MALIGNANT MELANOMA

ESSAY

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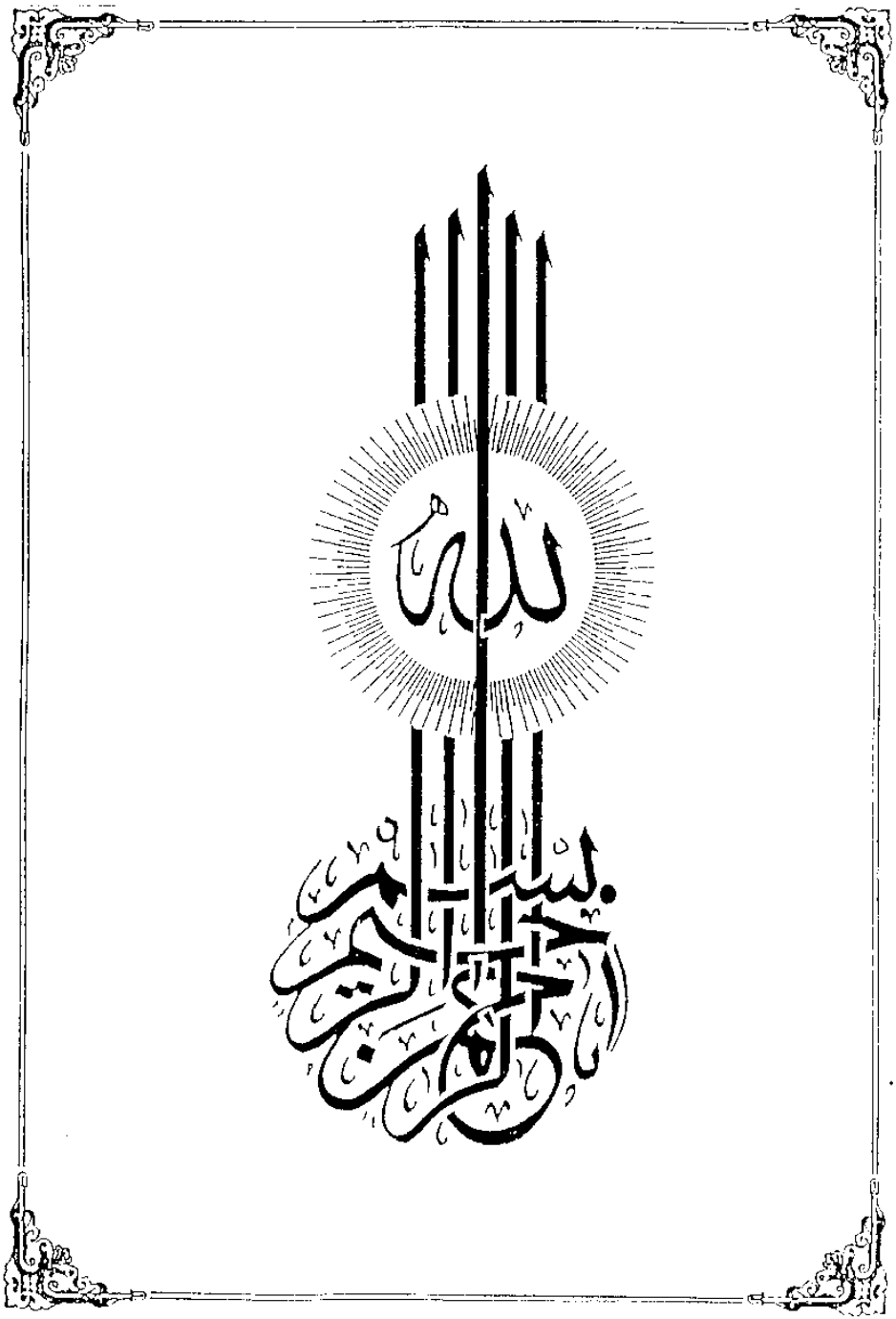

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The continuing rise in the reported incidence of malignant melanoma suggests that changes in exposure or behaviour may be responsible for the increase. The most widely accepted hypothesis Proposes that solar exposure makes a substantial contribution to the cause of the disease. Trauma has been proposed as an aetiological factor. Individuals with fair skin, blue eyes and naturally red or blond hair are more liable to malignant melanoma.

Clinically, primary cutaneous malignant melanoma may be classified into four major types: superficial spreading malignant melanoma, nodular malignant melanoma, lentigo malignant melanoma and acral lentiginous melanoma.

Histologically, malignant melanoma is classified by two ways: Clark's classification is based on depth of invasion of the tumour and Breslow's classification based on tumour thickness.

There have been many changes in the management of patients with malignant melanoma but surgery remains the only curative treatment and the patient's best chance of cure is adequate surgery on an early lesion. Immunotherapy of malignant melanoma is still considered experimental and has been employed in advanced disease. Chemotherapy either alone or combined with immunotherapy has also been employed in advanced cases. Malignant melanoma is considered to be one of the most radioresistant tumours but high fraction doses and hyperthermia may enhance the effect.

Recognition of the prognostic value of microstaging of the individual lesions has had a major effect on planning of more rational therapy. The combined determination of the level of invasion and the tumour thickness has resulted in a more logical approach to the surgical management of malignant melanoma.

The aim of this essay is to review malignant melanoma as regards its incidence, aetiology, classification, histopathology, clinical features, differential diagnosis, immunology, prognosis and treatment.

REVIEW OF LITERATURE

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HISTOLOGY OF THE SKIN

The skin consists of two layers of different origin and structure, the epidermis which is the thinner superficial layer formed of stratified squamous keratinized epithelium and the dermis which is the thicker deep layer formed of connective tissue. The epidermis is derived from the ectoderm while the dermis is derived from the mesoderm *(Lampe et al., 1983).*

I. The Epidermis: (Fig. 1)

The normal epidermis is a terminally differentiated stratified squamous epithelium. The major cell, making up 95% of the total, is keratinocyte, other cells present in the epidermis are the melanocytes, langerhan's cells and Merkel's cells. *(Thody and Friedmann, 1986).*

* Keratinocytes

They are the major cells of the epidermis, they move 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 *(Breathnach, 1975).*

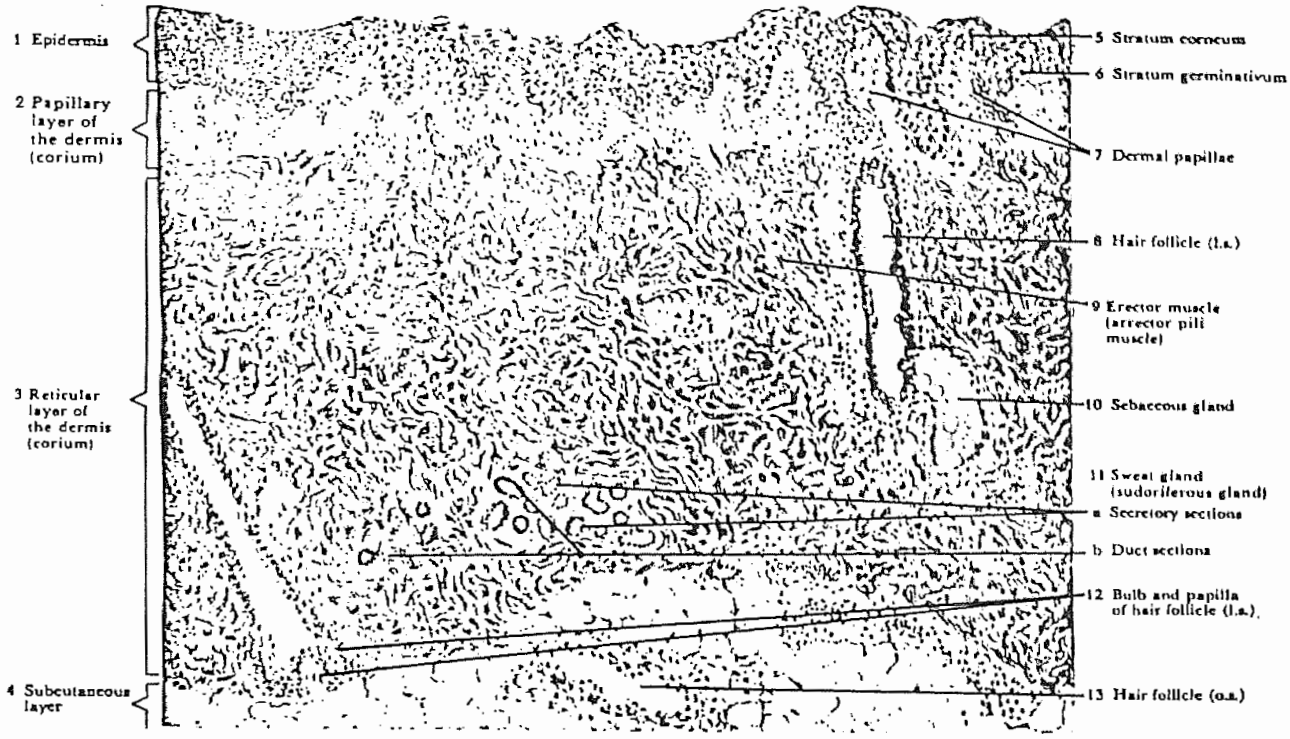

Fig. 1: Thin skin, general body surface *(Mariano and Flore, 1979)*

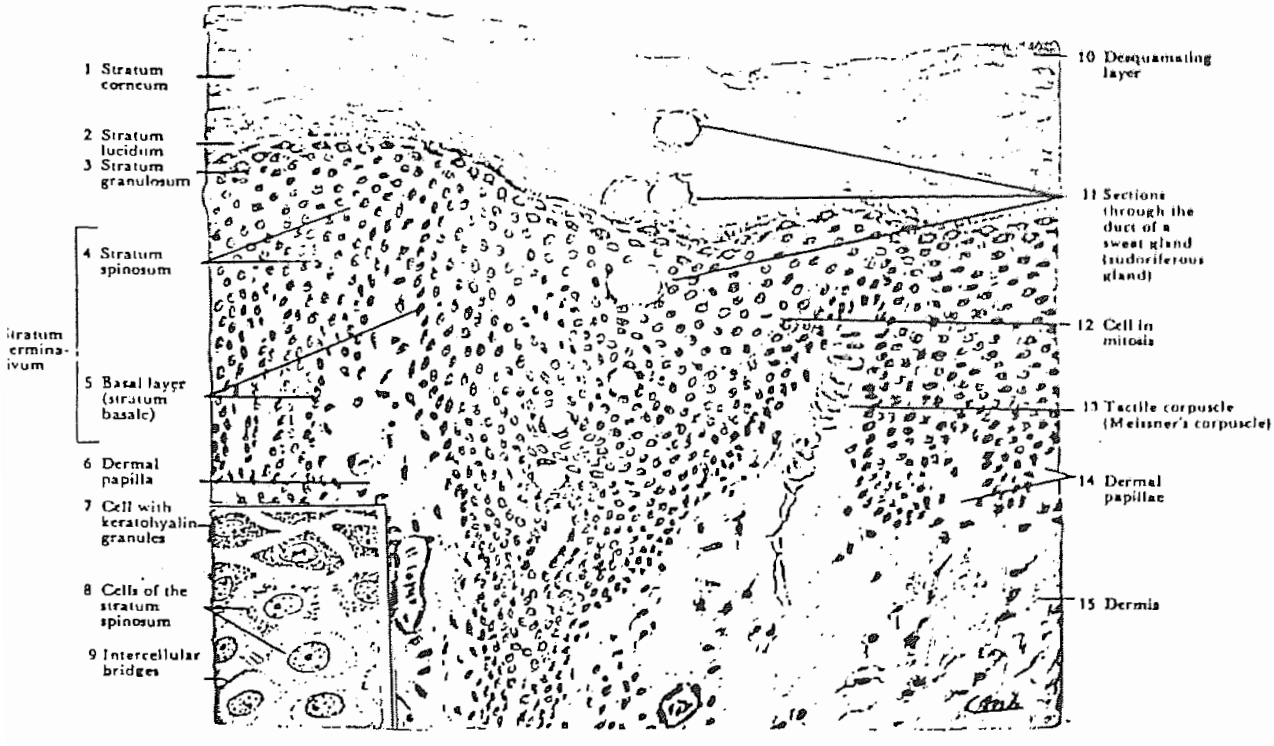

Fig. 2: Thick skin, palm: superficial layers *(Mariano and Flore, 1979)*

1) Stratum basale (stratum germinativum)

It is a continuous layer which is generally described as only one cell thick but may be 2-3 cell thick in hyperproliferative epidermis. The basal cells are small and cuboidal (10-14 nm) and have large dark staining nuclei and dense basophilic cytoplasm containing many ribosomes and dense tonofilament bundles. Mitotic figures are common in this layer. Their repeated mitosis is responsible for the regeneration of the entire epidermis (hence the name germinativum). The cells rest on a basement membrane and are anchored to it by hemidesmosome *(Breathnach, 1975).*

2) Stratum spinosum (Prickle cell layer)

Immedietly above the basal cell layer, the epibasal keratinocytes enlarge to form the spinous or Prickle cell layer which consists of 4-8 layers of polyhedral cells with rounded nuclei. The cells are larger near the basal layer but become smaller near the top. Mitotic figures are seen in the deeper layers. The cells have cytoplasmic processes which are joined to those of neighbouring cells by spot desmosomes. Cytoskeletal tonofilaments seem to attach close to desmosomes providing stability across the cell layers. Minimal intercellular substance allows the nutrients to diffuse from the capillaries of the dermis to the more superficial layers *(Breathnach, 1975).*

3) Stratum granulosum (granular layer)

Consists of 2-4 layers of flattened, diamond-shaped cells with flat nuclei. The cytoplasm contains basophilic granules of keratohyalin *(Matoltsy and Matoltsy, 1970).* The cytoplasm of cells of the upper spinous

layer and granular cell layer also contains smaller lamellated granules known as lamellated bodies, membrane - coating granules or Odland bodies. These are numerous within the spinous layer and migrate towards the periphery of the cell as it enters the granular cell layer. They discharge their lipid components into the intercellular spaces playing important roles in barrier function and intercellular cohesion within the stratum corneum *(Odland, 1960)*.

4) Stratum corneum

The outermost layer of the epidermis 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 granules responsible for keratin filament aggregation *(Lynley and Dale, 1983)*. The process of desquamation of keratin involves degradation of the lamellated lipid in the intercellular spaces and loss of the residual intercellular desmosomal interconnection *(Lampe et al., 1983)*.

In palmoplantar skin there is an additional zone, also electronlucent, the stratum lucidum, between the granulosum and corneum (Fig. 2). These cells are still nucleated unlike corneocytes but have opaque membranes and dense cytoplasm *(Lampe et al., 1983)*.

Kinetics of the epidermis:

The epidermis has classically been viewed as a stratified squamous epithelium maintained by cell division within the basal layer which is attached to the epidermal basement-membrane. Differentiating cells are gradually displaced outwards through the stratum spinosum to the stratum corneum. The anucleate corneocytes (squames), which protect the viable cell layers, are continually shed from the skin surface and the rate of production of cells in the basal layer must match the rate of loss from the surface to produce the normal skin thickness, although increased rates of loss and cell division occur in pathological states *(Pinkus, 1970).*

*** Melanocytes**

Malanocytes are the melanin producing cells. They are large branching cells present just under or inbetween the cells of the basal layers of the epidermis. Their cytoplasm contains tyrosinase enzyme which can convert tyrosine into melanin. The formed melanin granules pass to the tips of the cell processes to be injected into the neighbouring epidermal cells so both epidermal cells and melanocytes possess melanin and can only be differentiated by a histochemical reaction called DOPA reaction *(Thody and Friedmann, 1986).*

Melanocytes develop from an embryonic cell called melanoblast which migrates from the neural crest to the epidermis. It is a DOPA negative cell. Later on, it acquires tyrosinase enzyme and differentiates into a DOPA positive cell called clear cell (which is a melanocyte that has

not yet formed melanin granules) when the clear cell starts to form melanin granules in its cytoplasm it is called melanocyte *(Breathnach, 1971).*

*** Langerhans cells**

Denderitic cells of a form similar to melanocytes, but free from pigment, and dopa-negative, were first described by langerhans, who demonstrated their existence in human epidermis by staining with gold chloride *(Juhlin & Shelley, 1977).*

Under the electron microscope langerhans cells share with melanocytes a lobulated nucleus, a relatively clear cytoplasm and well-developed endoplasmic reticulum, Golgi complex and lysosomes. They differ in lacking melanosomes and in possessing a characteristic granule which is rod or racquet-shaped. They extend between the keratinocytes of the epidemis but not connected to them by desmosomes *(Zelickson and Mottaz, 1968).*

The origin of langerhans cells is mesenchymal, a view supported by the fact that they contain a similar range of hydrolytic enzymes to macrophages *(Riley, 1974).*

The function of the langerhans cell has been much debated. It has been argued that they could be concerned with the organization and function of the squamous epidermis *(Riley, 1974).* A role in keratinization was suggested by the fact that langerhans cells occur in epithelium from which they are normally absent such as the trachea and

urinary bladder, when squamous metaplasia is induced by vitamin A deficiency *(Wong & Buck, 1971).*

Another view was that langerhans cells are active as phagocytes. They are capable of limited phagocytosis *(Wolff and Schreiner, 1970).*

It is now evident that the major function of langerhans cells is to provide a reticulo-epithelial trap for contact antigens and to present them to T-cells *(Shelley and Juhlin, 1976).*

*** Merkel cells**

These are sensory receptors embedded in the basal layer of epidermal cells with which it has desmosomal connections. Each Merkel cell has a lobulated nucleus and characteristic granules in the cytoplasm. The nerve fibre loses its myelin, then loses the neurolemmal cells, then the naked nerve fibre penetrates the basement membrane to terminate as a terminal disc called Merkel tactile disc around the Merkel cell. Merkel tactile discs are present in the epidermis of soles and palms and they are touch receptors *(Winkelmann and Breathnach, 1973).*

II. The Dermis: (Fig. 1)

The dermis is bounded distally by its junction with the epidermis and proximally by the subcutaneous fat. It varies in thickness from about 1 mm on the face to 4 mm on the back and thigh. It is tough and reselient tissue which provides nutriment to the epidermis and cutaneous appendages and cushions the body against mechanical injury *(Wuepper et al., 1982).*