Dermatology : the past Milestones and the future Cross-currents

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Science in general and medicine in particular made truly momentous advances during the last century [1]. Dermatology too benefited from many of these and underwent some additional ones of its own. The path-breaking dermatological events of the last century, the epochal general scientific events of the period and the likely future of dermatology based on the present cross-currents are successively reconnoitered below [2].

Advances in the twentieth century pertaining to dermatology

Cellular biology : Revelation of biology of the cells of the epidermis and its junction with the dermis proved to be a major advance in understanding the cutaneous pathology in general and pathogenesis of bullous disorders in particular. Immunohistopathological (including prenatal), electron microscopic and immunofluorescence advances of the later part of 20th century enable accurate subtyping and thereby early appropriate management, genetic counselling and DNA based prenatal diagnosis for subsequent pregnancies of epidermolysis bullosa (EB), a group of inherited disorders with blistering of skin and mucous membranes after trivial trauma having diverse prognoses. Direct immunofluorescence (DIF) of mucosal pemphigus vulgaris (PV) and demonstration of specific antigens by immunoblotting, etc., led to its early specific diagnosis and improved prognosis. The blisters of staphylococcal scalded skin syndrome (SSSS) as well as pemphigus foliaceus were shown to be due to disrupted adhesive function of desmoglein 1 (Dsg 1) by exfoliative toxin or anti-Dsg1 immunoglobulin G respectively.

Topical corticosteroids : The discovery of compound E (cortisone) in 1935 heralded the arrival of topical corticosteroids. Numerous modifications of the corticosteroid molecule, viz. halogenation, esterification, hydroxylation, modification of side chains etc, and improvements in delivery systems have since significantly increased its anti-inflammatory activity as well as adverse effects. Discontinuation after prolonged

use of a potent steroid on the face or anogenital region can lead to a rash that subsides on their re-use and promptly recurs on discontinuance, hence getting the patient 'addicted' (topical steroid addiction syndrome) [3]. Tachyphylaxis and disguised morphology of non-steroid responsive dermatoses (scabies, tinea etc) can also result from their chronic use.

Superficial fungal infections: Griseofulvin, originally isolated from *Penicillium griseofulvum* was the first oral drug to be used during the second half of the 20th century to treat dermatophytosis, a superficial fungal infection with the potential of troubling the active and the obese all the year round particularly in the tropics. *Candida albicans*, the opportunistic 'marker' of immunosuppression was initially tamed by nystatin. The antifungal spectrum broadened subsequently with the arrival of azoles (ketoconazole, fluconazole, itraconazole, etc) and more recently allylamines.

Phototherapy : Although the Greeks were the first to use sun as a therapeutic light source three thousand years ago, modern heliotherapy began in 1923 with the use of UVB in psoriasis. PUVA, acronym for oral psoralen followed by long-wave ultra violet light (UVA), got FDA approval for psoriasis in 1982. It has also been used therapeutically (vitiligo, mycosis fungoides, atopic dermatitis, generalised lichen planus, urticaria pigmentosa, pityriasis rubra pilaris, etc) and prophylactically (polymorphic light eruption, solar urticaria, chronic actinic dermatitis, etc) for many chronic dermatoses. Narrow band UVB at 311nm, due to reduced risk of carcinogenicity compared to PUVA and more efficient clearing of psoriasis with reduced erythema compared to broadband UVB, was a natural corollary. Photodynamic therapy (PDT) sought to inactivate tumoral or aberrant psoriatic cells by generating highly reactive oxygen intermediates by exposing, after prior systemic or topical administration of a photosensitiser, to long wavelength emission of a visible or a laser light. In photopheresis, two hours after oral psoralen intake,

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blood is centrifuged to separate its lymphocyte-enriched fraction which after being exposed to UVA, is then returned to the patient whose immune system responds by destroying the altered or damaged malignant T lymphocytes. This mode of therapy is quite useful in Sezary syndrome, less so in systemic sclerosis and GVHD and is least effective in psoriasis, atopic dermatitis, pemphigus, SLE, etc.

Retinoids : Vitamin A (retinol) was extracted from egg yolk in 1909. Retinoids, its structural analogues, result naturally during vitamin A metabolism but most (more than 1500 since 1968) are synthesised by changing the polar end group, polyene side chain, or cyclic group of vitamin A. Vitamin A as well as retinoids affect epithelial tissue differentiation, general growth, visual function and reproduction. They act on cells as hormones by binding to retinoic acid receptors (RAR) and / or other retinoid X receptors (RXR), which have α , β and γ subtypes [3]. Topical (tretinoin, tazarotene and alitretinoin) as well as oral (isotretinoin and acitretin) retinoids are available for dermatological use. Though FDA approved only for acne, sun-induced skin aging and psoriasis, topical retinoids have also been used for flat warts, epidermal naevi, porokeratosis, melasma, keloids, scars, etc. Adapalene, a naphthoic acid derivative, also has a retinoid-like action but causes much less local irritation. Oral isotretinoin, though FDA approved only as a second line drug for severe recalcitrant cystic or nodular acne vulgaris, is the drug of choice for pityriasis rubra pilaris, severe lichen planus, Darier's disease and ichthyoses. It has also been found beneficial in oncology in combination with other agents such as cytokines. Likewise, acitretin has been used for many other dermatoses besides the FDA approved one of severe recalcitrant psoriasis.

Dermatosurgery : In 1936, Dr. Frederic Mohs of the University of Wisconsin developed Mohs "chemosurgery", a technique to remove cancers with maximum tissue conservation providing controlled, serial microscopic examination by frozen section of the excised tissue that had been directly fixed chemically applying zinc chloride paste. Subsequently, use of frozen sections of fresh tissue eliminated the need of zinc chloride paste. This technique is especially effective on basal cell and squamous cell carcinomas of the face and recurrent skin cancers [3].

The therapy of resistant vitiligo got revolutionised by grafting viz, Thiersch's grafts, epidermal grafts (by suction of freezing blisters) and minigrafting by punch. More and more procedures like nail surgery, single hair transplantation, dermabrasion, laser surgery, etc are being increasingly carried out by the dermatologists.

General scientific events of the twentieth century: Some of the general scientific events of the twentieth century left deep imprint on dermatology also.

Information, Communication and Entertainment The modern commercial television (1941) was the forerunner of the 'Information, Communication and Entertainment' era that has shrunk the world into a global village.

Genetics : The structure of DNA, the molecule of life was suggested in 1953. Less than half a century later, the human genome project furnished a tantalizing key to Pandora's box of nearly 4000 known (and countless unknown) genetic disorders by decoding the genetic instructions encoded in the estimated three billion base pairs of nucleotides within the 46 chromosomes. Gene therapy may not only enable rewriting of the blueprint of life itself (rather than treat its infirmities symptomatically) but also tackle many of the common, so called degenerative, diseases believed to be due to gene mutations. The molecular basis of genodermatosis and mosaic conditions (viz, Dowling-Meara form of EB, epidermolytic hyperkeratosis, palmoplantar keratoderma, pachyonychia congenita, oral white spongy naevus, monilethrix, etc) received a tremendous fillip about a decade ago with the engineering of a transgenic mouse model of a genodermatosis with a keratin 14 deletion [4].

Inflammation : The understanding of the cause and regulation of inflammation as well as its mediators, immune responses, oncogenesis and genetic defects has greatly advanced in the second half of the 20th century. Histamine, the first identified mediator of acute inflammation, released rapidly on stimulation of mast cells and basophils from their granular stores is pro-inflammatory as well as regenerative. Its formation and release is regulated by cytokines and its activity regulates formation of other cytokines contributing to their participation in inflammation and allergy. Stimulation of cells or perturbation of their phospholipid-rich membranes activates phospholipase 'A' releasing fatty acids which are then cleaved to form extremely potent mediators of inflammation. Cleavage of arachidonic acid by 5-lipoxygenase releases a product that on further degradation results in several chemically related leukotrienes, and cleavage of the essential fatty acids by the cyclo-oxygenase pathway gives rise to a group of cyclic endoperoxides, eg. prostaglandins, prostacyclin (PGI₂) and thromboxanes.

Cytokines : Organisms survive inside macrophages by subverting the innate killing mechanisms of these cells. Nonetheless, the macrophages can process small antigenic fragments (possibly of organisms which have spontaneously died) and place them on the host cell

surface.

A subpopulation of T-helper cells, primed to the combination of antigen with so-called class II MHC molecules on the macrophage surface, produce a variety of cytokines which are low molecular weight, soluble, proteins having pleiotropic biologic properties like stimulation as well as inhibition of differentiation, proliferation or function of immune cells acting virtually as an 'internet' to direct immune response by cell-to-cell communication. They are divisible into primary (eg. IL-1 and TNF α) and secondary namely JAK (Janus family kinases) or STAT (signal transducers and activators of transcription), interleukins (IL), interferons (IFN), growth factors, colony stimulating factors (CSF) and tumour necrosis factors (TNF). They have direct effect on macrophages and natural killer cell activation. Different cytokines can be made by various cell types and generally act at a short range on neighbouring cells. Some T-cell cytokines help B-cells to make antibodies while others such as gamma interferon act as macrophage activating factors switching on the previously subverted microbiocidal mechanisms of the macrophage and bring about death of intracellular microorganisms. IL-1, a product of many cell lines including keratinocytes, is secreted as a primary response to injury. IL-2, a T-cell product that causes the proliferation of not only T cells but also natural killer cells and LAK cells, has been found useful in combination protocols for malignant melanoma and possibly in atopic dermatitis. Interferons, proteins produced by cells in response to viruses to slow down viral replication, consist of IFN- α (a group of more than 20 structurally related proteins produced by mononuclear phagocytes, IFN- β (single protein produced by fibroblasts) and IFN- γ (a single protein produced by lymphocytes during cell mediated immune reactions). IFN α has been used in various viral dermatoses (recurrent HSV, *Herpes zoster* in the immunocompromised, HPV induced neoplasia and in early stage of HIV infection to prevent opportunistic infections), tumours (CTCL, early malignant melanoma and early stage of HIV associated Kaposi's sarcoma) and in certain inflammatory disorders. However, frequent relapses of LE/SCLE limit its clinical application. IFN- β has also been tried in viral (HSV, HIV) diseases as well as skin tumours as an adjuvant/palliative measure. Use of IFN- γ , in rheumatology (chronic polyarthritis, systemic sclerosis and Behcet's disease) is established, its role in psoriasis controversial, in atopic dermatitis promising, in leprosy and leishmaniasis experimental and in severe HPV and *Herpes zoster* probable [5].

Examples of other cytokines used in dermatology as immunomodulators/immunosuppressants are imiquimod

in viral dermatoses (HIV, HSV, molluscum contagiosum, etc) and to prevent scars after surgery, tacrolimus in atopic dermatitis, psoriasis and pyoderma gangrenosum, cyclosporine A in atopic dermatitis, lichen planus, psoriasis, mechanobullous disorders (epidermolysis bullosa acquisita), collagen vascular diseases (SLE and systemic sclerosis) and CTCL (cutaneous T cell lymphoma). Cytokines like etanercept, infliximab, alefacept and denileukin diftiox are being used in psoriasis, 1% pimecrolimus is being tried as a topical selective inflammatory cytokine inhibitor.

Chemokines, [5] small molecular weight peptide cytokines having target cell specificity, are divisible into three subfamilies ('C-X-C', 'C-C' & 'C') based on structural and genetic considerations. Acting through their receptors whose expression can be fine-tuned by other cytokines eg. IL-2 (strongly upregulates expression of CCR1 and CCR2 in circulating T cells), IL-4, TNF- α , IFN- γ , etc, chemokines may help control the movements of leucocytes precisely, inhibit autoimmune allergic or septic processes, provide more effective anti-tumour therapy with other cytokines and inhibit the progression of HIV infection. Significant rise of 72 amino acid variant of IL-8 seen in psoriasis could play a role in keeping up epidermal hyperproliferation and be correctable by future interventions. IP-10 is another important chemokine seen over expressed in biopsies of mycosis fungoides patients. One of the chemokine receptors (cc-CKR₅ for a group of β chemokines) serves as a co-receptor for primary macrophage tropic strains of HIV-1 and is a new target for HIV therapy.

Immunoglobulins : Microbes evade our immune defence through frequent mutations. Hence, the body obviously needed to 'devise' defence mechanisms, which could be dovetailed individually to each one of these. This need was met by fashioning an adaptor molecule, the antibody, with three main regions, two constant ones communicating with complement and the phagocytes (the biological functions) and the variable one for binding to an individual micro-organism (the external recognition function), being complementary in shape to some micro-organisms to which it could bind [6].

Adhesion molecules : Intercell and cell-substrate adhesion, an essential function of cell membranes, is subserved by adhesion molecules, which participate in every cell activity. These proteins may be latent, i.e. not expressed until the cell is stimulated as in platelets, or expressed very transiently eg. selectins between leukocytes and endothelium, cadherins between the keratinocytes or durably as the integrins between basal keratinocytes and the basement membrane. Besides regulating tissue growth, differentiation and repair, adhesion molecules also help leukocyte recruitment and

function [7].

L-selectin (CD₆₂L), E-selectin and P-selectin, the three structurally related proteins are readily inducible by cytokines. They mediate the initial tethering of leucocytes prior to their extravasation into tissues. L and E selectin are expressed respectively by leucocytes and endothelial cells, (TMF/ILPb induces expression on E selectin and also synthesis of P-selectin which is expressed on platelets and endothelial cells in chronic inflammatory settings. E selectin selectively recruits lymphocytes to cutaneous sites of inflammation through binding to the surface of T cells and circulating Langerhan's cells (LCs) through a carbohydrate moiety called cutaneous lymphoid antigen (CLA) that probably also helps the LCs to eventually localize to the skin. Firm adhesion of lymphocytes to the endothelium is mediated by two different groups of leucocyte integrins. The first group consists of β integrins (LFA-1 and Mac 1) which bind to intercellular adhesion molecule (ICAM-1/CD₅₄), causing cessation of rolling of leucocytes followed by their spreading out and slow crawl along the endothelial surface until they reach a cell junction where they move through the vessel wall into the tissues. The second group of integrins, the α 4 integrins (CD₄₉ α) may pair either with β 1 (CD₂₉) integrins to form very late activation antigen (VLA 4), restricted to monocytes, T cells, eosinophils and B cells) or with β 7 to form lymphocyte Peyer's patches adhesion molecule (LPAM), both of which bind to vascular cell adhesion molecule (VCAM/CD₁₀₆) which is an immunoglobulin superfamily member not normally expressed on endothelial cells, but is upregulated by TNF, IL-1b and selectively by IL-4 during Th₂ mediated diseases.

Cadherins including E-cadherin are homophilic adhesion molecules that maintain tissue integrity through interkeratinocyte adherence junctions and skin associated lymphoid tissue (SALT) integrity by helping to retain LCs in the skin. On antigenic stimulus, the epidermal LCs show decreased E-cadherin levels prior to their migration to the regional lymph nodes to present processed antigen to naive helper T cells that reside there.

Integrins comprise a large family of heterodimeric adhesion molecules that mediate cell matrix interactions and cell-cell interactions. They also help in LC migration across the basement membrane, the extracellular matrix (ECM) and afferent lymphatics to ultimately localize in the T cell-rich paracortical areas of regional lymph nodes.

As regards the role of adhesion molecules in common dermatological disorders, sequential changes in psoriasis are a prototype of T cells role after tethering to selectins, where chemokines activate cells via specific cell-surface

receptors. Chemokine activation enables integrins to bind to ICAMs and VCAMs, which mediate firm adhesion to the endothelium. T cells then migrate across the endothelium into the dermis in response to chemokines that are synthesized in psoriatic lesions. CD₈ T cells thereafter migrate into the epidermis according to chemokine gradients and adhesion molecules expressed on the T-cell subset and cause cytotoxicity. A role for endothelial activation by upregulation of E-selectins is envisaged in late phase responses of immediate hypersensitivity in atopic dermatitis, also in chronic urticaria and vasculitis. Adhesion molecules may have a role to play in the pathogenesis of spongiotic dermatitis, CTCL, pityriasis rubra pilaris, as well as benign (haemangiomas) and malignant (Kaposi's sarcoma) tumours. Tissue culture of keratinocytes : expansion of a small donor site upto 10000 - fold by this technique has made it feasible to treat major burns patients, deep dermal naevi, chronic leg ulcers, etc. Epithelial cell grafts can also be used in the oral/mastoid cavities and urethral/genital mucosae. Keratinocytes subcultured onto a complex matrix or dermal substitute form skin equivalent cultures [8].

Diagnosis of syphilis by visualising Treponema pallidum (TP) : Though discovered in 1905, the grace and elegance of the movements of TP could only be appreciated after the advent of dark ground illumination (DGI) microscopes, its structural details revealed by electron microscopy (EM) were further refined with the advent of freeze fracture EM technique. Detected by DIF in fixed tissue smears treated with conjugate of specific antibodies and a fluorescent dye, TP could be demonstrated in tissues by silver impregnation technique. Indirect immunofluorescence was employed to detect antibodies specific to it by fluorescent treponemal antibody absorption (FTA-ABS) test. The need to search and visualize TP has further increased in this HIV era, as it still cannot be grown on any of the laboratory biochemical media.

Viruses : Many of the viruses, microbes dependent on the host-cell ribosomes for their replication, remained unconquered during the 20th century. Their various proteins - regulatory, enzymatic and structural, together with the products of cell damage, probably contribute to the local and general response to the infection. Some viruses cause persistent infections, others cause cell proliferation. They are also implicated in the process of carcinogenesis e.g. in the development of cervical cancer (HPV types 16,18, 31, 33), hepatoma (HBV and HCV), Kaposi's sarcoma (HHV-8), Burkitt's lymphoma, Hodgkin's lymphoma and nasopharyngeal carcinoma (EBV), T-cell lymphoma (HTLV) and AIDS related malignancies (HIV), etc.

The relentless replication of HIV causes progressive immune suppression by direct cytotoxicity of CD4 T lymphocytes, antibody dependent cell cytotoxicity, persistent immunostimulation as a superantigen exhausting immunity and killing bystander T cells due to formation of syncytia.

DNA viruses affect antigen presenting MHC-I cell cycle at various steps viz, blockage of cleaving of its antigens, interference with complexing of transporter-associated protein to its peptide fragments (HSV) and interference with transfer/incorporation of the MHC-I peptide complex on to cell membranes after being processed in the Golgi bodies of the APCs (CMV and adenoviruses).

The immunomodulation by the viruses to cause neoplasia [9] can either be indirect, after a very long latency (retroviruses) by activating cellular proto-oncogene leading to indefinite cell growth or direct, after a long latency, by inducing cellular alterations in synergism with host cellular changes. The third mechanism which after a short latency, causes direct encoding of viral gene (usually of DNA viruses) proteins to induce malignancy in normal cells includes single step mutation by activation of anti apoptotic Bcl-2 genes (by HSV and adenoviruses), synthesis of epidermal growth factor (EGF) analogues (by pox viruses), B cell neoplasia encoded by proto-oncogenes eg 'myc' (by EBV) and inactivation of cellular proteins by tumour suppressor genes e.g. p 53 (by E₆ and E₇ proteins of HPV and E1A and E1B proteins of adenoviruses).

The clinical applications of the above pathogenesis of immune suppression by viruses include vaccines against HBV and HPV reducing incidence of malignancies and immune reconstitution following HAART reducing AIDS related malignancies and OIs.

Therapeutics : The discovery of penicillin in 1928, by Alexander Fleming, proved to be a watershed. Seventeen years later, Selman Waksman discovered streptomycin. Tetracyclines, quinolones and later a variable deluge of antibacterials followed. Their advent virtually eclipsed the dominance of venereology over dermatology till 1980s when HIV/AIDS darkened the horizon so much that the UN deliberated about it through an entire session of its security council (January 2000) and again in a special session of its general assembly (June 2001).

Immunosuppressive and cytotoxic drugs like methotrexate, cyclophosphamide, cyclosporine and mycophenolate mofetil have acquired a useful niche in the management of many autoimmune disorders like vasculitis, rheumatological disease, idiopathic nephrotic syndrome, inflammatory bowel disease, immunobullous

dermatoses, psoriasis, etc. Combination therapies have included use of isotretinoin with immune mediators like cytokines in oncology. In psoriasis, the risk of PUVA/UVB induced skin malignancies gets reduced when administered in combination with retinoids which also have additional beneficial effects on psoriasis.

Apoptosis : Advances in molecular biology and genetics were responsible for detecting, characterising and cloning normal tissue homeostasis. They also helped to delineate a Fas receptor (CD95) & Fas ligand (CD95L) pathway mediated process called apoptosis that maintains the balance between cell survival and death by genetically regulating the orchestrated collapse of a cell, as opposed to necrosis, the passive process of cell death in various diseases. Apoptosis not only eliminates unwanted, senescent and damaged cells without damage to the surrounding normal cells during several biological processes like embryogenesis, ageing, etc. but can also cause many disease processes ranging from autoimmune to malignant. Dermatological disorders like toxic epidermal necrolysis (TEN), lichen planus, etc., can also be a result of it. Study of altered apoptosis implies potentially great therapeutic advances to manage many such diseases that result when cells die that shouldn't or others live that should die. Following one such observation that antibodies present in pooled purified human immunoglobulin block Fas mediated keratinocyte apoptosis in vitro, followed the introduction of high dose IVIG in the treatment of TEN in 1998, radically altering the prognosis of this erstwhile "killer" disease. Antisense oligonucleotides, 16-20 base lengths of DNA, after injections are internalized by cells through endocytosis pathway and can block bcl-2 overexpression. Agents to halt apoptosis of uninfected CD4 T-cells in HIV and to increase the inadequate apoptosis in rheumatoid arthritis and SLE are likely to be developed in future. Caspase inhibitors are undergoing animal trials for treatment of neurodegenerative diseases and anti-Fas antibodies can be a potential mode of therapy in GVHD by blocking the Fas ligand expressed on the donor lymphocyte [10].

Cross-currents buffeting dermatology today

Concern for cutaneous health and appearance : The dermatological patients, who are fortunately no longer treated as pariahs and isolated, demonstrate a mounting awareness of their skin and cosmetic health. This augurs well for the nascent but actively developing chapters of cosmetology and dermatological surgery, whose practitioners' need to keep focus and strive actively to seek funds in the face of competing life-threatening conditions. Cost effective management of the more difficult cosmetic problems needing expensive technology is better left to a few select centres of

excellence. Dermatologists must however, not remain obsessed with cosmetology only and opt out of treating less glamorous but important endemic conditions.

Preventive dermatology : While the genetic basis of disease remains paramount, role of environmental factors like climate will increase. Efficient preventive education as regards avoidance of solar radiation should specially address the young high-risk group. Unless pollution and environmental degradation is restricted there will be no let up in the progressive increase of cutaneous and nasobronchial allergies.

Patient education : The ever-improving tools of communication offer exciting prospects. Rather than dispense just topicals, pertinent information and knowledge should be imparted to the patients, increasing their compliance as well as satisfaction and decreasing complications and exploitation due to wrong prescriptions by quacks.

Complementary medicine : Antibiotic resistance, diabetes, asthma, eczema etc. have surfaced in epidemic proportions, perhaps as a result of winning the battle against infection. This has encouraged votaries of alternative paradigms. However, the soldiers of scientific medicine must continue their battle, there being no alternative to scientifically proven therapies.

Standardizing dermatological vocabulary : Lest the lack of standard definitions of dermatological terms continues to stunt the growth of dermatology into an authentic speciality, a precise dictionary of the subject is mandatory [11].

Priorities in future research : As the aetiopathogenesis of many dermatoses like psoriasis, vitiligo, alopecia areata, atopic dermatitis and the mechanism underlying the commonest dermatological symptom of pruritus are not clearly understood, a high priority in future research to unravel these mysteries will facilitate their prevention and treatment.

Art of dermatological practice : As improved scientific knowledge has made practice of evidence-based medicine mandatory, there is a real danger of the very 'art of medicine' being swept away by this 'science of evidence' [12]. The progress in dermatopathology has led to the downplaying of clinical skills and shrinkage of the textbook coverage of principles of clinical diagnosis. This trend must be reversed by thoughtful and critical appraisal to strike a judicious balance between logic and intuition integrating the wisdom of

the historical lessons absorbed from the patients' bedside with the strengthened morphology, the very foundation of dermatology, is inescapable.

Tele-dermatology : With increasing bandwidth, cheaper and efficient 3D web cameras, tele dermatology has come to stay and is sure to rapidly evolve as a cost effective mode of delivering dermatologic health care to remote locations. Besides clinical management and follow up of patients, easy references to textbooks, journals, and on-line atlases over the web are additional advantages of information technology.

Lest the challenging crosswinds blow the speciality off course, the practitioners of dermatology need to instill discipline of basic philosophies and aim for the humanization of the subject. Let the acronym 'I.C.E' be supplanted by a warmer one namely, 'Inspiration, Compassion, and Ethics'; for the succour that we may bring to the suffering humanity will be the best tribute to our forebearers!

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