherapy (Michaelson G 1980).

The interrelationships of the dermis, epidermis, and various metabolic modulatory pathways discussed earlier are complex. For example, drugs that affect the cyclic nucleotide system, such as prostaglandins or propranolol, can influence collagen synthesis (Berg RA 1981). Also, normal levels of cyclic nucleotides are necessary for a proper microtubular-microfilament array affecting cell communication and morphology (Voorhees J.J1981). **The skin has a finely orchestrated series of molecular events, each interdependent on one another. Any perturbation of one**

pathway usually sets off a series of "corrective" changes in another pathway, resulting in "Homeostasis." Major insults to critical pathways may result in disease. It is reasonable to postulate that lipid compounds such as cortisol or vitamin A render a certain "set" of instructions to genome DNA. Then other cell surface events such as receptor binding or cell membrane damage result in certain "triggers" to biochemical events that lead to a temporary new set of instructions. Lastly, metabolic events within the cell can produce changes that again alter the instructions to the genome, starting the cycle once more. This process continues in a very complex fashion until the cell is replaced with new progeny to carry on and /or terminally differentiate and die. **Alteration of cellular activity can result from injury, pharmacologic change, or metabolic perturbation of hormonal or immunologic systems.**

1.1d Skin Permeability

Skin is neither an impregnable, impermeable envelope nor a fragile, freely permeable membrane. It is a durable, selectively permeable (more impermeable than permeable) cover, showing regional variations in absorptive capacity**. Skin owes its durability to the dermis, but its chemical impermeability resides in the epidermis and almost exclusively in its dead outer layer, the stratum corneum.** The cutaneous permeability of man cannot be equated with that of any other species, although, in this property at least, the skin of the pig and guinea pig comes closest to that of man.

Skin should be viewed both as a membrane that limits water loss from the body and as a protective sheath that regulates the penetration of water and other chemicals into the system. In the latter role, skin is both a barrier to the absorption of most substances and a system of routes or pathways permitting the selective entry of others.

Percutaneous absorption

When a drug system is applied topically, the drug diffuses passively out of its carrier or vehicle and , depending on where the molecules are placed down , it partitions into either the stratum corneum or the sebum-filled ducts of the pilosebaceous glands i.e. transepidermal route or transfollicular route. Inward diffusive movement continues from these locations to the viable epidermal and dermal points of entry. In this way a concentration gradient is established across the skin up to the outer reaches of the skin's microcirculation where the drug is swept away by the capillary flow and rapidly distributed throughout the body (Gordan L.Flynn 2002).

1.2 Psoriasis

Psoriasis is a chronic disease with a variety of treatment options and strategies. This multifactorial disorder affects 1% to 3% of world's population and occurs equally among men and women. Age of onset varies according to type of psoriasis, generally occurring at age 20 to 30 years or 50 to 60 years (Griffiths CEM, 2007, West DP, 2005)

Multiple genetic and environmental factors are involved in psoriasis. The genetic component is still not well understood though many theories have been postulated. However, the disease affects more than one immediate family member in approximately 30% of patients with psoriasis, and the incidence is higher in monozygotic twins than in dizygotic twins. There is an 8.1% chance of developing psoriasis when one parent has the disease, the risk increases to 41% when both parents have it. Additionally, certain genes have been identified that increase the likelihood of developing psoriasis by 9 to15 times (West DP 2005 , Baxi Sneha 2008).

1.2a Types of psoriasis

There are different types of psoriasis and the area typically affected by psoriasis is scalp, belly button, knees, elbows and back.

(1) Psoriasis vulgaris (plaque psoriasis):

Plaque psoriasis is the most common type of psoriasis; typically one will see well defined red patches with dry, silvery scales on scalp, elbows, knees, lower back and around the belly-button. Face will not usually be involved. If the scales are picked off, small points of bleeding will typically occur. One may see thick areas of scaling on the palms of hands and the soles of feet, individual patches may last for months to years, and may come and go.

(2) Guttate Psoriasis

Guttate psoriasis is named after the French word for drop "goutte" since the lesions are multiple, small (5-15 mm), round, or oval and drop-like in shape. They will typically cover trunk, arms, legs, face and scalp. This form of psoriasis is seen mainly in children and young adults after a Streptococcal throat infection. It is the presenting form of psoriasis in approximately 15% of people and often goes away on its own within a few weeks or months.

(3) Pustular Psoriasis:

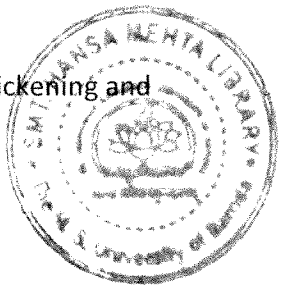
Pustular psoriasis may be found in one localized area or spread over many parts of body. Pustules do not represent infections and are not contagious.

((4) Nail psoriasis:

Nail changes occur in 25-50% of people who have psoriasis, they are more common in people who also have psoriatic arthritis.

Small indents in the nails ("pitting") are the most common nail changes, other

changes include lifting up of the nails ("onycholysis"), discoloration, thickening and crumbling.



(5) Psoriatic arthritis:

Psoriatic arthritis occurs in approximately 5-10% of people who have psoriasis. It is more common in men when the psoriasis is generalized and/or pustular, the most common form involves only one or a few joints, often the knees. The small joints of the hands and feet may be swollen and deformed, nail changes are common if the arthritis affects the hands and feet. Back pain may indicate arthritis of the spine and/or sacroiliac joints.

1.2b Exogenous factors which may precipitate or aggravate psoriasis

Environment

Cold weather is thought to increase dry skin which in turn triggers scaling of plaques conversely warm weather and sunlight may improve psoriasis in 80% of patients. Many researches have been done on climatotherapy at Dead Sea for psoriasis where average year round temperature is nearly 30°C and relative humidity is 27% in summer and 38% in winter (Shani J 1997, Even-Paz Z 1989, Drugan A. 1979, Dostrovsky A 1959). The dense oxygen rich haze, the relaxing atmosphere and the ecological determinants at Dead Sea all contribute to a situation where healing and recovery are smooth, safe, and effective.

Psychological stress:

Psoriasis, a chronic inflammatory skin disease, is believed to be exacerbated by stress. The exact mechanism of this phenomenon is not fully understood, however, it has been postulated that different substances released from dermal nerve endings during stress may take part in initiation or modulation of psoriasis. One of the most interesting groups of mediators is polypeptides, also named as neuropeptides that

possess vasoactive properties. It was documented that these polypeptides could not only be released from nerve endings, but may also be directly synthesized in the skin and liberated from numerous dermal cells. Moreover, these substances are not only released by different cells, but may activate various cell types showing a wide spectrum of biological actions. Thus, this complex system of interactions seems to be important component of psoriatic pathological reaction. The significant role of these neuromediators has also been postulated in other chronic skin diseases, like palmoplantar pustulosis, atopic and irritant eczema, rosacea, lichen sclerosus, vitiligo, pigmented urticaria or prurigo nodularis. Among different neuropeptides, substance P, calcitonin gene-related peptide, vasoactive intestinal peptide (VIP) and neuropeptide Y have been mostly studied in psoriasis (Reich A 2008, Saraceo R 2006, Pincelli C 1994).

Dietary factors

Diet has been suggested to play a role in the aetiology and pathogenesis of psoriasis. Fasting periods, low energy diets and vegetarian diets improved psoriasis symptoms in some studies, and diets rich in n-3 polyunsaturated fatty acids from fish oil also showed beneficial effects. **All these diets modify the polyunsaturated fatty acid metabolism and influence the eicosanoid profile, so that inflammatory processes are suppressed (Walters M 2005).** It was observed that during fasting that some patients with psoriasis experienced an improvement, which persisted during the vegetarian diet (Lithell H 1983). **The most important reason is probably the lack of arachidonic acid (AA) intake, (food sources of AA are only animal-derived foods such as meat and egg yolk)resulting in lower leukotriene (LT) B4 production** . During fasting, CD4+ T- cell activation is reduced and anti-inflammatory cytokines such as interleukin (IL) -4 increase (Fraser DA 1999). Another reason may be a reduction of oxidative stress due to calorie restriction, because psoriasis appears to be associated with oxidative stress. The consumption of vegetables and fruits may be beneficial in psoriasis due to their high content of various antioxidants such as carotenoids, flavonoids and vitamin C (Briganti S 2003, Rocha PP 2001). A vegetarian diet may be beneficial because it is associated with a reduced AA intake.

As psoriasis is positively connected with body mass index (BMI) weight reduction is recommended for obese patients (Henseler T 1995, Naldi L 1994).

There have been several observations indicating that alcohol consumption is highly prevalent in patients with psoriasis (Polkolainen K 1994, Polkolainen K 1999). As alcohol stimulates the release of histamine, skin lesions can aggravate as a consequence (Smith KE 2000). Moreover, a high alcohol intake may be accompanied by an excessive intake of high fat foods and saturated fats and a low intake of vegetables and fresh fruit (Naldi L 1994, Zamboni S 1989). Therefore alcohol intake should be restricted in psoriasis.

Vitamin B 12 may influence psoriasis due to its role in nucleic acid synthesis. In vitro studies also demonstrated immunomodulatory effects of vitamin B 12 on T lymphocytes and cytokines (Sakane T 1982, Yamashiki M 1992).

Free arachidonic acid (AA) in epidermal cells is found to be a causative factor in psoriasis and humans obtain AA chiefly from two dietary sources: the membranes of red meat and also certain green leafy vegetables and vegetable oils contain linoleic acid, which is desaturated and elongated by the body to form AA (Voorhees JJ 1983). Dietary linoleic acid is converted to arachidonic acid, which is metabolized through the lipoxygenase and cyclooxygenase pathways to potent inflammatory derivatives (Santoli D 1990, Rappaport RS 1982, Crawford MA 1983). The levels of some of these products are markedly increased in psoriatic plaques, and they may be involved in the pathogenesis of psoriasis through their chemotactic and proliferative effect in human skin (Voorhess JJ. 1983, Kragballe K 1985). When dietary n-3 fatty acids (seal and fish oils) are consumed, they are incorporated into cell membranes and compete with n-6 fatty acids (especially linoleic acid obtained mainly from vegetable sources and animal fat) as substrates for the cyclooxygenase and lipoxygenase pathways (Drevon CA 1992). Eicosanoids from fatty acids of the n-3 series are generally less potent than metabolites from the n-6 series, and the inflammatory reaction is therefore smaller (Lee TH 1985, Miller CC 1989, Elisabeth S 1993).

Infection factor

The role of an infectious aetiology in triggering psoriasis has been well documented in cases of bacterial, viral and fungal infections (Duvic M 1987, Swerlick RA 1986).

Most noteworthy is the association between groups A ß-haemolytic streptococci and the acute onset of guttate psoriasis, as well as the exacerbation of chronic psoriasis (Valdimarsson H 1997). It is also postulated that bacterial endotoxins can act as superantigens, resulting in a complex cascade involving T cell, macrophage, Langerhans cell and keratinocyte activation and interaction (Ortonne JP 1999).

Medications

Medications reported to initiate or exacerbate psoriasis include ß-blockers, (Gold MH 1988) angiotensin-converting enzyme inhibitors (Wolf R 1990), antimalarials (Baker H 1971) and lithium (Lazarus GS 1979).

1.2c Endogenous factors causing psoriasis

There are many endogenous factors which claim to cause psoriasis. Amongst them one pathway points towards the **disruption in the normal cutaneous biochemistry** and the other pathway points towards the **immunomodulatory changes.** Several processes which involve disruption in normal cutaneous biochemistry leading to psoriasis, eczema and acne have already been discussed in the 1.1c section. **Whatever may be the cause, the resultant pathological condition reveals unregulated proliferation and differentiation of epidermal cells.** As stated earlier the proliferative compartment of normal epidermis has a cell cycle duration (Tc) of 311 hrs or say the mean epidermal turnover time of the entire tissue is 39 days whereas in psoriasis (Tc) is just 36 hrs 8 fold shorter.i.e. before the upper stratum corneum is removed (39 days in normal humans) the next layer beneath it, is ready within 36 hrs and so repeated deposition of layers create plaques of psoriasis. The process of keratinization results in a stratum corneum with corneocytes without a cell nucleaus filled with proteins keratins and filaggrin) surrounded by a cornified

envelope and a lipid bilayer, which is formed by lipids extruded from the cell envelope (Placek W 1988).

The idea, that the germinative cells in normal and in uninvolved psoriatic epidermis (during clinical remission) exist primarily in the non-cycling G1 and G2 blocked states, leads to the suggestion that one should focus attention on non-cycling cells for the control and treatment of psoriasis. It may eventually turn out that the effective therapy for psoriasis is not to treat the patient during psoriatic flare-ups (with durgs which kill cycling cells), but rather that effective therapy be administered during periods of clinical remission by applying factors which would keep the germinative cells in the non-cycling state i.e.which would open and close the G1 and G2 blocks of the cell cycle (Gelfant S 1976).

1.2d The development of the psoriatic lesion in patients with psoriasis

Several models are available to study the psoriatic lesion in patients with psoriasis:

In **the first** model, the artificial elicitation of psoriatic lesions following injury of the symptomless skin induces a psoriatic lesion in 25% of patients with psoriasis. (Eyre RW 1982). Furthermore, it was shown that a dermal injury (intradermal injections of chymotrypsin) never resulted in a psoriatic lesion: the epidermis has to be injured as well (Stratis A 2006). Vice versa, removal of the stratum corneum by tape stripping of the epidermis **rarely results in psoriatic lesions in normal patients** but in patients with psoriasis, partial stripping of the stratum corneum induced minute erythematous and edematous, nonscaling papules six hrs to seven days later (Stefania Jablonska 1982). The observations following standardized injury of the symptomless skin in patients with psoriasis suggest that both epidermis and stroma are driving the pathogenesis of psoriasis and that both have to be affected in order to induce psoriatic lesions efficiently (Van de Kerkhof PCM 2007).

Studies during relapse of psoriasis following discontinuation of treatment represent **another model** to obtain insight into the order of events. In these studies, the first

changes were accumulation of monocytes and mast cells and that the suprabasal compartment anticipates full epidermal proliferation. Mast cells may reflect an early role of the functioning of the microvasculature in the development of the lesion (Schubert C 1985).

In **a third model**, which explains immunomodulatory changes, the margin zone of the spreading psoriatic plaque has been used to study the transition between symptomless and lesional psoriatic skin (Van de Kerkhof PCM, 1996). The changes in front of the transition may be expected to represent the most primary phenomena, whereas the changes closer to the lesion are likely to be secondary. Earlier studies have suggested a three-stage transition model. The first phase of transition from symptomless to lesional skin involves the stroma and is characterized by increased expression of tenascin X and alkaline phosphatase activity, indicative for endothelial cell activation and T-cell activation by cytokines released (Chang EY 1992). By means of Doppler flowmetry, it has also been shown that increased blood flow is an initial event in the development of the lesion (Hull SM 1989). The second phase is the appearance of the inflammatory infiltrate with CD8+ and CD45RO+ cells, CD2+ and CD25+ cells as early invaders (Nickoloff BJ 2000). However, in distant uninvolved skin already some increases of CD4+ cells have been reported. In the second phase of development suprabasal expression of keratin 16 and suprabasal expression of β 1 integrin-dim cells and Ki-67+ nuclei have been reported (Korver JEM 2006). The third phase is the simultaneous appearance of Ki-67+ nuclei in the basal cell layer, accumulation of CD4+ cells and NK-T cells and increased expression of involucrin with decreased expression of filaggrin and CD3+, CD56+ cells were decreased in peripheral blood (Koreck A 2002).

More recently it was shown that plasmacytoid dendritic cells are increased in the "nearly" symptomless skin, suggesting early involvement of this class of APCs (Nestle FO, 2005). Apart from the cellular development of psoriasis lesion as seen above there are many other observations in lesional and symptomless skin and peripheral blood of patients with psoriasis which are tabulated in table no. 01. These

observations either trigger cell proliferation or malkeratiization or are manifestations of increased cellular mass.

Table No: 01 Molecules that are expressed in the psoriatic plaque but are absent or have a restricted expression in Normal skin.

Sr.No.	Molecule	Reference
01	CD1d	Bonish B, Jullien D, Dutronc Y., Overexpression of CD1d by keratinocytes in psoriasis and CD1d dependent IFN-γproduction by NK-T cells., J Immunol, 2000;165:4076-85.
02	Complement proteins C3a, C4a, C5a, C4d, Bb, C5b-9	Priestly FC, Adams LW , Hyperactivity of fibroblasts cultured from psoriatic skin. I Faster proliferation and effect of serum withdrawal , Br J Dermatol ,1983; 109: 149-56, Pasch MC, Bos JD, Asghar SS, Activation of complement in psoriasis. Clin Exp Dermatol, 1998; 23: 189-90, Pasch MC, Timar KK, van meurs M et al. In situ demonstration of CD40- and Cd154- positive cells in psoriatic lesions and keratinocyte production of chemokines by CD 40 ligation in vitro. J Pathol, 2004; 203: 839-48.
03	Keratin 6, 16,17	De Jong EMGJ van Vlijmen IM, van Erp PEJ. Keratin 17: a useful marker in anti-psoriatic therapies. Arch Dermatol Res 1991; 283:480-2
04	Skin-associated antileucoprotease	Schalkwijk J, Chang A, Janssen P et al. Skin derived antileucoproteases (SKALPs) characterization of two new elastase inhibitors from psoriatic epidermis , Br J Dermatol, 1990; 122: 631-41
05	Psoriasis-associated fatty acid binding protein	Siegenthaler G, Hotz R, Chatellard- Gruaz D et al. Characterization and expression of a novel human fatty acid binding protein: the epidermal type (E-FABP) Biochem Biophys Res Commun 1993; 190: 482-7
06	Psoriasin	Madsen P, Rasmussen HH, Leffers H et al Molecular cloning, occurrence, and expression of a novel partially secreted protein "psoriasin" that is highly up regulated in psoriatic skin. J Invest Dermatol 1991; 97: 701-12
07	Transforming growth factor-α	Elder JT, Fisher GJ, Lindquist PB et al. Over expression of transforming growth factor alpha in psoriatic epidermis. Science 1989;243:811-814
08	Amphiregulin	CookPW, Pittelkow MR, Keeble WW, et al. Amphiregulin messenger RNA is elevated in psoriatic epidermis and gastrointestinal carcinomas. Cancer Res

		1992; 52;3224-7
09	Epidermal growth factor receptor	Nanney LB, Yates RA, King LE JR. Modulation of epidermal growth factor receptors in psoriatic lesions during treatment with topical EGF. J Invest Dermatol 1992; 98:296-301
10	Interleukin -1ra	Hammerberg C, Arend EP, Fisher GJ et al. Interleukin -1 receptor antagonist in normal and psoriatic epidermis. J Clin Invest 1992; 90: 571-83
11	Interleukin-1β,6	Schmid P, Cox D, McMaster GK, ITIN P. In situ hybridization analysis of cytokine, proto-oncogene and tumor suppressor gene expression in psoriasis , Arch Dermatol 1993; 285:334-40
12	Interleukin -8	Nickoloff BJ, Karabin GD, Barker JN et al . Cellular localization of interleukin -8 and its inducer, tumor necrosis factor –alpha in psoriasis. Am J Pathol 1991; 138: 129-40
13	Growth related oncognene α/β/γ	Tettlebach W, Nanney L, Ellis D et al. Localization of MGSA/GRO protein in cutaneous lesions. J Cutan Pathol 1993; 20: 259-66
14	Fibronectin	Bernard BA, Asselineau D, Schaftar D, Darmon MY.Abnormal sequence of expression of differentiation markers in psoriatic epidermis: inversion of two steps in the differentiation program? J Invest Deramtol 1988; 90: 801-5.
15	B-defensin-2, and 3	Lew W, Bowcock AM, Krueger JG., Psoriasis vulgaris : cutaneous lymphoid tissue supports T-cell activation and type1 inflammatory gene expression . Trends Immunol 2004; 25: 295-305.
16	Cathelicidin	Chang EY, Hammerberg C, Fisher G et al. T-cell activation is potentiated by cytokines released by lesional psoriatic but not normal epidermis, Arch Dermatol 1992; 128: 1479-85.
17	TLR1, TLR2 ,TLR5	Baker BS, OVigne JM, Powles AV et al. Normal keratinocytes express toll-like receptors (TLRs) 1, 2 and 5: modulation of TLR expression in chronic plaque psoriasis. Br J Dermatol 2003; 148: 670-9.
18	HSP 27, HSP 60, HSP 70 (Heat shock protein)	Curry JL, Quin JZ, Bonish B et al. Innate immune related receptors in normal and psoriatic skin. Arch Pathol Lab Med 2003; 127: 178-86.
19	Polyamines(increased)	Polyamines and Psoriasis Editorial Arch Dermatol 1979; 115; Aug 943-4, Proctor , David IW ,Elaine KO, Eugene MF, Lowered cutaneous and urinary levels of Polyamines with clinical improvement in treated psoriasis. Arch Dermatol 1979; 115 Aug: 945-9,

		Editorial. Voorhees JJ, Polyamines in Psoriasis. J Invest Dermatol. 1983 ;81: 385-387;
20	Extracelllular calcium (increased)	Karvonen SL, Korkiamaki T, Yla-Outinen H, Nissinen M, et al Psoriasis and altered calcium metabolism: downregualted capcacitative calcium influx and defective calcium-mediated cell signaling in cultured psoriatic keratinocytes. J Invest Dermatol. 2000;apr: 114(4): 693-700, Korkiamaki T, Outinen YH ,Leinonen P, Koivunen J, PeltonenJ,. The effect of extracellular calcium concentration on calcium-mediated cell signaling in NF-1 tumor suppressor – 29eficient keratinocytes. Arch Dermatol Res. 2005 Apr; 296(10): 465-72, Calcium salts for the treatment of psoriasis, dermatitis and dandruff patent WO /2005/097084 .,Pallon J, Malmqvist KG,Werner LY, Forslind B, Pixe analysis of pathological skin with special reference to psoriasis and atopic dry skin. Cell Mol Biol (Noisy-le-grand).1996 Feb; 42 (1): 111-8 . ,Fairley JA Calcium metabolism and the pathogenesis of dermatologic disease . Semin Dermatol . 1991 Sep; 10(3): 225-31. Menon GK Elias PM . Ultrastructural localization of calcium in psoriatic and normal human epidermis. Arch Dermatol 1991 Jan; 127(1): 57-63
21	Sodium chloride (increase in sweat, saliva),K and P	Wanjura HJ Psoriasis and sodium chloride Derm Beruf Unwelt. 1986 Mar-Apr; 34(2): 41-2, Singh G, Rajashekar TS, Janeef KN. Salivary electrolytes in psoriasis; A preliminary study. Indian J Dermatol 2006; 51:192-3, Hajini GH, Hussain ST, Shah SN . Sodium, potassium and phosphorus content of normal and psoriatis skin. Br J Dermatol 1976 Dec; 95(6): 674-5., Hodgson C. The sodium and potassium content of the epidermis in eczema, psoriasis and lichen simplex. Br J Dermatol 1960 Nov; 72: 409-15., Levy R, Reinberg A, Sidi E, Hincky M., Reduction in plasma potassium in the course of clinical improvement of psoriasis. Sem Hop. 1955 Jun 6; 31(34)., Wanjura HJ Psoriasis, sodium potassium , chloride –analysis in sweat, saliva and urine-selective ultraviolet phototherapy Z Hautkr. 1987Jul:1:62(13): 1029-34.
22	Protein kinase C	Zhao Y, Fishelevich T, Petrali Jp, Zheng L., et al Activation of keratinocyte protein kinase C Zeta in psoriasis plaques.J Invest Dermatol 2008;Sep; 128(9) 2190-7, Rasmussen HH, Celis JE., Evidence for an altered protein kinase C(PKC) signaling pathway in psoriasis. J Invest Dermatol 1993 Oct; 101(4): 560-6.
23	Nitric Oxide	Morhenn Vb. Langerhans cells may trigger the psoriatic disease process via production of nitric oxide. Immunol Today 1997 Sep; 18(9): 433-6
24	ATPase, HLA-DR, B7 molecules and cytokines	Sxhempp CM, Dittnar HC, Hummier D, et al

		Magnesium ions inhibit the antigen-presenting function of human epidermal Langerhans cell in vivo and in vitro. Involvement of ATPase, HLA-DR, B7 molecuels, and cytokines. J Invest Dermatol 2000 Oct; 115 (4): 680-6.
25	Phosphorus and phosphorylase kinase activity	Zemtsov A,Dixon L, Cameron G. Human in vivo phosphorus 31 magnetic resonance spectroscopy of psoriasis. A noninvasive tool to monitor response to treatment and to study pathohysiology of the disease. J Am Acad· Dermatol. 1994 Jun; 30(6): 959-65., Hena MC, Sona MK, Hena MK Elevated phosphorylase kinase activity in psoriatic epidermis: correlation with increased phosphorylation and psoriatic activity. Br J Deramtol. 1994 Mar; 130(3): 298-306, Burkhart Cg, Burnham JC. Elevated phosphorus in psoriatic skin determined by energy dispersive x-ray micro-analysis. J Cutan Pathol/ 1983 Jun; 10(3): 171-7. Mier PD, Mccabe MG ., The distribution of phosphorus in the lesions of eczema, psoriasis and seborrhoeic dermatitis. Br J Dermatol 1963 Aug-Sep; 75: 354-7.
26	Ca^{2+} binding proteins	Plavina T, Hincpie M. Wakshull E. Subramanyam M, Hancock WS Increased plasma concentrations of cytoskeletal and Ca2+ binding proteins and their peptides in psoriasis patients. Clin Chem. 2008 Nov: 54(11):1805-14. Benoit S, Toksov A, Ahimann M,Schmidt M, et at Elevated serum levels of calcium-binding S100 proteins A8 and A9 reflect disease activity and abnormal differentiation of keratinocytes in psoriasis. Br J Dermatol 2006 (Jul) 155(1) 62-6, Szabo Ak, Bos JD, Das PK. Hyperproliferation of normally quiescent keratinocytes in non –lesional psoriatic skin due to high calcium concentration (an organotypid culture model) Acta Microbiol Immunol Hung. 2002; 49(1); 129-40.
27	Vasoactive intestinal peptide (VIP)neurotransmitter	Ionov DL. Self sustaining pathological processes in skin psoriasis. Med Hypotheses 2009 Feb 72(2) 171-3., Saraceno T, Kleyn CE, Terenghi G, Griffithi CE., The role of neuropeptides in psoriasis. Br J Dermatol 2006 Nov 155(5) 876-82,., ,Pincelli C, Fantini F, Magnoni C, Giannetti A., Psoriasis and nervous system Acta Derm Venereol Suppl (Stockh) 1994;186: 60-1.
28	Free Arachidonic acid and 12HETE,PGE_2 and PGF_2	Voorhees JJ Leukotrienes and other lipoxygenase products in the pathogenesis and therapy of psoriasis and other dermatoses Arch Dermatol 1983 Jul 119: 541-7, WA Khan, GC Blobe, YA Hannun Arachidonic acid and free fatty acids as second messengers and the role of Proein Kinase C . Cellular signaling 1995 : 7 (3): 171-184.
29	**Decreased cAMP**	Voorhees JJ, Duell EA,Bass LJ, Harell ER. Decreased

		cyclic AMP in the epidermis of lesions of psoriasis. Arch Dermatol 1972 May 105:695-701., Voorhees JJ, Duell EA , Mirch AA., Psoriasis as a possible defect of the adenyl cyclase –cyclic AMP cascade. A Defective chalone Mechanism? Arch Dermatol 1971 Oct; 104:352-358., Voorhess JJ Commentary: Cyclic Adenosine Monophosphate regulation of normal and psoriatic epidermis . Arch dermatol 1982 Oct; 118: 869-872,
30	Ki-67^{+} nuclei	Mare S De., Jong E.De ,.Van Erp P.E.J and P.C.M. van de Kerkhof .Markers for proliferation and keratinization in the margin of the active psoriatic lesion. Br J Dermatol 1990 122;469-475
31	Eicosanoids,Prostaglandins,thrombozane, leukotrienes HETE(Hydroxyeicosatetranoic acid)	Ikai K., Psoriasis and arachidonic acid cascade . J Dermatol Sci 1999 Nov ; 21(3): 135-146.
32	Serum apo B,C-II and Ciii	Seishma M,. Mori S. Noma A., Serum lipid and apolipoprotein levels in patients with psoriasis. Br J Dermatol 1994,; 130: 738-742
33	PPAR α & PPARγ is decreased while PPARβ/δ is increased.(Peroxisome proliferator-activated receptor)	Pit Sertznig, Markus Seifert, Wolfgang Tilgen and Jörg Reichrath ., Peroxisome Proliferator-Activated Receptors (PPARs) and the Human Skin: Importance of PPARs in Skin Physiology and Dermatologic Diseases, Am J Clin Dermatol. 2008;9(1):15-31.
34	Glycogen accumulation in epidermis	Stankler L ,.Walker F., Periodic acid –Schiff (PAS) staining for glycogen in clinically normal psoriatic and non-psoriatic skin . British J Dermatol ,1976 ; 95; 599-601.
35	Staphylococcus aureus	Aly B., Maibach HI , .Mandel A . Bacterial flora in psoriasis. British J Dermatol 1976; 95: 603-606.
36	Na,Mg,P,S,Cl,K,Ca,,Na/K ratio increased	Grundin TG., Roomans GM, Forslind B, Lindberg M, WernerY. X-ray Microanalysis of Psoriatic skin. J Invest Dermatol 1985; 85: 378-80. HajiniGH, Hussain ST, .Shah SNA . Sodium, potassium and phosphorus content of normal and psoriatic skin.. J Invest Dermatol 1985;85:674-5.
37	Calmodulin content of epidermis increased in psoriasis	MaeNeil S, Tucker WF, Dawson RA, et al: The calmodulin content of the epidermis in psoriasis Clin Sci 69:681-688, 1985

Thus it can be observed that psoriasis is a very complex disease and to have a single drug having the capabilities to act on all the above molecules is next to impossible. So to treat psoriasis, both exogenous as well as endogenous triggers should be taken care of.

1.2e Treatment of Psoriasis:

(1)Topical treatment:

Topical coricosteroids, calcipotriol, tazarotene, tars, and anthralin.

These are either used alone or in combination .They are available in creams, ointments, gels ,lotions , solutions, oils, and shampoos.

Topical corticosteroids usually don't show any side effects with short term use. However, longer use particularly with stronger preparations, may cause thinning of the skin, stretch marks, dilated blood vessels, rosacea, perioral dermatitis, bruising, and hair growth. Side effect may include, progression to a more active form of psoriasis for example, pustular or erythrodermic psoriasis, increased susceptibility to infections, and a flare up of the psoriasis when the medication is stopped.

Tazoretene should be avoided on genitals, skin folds, and during pregnancy and should be applied only on the affected part of the skin. Side effects include redness and burning. Anthralin cause staining of skin, clothes, and hair which limits its use.

(2) Oral Treatment:

Methotrexate, Acitretin, Cyclosporine, are used for oral treatment of psoriasis. Oral corticosteroids are also used.

We are entering a very exciting stage in medical treatment in that drugs have been designed to specifically hit immunological targets that are involved in specific conditions. Previous immune therapy has involved drugs that have a general suppressing effect on the immune system which consequently prevents high doses being used because of the fear of side effects. Theoretically, the more specific the target to be blocked, the less interference with other biological functions - making the drug safer. These new drugs are known as biological drugs. They are created in living cells. The technique has been used for a long time for drugs such as insulin or interferon.

Alefacept(Amevive), Inflixiamab(Remicaide), Efalizumab(Raptiva), Etanercept(Enbrel) are some biologics.

(3) Other therapies include UVB (Ultraviolet Broad Band), 290-320nm, and PUVA (Psoralen (a medication that sensitizes your skin to ultraviolet A light waves) + UVA (ultraviolet A, with a wavelength range of 320-400 nm). Climatotherapy at Dead Sea is also adopted by many patients. Tar is also used and tar with light therapy known as Goekermann therapy is also used traditionally. Anti yeast preparations e.g. Nizoral cream is useful on face.

Mud therapy is also used by many people in USSR (Vetchinkin VD 1977).

(4)Keratolytics

Agents used to soften and exfoliate the thickened psoriatic scales are often incorporated into therapy. While they do not address the underlying problems that cause psoriasis, thinning and smoothing out thickened, often cracking skin can palliate discomfort as well as improve the overall skin aesthetics.e.g. urea, lactic acid, glycolic acid etc. Vitamin D3 derivative Dovonex and Vitamin A topical (Tazorac) give good results.

1.3 Eczema (Atopic Dermatitis)(AD)

Eczema is an inflammatory skin reaction characterized histologically by spongiosis with varying degrees of acanthosis, and a superficial perivascular lymphohistocytic infiltrate. The clinical features may include itching, redness, scaling and clustered papulovesicles.

Eczema or Atopic Dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease affecting, more than 10 to 20% of children and 1-3% of adults. Pruritus and a chronic relapsing remitting course are hallmarks of the disorder, and sleep disturbance can occur in both the patient and family.

The pathomechanism of AD is still not completely understood, but the disorder appears to result from the complex interaction between various susceptibility **genes, defects in skin barrier function, immunological responses, host and environmental factors and infectious agents.** It can be classically separated into two distinct types: **intrinsic (nonallergic) AD,** which affects 20 to 30% of adult patients and is characterized by the absence of any observable sensitization to environment allergens and low serum IgE levels; and **extrinsic (allergic) AD,** which affects 70 to 80% of adult patients and is characterized by sensitization to environment allergens and increased serum IgE levels.(Novak N 2003).

1.3a Types of eczema

Eczema can broadly be classified in two main categories:

1. Exogenous or Contact Eczema, which is caused by skin contact with an external substance that may be natural or synthetic. For example extreme hot or cold conditions, or harsh chemicals.
2. Endogenous or Constitutional Eczema, which is caused by an inherent tendency of the body and may affect a person even if they lived in a highly sanitized environment. People who suffer from this kind of Eczema will react to triggers that cause Exogenous or Contact Eczema also. They seem to have a highly sensitive system that reacts to slightest changes. This kind of Eczema is more likely to be inherited.

Endogenous or Constitutional Eczema can be of the following kinds:

· Atopic eczema
· Seborrhoiec Eczema
. Discoid Eczema
· Dyshidrotic Eczema
. Asteatototic (dry) Eczema

1.3b Evolution of eczematous lesion

The inflammatory cascade resulting in AD skin lesions begins when circulating T_h2 cells express cutaneous lymphocyte-associated antigen (CLA), the skin-homing receptor, and recirculate through the skin, where they engage allergen –triggered IgE+ Langerhans cells and mast cells.(Leung DYM 2004). Subsequently, skin injury by allergens, scratching, or microbial toxins activates keratinocytes to release cytokines (e.g. tumor necrosis factor {TNF}-I± and IL-1) and chemokines that induce expression of adhesion molecules on vascular endothelium and facilitate extravagation of inflammatory cells into the tissues.IL-16, the chemoattractant cytokine for activated CD4+ T_h cells, is derived from Langerhans cells and is increased in acute skin lesions in AD. Additionally, the CC chemokine ligand 27 is highly upregulated and preferentially attracts CLA+ T cells. (Leung DYM 2004). Keratinocyte derived thymic stromal lymphopoietin, and IL-7- like cytokine, further contributes to the allergic cascade by inducing migration of Langerhans cells into lymph nodes, stimulating dendritic cells to prime naïve T cells to produce IL-5, Il-13, and TNFI±, and initiating the production of macrophage-derived chemokine or TARC (thymus and activation-regulated chemokine), which attract T_h2 cells (Soumelis V 2002, Kakinuma T, 2001, Novak N,2003). A schematic representation of inflammatory cascade is shown in figure no. 02.

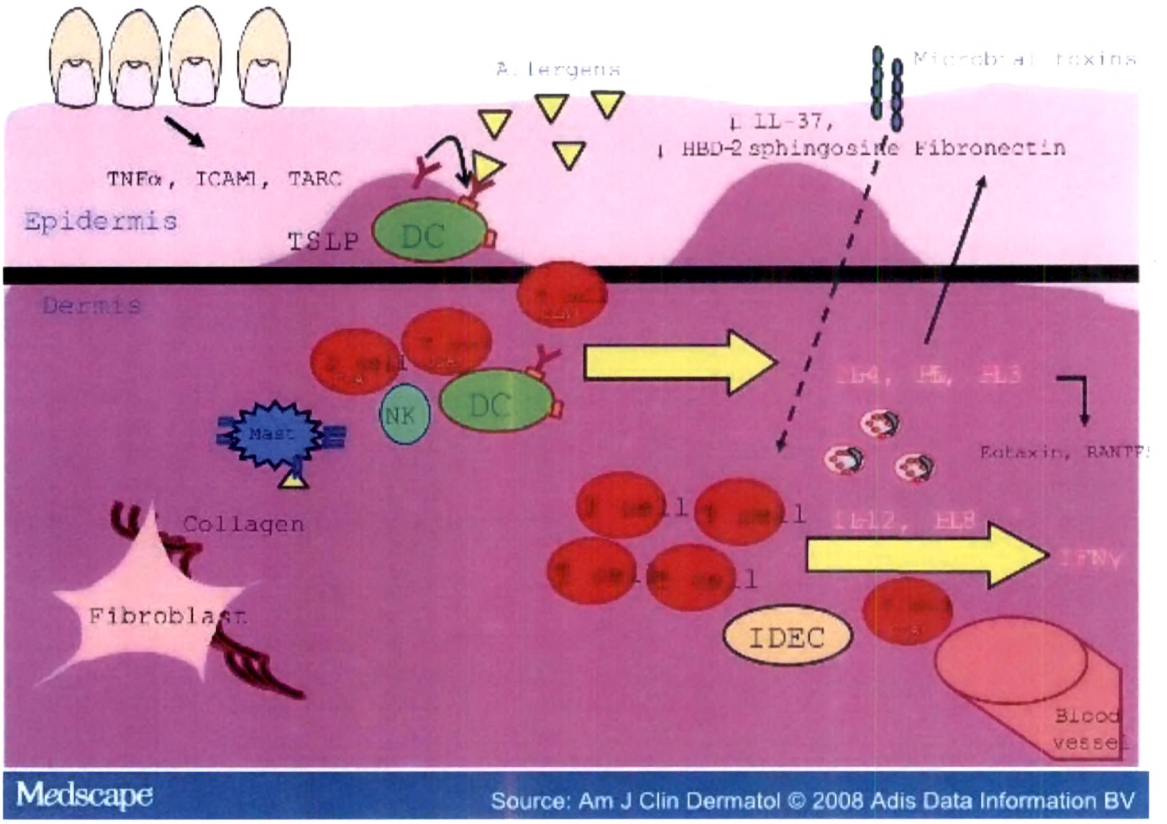


Figure no 02. The inflammatory cascade in atopic dermatitis and tissue injury by allergens, scratching, or microbial toxins.(JM Spergel Immunology and treatment of Atopic Dermatitis Am J Clin Dermatol 2008; 9 (4) 233-39.)

CLA = cutaneous lymphoid antigen; DC = dendritic cell; HBD-2 = human β-defensin 2; ICAM-1 = intercellular adhesion molecule-1; IDEC = inflammatory dendritic epidermal cell; IFNγ = interferon-γ; IL = interleukin; LL-37 = cathelicidin-type antimicrobial peptide; NK = natural killer; RANTES = regulation on activation, normal T cell expressed and secreted; TARC = thymus and activation-regulated chemokine; TNFα = tumor necrosis factor-α; TSLP = thymic stromal lymphopoietin

1.3c Factors causing eczema

Genes

Several genetic analyses have identified different chromosome regions with a linkage to AD, including linkages for asthma (MacLean J 2001), psoriasis (Cookson W 2001, Cookson W,2002) and several single –gene Mendelian disorders, such as hyperimmunoglobulinemia E syndrome, Wiskott-Aldrich syndrome and Netherton syndrome (Walley A 2001).

There have been other chromosomal loci and candidate genes associated with AD (Möhrenschlager 2006, Tamura K 2003, Novak N 2002, Weidinger S 2004) that encode various immunomodulators. These genes encode cytokines that control IgE synthesis and include IL-4, -5 and -13. Th2 cells elaborate these cytokines, which are thought to play an important role in the initiation of the AD inflammatory process.

The genetic basis for an impaired epidermal skin barrier in AD has been linked with loss of function mutations with the filaggrin (FLG) gene, which encodes a structural protein essential for skin barrier formation (Joseph Lam 2008).

Skin barrier Dysfunction

The epidermis of individuals with AD shows a decreased content of ceramides that probably affects both the barrier function and inflammatory responses of skin (Sator PG 2003). These lipids evolve from lamellar bodies, which are extruded from keratinocytes in the upper portion of the epithelium. The abnormal barrier function of atopic skin leads to increase transepidermal water loss (TEWL) and increased penetration of irritant, allergens and microbes. Alteration of the skin barrier in AD patients is evidenced by the reduction in the water-content of the SC (stratum corneum) and by an increase in TEWL (Seidenari 1995, Werner Y 1985). Barrier dysfunction with increased water loss is responsible for the dry skin (xerosis) that ultimately results in dry, scaly, rough, dull, slightly wrinkled skin, hallmarks of AD and is responsible for the pruritus that increases the penetration of allergens (Goerdt S 1999, Krasteva M 1999, Thestrup-PK 1997). Additionally, atopic skin exhibits

disturbed lipid composition and altered sphingomyelin metabolism, resulting in decreased ceramide concentrations and disruption of barrier function (Lee SH 2006, Jenson JM 2004).

In healthy individuals, the skin barrier undergoes constant renewal; the corneocytes at the outermost skin surface are continually shed and are immediately replaced by keratinocytes undergoing terminal differentiation. Thus, through desquamation, the stratum corneum is maintained at a constant thickness. In patients with a genetic predisposition towards AD, upregulation of the stratum corneum chymotryptic enzyme results in premature breakdown of the corneodesmosomes and thinning of the stratum corneum (Jonathan MS 2008). Figure no 03 shows both normal and eczematous epidermis and how chemicals disrupt the epidermis and Figure no 04 depicts skin barrier dysfunction.

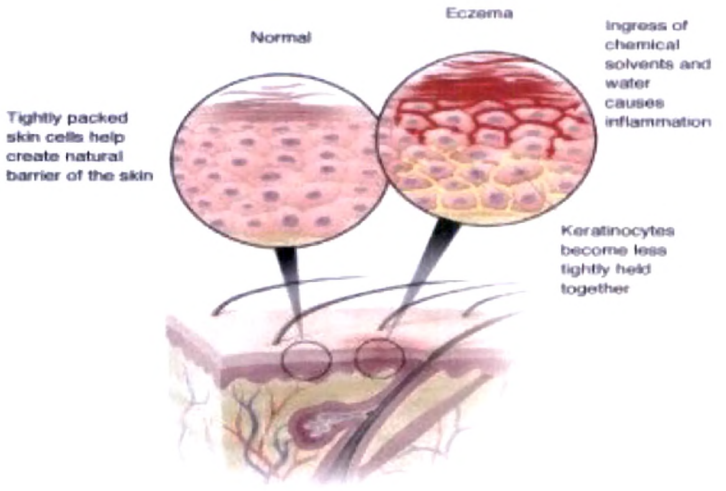


Figure no 03 Schematic diagram of normal and eczematous skin

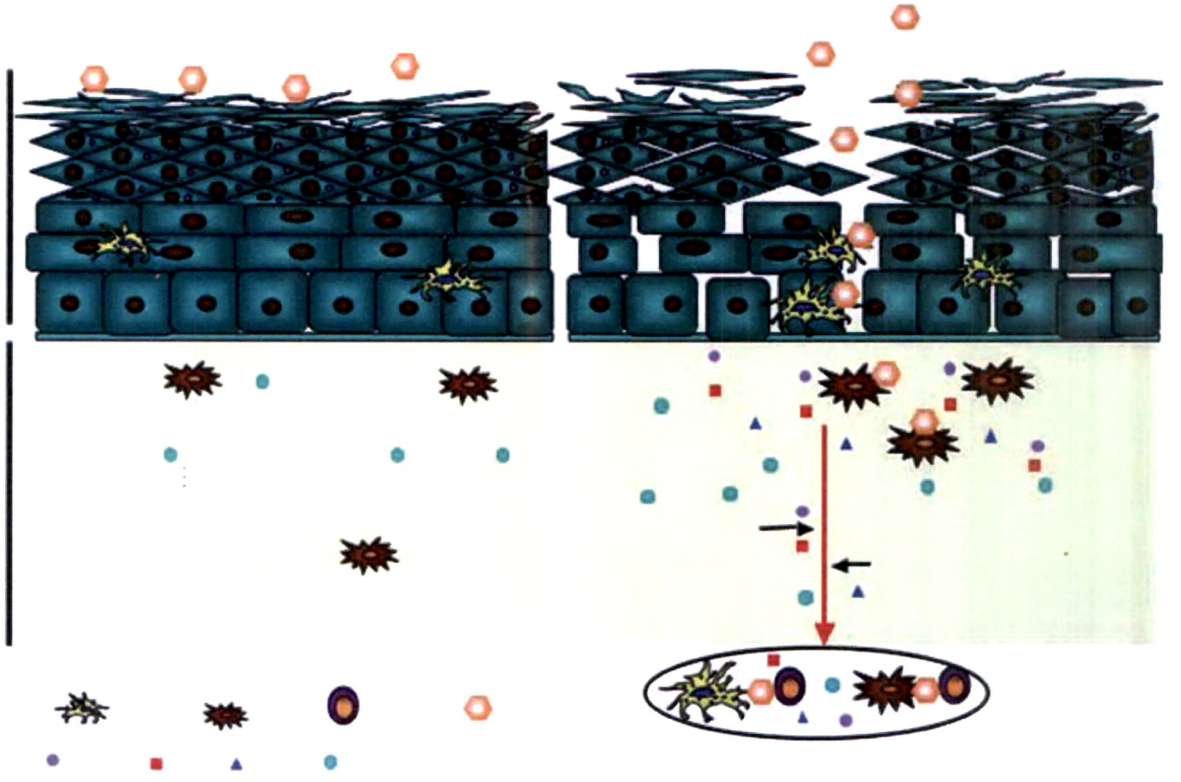


Figure no. 04 Skin barrier dysfunction in AD. An intact skin barrier (left panel) prevents allergens from entering normal skin. Damage to this barrier (right panel) allows allergens to penetrate into the subepidermal layer and interact with APCs, and induces cytokines by keratinocytes that includes TSLP, IL-1, IL-6, and TGF-b. This leads to maturation and migration of APCs to DLN where they present antigens to naive T cells, resulting in Th2-dominated immune response.

Immunological responses

Langerhans cells may possess high affinity receptors for IgE on their surfaces which avidly bind allergens, such as food, aeroallergens and microbial superantigens. Such linkage induces the release of chemotactic signals and recruitment of IDECs and T cells. Cytokines and chemokines are key factors in the elaboration of AD.Th2 cytokines (IL-4 and 13) mediate isotype switching to IgE synthesis and upregulate **expression of adhesion molecules on endothelial cells (**Hamid Q, 1994). The eosinophilic cationic protein and IL-16 are also elevated in the acute AD phase (Akdis

CA 2006). The imbalance of Th 1 and Th2 in AD may depend on polymorphisms in the IL-18 gene on peripheral mononuclear cells, which react after stimulation with superantigens through the upregulation of IL-18 and the downregulation of IL-12 (Toda M, 2003).

A variety of pharmacophysiologic abnormalities have also been described. Leukocytes, and especially monocytes from atopic patients demonstrate elevated phosphodiesterase activity, leading to decreased levels of cAMP andincreased production of prostaglandin and IL-10 , which inhibit Th1 function and enhance IgE production (Toda M, 2003).

Staphylococcus aureus

Atopic dermatitis skin has been found to be deficient in antimicrobial peptides needed for host defense against bacteria, fungi and viruses (Ong PY 2002). Antimicrobial peptides such as the cathelicidins represent the first-line defense against many infections, and are produced by keratinocytes following attachment of appropriate bacterial, viral or fungal antigens to Toll-like receptors present on the keratinocyte surface.IL-4 is known to suppress production of cathelicidins, and it has been theorized that this is the etiology of decreased levels of cathelicidin in atopic patients given that they possess elevated IL-4 levels.
Most patients with AD are colonized with Staphylococcus aureus and experience exacerbation of their skin disease after infection with this organism (Leung DY 2003). Superantigens of *S.aureu* , such as staphylococcal enterotoxin, can cause defects in regulatory T-cell function and promote skin inflammation. Most patients with AD make specific IgE antibodies directed against staphylococcal superantigens, which correlate with skin disease severity (Hofer MF 1995).

High expressions of adhesion molecules, specifically, intercellular adhesion molecules -1 and -3, E-selectin and L-selectin in skin lesions of AD patients suggest

that they may be additional factors in the pathogenesis of AD and may be of clinical relevance for the management of AD (Chien YH 2007).

Environmental factors:

Factors that contrinute to AD include aspects of the patient's home environment (presence or absence of pets, number of siblings, proximity to farm animals) that affect immunologic development (Cookson W 2004). Additionally, use of soap and detergents can exacerbate the disease process by promoting xerosis, which allows penetration of irritants and allergens through the skin barrier (Abramovits W 2005).

The summary of the different pathological and biochemical processes in the etiology of eczema is given in table no.02.

Table no .02 Various pathological and biochemical processes in etiology of eczema

Sr No.	Molecules	Reference
01	Filaggrin	Irvine AD, McLean WH. Breaking the (un)sound barrier: filaggrin is a major gene for atopic dermatitis. J Invest Dermatol 2006; 126 (6): 1200-2.
02	Decreased ceramides	Sator PG, Schmidt JB, Honigsmann H: Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. J. Am.Acad. Dermatol.2003; 48:352-358 .
03	Stratum corneum chymotryptic enzyme	Jonathan M. Spergel Innunology and treatment of atopic dermatitis. Am J Clin Dermatol. 2008;9 (4):233-243.
04	IL-4,IL-5,IL-13 mRNA expressing cells increased	Leung DYM, Boguniewicz M, Howell MD, et al. New insights into atopic dermatitis. J Clin Invest 2004; 113 (5): 651-7
05	Reduction in natural killer cells	Ilhan F, Kandi B, Akbulut H, et al. Atopic dermatitis and Vî±24+ natural killer T cells. Skinmed 2007; 6 (5): 218-20
06	Decreased cathelicidins and defensins	Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med 2002; 347 (15): 1151-60
07	Microbial superantigen	Cardona ID, Cho SH, Leung DY. Role of bacterial superantigens in atopic dermatitis: implications for future therapeutic strategies. Am J Clin Dermatol 2006; 7 (5): 273-9
08	IL-10,TGFI^2 increased	Verhagen J, Akdis M, Traidl-Hoffmann C, et al. Absence of T-regulatory cell expression and function in atopic dermatitis skin. J Allergy Clin Immunol 2006; 117 (1): 176-83

09	ICAM-1 and 3,E-selectin,L-selectin	Chien YH, Hwu WL, Chiang BL: The genetics of atopic dermatitis. Clin. Rev. Allergy Immunol. 2007;33(3):178-190 .
10	Elevated phosphodiesterase activity, and decreased cAMP	Toda M, Leung DY, Molet S *et al.*: Polarized *in vivo* expression of IL-11 and IL-17 between acute and chronic skin lesions. J. Allergy Clin. Immunol. 2003; 111,875-881.

Thus it can be observed that like psoriasis, eczema too is caused by immunological factors and so some of the medicines are common to both.

1.3d Treatment of eczema

Topical treatment

Corticosteroids: Betamethasone valerate, Fluocinonlone acetonide, Fluticasone propionate, Clobetasone 17 Butyrate, and many others are used. The main side effects are : Corticosteroids should not be used on ulcerated or atrophic skin. Sudden discontinuation should be avoided, after prolonged use, to prevent rebound phenomenon. It also causes atrophy, perioral dermatitis, rash like rosecea, increase hair growth, glaucoma and cataracts when used around eyes and systemic side effects include growth suppression and adrenal suppression.

Other topical preparations include tar preparations, antibiotics like fucidic acid, (Fucidin) and mupirocin (Bactroban), Anti itch creams like Promoxine or Doxepine may also be used .

Topical immunomodulators: Pimecrolimus, (Elidel), Tacrolimus (Protopic)

Elidel is a non-steroid medication with proven efficacy to provide relief of itch, rash & redness, and is the only eczema treatment proven by studies to reduce flares over time & increase the time to the next flare. Studies have demonstrated safety in infants, children and adults. This drug is well absorbed into the skin but not into the blood stream. A burning sensation may occur initially in some users. However, the cream formulation makes it attractive for use on the face, with children, or ointment may also be used.

Tacrolimus: This is a new generation of topical immunomodulating agents. It is a calcineurin inhibitor which in turn inhibits the activity of white blood cells called T lymphocytes which produce a cascade of chemicals that increase inflammation The drug has been studied in both children and adults and has been shown to be effective. It is a non-steroid. The most common side effect is of transient burning. It appears to be safe for long term use.

Marked to excellent improvement was seen in moderate to severe eczema in the majority of patients using Tacrolimus 0.1% ointment over a one year period (www.eczemavoice.com).

Oral Treatment

Possible oral treatments for eczema are antibiotics, antihistamines, corticosteroids and cyclosporine A (Neoral).

Antibiotics like Bactroban, fucidin, cloxacillin, erythromycin may be used to reduce bacterial load in certain difficult cases.

Corticosteroids:

Short courses of oral prednisone are occasionally used in severe intractable cases. Rebound of eczema is a concern as well as long-term side effects in those who demand or are unable to quickly wean off the medication.

Cyclosporine A (Neoral):

This is restricted for severe cases. It allows significant improvement. It is often started at a dose of 3mg. per kg. per day and is used to a maximum of 5mg. per kg. per day. Concerns about hypertension and renal problems are important concerns for this drug.

Light therapy

Phototherapy, PUVA, narrow band UVB (311nm) has been useful in certain stubborn chronic dermatitis. Mud therapy is also used for treating eczema (Vetchinkin VD 1977).

1.4 Acne

Acne vulgaris is a common skin disease that affects 60-70% of human population at some time during their lives. Twenty percent will have severe acne, which results in permanent physical and mental scarring. Acne vulgaris is characterized by noninflammatory, open or closed comedones and by inflammatory papules, pustules, and nodules. Acne vulgaris affects the areas of skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back.

The pathogenesis of acne vulgaris is multifactorial. The key factor is genetics (Goulden V 1999). If both parents have acne, 3 of 4 children will have acne. If 1 parent has acne, then 1 of 4 of the children will have acne. However, similar to other genetic conditions, not every family will have the same pattern, with acne vulgaris sometimes skipping generations. What is inherited is the propensity for follicular epidermal hyperproliferation with subsequent plugging of the follicle. Additional aggravating factors include excess sebum, the presence and activity of *Propionibacterium acnes,* and inflammation.

1.4a Types of acne

Figure no.05 shows normal and inflamed sebaceous gland resulting into inflamed tissue. Fig.no.6a, b,c shows different types of acne : noninflammatory (a) and inflammatory (b),(c). Fig.no 6a shows comedones, which can be black head or white head. The inflamed portion is covered inside the epidermis in white head while in black head, it is exposed and so dust collects on it. Pustule shown in fig.6b contains

pus while papule does not contain pus. Nodules and cysts shown in fig.6c are very large and resistant to healing.

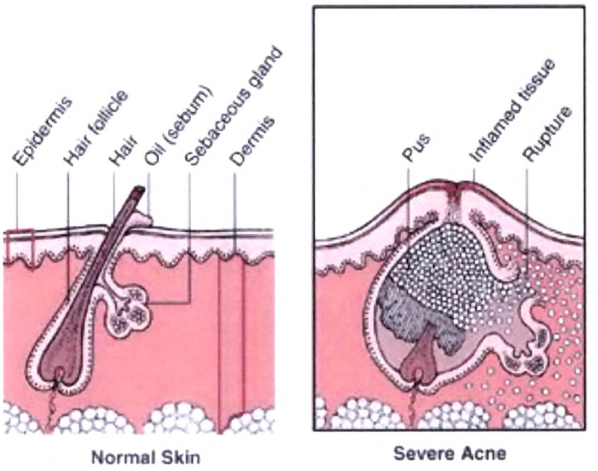


Fig.no.05 Schematic diagram of normal skin and acne

Types of acne

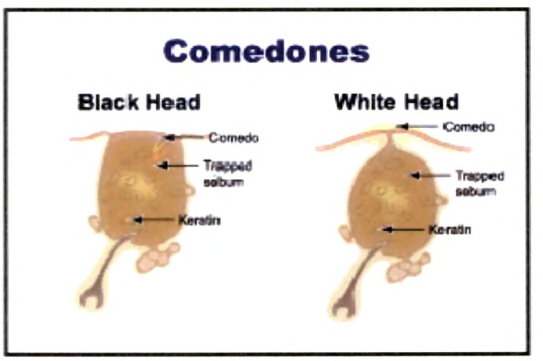


Fig.no: 06a Comedones

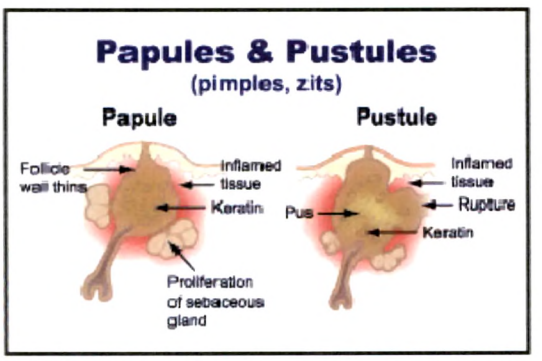


Fig. no: 06b Papules & Pustules

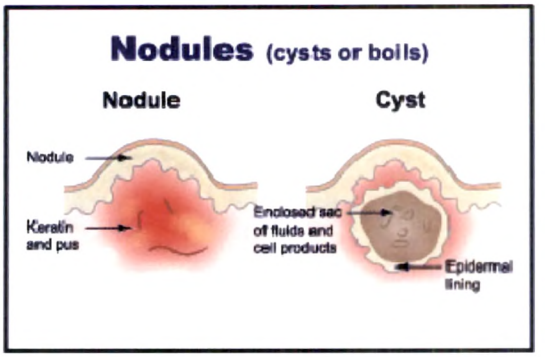


Fig.no: 06c Nodule and cyst

1.4b Pathophysiology and factors of acne

Hormone

Retention hyperkeratosis is the first recognized event in the development of acne vulgaris (Norris JF 1988). The exact underlying cause of this hyperproliferation is not known. Currently, 3 leading hypotheses have been proposed to explain why the follicular epithelium produces cells at a rapid rate that are retained in individuals with acne.

First, androgen hormones have been implicated as the initial trigger (Thiboutot D 1999) . Comedones, the clinical lesion that results from follicular plugging, begin to appear around adrenarche in persons with acne in the T-zone area. Furthermore, the degree of comedonal acne in prepubertal girls correlates with circulating levels of the adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) (Lucky AW 1997). Additionally, androgen hormone receptors are present in sebaceous glands; individuals with malfunctioning androgen receptors do not develop acne (Holland DB 1998).

Excess sebum is another key factor in the development of acne vulgaris. Sebum production and excretion are regulated by a number of different hormones and mediators. In particular, androgen hormones promote sebum production and release (Pochi PE 1988). Still, most men and women with acne have normal circulating levels of androgen hormones. An end-organ hyperresponsiveness to androgen hormones has been hypothesized. Androgen hormones are not the only

regulators of the human sebaceous gland. Numerous other agents, including growth hormone and insulin like growth factor, also regulate the sebaceous gland and may contribute to the development of acne.

Propionibacterium acnes

P. acnes is an anaerobic organism present in acne lesions. The presence of *P acnes* promotes inflammation through a variety of mechanisms. *P acnes* stimulates inflammation by producing proinflammatory mediators that diffuse through the follicle wall. Studies have shown that *P acnes* activates the toll-like receptor 2 on monocytes and neutrophils (Kim J 2002). Activation of the toll-like receptor 2 then leads to the production of multiple proinflammatory cytokines, including interleukins 12 and 8 and tumor necrosis factor. Hypersensitivity to *P acnes* may also explain why some individuals develop inflammatory acne vulgaris while others do not (Webster GF 1998).

Inflammation may be a primary phenomenon or a secondary phenomenon. Most of the evidence to date suggests a secondary inflammatory response to *P acnes*. However, interleukin 1-alpha expression has been identified in microcomedones, and it may play a role in the development of acne (Ingham E 1992).

Immunological factors

Jeremy et al (Jeremy AH 2003) investigated the initiating events for acne lesions, and found that immune changes and inflammatory responses occur before hyperproliferation of keratinocytes, with a pattern similar to a type IV delayed hypersensitivity response. The immune response is led by CD4 lymphocytes and macrophages (Jeremy AH, 2003). These researchers hypothesize that the subsequent production of cytokines activates local endothelial cells, up-regulating inflammatory vascular markers (E-selectin, vascular cell adhesion molecule-1 [VCAM-1], intercellular adhesion molecule-1 [ICAM-1], and human leukocyte antigen- DR [HLA-DR]) in the vasculature around the pilosebaceous follicle (Jeremy AH 2003). They further have postulated that the entire process is initiated by interleukin (IL)-1a up-

regulation in response to a relative linoleic acid deficiency caused by excess sebum and perturbation of barrier function within the follicle. This provided additional evidence that inflammatory cytokines, working via autocrine and paracrine mechanisms through their respective receptors, amplify the signaling pathways that activate the activator protein (AP)-1 transcription factor (Kang S 2005).

Activation of AP-1 induces MMP genes, whose products degrade and alter the dermal matrix. Retinoids are known to inhibit AP-1(Czernielewski J 2001). Very recent studies indicate that retinoids can induce monocytes to develop into CD209+ macrophages that phagocytose *P .acnes* bacteria (Liu PT 2008).

Sebaceous glands

The sebaceous gland acts as an independent endocrine organ in response to changes in androgens and hormones, and is the control center for a complex regulatory neuropeptide program that acts like the hypothalamus-pituitary- adrenal axis (Zouboulis CC 2008). This aspect of sebaceous gland function is primarily influenced by corticotrophin releasing hormone, its binding protein, and corticotrophin receptors (Zouboulis CC 2004, Ziegler CG 2007, Slominski AT 1999).

Corticotrophin-releasing hormone levels change in response to stress, and its role in regulating sebaceous gland function is likely a link in the brain-skin connection that is thought to explain the relationship between stress and skin disorders with an inflammatory component such as acne. The improved understanding of acne development on a molecular level suggests that acne is a disease that involves the innate and adaptive immune system and inflammatory events. Treatment that targets both immune system activation and inflammatory pathways is, therefore, desirable.

More has been learned about the role of seborrhea in acne as well. Sebaceous lipids are at least partly regulated by peroxisome proliferator-activated receptors(PPAR) and sterol response element binding proteins (Trivedi NR 2006, Smith TM 2006).

Peroxisome proliferator-activated receptor nuclear receptors act in concert with retinoid X receptors to regulate epidermal growth and differentiation and lipid metabolism (Trivedi NR, 2006).

Sebocytes are capable of metabolizing and synthesizing the primary vitamin D metabolite 1,25-dihydroxyvitamin D3 (Zouboulis CC 2006). Several lines of evidence suggest that the vitamin D endocrine system is involved in regulating sebocyte function and physiology, including production of sebum. Further, vitamin D analogues may potentially be useful in normalizing sebaceous gland physiology in patients with acne (Zouboulis CC 2008).

Papakonstantinou et al (Papakonstantinou E 2005) investigated the role of MMPs in acne. These enzymes, which include collagenases, gelatinases, stromelysins, and matrilysins, have a prominent role in both inflammatory matrix remodeling and proliferative skin disorders. Sebum includes several MMPs, which are thought to originate in keratinocytes and sebocytes.

Using a human keratinocyte cell line, Ottaviani et al (Ottaviani M 2006 showed that peroxidation of sebum lipids can activate inflammatory mediators, including IL-6 and lipoxygenases. Oxidized squalene can also stimulate hyperproliferative behavior of keratinocytes, suggesting that this lipid may be partly responsible for comedo formation. Zouboulis et al (Zouboulis CC 2003, Zouboulis CC 2005) have hypothesized that lipoperoxides exert a proinflammatory effect on the pilosebaceous duct. Lipoperoxides produce leukotriene B4, which is a powerful chemoattractant that can recruit both neutrophils and macrophages, and stimulate production of proinflammatory cytokines (Alestas T 2006).
In addition, the sebaceous gland has both direct and indirect antibacterial activities. Sapienic acid, a lipid in sebum, has innate antimicrobial activity and is up-regulated by activation of TLR-2 by skin bacteria (Wille JJ 2003 , Georgel P 2005).

Further, the sebaceous gland has ubiquitous expression of antibacterial peptides and proinflammatory cytokines/chemokines; these substances are induced in sebocytes by the presence of bacteria (Boehm KD, 1995).

Summary of the molecular expression in acne is given in table no. 03.

Table no: 03 Table showing molecule expression in acne

Sr.no.	Molecule	Reference
01	CD4, VCAM,ICAM	Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003;121:20-7.
02	IL-1,upregulation &linoleic acid deficiency	Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003;121:20-7.
04	AP-1 and MMP genes	Czernielewski J, Michel S, Bouclier M, Baker M, Hensby JC. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. J Eur Acad Dermatol Venereol 2001;15 (Suppl):5-12.
05	PPAR (increased)	Trivedi NR, Cong Z, Nelson AM, Albert AJ, Rosamilia LL, Sivarajah S, et al. Peroxisome proliferator-activated receptors increase human sebum production. J Invest Dermatol 2006; 126:2002-9),
06	Matrix metalloproteinase	Papakonstantinou E, Aletras AJ, Glass E, Tsogas P, Dionyssopoulos A, Adjaye J, et al. Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by isotretinoin. J Invest Dermatol 2005;125:673-84.
07	Per oxidation of sebum lipids	Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, Zouboulis CC, Picardo M. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris. J Invest Dermatol 2006;126:2430-7.)

1.4c Treatment

(1) Topical Treatment:

The most commonly used topical acne treatments include benzoyl peroxide, retinoids, topical acne antibiotics, azelaic acid, and combination topical products.

1) Benzoyl Peroxide

Benzoyl peroxide can improve acne by killing the acne bacteria and by unblocking oil gland pores. There are many different benzoyl peroxide products available. The lower concentrations can be obtained over the counter (OTC), while higher strengths require a prescription.

2) Retinoids

These products are the most effective type of medications for unblocking the pores of oil glands. They are generally considered to be the first choice of treatment for whiteheads and blackheads (comedones). Although there are a variety of topical retinoids, physician can choose the one that is best suited to ones needs.

- Tretinoin
- Adapalene
- Tazarotene
- Isotretinoin

3) Topical Antibiotics - Antibacterial/Anti-Inflammatory:

- Clindamycin
- Erythromycin
- Sulfacetamide

4) Azelaic Acid - Antibacterial/Anti-Inflammatory:

5) Combination Topical Products:

- Topical retinoid with erythromycin (Stievamycin® by Stiefel) - Available only in Canada
- Topical benzoyl peroxide with erythromycin (Benzamycin® by Dermik)
- Topical benzoyl peroxide with clindamycin (CLINDOXYL® by Stiefel in Canada, Duac® by Stiefel in the USA)

General side effects:

- Skin irritation - dry, red, scaly skin, inflammation of the skin can result in a short term increase or decrease in pigmentation
- Photosensitivity
- Initial flare of acne may occur .

Oral Antibiotics

The most commonly used antibiotics are:

- Tetracycline
- Minocycline
- Doxycycline
- Erythromycin
- Trimethoprim
- Azithromycin

Gastrointestinal upset is a common side effect of oral acne antibiotics.

1.5 Alternative approaches (Ayurvedic, Siddha and Naturopathy) to treat psoriasis, eczema and acne

Ayurved, Siddha and naturopathy are all indigenous traditional systems of medicine. The basic principles of treatment (*cough, vayu and pitta*) incorporated with the basic five elements viz. sky, air, fire, earth water is common to all the three systems of medicine.

The physiological function of the body is mediated and maintained by Three Forces. (Joseph J Thas 2008). They are Vali (*Vatham*), Azhal (*Piththam*), and Aiyam (*Kapam*). The terms given in parenthesis are common to Siddha and Ayurveda. As any other

substance of the body, these Three Forces are also made up of Five Elements. Vali is made up of Sky (*Avakash*) and Air (*Vayu)*. Azhal is made up of Fire (*Agni*), Aiyam is made up of Earth(*Prithvi*) and Water(*Jal)*. In each living cell, these Three Forces coexist and function harmoniously. When these Three Forces are in balance one is healthy. Any imbalance will result in diseases. In a disease, these Three Forces are called Three Faults (Mukkuttram).

Seven pillars or fundamental tissues called *Thathus* support every living body. They are *Charam*{ (lymph), *Ras* } ,*Kurudhi*{ (blood), *Rakata* }, *Oon*{ (muscle), *mamsa*}, *Kozhuppu*{ (adipose tissue), *Meda*}, *Elumpu* {(bones), *Asthi* }, *Moolai*{ (marrow), *Majja* } and *Venneer* {(reproductive tissue) *Shaukra* }. (Shanmuka Velu M 1987). There are 21 types of' Agni' which gives energy to the body. (Five *agni* in five elements, seven *agni* in seven *thathus* and last one *jatharagni*). In these tissues, one or the other of the Three Forces predominate. For instance, *Vali* is predominant in bones, *Azhal* in blood, and *Aiyaam* in other tissues. **When the Three Forces are vitiated, the tissues with which they are associated are also diseased** (Narayansami V. 1975). **This is the basis of expression of disease according to ayurved.**

Thus for skin diseases Aiyaam (*Kapam)* gets imbalanced and so the body has to get rid of excess of cough. This theory has been supported by Naturopathy also. According to Charak Samhita the definition of "health" is

Shamdosha Samagni cha Samdhatu Malkriya
Prasanna Aatmendriya Swastha eti Abhidhiyate II

"A person is said to be 'healthy' if he has balanced *Doshas, Agni, and Thatu* and who is in a joyful state of *Aatma* and *Indriya* (senses)."

Charak Samhita describes skin diseases broadly as *Kustha* (normal skin diseases) and *Mahakustha*(Leprosy) and gives three main reasons for its cause.(i) *Gon* (minor) which include age, season, and which vanish once that natural trigger is crossed.(ii)' *Uddipuc'*(catalyst) external factors and excitatory triggers which are incorporated in daily *'Aahar'* and ' *vihar'* i.e. diet and life style. (iii) *'Aupsargic'* (infectious) i.e.

caused by bacteriological, fungal, viral infections. It claims that *dosh* in *Kapha* and *Pitta* causes skin disease and so treatment should be given accordingly. Since Aiyam *(kapha)* is made of earth *(Prithvi)* and water *(jal)* treatment by these forces helps relieve the diseases.

Mention of mud being used for the treatment for disease is made in Ayurved.

Vaidurya Muktamapi Gairikanam
Mruchhang Hemahb ladho Kodakanam I
Madhu dakasyekshu Rasasya Chaiva
Panachha Mam Gachhati Raktapittam II
Ref: Charak Samhita Chikitsasthan Adhayay 4 Shloka 79

"Mud application along with honey and ghee is used for *'Raktapittam'* (condition when *Pitta* has increased in blood)."

Krishnamrunmadhyukam Shankham Rudhiram Tandu lodakam
Pittama Ekatra Sakshodram Rakta Sangrahanam Param II
Ref: Charak Samhita Chikitsasthan Adhyaya 19 shloka 82
"Black soil of Rafda (ant's house) alongwith ghee is applied for bleeding"

In Ayurveda the treatment of an ailment takes into consideration both drug and host factors. The English translation of characteristics of Drug and Host factors are mentioned in table no. 04a and 04b respectively (Virender Sodhi 1999).

Table no . 04a Drug factors influencing Ayurvedic treatment

Pakriti	Constitution of the drug
Guna	Properties
Prabhava	Activity (potency)

Desh	Place
Ritu	Season
Grahan	Storage
Nihit	Transport
Sanskar	Refinement(removal of toxin)
Matra	Dose
Sanyog	Combination
Adhishthan	Ability to reach site of action

Table no: 04b Host factors influencing Ayurvedic treatment

Pakriti	Constitution of host
Vayam	Age
Vikriti	Pathological condition
Sar	System strength
Satamya	Tolerability
Satva	Psychological state
Ahar Shakti	Digestive capacity
Vyaaym shakti	Exercise tolerance
Balam	Strength of host

To summarize,it can be observed that medicinal therapy is highly individualized in Ayurved (Sasdri RD 1949). The choice and dose of medicine are influenced not only by disease, but by the individual's constitution and the environmental conditions likely to affect that individual's *Doshas.* For treating skin diseases, the ayurved practitioners give medicines which clears bowels, (*guggul, triphala, harde etc)*, which reduces *pitta a*nd cough *parkriti (khardi,haridra,tallattak*) and oils which emolliate (*karanj, sarsav, chakramad etc.).*

In Naturopathy, the whole body i.e.physical ,emotional , and spiritual level (holistic approach) is treated by the five elements.(earth, water, fire, air , space).The location of the five elements in the body and the therapy applied to balance them are given in table no. 05.

Table no : 05 Therapies indicated in naturopathy to balance five elements.

Tatva	Location in body	Therapy
Aakash (Space)	Intercellular space	Fasting
Air	Oxygen and void spaces	Massage therapy,Pranayam
Fire	Energy producing process	Solar radiation , color therapy
water	80% of body	Hydrotherapy
earth	Mineral constituents of cells	Mud therapy, diet therapy

All the therapies applied together will balance the five elements and thus keep a man healthy. Thus for treating skin diseases, similar to ayurved, naturopathy also believes in treating the whole patient i.e. balancing all the five elements by all the modalities simultaneously and treating him at emotional and spiritual level. This will help the elements to work harmoniously in body.

MacLean J (2001) and Cookson W (2002) have identified different chromosome regions with a linkage to Atopic Dermatitis, including linkages for asthma and psoriasis. This is an important finding which indicates linkages of AD to asthma and psoriasis because it is very often noticed that if AD is relieved then the person starts suffering from asthma.(i.e. chromosomal linkages to AD, asthma, psoriasis).This is very well documented in ayurved stating that skin disease is influenced by *kapha* and so if this *dosh* is not balanced then suppression in one region (skin) will show expression in the other (lungs), suggesting that in treating the skin disease the whole body should be treated and not a particular organ because a diseased organ is the manifestation of *'tri guna dosha'* in the whole body and largely in that particular organ. Probably this may be the reason why allopathic medicine is not successful in curing the skin disease like psoriasis, eczema and acne because they target only the skin symptoms which is the manifestation of so many causative factors. Unlike ayurved it does not consider the drug and host factors in treating the person.

1.6 Mud

Wet soil is called mud and so before utilizing it for skin disorders, it becomes utmost necessary to study the **soil,** its genesis, its variability, and its physicochemical properties. Most of the pedologists have briefly defined the soil to be the outermost weathered layer of the earth's crust. Joffe JS (1945) who is one of the representative of the Russian school of Pedology has defined the soil to be a natural body which has been differentiated into horizons and which is usually unconsolidated, of variable depth, and which differs from the underlying material in morphological characteristics, physical properties and chemical composition and properties and biological characteristics. Biswas and Mukherjee (1987) have given the undermentioned definition: "The soil is a dynamic natural body (i) which has been formed as the result of pedogenic processes taking place during and after weathering of rocks (ii) which is constituted of inorganic, and organic substances, (iii) which possess definite physical, mineralogical chemical and biological properties, (iv) which is of variable thickness and (v) which acts as a medium for growth of terrestrial plants" .

Soils are natural bodies that exhibit three dimensional sequences of characteristics. First, the properties gradually change downwards from the surface to the bed rock. The unconsolidated material lying above the bed rock is called the regolith. The upper portion of the regolith is different from the lower portion. Being nearer the atmosphere, this upper zone has been subjected to the weathering action of wind, water and heat. Plant roots are found in this zone. Organic matter delivered as fallen leaves on the surfaces and dead roots below the surface are decomposed to form humus. The humus and partially decomposed organic matter is mixed with the soil at the surface layer. Primary minerals are decomposed to form clay. This upper and biochemically weathered portion of the regolith is called the solum (Kolay AK 1993).

Scientists have considered the soil to be a natural body possessing both depth and surface area. The properties of soil change vertically because the intensity of weathering of primary minerals decreases from the surface downwards and also

because the organic matter is incorporated into surface layer, and decomposed there. The characteristics of soils also changes in the horizontal direction due to change in topography and parent material (Foth HD 1984).e.g. Soil developed from granite tends to be coarse textured , whereas soil developed from limestone tends to be fine textured.

1.6a Formation of soil

Rocks were slowly broken down to smaller and smaller pieces by physical weathering, then decomposed by chemical weathering to form the parent material, which may be defined as the weathered material from which the soil was synthesized. The parent material was further decomposed by the action of atmospheric gases like water vapour, carbon-dioxide, sulphur dioxide, nitric oxide etc. at different temperatures. Some of the primary minerals present in rocks were altered to form some secondary minerals. Some were completely decomposed and the products of decomposition recombined with each other to form some secondary minerals, which also included clay minerals. These clay minerals or simply the clay remained intimately mixed with primary minerals like quartz or sand to form some soil. Some lower plants like algae, moss, lichens etc began to grow on the bare rocks and on this thin layer of soil, respiring to produce carbon dioxide, which reacted with water to form carbonic acid that decomposed the primary minerals to form clay. Later on, higher plants began to grow and continued this process. These plants continued to add organic matter to the soil in the form of leaves, roots etc. which decomposed in the soil to form humus that combined with the clay to form the clay-humus complex. Hence the colour of the surface soil gradually darkened. This process continued till a darker layer of soil of about one foot in thickness was developed. Soil forming factors like, parent material, climate, vegetation topography and time, are considered more or less independent of each other. But the simultaneous interaction of all these soil forming factors results in the particular soil forming process (Jenny H 1941).

Soil is the collection of natural bodies occupying portions of the earths surface, possessing properties due the integrated effects of climate and living matter, action upon parent material as conditioned by relief over periods of time.

A parent material may be defined as the unconsolidated, fully or partially weathered material from which the solum has been presumed to have developed. Parent materials has been classified on the basis of their silica content as acidic or Felsic, intermediate, basic or mafic and ultra basic or ultra mafic. The influencesof the parent material is more clearly seen in the earlier stage of soil development. But as the time passes, basic elements and plant nutrients are gradually washed down from soils that had developed from weathering of basic parent material. Consequently, the soils developed from the basic parent material become poor in basic elements and plant nutrients, and become acidic in reaction over a long period.

Soluble neutral salts of sodium, calcium and magnesium originate mainly from the decomposition of primary minerals in the soils of arid regions. When water evaporates from the surface of the soil, the water containing soluble salts moves from the deeper layers to the surface of the soil and deposits them at the surface of the fields, which are covered with a white crust of soluble salts in patches. This process of soil development is known as salinization. The soil obtained from Dwarka for study, may have been formed due to process of salinization because Dwarka gets less rainfall.

If these soluble salts are removed to the layer by a limited amount of rainfall occurring in the arid regions, then calcium and other ions are replaced from the clay and humic micelle, by sodium ions. Consequently the soil becomes sticky and plastic when wet and very hard when dry and black due to the dissolution of humus in the alkaline medium. This process of soil formation is known as alkalization.

If the rainfall increases a little, sodium ions are replaced from the clay and humic micelle, by hydrogen ions, the silicate clay is decomposed to release silica which is deposited on the soil particles. Consequently an ash grey colour develops on the soil. This process of soil formation is known as dealkalization.

1.6b Formation of soil organic matter

The organic part of the soil consist of a complex system of substances, the dynamics of which is determined by the continuous admission of organic residues of plant and animal origin into the soil and their continual transformation under the action chiefly of biological factors, but also, to some extent, of chemical and physical factors. This explains the fact that in the organic part of the soil various substances are present which represent the components of organic residues undergoing decomposition, metabolic products of micro-organisms utilizing organic residues as a source of energy, products of secondary synthesis in the form of bacterial plasma and strictly humus substances (Kononova MM 1966).

The term SOM(Soil Organic Matter) has been used to encompass all organic materials found in soil (Stevenson 1994) excluding charcoal (Oades 1988) or excluding non decayed plant and animal tissues, their partial decomposition products, and the living soil biomass (MacCarthy 1990). The definitions of SOM and its components have been derived from several sources (Oades 1988, MacCarthy 1990b, Stevenson 1994) and are compiled in table no. 06 in an effort to reduce existing variations in the use of the terms.

Table no: 06 Definitions of soil organic matter and its components (the letters in bold indicates the components which are studied in our work)

Component	Definition
Soil organic matter (SOM)	Thermally altered ,biologically derived ,organic material found in the soil or on the soil surface , whether it is living or dead or stage of decomposition but excluding the plants.
Living components phytomass	Living tissues of plant origin. Standing plant components which are dead (e.g. standing dead trees) are also considered as phytomass.
Microbial Biomass	Organic matter associated with cells of living soil microorganism.
Faunal Biomass	Organic matter associated with living soil fauna.
Nonliving components Particulate organic matter	Organic fragments with a recognizable cellular structure derived from any source but usually dominated by plant derived materials.

Litter	Organic materials devoid of mineral residues located on the soil surface.
Macroorganic matter	Fragments of organic matter >20um or >50um contained within the mineral soil matrix and typically isolated by sieving a dispersed soil
Light fraction	Organic materials isolated from mineral soils by flotation of dispersed soil suspensions on water or heavy liquids of densities 1.5-2.0Mg/ m^3
Dissolved organic matter	**Water soluble organic compounds found in the soil solution which are <0.45 um by definition. Typically this fraction consist of simple compounds of biological origin (e.g. metabolites of microbial and plant processes) including sugars, amino acids, low molecular weight organic acids (e.g. citrate, maleate etc) but may also include large molecules.**
Humus	Organic materials remaining in the soil after removal of macroorganic matter and dissolved organic matter.
Non humic biomolecules	Identifiable organic structures which can be placed into discrete categories of biopolymers including polysaccharides and sugars, proteins and amino acids, fats ,waxes and other lipids, and lignin,
Humic substances	Organic molecules with chemical structures which do not allow them to be placed into the category of non-humic biomolecules.
Humic acid	**Organic materials which are soluble in alkaline solution but precipitate on acidification of the alkaline extracts.**
Fulvic acid	Organic materials which are soluble in alkaline solution and remain soluble on acidification of the alkaline extracts.
Humin	Organic materials which are insoluble in alkaline solution.
Inert organic matter	Highly carbonized organic materials including charcoal, charred plant materials , graphite and coal with long turnover times.

The **organic fraction** of soils often accounts for a small but variable proportion of total soil mass. Despite its often minor contribution to the total mass of mineral soils, the organic fraction can exert a profound influence on soil properties, ecosystem functioning, and the magnitude of various obligatory ecosystem processes as shown in table no. 07.

Table no : 07 Properties and functions of organic matter in soil

Property	Function
<u>Biological Properties</u> Reservoir of metabolic energy	Organic ,matter provides the metabolic energy which drives soil biological processes.

Source of macronutrients	The mineralization of soil organic mater can significantly influence (positively or negatively) the size of the plant available macronutrient (N,P,and S) pools.
Stimulation and inhibition of enzyme activity and plant and microbial growth	The activity of enzymes found in soils and the growth of plants and microorganisms can be stimulated or inhibited by the presence of soil humic materials.
Physical Properties Stabilization of soil structure	Through the formation of bonds with the reactive surfaces of soil mineral particles, organic matter is capable of binding individual particles and aggregations of soil particles into water-stable aggregates at scales ranging from <2um for organic molecules through to 1 mm for plant roots and fungal hyphae.
Water retention	Organic matter can directly affect water retention because of its ability to absorb up to 20 times its mass of water and indirectly through its Impact on soil structure and pore geometry.
Low Solubility	Ensures that the bulk of the organic materials added to the soil are retained and not leached out of the soil profile.
Chemical properties Cation exchange capacity	The high charge characteristics of soil organic matter enhance retention of cations(e.g. Al^{3+}, $Fe^{3+,}$ Ca^{2+},Mg^{2+},NH_4^+ and transition metal micronutrients).
Buffering capacity and pH effects	In slightly acidic to alkaline soils, organic matter can act as a buffer and aids in the maintenance of acceptable soil pH conditions,
Chelation of metals	Stable complexes formed with metals and trace elements enhance the dissolution of soil minerals, reduce losses of soil micronutrients, reduce the potential toxicity of metals, and enhance the availability of phosphorus.
Interactions with xenobiotics	Organic matter can alter the biodegradability, activity and persistence of pesticides in soils.

The great diversity of soil organic substances, present often in negligible amounts, their dynamic state and the difficulty of isolating them from the soil in unchanged form (particularly the fraction occurring in the form of organo-mineral compounds), have so far been serious obstacles to the study of soil organic matter. However a

whole range of chemically individual compounds was isolated from the soil and identified by many investigators.

The list of organic substances of non-specific nature isolated from soils by numerous investigators was classified by Shmuk (1930) and Maiwald (1931), as follows:

(1)Carbohydrates:

(a)Pentoses, pentosans: (b) hexoses: (c) cellulose and early products of its decomposition.

(2) Hydrocarbons:

(3) Organic acids of the fatty series and their esters:

Oxalic acid $(COOH)_2$, Succinic acid $(CH_2COOH)_2$, Saccharic acid $(CHOH)_4(COOH)_2$, Crotonic acid $CH_3CH=CHCOOH$, Lignoceric acid $C_{24}H_{48}O_2$, Monohydroxystearic acid $C_{18}H_{36}O_4$,Acrylic acid $CH_2=CHCOOH$, Benzoic acid C_6H_5COOH and a number of others.

(4) Alcohols

Mannitol $C_6H_8(OH)_6$

(5) Esters

Glycerides of caproic and oleic acids

(6) Aldehydes:

Salicylaldehyde (o-hydroxybenzaldehyde) C_6H_4OHCHO, Vanillin $C_6H_3(OCH_3)OHCHO$ and a number of others.

(7) Resins

Resin acids and their derivatives.

(8) Nitrogen-containing compounds:

Trimethylamine $(CH_3)_3N$, Choline $C_5H_{15}O_2N$, Histidine $C_6H_9O_2N_3$, Arginine $C_6H_{14}O_2N_4$, Hypoxanthine, cytosine $C_4H_5ON_3$, Xanthine $C_5H_4O_2N_4$, Creatinine $C_4H_2ON_3$,Derivatives of pyridine and a number of monoamino-acids.

(9) Humic and fulvic acids, which are by-products of soil organic matter degradation, are naturally present in the environment (soil and water). Their chemical composition is complex and is still under investigation, although resorcinol, vanillic acid, ferullic acid and benzoic acid represent recurrent components (Sato T 1987).

An essential difficulty in studying organic compounds of an individual nature is the fact that they only occur in small amounts in the soil. But it cannot be assumed that, because these compounds occur in small amounts in the soil, they are of lesser interest, as many of their functions as antibiotics and as vitamins are manifested only **when they are applied in small amounts.**

1.6c Mud as a therapeutic agent

Mud has been used as a therapeutic agent since the creation of earth. Its importance has been demonstrated by Lord Shri Krishna by somersaulting in the fine silty soil at beach of Yamuna River (Raman reti). Medicinal value of geophagy i.e.deliberate ingestion of mud is also very old and it has been incorporated into religious ritual by putting a pinch of *Charnamrut* (mud of Yamuna river basin) on tongue daily in the morning, in *Vaishnav* clan.

It is widely used as a therapy in Israel using Dead Sea mud for psoriasis (Jashovam S 1999). It is also very prevalent in Russia and much research work is done on mud of that country (Mar'iasis ED 1979). There is a mud festival celebrated in European countries (France, Bulgaria) where a mud pond is made and people play in it as it is believed to improve general health. In India its importance as a therapeutic agent is well established in Nature Cure Centres (NCC) and by Ayurvedic & Siddha practitioners. Its use as rejuvenation therapy, for constipation, and acne, was also encouraged by Gandhiji.

Mud is a major therapeutic agent in Naturopathy and its reference is there in Ayurved system of medicine also. Naturopathy is more prevalent in European countries and Dead Sea mud is more investigated regarding its therapeutic activity. Due to Dead Sea, Israel has good revenue in medical tourism. A lot of work is also done in Russia (USSR) on mud and its activity, too. It has multifaceted actions due to its several properties and so its use in psoriasis, eczema and acne is widespread.

Its use in other fields viz poliomyelitis (Stepina NG 1965), pneumonia (Redchits IV 1976), encephalopathies (Khil'ko AS 1986) and rheumatoid arthritis (Aleksandrov VV 1971) has also been studied.

Various therapeutic activities of mud demonstrated by several researchers are summarized as follows.

(1) Heite JH (1967) indicated that high salt concentrations of mud decreased the mitotic rate of mouse epidermal cells. Madeleine Duvic (1986) stated that since psoriasis may involve abnormally regulated metabolic pathways comprising the arachidonic acid pathways, certain minerals may play an important role as enzymatic cofactors or regulators of epidermal proliferation

(2) Comacchi C (2004) reported that a single mud application in patients suffering from seborrhoeic dermatitis improves the values of stratum corneum hydration, TEWL, (Total Epidermal Water Loss), skin surface pH and sebum content. These are important parameters for integrity of the skin and thus, creating occlusion to the skin by applying mud, improves dermatitis condition.

(3) Skin microcirculation has been markedly increased by single mud pack treatment and this effect was disproportionately large compared to the modest increase in local skin temperature. The mechanism may perhaps be related to transcutaneous ion transfers (Poensin D 2003).

(4) Though mud is a store house of micro-organisms, it also has antimicrobial activity. One of the cause of psoriasis, eczema and acne is S.aureus infection

and mud has a good antibacterial activity against S.aureus and other organisms, thus helping to relieve the symptoms of the diseases (Maor Z. 2006).

(5) Aqueous peat (mixture of decayed vegetation, mud and water found naturally) extract shows excitatory action on the spontaneous contractile activity of the smooth muscles in vitro (Beer AM 2002).

(6) Because of reduced water content of balneological peat, (or thermal peat i.e. due to intentional microbial interaction for approx. three months the temperature of peat is increased), its thermical features were deteriorated. This goes for peat with a humidity factor < 60 %.(Beer AM 2005). The thermical features are associated with increased blood flow.

(7) The stabilizing effect of peloid (or balneological peat) on the intracellular pool and compartmentalization of thiamin in myocarditis , involved equilibration of the anabolic and catabolic reactions in the coenzyme metabolism, mainly due to selective inhibition of the thiamin pyrophosphatase activity stimulated under these conditions (Leus NF 1986).

(8) Bathing in the Dead Sea (penetration of salts through skin), caused histologically an overall reduction in Malpighian layer thickness by 63.4% and keratinocyte hyperplasia by78%. These changes were accompanied by normalization of keratin 16 expression in 90% of psoriasis patients. T lymphocytes were totally eliminated from the epidermis (depletion of >90% of CD 4+ and CD25+ cells) with only a low number remaining in the dermis (depletion of 69.4% of CD3+ cells and 77% of CD25+ cells). This reduction in activated T cells was accompanied by a marked reduction in HLA-DR expression by epidermal keratinocytes (Emmilia Hodak 2003). Probably this may be the reason why bathing in Dead Sea gives beneficial results against psoriasis, where increase in T lymphocytes is a major causative factor.

Apart from the activities described above, there are other modes of actions of mud due to its constituents which are summarized in table no.08. The activity shown in bold letters refers to its activity against skin disease.

Table No: 08 Different activities of mud through expression of biochemical factors

SR.No	Activity	Reference
01	Serum amino acid levels of tryptophan, cysteine and citrulline are increased.	Bagnato G,Morgante S, et al Clinical improvement and serum amino acid levels after mud-bath therapy. Int J Clin Pharmacol Res. 2004;24(2-3):39-47.
02	Activity due to Phospholipids , phytosterols,terpenes present in mud	Curri SB,Bombaidelli E, Grossi F,. Observations on organic components of thermal mud: morphohistochemical and biochemical studies on lipid components of mud of the Terme dei Papi (laghetto dei Bagnaccio, Viterbo). Chemical basis of the interpretation of biological and therapeutic actions of thermal mud. Clin Ter 1997 Dec 148 (12) 637-54
03	Change in catecholamines in animal tissue	Zolnikova Al, Kubil Skh, Nestrueve Vis Change in catecholamines in animal tissue under the effect of application of mud of various chemical composition. Vopr Kurortol Fizioter Lech Fiz Kult, 1967 Sept-Oct 32(5) 439-444.
04	**Inhibitors of Matrix mettalloproteinases produced in vivo**	**Bellometti S,Richelmi P, Tassmi T,Bente F. Production of matrix metalloproteinases and their inhibitors in osteoarthritic patients undergoing mud bath therapy. Int J Clin Pharmacol Res 2005 25(1) 77-94.**
05	**Activation of oxidant activity of neutrophils, and elimination of intracellular products of inflammation**	**Starichkov AA,Bondareva ZG,. The role of leukocytes in mechanism of action of balneopeloidotherapy. Vopr Kurortol Fizioter Lech Fiz Kult,2004: Sep-Oct; (5):29-31.**
06	**Production of prostaglandins by microorganisms of mud**	**Katrich EM ,ISai SV., The microorganisms of therapeutic mud as a possible producer of prostaglandins. Vopr Kurortol Fizioter Lech Fiz Kult 1994;Jan-Feb (1) 37**
07	**Modulating production of interleukin-1,decreases TNF-α and increases insulin growth factor**	**Simona Bellometti, Maurizio Cecchettin L. Galzigna. Mud pack therapy in osteoarthrosis : Changes in serum levels of chondrocyte markers. Clinica Chimica Acta, Volume 268, Issues 1-2, 10 December 1997, Pages 101-106., Bellometti S et al Cytokine levels in osteoarthrosis patients undergoing**

		mud baththerapy. Int J Clin Pharmacol Res 1997; 17(4): 149-53
08	**Nitric oxide, myeloperoxidase and glutathione peroxidase serum levels decreased by mud**	**Bellometi S, Poletto M, Greogotti C, Richelmi P, Berte F. Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients .Int J Clin Pharmacol Res 2000 20(3-4) 69-80**
09	Peloid balneotherapy normalized acid function of the stomach in duodenal ulcer	Petrakova VS., Possibility of using intensive peloid balneotherapy on duodenal ulcer patients . Vopr Kurortol Fizioter Lech Fiz Kult 2001 Sep-Oct (5) 20-3
10	**Alkaline phosphatase, plasma calcium, non-organic phosphorus coefficient Ca/P reduced**	**Dicheva MA, Khyshikutev BS, Anikina LV, Popov VM., Changes in the mineral metabolic indices of osteoarthrosis patients with the use of radon therapy and mud therapy. Vopr Kurortol Fizioter Lech Fiz Kult 1998 May-Jun;(3): 37-8.**
11	**Serum sTNF-R75 level reduced**	**Bellometti S., Galzigna L, Tichelmi P., Gregotti C, Berte F. Both serum receptors of tumor necrosis factor are influenced by mudpack treatment in osteoarthriic patients. Int J Tissue React 2002; 24 (2): 57-64**
12	**Plasma cytokine and soluble adhesion molecule levels decreased in healthy volunteers**	**Basili S, Martini F, Ferroni P, Grassi M, Sili SA., Effects of mud-pack treatment on plasma cytokine and soluble adhesion molecule levels in healthy volunteers. Clin Chim Acta 2001 Dec:314(1-2): 209-14.**
13	**Beta-endorphin and stress hormones(ACTH and Cortisol) decreased**	**Pizzoferrato A,Garzia I, Cenni E, Pratelli L, Tarabusi C. Beta-endorphin and stress hormones in patients affected by osteoarthritis undergoing thermal mud therapy. Minerva Med 2000 Oct: 91(10): 239-45.**
14	Increase in estradiol level in postmenopausal females,levels of soluble Interleukin-2 altered	Beer AM, Fey S, Walch S, et al The effect of peat components on endocrine and immunological parameters and on trace elements-results of two pilot studies. Clin Lab 2001; 47(3-4): 161-7.
15	Progesterone and estradiol in blood increased and excretion of adrenaline and noradrenaline increased in urine in women with insufficient corpus luteum	Bromirska D., Effect of hyperthermic and isothermic mud application on hormonal function of normal and insufficient corpus luteum in women. Ann Acad Med Stetin 1993; 39: 133-46
16	**Inhibition PGE2 production**	**Kim JH, Lee J, Lee HB, Shin JH, Kim EK. Water-retentive**

		and anti-inflammatory properties of organic and inorganic substances from Korean sea mud. Nat Prod Commun. 2010 Mar;5(3):395-8.
17	**Peloid therapy stimulates a monocytic (macrophagal) lineage of hemopoiesis directed to elimination of intracellular microflora and products of inflammation.**	**Starichkov AA, Bondareva ZG. The role of leukocytes in mechanism of action of balneopeloid therapy Vopr Kurortol Fizioter Lech Fiz Kult. 2004 Sep-Oct;(5):29-31.**
18	Enhances bile lithogenesis and gall bladder motility	Shvarts VIa, Bolatchieva LK, Makaeva IM, Alimova SF, Fidirko LP, Rassvetaeva GI. The effect of mud treatment on the function of the bile-secreting system.Vopr Kurortol Fizioter Lech Fiz Kult. 1991 Nov-Dec;(6):30-4.
19	**Induces involucrin, loricrin, transglutaminase-1 and filaggrin gene expression in primary human epidermal keratinocytes.**	**Grether-Beck S, Mühlberg K, Brenden H, Felsner I, Brynjólfsdóttir A, Einarsson S, Krutmann J Bioactive molecules from the Blue Lagoon: in vitro and in vivo assessment of silica mud and microalgae extracts for their effects on skin barrier function and prevention of skin ageing. Exp Dermatol. 2008 Sep;17(9):771-9. Epub 2008 Feb 28**

The activities shown in bold are related to psoriasis, eczema or acne.

Thus, it can be observed that mud exerts its action on various biochemical factors, resulting in normalizing their levels and thus finally leading to its healing process. It is rightly said in our literature that our body is made up of mud and we merge in mud after death. It is also believed that we are made up of the mud of the place where we live.

Annadbhanti Bhutani Parjanyadann Sambhavah ॥

i.e. our body is made up of the minerals through the food we eat and eventually of the mud from which those plants grow. Thus the land and the environment we live in, influence our body constitution.

Lots of research work has been conducted on beneficial effects of mud in skin disorders in various places in the world. e.g. Active properties and therapeutic effects of San Giovanni Spa (Italy) mud was studied (Agostini G 1996). Argenziano G (2004) of Italy studied effect of mud and bath therapy on acne cure. Vetchinkin VD

(1977) conducted a study on treatment of eczema and psoriasis with Altai territory mud, in Russia. A study of inhabitants of different climatogeographic zones of USSR with respect to psoriasis was done by Mariasis ED (1972). Ereshov ME(1973) experienced treating psoriasis and eczema in Alamyshik Balneological Health Resort (USSR). Montgomery BJ (1979) studied the effects of bathing in Dead Sea(Israel) on psoriasis.

To our knowledge, no such work is done on Indian soil and our work is the first effort to study four different types of Indian muds which are used traditionally as a health replenisher and anticonstipating agent.

If a person comes in constant contact with some **polluted** surface soils, then there are chances of geohelminth infection (Gilles HM 1991), arsenic poisoning (Lee RC 1995), hookworm infection (Wong MS 1991), tetanus (Waldron HA 1985) and podoconiosis (Price EW 1990) etc.

Hence, the soil used for therapy is dug from 3 to 4 ft under the soil surface, so that it is free from such contaminants like pesticides, worms and their eggs, litter and surface heavy metal pollutants. It is then milled and dried in sun for 10 days, for assuring freedom from vegetative microorganisms, sifted and stored in air tight containers.

An interesting study has been made by Jashovam Shani (1999) comparing different modalities used for treatment of psoriasis with respect to economy and efficacy. The results are shown in table no. 09.

Table No : 09 % Clearance, length of treatment, and remission of various therapies of psoriasis (numbers in parentheses indicate the superiority score for each parameter, "1" being the best)

Sr.no	Mode of psoriasis therapy	Percentage of patients Cleared >75%	Length of treatment(weeks)	Mean remission time (weeks)
01	Topical corticosteroids	45 (15)	20.0 (15)	>24 (7)
02	Ingram regimen*	58(13)	4.0 (2)	14(10)
03	UVB 280-350nm	87(4)	8.1 (9)	14(11)
04	UVB 311 nm	89(2)	4.4(3)	12(14)
05	UVB+Dithranol	86(5)	11.0(11)	32(1)
06	Goeckerman outpatient #	94(1)	6.0(6)	14(12)
07	Goeckerman inpatient	78(12)	9.0(10)	18(8)
08	Etretinate	82(10)	24.0(16)	8(15)
09	PUVA	85(7)	7.6(7)	25(5)
10	Cyclosporine(1.5mg/kg/day)	21(16)	20,0(13)	8(16)
11	Cyclosporine(3mg/kg/day)	57(14)	20.0(14)	18(9)
12	Cyclosporine(5mg/kg/day)	81(11)	16.0(12)	26(3)
13	Methotrexate	84(8)	8.0(8)	24(6)
14	**Balneophototherapy**	**83(9)**	**6.0(5)**	**25(4)**

15	Heliotherapy	86(6)	5.0(4)	12(13)
16	Climatotherapy	87(3)	4.0(1)	28(2)

(Balneophototherapy includes mud+PUVA therapy). ,(Ingram regimen : anthralin in Lassar's paste, coal –tar baths and UVlight,) (Goeckerman : UVB and crude coal-tar in a petrolatum base.)

It can be observed from the table that balneophototherapy scores 9^{th}, 5^{th}, &4^{th} in percentage of patients cleared, length of treatment , mean remission time respectively, when compared with 16 types of psoriasis therapy. Thus balneophototherapy can be said to be superior to many allopathic treatments. Hence, we have attempted to study the efficacy of only **balneotherapy** (only mud therapy) using different types of formulations in our present research work.

Summary of pathophysiology of skin disorders and action of mud in their treatment.

Various causes for psoriasis, eczema and acne and also the varied reported actions of mud have been discussed earlier in detail. An effort has been made to summarize all these factors in one single schematic diagram (fig.no.7) which gives an overview, stressing the concept of cell pathophysiology of psoriasis, eczema, acne and correlating actions of mud in their treatment. The key and reference details for the fig. are shown in table no.10. The suffix 'm' indicates activity of mud, 'p', trigger factor for psoriasis, 'e', trigger factor for eczema and 'a', trigger factor for acne.

The causative factors of psoriasis, eczema and acne are shown in the three different colour layer. The brown coloured layer with dashes shows the reported activity of mud with regards to these triggers.

UNIFYING CONCEPT CORRELATING PATHOPHYSIOLOGY OF PSORIASIS, ECZEMA, ACNE AND ACTION OF MUD IN THEIR TREATMENT

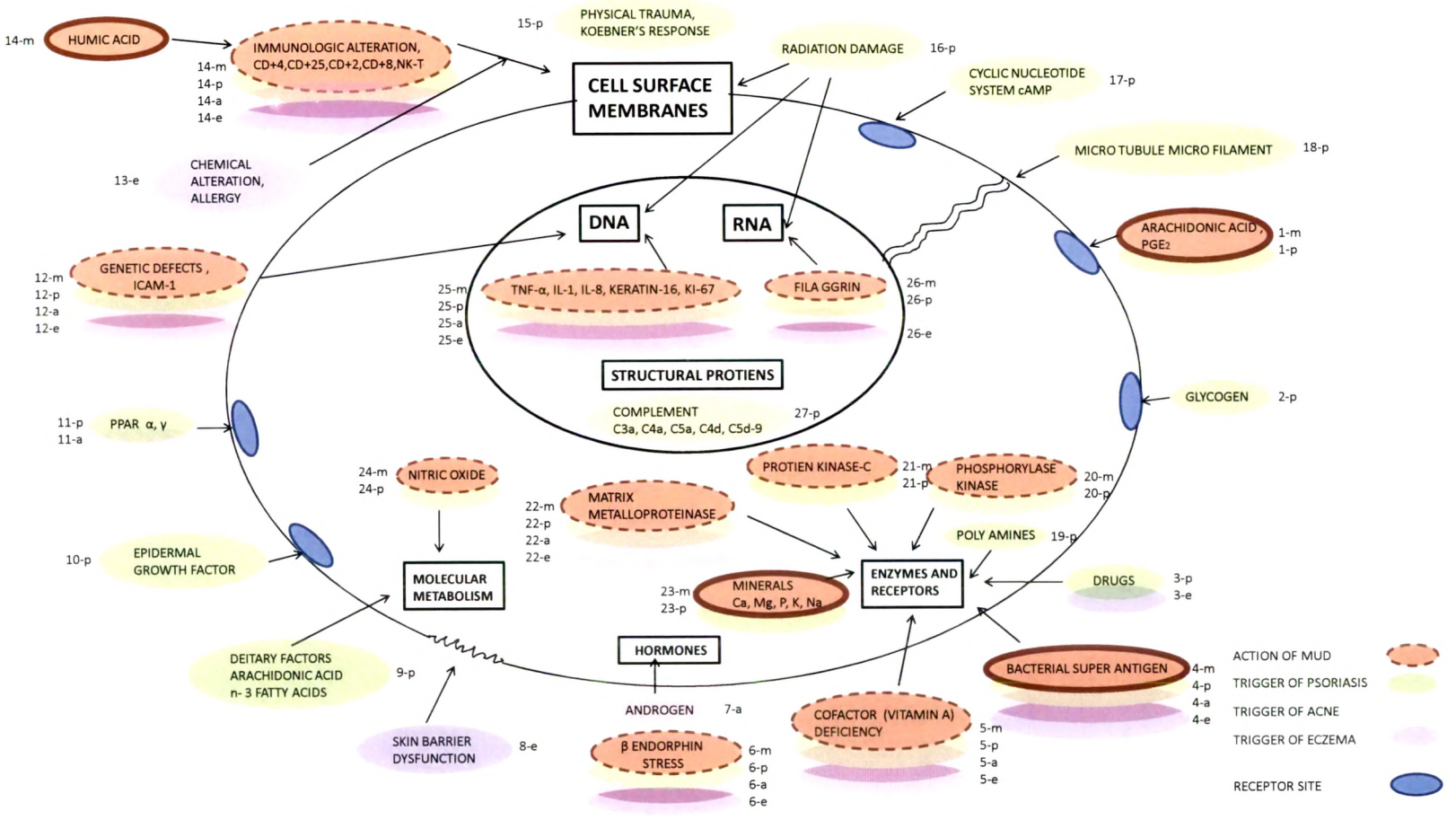


Table no.10 References to fig.no.07

m= mud, p=psoriasis, e=eczema, a=acne

Sr.no	ref. no.	Activity or causating factor	Reference
01	1-m	Inhibits PGE2 production	Kim JH, Lee J, Lee HB, Shin JH, Kim EK. Water-retentive and anti-inflammatory properties of organic and inorganic substances from Korean sea mud. Nat Prod Commun. 2010 Mar;5(3):395-8.
02	1-p	Free Arachidonic acid and 12HETE,PGE_2 and PGF_2	Voorhees JJ Leukotrienes and other lipozygenase products in the pathogenesis and therapy of psoriasis and other dermatoses Arch Dermatol 1983 Jul 119: 541-7,,,,,,WA Khan, GC Blobe, YA Hannun Arachidonic acid and free fatty acids as second messengers and the role of Proein Kinase C . Cellular signaling 1995 : 7 (3): 171-184
03	2-p	Glycogen accumulation in epidermis	L. Stankler, F.Walker Periodic acid –Schiff (PAS) staining for glycogen in clinically normal psoriatic and non-psoriatic skin. British J Dermatol (1976) ; 95; 599-601.
04	3-p	Lithium,betablocker, antimalarials,angiotensin converting enzyme inhibitor	DikaE, Bardazzi F, Balestri R, Maibach HI. Environmental factors and psoriasis. Curr Probl Dermatol 2007; 35:118-135
05	3-e	Drugs,(soap, detergents)	Novak N, Bieber T, Leung DYM.Immune mechanisms leading to atopidc dermatitis J Allergy Clin Immunol 2003; 112(6 suppl):S 128-39
06	4-m	Bacterial superantigen	Z. Maor, Y Henis, Y Alon, E. Orlov, K.B.Sorensen, A. Oren. Antimicrobial properties of Dead Sea black mineral mud. Int J Dermatol2006; 45:504-511
07	4-p	Streptococcal superantigens	Valdimarsson H, Sigmundsdottir H, Jonsdottir I Is psoriasis induced by streptococcal superantigens and maintained by M-protein-specific T cells that cross-react with keratin? Clin Exp Immunol. 1997 Jan:107 Suppl 1:21-4
08	4-e	Bacterial infection	Ong PY, Ohtake T, Brandt C et al:Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N. Engl . J Med 2002;347:1151-1160
09	4-a	P. acnes	Webster GF. Inflammatory acne represents hypersensitivity to Propionibacterium acnes. Dermatology.1998;196(1):80-1
10	5-m	Vitamin A presence	Shmuk A.A. The chemical nature of soil organic matter, Byull. Pochvoveda, 1930, (5-7)

11	5-p	Vitamin A deficiency	Treatment with vit A retinoids combination therapy
12	5-e	" "	" "
13	5-a	" "	" "
14	6-m	Beta-endorphin and stress hormones(ACTH and Cortisol) decreased	Pizzoferrato A,Garzia I, Cenni E, Pratelli L, Tarabusi C. Beta-endorphin and stress hormones in patients affected by osteoarthritis undergoing thermal mud therapy. Minerva Med 2000 Oct: 91(10): 239-45.
15	6-p	Psoriasis &neuropeptides	Pincelli C, Fantini F, Magneoni C, Giannetti A.,Psoriasis and Nervous system. Acta Derma Venereol suppl (Stockh) 1994;186:60-1
16	6-e	Stress hormones	Chien YH, Hwu WL,Chiang BL: The genetics of atopic dermatitis.Clin.Rev Allergy Immunol 2007 ;33(3):178-190
17	6-a	"" "	Zoubilis CC, Baron JM, Neuroendocrine regulation of sebocytes and pathogenetic link between stress and acne. Exp Dermatol 2004; 13 (suppl):31-5
18	7-a	androgen	Zeigler CG, Krug AW, Zouboulis CC, Bornstein ST. Corticotropin releasing hormone and its function in the skin . Horm Metab Res 2007:39:106-9
19	8-e	Skin barrier dysfunction	Lee SH, Jeong SK, Ahn SK. An update of the defensive barrier function of skin. Yonsei Med J 2006; 47(3):293-306
20	9-p	Dietary factors	Elisabeth S, Jurgen F, Georg R, Morten S., PerT., et al Effect of dietary supplementation with very long chain n-3 fatty acids in patients with psoriasis. The New England Journal of medicine June 1993;328(25) 1812-16
21	10-p	Epidermal growth factor receptor	Nanney LB,Yates RA, King LE JR.,Modulation of epidermal growth factor receptors in psoriasitc lesions during treatment with topical EGF. J Invest Dermatol 1992; 98: 296-301
22	11 a	PPAR α,γ	Trivedi NR., Cong Z.,Nelson AM., Albert AJ., Rosamilia LL., Sivarajah S,. et al. Peroxisome proliferator-activated receptors increase human sebum production. J Invest Dermatol 2006; 126: 2002-9
23	11-p	PPAR α,γ	Pit S.,Markus S., Wolfgang T., Jorg R.,Am J Clin Dermatol 2008;9 (1): 15-31
24	12-m	Cellular adhesion molecule	Basili S., MartiniF., Ferroni P., Grassi M.,Sili SA., Effects of mud pack treatment on plasma cytokine and soluble adhesion molecule levels

			in healthy volunteers. Clin Chim Acta 2001 Dec: 314 (1-2): 209-14
25	12-p	Cellular adhesion molecule	Chang EY., Hammerberg C., Fisher G. et al T-cell activation is potentiated by cytokines released by leisonal psoriatic but not normal , epidermis. Arch Dermatol 1992;128: 1479-1485.
26	12-e	Genetic defects,ICAM-1	Chien YH, Hwu WL., Bhiang BL; The genetics of atopic dermatitis. Clin. Rev. Allergy Immunol 2007; 33(3):178-190, Hamid Q., Boguniewicz M.,Leung Dy Differential in situ cytokine gene expression in acute versus chronic dermatitis J Clin Invest 1994; 94:870-876
27	12-a	Genetic defect,ICAM-1	Goulden V., McGeown Ch., Cunliffe WJ., The familial risk of adult acne: a comparison between first –degree relatives of affected and unaffected individuals. Br J Dermatol. Aug 1999; 141(2): 297-300., Jeremy Ah., Holland DB., Roberts SG.,Thomson KF., Cunliffe WJ., Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003;121: 20-7
28	13-e	Allergy & chemical alteration	Goerdt S., Birk R., Dippel E., Orfanos. CE. Beyond inflammation: Tolerance, immunotherapy and more . Eur. J Dermatol 1999;9:507-513 Abramovtis W., A clinician's paradigm in the treatment of atopic dermatitis. J A, Acad Dermatol 2005; 53®1Suppl): S70-7
29	14-m	Immunologic alteration CD+4, CD+25 ,CD+2,CD+8 NK-T	Emmilia H., Gottlieb AB., Segal T., Politi et al Climatotherapy at the Dead Sea is a remittive therapy for psoriasis:Combined effects on epidermal and immunologic activation. J Am Acad Dermatol 2003;49; (3): Sep 451-457.
30	14-p	CD+4.CD+25, NK-T , CD +2, CD+8	Nickoloff BJ., Bonish B., Huang BB., Porcelli SA.,Characterization of a T cell line bearing natural killer receptors and capable of creating psoriasis in a SCID mouse model J Dermatol Sci 2000; 24: 212-25
31	14-e	CD+4,	Leung DYM., Boguniewicz M, Howell MD., et al . New insights into atopic dermatitis. J Clin Invest 2004;113(5): 651-7
32	14-a	CD+4	Jeremy AH., Holland DB., Roberts SG., Thomson KF.,Cunliffe WJ., Inflammatory events are involved In acne lesion initiation J Invest Dermatol 2003; 121: 20-7
33	15-p	Eyre	Eyre RW., Krueger GP. Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity Koebner reactions. Br J Dermatol 1982; 106: 153-9

34	16-p	Radiation damage	Sneha Baxi Psoriasis and its treatment US Pharmacist April 2008
35	17-p	Cyclic nucleotide system cAMP	Voorhees J., Duell EA, Bass LJ., Harell ER. Decreased cyclic AMP in the epidermis of lesions of psoriaisis. Arch Dermatol 1972 May 105: 695-701
36	17-m	Cyclic nucleotide system cAMP	Madeleine D Possible mechanisms of effectiveness of Dead Sea balneotherapy Am Acad Dermatol Correspondence ; Nov 1986; 5: 1061
37	18-p	Micro tublule microfilament	Puck TT., Cyclic AMP, the microtubule-microfilament system, and cancer. Proc Natl Acad Sci 1977;74: 4491
38	19-p	Polyamines	Voorhees JJ Cyclic nucleotides, arachidonic acid, and polyamines in the pathophysiology of inflammatory proliferative skin diseases. In Safai, B. and Good, R Immunodermatology New York Plenum Press, 1981
39	20-p	Phosphorylase Kinase	Hena MC.,Sona MK.,Hena MK Elevated phosphorylase kinase activity in psoriatic epidermis: correlation with increased phosphorylation and psoriatic activity. Br J Dermatol 1994 Mar; 130(3):298-306
40	20-m	Phosphorylase Kinase	Dicheva MA,Khyshikutev BA, Anikina LV, Popov VM., changes in the mineral metabolic indices of osteoarthrosis patients with the use of radon therapy and mud therapy . Vopr Kurortol Fizioter Lech Fiz Kult 1998 May –Jun ; (3)37-8
41	21-m	Protein Kinase -C	Hart RM., Jones HL.,Jones VLE.,Malik S., Kenny MA.,Love B., Harnisch JP., Compositions and methods of treatment using peat derivatives US Patent 6267962 2001
42	21-p	Protein Kinase - C	Zhao Y., Fishelevich T., Petrali JP., Zheng L. et al Activitaion of keratinocyte protein kinase C Zeta in psoriasis plaques. J Invest Dermatol 2008;Sep: 128 (9)2190-7
43	22-m	Matrix meralloproteinase	Bellometti S., Richelmi P., Tassmi T., Bente F., Production of matriz metalloproteinases and their inhibitors in osteoarthritic patients undergoing mud bath therapy.Int. J Clin Pharmacol Res 2005 ; 25⊛1): 77-94
44	22-p	Matrix metalloproteinase	Reich E., Rifkin DB. Shaw E., (eds): Proteases and Biological Control . New York, Cold Spring Harbor Laboratory. 1975

45	22-a	Matrix metalloproteinase	Papakonstantinou E., Aletras AJ, Glass E., Tsogas P., Dionyssopoulos A .,Adjaye J et al Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by Isotretinoin J Invest Dermatol 2005; 125: 673-84
46	22-e	Matrix metalloproteinase	Novak N. Bieber T. Leung DYM. Immune mechanisms leading to atopic dermatitis. J allergy cllin Immunol 2003; 112(6suppl): S128-39
47	23-m	Minerals Ca,Mg,P ,K, Na	Heite JH,Schumann JW: Untersuchungen am Scanthose-test uber die wieksamkeit kochsalzhaltiger, salben Arch Klin Exp Derm 1967;228:266-275
48	23-p	Minerals increased expression	Szabo AK. Bos JD , Kas PK/ Hyperproliferation of normally quiescent keratinocytes in non-lesional psoriatic skin due to high calcium concentration (an organotypid culture model) Acta Derm Venereol suppl (Stockh) 1994;186:60-1
49	24-m	Nitric oxide	Bellometti S., Poletto M., Greogotti C., Richelmi P., Berte F., Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients Int J Clin Pharmacol Res 2000; 20 (3-4): 69-80
50	24-p	Nitric oxide	Morhenn VB.,Langerhans cells may trigger the psoriatic disease process via production of nitric oxide. Immunol Today 1997 sep 18(9): 433-6
51	25-m	TNF-α, IL-1, IL-8, Keratin-16, Ki - 67	Bellometti S., et al Cytokine levels in osteoarthrosis patients, undergoing mud bath therapy Int J Clin Pharmacol Res 1997; 17(4):149-53
52	25-p	TNF-α, IL-1, IL-8, Keratin-16, Ki - 67	Nickoloff BJ., Karabin GD., Barker JN et al Cellular localization of interleukin -8 and its inducer, tumor necrosis factor –alpha in psoriasis. Am J Pathol 1991;138:129-40
53	25-e	TNF-α, IL-1, IL-8, Keratin-16, Ki - 67	Novak N. Bieber T Leung DYM. Immune mechanisms leading to atopic dermatitis J Allergy Clin Immunol 2003; 112(6suppl): S128-39
54	25-a	TNF-α, IL-1, IL-8, Keratin-16, Ki - 67	Jeremy Ak. Holland DB., Roberts SG., Thomson KF., Cunliffe Wj. Inflammatory events are involved in acne lesion initiation J Invest Dermatol 2003; 121: 20-7
55	26-m	Filaggrin	Grether BS. Muhlberg K., Brenden H. Felsner.I., Brynjolfsdottir A., Einarsson S., Krutmann J., Bioactive molecules from the Blue Lagoon: in vitro and in vivo assessment of silica mud and microalgae extracts for their effects on skin barrier function and prevention of

			skin ageing. Exp Dermatol 2008; Sep; 17(9): 771-9
56	26-p	Filaggrin	Koreck A., Suranyl A., szony Bj., Farkas A et al CD 3+, CD56+, NK-T cells are significantly decreased in the peripheral blood of patients with psoriasis. Clin Exp Immunol 2002 Jan 127(1):176-82
57	26-e	Filaggrin	Irvine AD., McLean Wh., Breaking the (un)sound barrier: filaggrin is a major gene for atopic dermatitis . J Invest Dermatol 2006; 126 (6): 1200-2
58	27-p	Complement C3a, C4a, C5a, C4d, C5d-9	Pash MC., Bos JD., Asghar SS., Activation of complement in psoriasis. Clin Exp dermatol 1998; 23: 189-90

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