Chapter 1: Background & Basic Science

Introduction:

This chapter outlines the structure of normal skin and then discusses the most common benign and malignant pigmented lesions.

1.1 The skin:

Skin is the largest organ of the body weighing one-sixth of the total body mass of the average human. It is a homeostatic organ for heat and fluid balance, intrinsically linked with the endocrine system both as a primary and target organ, a protective organ against microbial invasion and external trauma, and, of course, a sensory organ providing tactile, thermal and noxious information about the external environment [Wheater *et al.,* 1987, Lever & Schaumburg-Lever, 1983]. Its basic structure is the same but it varies widely in thickness and pigmentation and in its composition of adnexal structures of hair, glands, nails, and sensory receptors from region to region of the body. The skin can be divided into two general regions - epidermis and dermis - bounded by the dermo-epidermal junction or basal lamina.

1.1.1 Epidermis:

The epidermis is a stratified squamous epithelium (figure 1.1) consisting of ectodermal cells that undergo keratinisation and melanocytes, embryologically derived from the neural crest, that produce melanin pigment. Keratinisation is a dynamic process - keratinocytes that form 95% of the cell population of the epidermis are produced by mitosis of the basal cells at the dermo-epidermal junction and migrate superficially, filling with keratin and losing the nucleus as they go. Eventually, keratinocytes are shed by mechanical trauma and friction. Thus, the stratified structure of the epidermis seen on microscopy represents stages in this dynamic process. The stratum corneum shows regional variation so that the plantar and palmar surfaces have the thickest layers of the human body as would be expected from the amount of friction and trauma sustained by these areas.

The stratum germinativum or basal layer consists of a single layer of cells anchored to the dermo-epidermal junction. In conjunction with the next layer, the stratum spinosum, a unit called the Malpighian layer (stratum Malpighii) is formed and here resides the melanocyte. More superficially are the stratum granulosum and the stratum corneum. The former is approximately five cells deep and consists of nucleated cells packed with keratin and its

precursors. The latter consists of flattened anucleated cells loaded with keratin, which often separates off in histological preparation. The epidermis has a remarkable rate of renewal and transit time of a cell from mitosis in the basal layer to being shed is usually 60-75 days [Lever & Schaumburg-Lever, 1986].

1.1.2 Melanocytes:

With the exception of the uvea, melanocytes are derived from non-pigmented precursor cells - melanoblasts- that migrate from the neural crest [Weston, 1970]. They migrate in the first trimester of gestation; reaching the epidermis by 8-10 weeks in a cranio-caudal fashion colonising the stratum germinativum and hair follicles [Sagebiel & Rorsman, 1970].

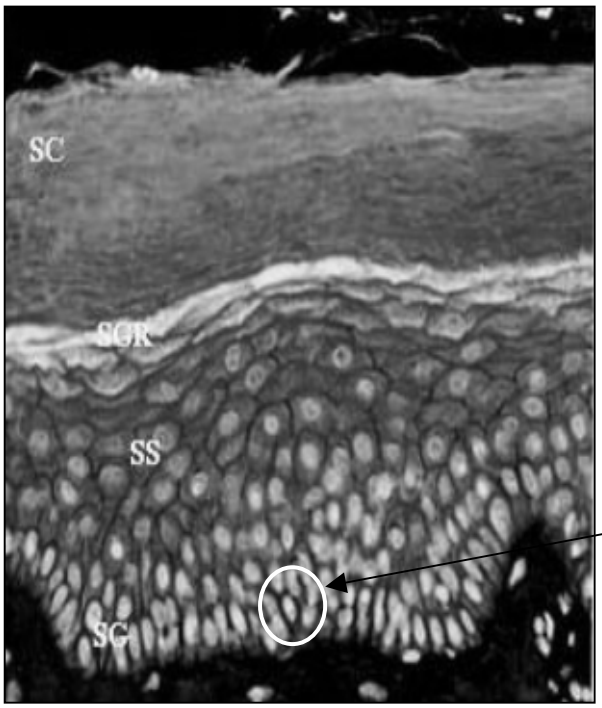


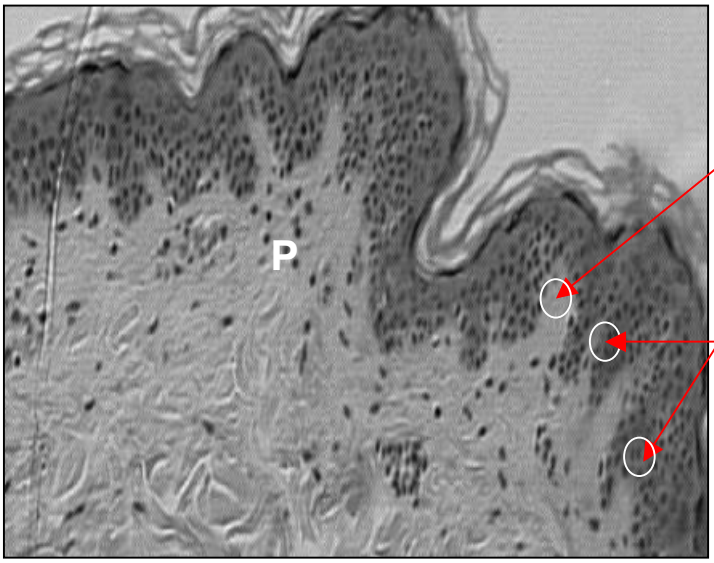
Figure 1.1: Epidermis of human skin x500
SC = Stratum Corneum
SGR = Stratum granulosum
SS = Stratum Spinosum
SG = Stratum Germinativum

The number of epidermal melanocytes shows a regional variation modified by the subject's age and sun exposure. On the face and genitalia, there are more than 2000/mm^3 epidermal melanocytes and here they are the most numerous. This contrasts with the upper arm where there are less than 1100/mm^3 [Fitzpatrick & Szabo, 1959]. The ratio of melanocytes to keratinocytes varies from 1:4 to 1:10. With advancing age not only does the number of melanocytes decrease but also so does the production of melanin [Gilchrest et al., 1979]. This is most obvious at the hair follicles where the subject's hair usually turns grey.

Epidermal melanocytes are scattered discretely throughout the Malpighian layer and have cytoplasmic projections between keratinocytes (figure 1.2). They convert the amino acid

tyrosine via the intermediate DOPA to melanin and contain the enzyme tyrosinase for this purpose [Lerner & Case, 1957]. Various hormones stimulate this process especially melanocyte stimulating hormone (MSH), adrenocorticotrophic hormone and the sex hormones. There are two main types of melanin produced by the melanocytes. Eumelanin is brown-black, phaeomelanin is reddish-yellow, and is the predominant melanin found in red-haired people. The melanin accumulates in vesicles called melanosomes that are transferred to keratinocytes by phagocytosis of the cytoplasmic processes [Cruikshank & Harcourt, 1964]. Most basal keratinocytes contain melanin and the inter-racial variation of skin pigmentation arises from the concentration of this and not the number of epidermal melanocytes that remains remarkably

Figure 1.2 Micrograph of human skin x40



PD = Papillary Dermis; RD = Reticular Dermis

constant [Starrico & Pinkus, 1957; Szabo, 1954]. A melanocyte and the keratinocytes that it supplies are collectively termed an ‘epidermal melanocyte unit' [Fiztpatrick *et al.,*1967]. With supra-basal migration and keratinisation, the melanin within the keratinocyte is broken down so that the superficial part of the epidermis is usually not pigmented. Conversely, pathology of the epidermis may produce shedding of melanin into the dermis termed 'pigmentary incontinence'. The melanin is phagocytosed by macrophages that are then termed as 'melanophages'.

When viewed with the light microscope the melanocyte usually appears as a small cell bulging at the dermo-epidermal junction separated from its fellows by several keratinocytes.

1.1.3 Dermis:

The dermis is the layer derived from mesoderm and consists of a thick supporting matrix of proteins- mostly collagen and elastin. It contains the epidermal appendages, blood vessels and nerves of the skin, its cellular component consists mainly of fibroblasts that produce the supporting matrix, and macrophages and mast cells concerned with host defence and repair of the dermis. It varies in thickness from 600 micrometres at the eyelid to greater than 3mm on the sole and palms, is generally thicker on the posterior surface of the body than the ventral and in males rather than females [Shuster *et al.,* 1975]. The dermis can be subdivided into papillary dermis and reticular dermis the thickness ratio being approximately 1:9 respectively.

1.1.4 Papillary dermis:

This is the layer of the dermis bounded superiorly by the dermo-epidermal junction, inferiorly by the sub-papillary vascular plexus and reticular dermis and laterally by the epidermal projections termed 'rete ridges' [McKee 1989]. It measures approximately 200 microns from superficial to deep but also shows wide regional variation. The papillary dermis undulates in a sinusoidal manner superficially and its projections, called 'dermal papillae', interlock with the rete ridges of the epidermis at the dermo-epidermal junction. These undulations show regional variations too. At the face and to a lesser extent the thigh and lower leg, the dermo-epidermal junction is smooth while the skin of the sacral and scapular regions shows elongation of the papillae [Moretti *et al.*, 1959]. Ageing produces a flattening of the dermo-epidermal junction and this can be seen most pronounced in the balding scalp. The deep surface of the papillary dermis has a smooth interface with the reticular dermis called the dermo-dermal junction. The papillary dermis consists mainly of type III collagen thrown into loose bundles of narrow-diameter and short fibres. Also found in this layer, intimately associated with the collagen fibres, are elastic fibres composed of the protein elastin running perpendicular to the skin surface. These fibres are 11nm in diameter and render the dermis retractile. All the structures are embedded within the ground substance that is a ubiquitous milieu synthesised by fibroblasts and consisting of fibronectin and glycosaminoglycans [McKee 1989].

1.1.5 Reticular Dermis:

This layer is bounded superiorly by the papillary dermis and inferiorly by the hypodermis that is mainly composed of subcuticular fat The boundaries are not self-evident on examination under the light microscope and therefore make measurements of thickness of this layer approximations at best. The reticular dermis consists of tightly woven, long and broad-width bundles of type I collagen arranged parallel with the surface of the skin. This is an important observation surgically as an incision placed in the same axis as these bundles will heal with a fine scar and the converse will produce a broad, heaped scar. Elastic fibres are found in large

quantities especially in the deeper region of the reticular dermis and they are arranged in parallel with their collagenous fellows.

1.1.6 Collagen:

Collagen is a complex protein secreted principally by the fibroblast in the skin. Initially procollagen molecules are synthesised and are combined into three pro-alpha chains that differ in the polypeptide residues at both the amino- and carboxyl terminals from collagen. Multiple enzymatic steps are involved to convert this precursor into collagen that includes co-enzymes ferrous iron and vitamin C and requires the presence of oxygen. The collagen chain contains three alpha chains composed of 1000 amino acids. These amino acids are composed of units of three with glycine occupying the third position. The other two positions contain various amino acids but principally these are proline in the first position followed by hydroxyproline in the second. The proline/hydroxyproline/glycine triplet lends to the structural integrity of collagen. The left-handed triple helix molecules of collagen are then intertwined with each other to form a right-handed superhelical model and the final rod measures approximately 300nm in length - several rods are then combined to form fibres or bundles.

Collagen molecules can be subtyped according to the variety of alternative amino acids and cross-linking that occurs with the molecule. The predominant collagen molecule is type I and this is found in most body tissues and is predominantly in the reticular dermis in the skin. The fibres here have a diameter of 2-15 micrometres. Type III collagen, also known as reticulin comprises the majority of the papillary dermis and measures 200 - 1000 nm in diameter while type IV collagen forms the basement membrane [Pope *et al.,* 1983].

There are a variety of inherited disorders described that result in faulty production of collagen including Ehlers-Danlos syndrome and pseudoxanthoma elasticum [McKee, 1989]. Clinically these patients have not only hyperextensile skin and poor scarring but also disorders of the vasculature, joints and eyes because of the quality of the connective tissue produced in these regions.

1.1.7 Vascular Supply and Arrangement:

The dermis receives a rich blood supply from subcutaneous arterioles that are derived from three main sources - the direct cutaneous system of vessels, fasciocutaneous system and musculocutaneous perforators [Cormack & Lamberty, 1986]. The arterioles lay in the subcutaneous tissue and branches from these supply the vascular plexus at the deep dermis and hypodermis level. This plexus gives off small branches that supply the deepest portion of

hair follicles, sweat glands and subcuticular fat. Superficially larger branches are given off that enter the dermis vertically and supply the epidermal appendages, smooth muscle fibres and nerves to end at the subpapillary plexus at the dermo-dermal junction that is arranged parallel to the skin surface. The subpapillary plexus supplies the upper dermis and forms capillary networks around the superficial epidermal appendages. In addition, capillary loops are given off into each of the dermal papillae and it is the blood within these loops that substantially contribute to the colour of the skin. The number and length of papillary loops in the skin shows regional variation that correlates with the number and development of dermal papillae and with the age of the subject. The epidermis has no vascular supply, both receiving nutrients and oxygen and exchanging metabolites by diffusion across the dermo-epidermal junction. Venous drainage conforms to the arteriolar supply but there is an additional venous plexus at the mid-dermal level. Also at this level are to be found arteriovenous anastomoses that allow shunting of blood proximal to the subpapillary plexus.

Many pathological conditions affect the vascular patterns of the skin. In wound healing there is an increase in the number of capillary loops seen in granulation tissue, basal cell carcinomas show visible telangectasiae especially at their peripheral margins and radiation and burns, in particular, produce a marked deterioration in the number and quality of the dermal vasculature. Portwine stains demonstrate specific anatomical abnormalities resulting in an increase in the number and diameter of the vessels - abnormal dilatation of the vessels is termed 'ectasia' [Barsky *et al*., 1980]. Ectasia is maximal at the subpapillary plexus level and can measure up to 400 microns in diameter.

1.1.8 Epidermal Appendages:

The epidermal or skin appendages are derived from cells originating in the ectoderm that migrate into the dermis and differentiate [Lever & Schaumburg-Lever, 1986]. Principally they form the hair follicles, sebaceous glands and sweat glands that are sheathed in connective tissue and basement membrane, and are surrounded by capillary plexus supplied by the dermal vascular arcades.

1.1.9 Nerves:

The skin has a rich supply of nerves: the efferent autonomics regulate vasculature, skin appendages and arector pili muscles and the afferent somatics to convey tactile and nociceptive information from the papillary dermis and hair follicles. There are a variety of nerve endings and types found within the skin to convey specific classes of information to the central nervous system.

1.2 Acquired melanocytic naevi:

Introduction:

A naevus is an area of skin that has an increased number of melanocytes with an increased amount of melanin [Browse, 1991]. Acquired naevi are classified according to the position of the melanocytes in relation to the dermo-epidermal junction. Thus a lentigo simplex and junctional naevus contains epidermal melanocytes, an intra-dermal naevus consists of dermal melanocytes and a compound naevus contains both [Mooi & Krausz, 1992a]. However, it will become clear from the discussion of these lesions that they do not remain as separate entities but represent phases in the cycle of the 'common acquired melanocytic naevus' in its journey from the epidermis to the dermis.

All Caucasians have naevi at some point in their lifetime. They emerge in childhood and are most numerous in early adulthood. At the extremes of life they are usually absent.[Nicholls, 1973; Cooke *et al.,* 1985]. One UK study attempted to quantify the average number of naevi in young Caucasian adults and found a wide variation between individuals and between the sexes with females having the greater number [MacKie *et al., 1985*]. The early emergence of naevi in childhood correlated with a greater number in adulthood. A Canadian study found that naevi in adolescent males tended to be distributed to the head, neck and trunk regions contrasting with the limbs in the females and were especially more common in the areas exposed to intermittent sunlight [Gallagher *et al.*,1990]. Epidermal naevi are most common in adolescence and early adulthood; compound and intra-dermal naevi are the predominant types of naevi later in life.

1.2.1 Lentigo Simplex:

The lentigo simplex is the first step in the development of acquired naevi. It is formed by a proliferation of melanocytes at the dermo-epidermal junction without the formation of nests and results in an increased pigmentation of keratinocytes [Mooi & Krausz, 1992a].Clinically it appears as a small pigmented macule on the skin and can be located anywhere on the skin or mucous membranes. The lesion is usually flat, symmetrical, impalpable and less than 4mm in diameter. They arise in childhood and become junctional and compound naevi in adulthood. However those on palmar or plantar skin and the vermilion border of the lip may persist.

Several clinical syndromes are associated with multiple lentigines including Peutz-Jeghers syndrome (an autosomal dominant disorder characterised by circumoral and buccal lentigines and is associated with gastrointestinal polyposis), LEOPARD syndrome and xeroderma pigmentosum - an autosomal dominant inherited disorder that produces a defect of

chromosomal repair leading to a high incidence of cutaneous malignancies caused by ultraviolet light [Dormandy, 1956; Voron *et al.*, 1976; Lynch *et al.*, 1977].

Under the light microscope, lentigo simplex is characterised by an absence of nesting of the melanocytes, thin, elongated rete ridges that are evenly spaced and regular in distribution and prominent pigmentation of the basal and suprabasal keratinocytes. In addition, the lentigo simplex may have some subepidermal fibrosis, melanophages in the superficial dermis and perivascular lymphocytic infiltrate. The melanocytes themselves have normal features with increased cytoplasm and may sometimes contain large melanosomes termed 'macromelanosomes'.

1.2.2 Junctional Naevus:

The junctional naevus represents the next step on the pathway of the acquired naevus though they may arise without a lentiginous route. Clinically they appear as symmetrical, sharp-bordered lesion often smaller than 8 mm and occur in childhood and adolescence. They may be just palpable and very dark in colour. Some occur on plantar and palmar skin and these may persist to adulthood.

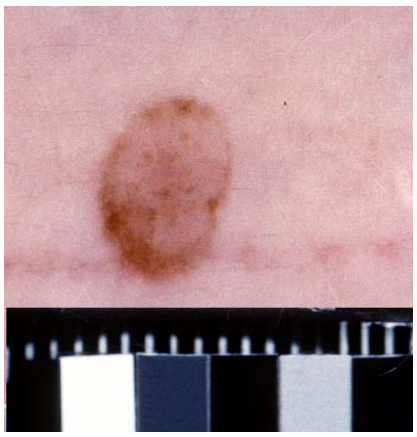


Figure 1.3

A Junctional Naevus

Under the light microscope, the junctional naevus may have lentiginous proliferation of melanocytes as described above but the feature that differentiates them from lentigos is the presence of naevus cell nests and these are confined to the epidermis. The nests are round or oval in shape and are present at the tip of rete ridges in most instances. The rete ridges themselves are often elongated within the naevus. The nests are usually symmetrically distributed and similar in size throughout the lesion [Mooi & Krausz, 1992a]. In the dermis, there may be some fibrosis in the papillary dermis and this is usually related to the lentiginous portion. At the level of the papillary plexus there may be some melanophages and perivascular lymphocytic infiltrate.

1.2.3 Compound Naevus:

The next stage of development is the migration of the nests of melanocytes into the dermis and this defines the compound naevus. Clinically, these small lesions are round or oval in shape with slight elevation from the surrounding normal skin. They occur in adolescence and early adulthood. There may be some hairs in the lesion and the surface may be smooth or corrugated. Thus, there is a large variation in the macroscopic appearance of these lesions from individual to individual but the lesion itself should be symmetrical and similar throughout.

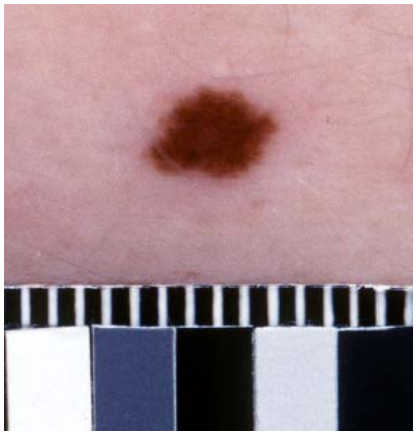


Figure 1.4

A Compound Naevus

When viewed under the light microscope, the epidermal or junctional component should be similar to a junctional naevus with the exception of rete tip preference of the nests and this is most pronounced in the thick, papillomatous naevi. The rete ridges, again, are often elongated and infrequently there may be a lentiginous proliferation of melanocytes especially towards the periphery. The nests of melanocytes become entrapped in the thickened papillary dermis until contact is lost with the epidermal component and are completely swathed in connective tissue - a process known as 'dropping off'. However, in the majority of compound naevi the nests remain confined to the thickened papillary dermis though there may be some projection into the superficial reticular dermis.

The melanocytes within these dermal nests undergo changes in their state of differentiation - the nucleus becomes smaller and there is less cytoplasm. The cells can be classified as types A,B & C representing points on a continuous spectrum of this change [Lever & Schaumburg-Lever, 1986]. However, the most striking feature in the deeper melanocytes is that they are generally devoid of melanin. This process has been termed 'maturation' but is roundly condemned by Mooi & Krausz (1992a) as inappropriate who would prefer the use of 'atrophy' as proposed by Goovaerts & Buyssens(1988). This is an important point to remember in the context of this thesis and means that by far the greater part of the colour of a compound naevus is derived from the superficial portion of that lesion.

1.2.4 Intradermal Naevus:

The final stage of the development of the acquired melanocytic naevus is the intradermal naevus that often decreases in size over the remaining years or may disappear altogether. As the name suggests, the junctional or epidermal component is lost except at the genitalia and plantar/palmar regions where there may be some lentiginous proliferation that remains. Clinically, it is occasionally slightly pigmented but usually the naevus is a small, dome-shaped lesion the same colour as the surrounding skin.

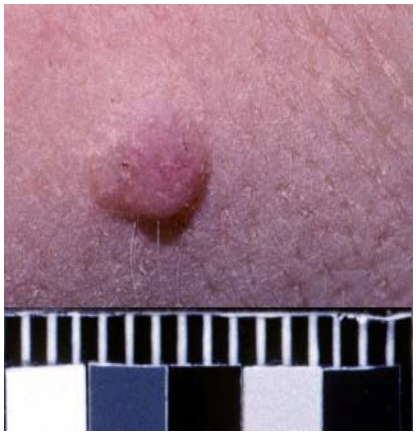


Figure 1.5

An Intradermal Naevus. Note the raised appearance and flesh colour.

Under the light microscope, there is a smoothing and flattening of the usual sinusoidal contour of the demo-epidermal junction. The naevus may also display some features of regression that includes fatty infiltration, fibrosis, myxoid change and an inflammatory response. The dermal component is otherwise similar to the compound naevus with maturation of the melanocytes.

1.2.5 Dysplastic Naevi:

Melanomas can arise at the site of a pre-existing acquired naevi and several studies have demonstrated remnants of acquired naevi at the periphery of histological specimens [Ackerman & Mihara, 1985; Black, 1988]. This finding has directed researchers to look for a particular subtype of naevi that carry a clinically significant risk of becoming melanomas. The dysplastic naevus was first described in two families with a predisposition to melanoma but has since been advanced as a premalignant lesion. This has created many debates and Mooi & Krausz

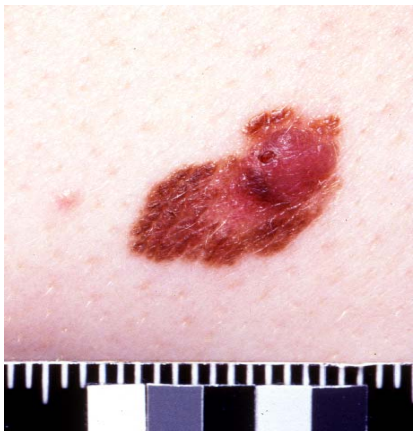


Figure 1.6

A Dysplastic Naevus. This lesion is clinically suspicious due to it demonstrating asymmetry, several colours, a diameter over 6mm and elevation.

(1992a) highlight the main areas of controversy. These include no consensus of definition, differences in terminology used to describe them, insufficient follow-up (if the lesion has been removed then its natural history cannot be observed) and a similarity in morphology between dysplastic naevus and melanoma meaning that one progresses to the other may be an incorrect assumption. This lack of consensus and definition has led to some authors abandoning the diagnosis altogether [Hastrup, 1994]. Melanocytic intraepidermal neoplasia (MIN) is another term that has been used to define this difficult category of lesions [Cook *et al.,* 1996: Cook *et al.,* 1997] and includes the dysplastic naevi and melanoma in situ subsets. However, this creates problems in turn as many dysplastic naevi are compound and are not, therefore, confined to the epidermis. Thus, the term dysplastic naevus, despite its shortcomings, prevails [Mooi, 1997].

Clinically the dysplastic naevus is often a symmetrical, slightly raised, irregularly pigmented lesion greater than 6mm in diameter. They often occur on areas where other naevi are absent such as the buttock, breasts, genitalia and dorsum of foot. The peripheral border often is blurred and has a hyperaemic ring around it. Under the light microscope, several architectural features are commonly seen. In the epidermis, there are nests as well as lentiginous proliferations and the rete ridges are irregular and elongated. The dermal component is centrally placed and contains nests and strands of melanocytes. The subepidermal region shows increased fibrosis especially around the papillary vessels that are invariably increased in number and show perivascular lymphocytic infiltration. The diagnosis of dysplastic naevus also depends on the analysis of the cytological features of the lesion. The histopathologist is looking for nuclear atypia and pleomorphism that is usually most apparent in the junctional component of the lesion. In contrast to melanomas, this nuclear atypia is evenly distributed throughout the lesion.

1.2.6 Other Naevi:

For completeness there will follow a short description of blue, Spitz and congenital naevi.

1.2.7 Blue naevus:

These naevi are thought to arise from the dermis rather than the epidermis and can be subdivided into common and cellular naevi. Common naevi are usually symmetrical bluish-grey nodules that are found most commonly on the dorsum of the hands and feet and the face and scalp. The cellular blue naevus tends to be larger and is located at the buttock and sacrococcygeal regions. They can be congenital or acquired - the latter occurring in the 3rd to 5th decade with a female bias of 2:1. [Rodriguez & Ackerman 1968]. Malignant transformation

in a common naevus is exceedingly rare but in a cellular naevus, while still comparatively rare, has been well documented.

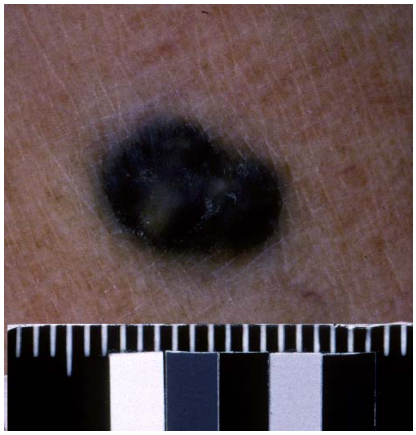


Figure 1.7

A Cellular Blue Naevus. The smooth, domed shape and the ink blue appearance are typical of this type of naevus.

Under the microscope, the common blue naevus has a proliferation of melanocytes mainly in the reticular dermis that may extend into the subcutis in an infiltrative pattern. However, there may be a narrow subepidermal zone free of melanocytes that is termed a Grenz zone. Often there is accompanying fibrosis in the dermis and the nests show a predilection for vessels, nerves and adnexae. Unlike intradermal naevi, there is no maturation of the melanocytes that are uniform from superficial to deep within the lesion. The cellular blue naevus demonstrates a biphasic pattern of melanocytes with an irregular distribution of melanin that distinguishes it from the common type. The lesion may extend into the subcutis, described by Mooi & Krausz (1992a) as a 'pushing' manner with an abrupt cut-off.

A combined naevus is the mixture of an acquired naevus and a blue naevus of either type. These uncommon naevi usually occur on the faces of females in a broad age-range and are mentioned as they can be easily confused clinically with a melanoma.

1.2.8 Spitz naevus:

This lesion was first described by Spitz (1948) as a separate entity from childhood melanoma. The Spitz naevus occurs in young adults and children with an even sex-distribution. They appear mainly as fleshy, pink nodules or polyps especially on the face and lower extremities but can be heavily pigmented on occasion. Under the light microscope, they may be junctional, compound or intradermal in nature though the majority are compound. There are large and pleomorphic spindle or epithelioid cell nests that are regular in distribution and often penetrate into the reticular dermis. The epidermis is usually hyperplastic with markedly elongated rete ridges. The dermis shows fibrosis and vascular proliferation with telangectasiae.

1.2.9 Congenital Naevi:

By definition these naevi are present from birth and are classified according to their size – small are less than 1.5cm, intermediate are less than 20cm and large are greater still [Consensus Conference, 1984]. There are also several eponymous congenital blue naevi viz. Naevus of Ota, Naevus of Oto, Sun's Naevus and the Mongolian Blue Spot.

This heterogeneous group varies greatly in their clinical presentation, being diffuse or well-demarcated, blue to pale brown and the larger ones may be covered in coarse hairs. There may be associated melanocytic meningeal proliferations involving both the brain and spinal cord coupled with neurological symptoms that are associated with a poor prognosis. Under the light microscope, the smaller lesions may be indistinguishable from their acquired cousins but the larger lesions tend to engulf and infiltrate the epidermal adnexae and arrector pili muscles. Penetration is often deep into the reticular dermis.

The risk of malignant transformation of these lesions has been debated. The largest lesions have a risk of approximately 8% and this occurs in childhood and early adolescence [Quaba & Wallace, 1986]. Histopathologically they are the naevi with subcutaneous involvement and unfortunately, this is usually the location of malignant transformation. Early surgery is therefore advocated for these lesions. One study showed no cases of malignant transformation in lesions covering less than 5% of the total body surface area and no increased risk of non-melanoma cancers [Swerdlow *et al*., 1996]. However, this result was interpreted with caution by the authors and called for a systematic review or meta-analysis to quantify the risk according to size and to allow appropriate clinical management.

This concludes the section on benign naevi and the reader is directed to table 1.1 for a summary of the clinical and histopathological features of these groups that is derived in large part from Mooi & Krausz (1992a).

Table 1.1: Summary of features of benign naevi

Type	Lentigo Simplex	Junctional	Compound
Clinical Features	Small macule Found anywhere Children & young adults	Small macule Symmetrical & sharp demarcation Children & Young adults	Palpable papule Large variation in appearance but symmetrical Young adults
Histopathological Features	Absence of nesting Elongated rete ridges +/- Subepidermal fibrosis +/- melanophages	Nesting of melanocytes Rete tip preference & elongation +/- fibrosis +/- melanophages	Elongated rete ridges Nests 'dropping off' in papillary dermis Maturation or atrophy of melanocytes Thickened papillary dermis
Other Comments	As part of a syndrome e.g. Peutz-Jehgers		

Type	Intradermal	Dysplastic	Blue
Clinical Features	Regular, raised fleshy or light pigmented nodule Adults	Symmetrical, irregular pigmented >6mm found at uncommon/covered sites	Regular small nodule 3rd to 5th decade hands, feet & head F:M 2:1
Histopathological Features	Rete ridges absent or flattened Regression, fibrosis, myxoid change. Melanocytes +/- melanin	Rete ridges elongated & irregular Nesting & lentiginous change Increased vascularity +/- fibrosis Nuclear pleomorphism & atypia	Proliferation into reticular dermis +/- subcutis Surrounds adnexae
Other Comments		Dysplastic naevus syndrome Possible increased risk of melanoma Controversy over criteria – some pathologists do not use the term	Malignant transformation rare but can occur in cellular type Eponymous congenital types

Type	Spitz	Congenital
Clinical Features	Children & young adults Often a fleshy pink nodule Face	Heterogeneous group Scalp, back & sacrum Pigmentation varies
Histopathological Features	Majority are compound Pleomorphic cell types Markedly elongated rete ridges Into reticular dermis	Smaller lesions indistinguishable from acquired naevi Infiltrates deep tissues Engulf adnexae
Other Comments	Sometimes impossible to distinguish from melanoma	Associated meningeal lesions +/- Neurological symptoms (poor outcome) Definite risk of malignant transformation in >20cm lesions Risk uncertain in others

1.3 Non-Melanocytic Pigmented Lesions

In this section the solar lentigo, basal cell papilloma (BCP) and basal cell carcinoma (BCC) will be considered as a group. They are not melanocytic in origin but share the ability to stimulate adjacent melanocytes to produce increased amounts of melanin [Mooi & Krausz, 1992a] that is then transferred to the tumour cell. In the case of BCC's, these tumours appear histologically identical to their non-pigmented counterparts.

1.3.1. Pigmented Basal Cell Carcinoma

The BCC is the commonest skin tumour of humans and occur in regions of sun-damaged skin in the white-skinned population [Kirkham, 1991]. As can be expected, given that the length of exposure to sunlight is the main risk factor, this is a disease of the elderly population. However, genetic disorders such as Gorlin's syndrome and Xeroderma Pigmentosum predispose patients to multiple BCC's. Histologically, the tumour consists of regular cells that, as the name suggests, are derived from the basal cell layer. These cells are strongly haemotoxophilic, with large nuclei and little cytoplasm, that arrange themselves into nests and groups of varying size and shape. The propagating element of the tumour is found at the peripheral nodules of the lesions. This fact accounts for the progression of the tumour by local invasion and destruction with metastasis occurring extremely rarely. Subtypes of the tumour include nodular, cystic, morpheic and sclerosing. The lesion can be multifocal and its cells can be well or poorly differentiated. These subclasses help to define the clinical progress of these tumours in terms of depth and margins of invasion, aggression and likelihood of recurrence. With pigmented BCC's, the melanin tends to accumulate mainly within the necrotic centre of the tumour nest [Mooi & Krausz, 1992a] and this accounts for its distinctive appearance when viewing with the skin surface microscope [Soyer *et al.,* 2001]. Treatment is normally by surgical excision and repair that depends upon the extent of the invasion of the tumour.

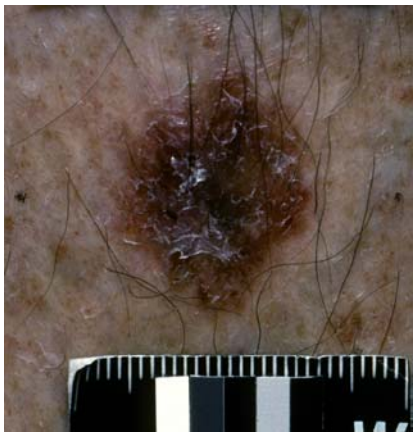


Figure 1.8

Pigmented Basal Cell Carcinoma. This lesion demonstrates the how a BCC can mimic melanoma. A 'rolled edge' that is not appparent from this photograph was the only clue.

1.3.2 Solar Lentigo & Basal Cell Papilloma

The solar lentigo is a pigmented macule that occurs on sun-exposed areas of the skin in elderly, white patients [Mooi & Krausz, 1992a]. Clinically these lesions may be mistaken for early lentigo maligna and are relevant for that reason. Alternative names for this lesion include the 'liver spot' and 'senile lentigo'. Histologically, there is an increase in pigmentation compared to the surrounding skin but the number of melanocytes is normally unchanged. Often there is some subepidermal fibrosis with melanophages and elongation of the rete ridges. The lesion is related to the basal papilloma [Mooi & Krausz, 1992a].

The basal cell papilloma is an extremely common benign lesion that appears as a warty growth on older patients. The alternative name, 'seborrheic keratosis' is derived from its

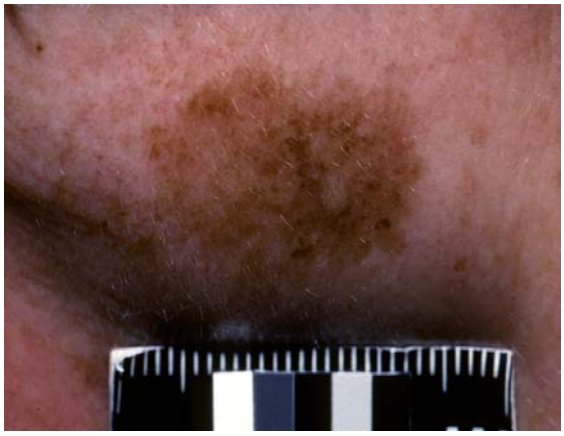


Figure 1.9

Seborrheic Keratosis. A large, irregularly shaped and pigmented macular seborrheic keratosis such as this can be difficult to distinguish from a superficial spreading melanoma or a lentigo maligna.

distribution to mainly the 'seborrheic' regions of the body, namely forehead, back & chest [McQueen & Smith, 1988]. Clinically it usually appears as a soft, pigmented raised lesion that is classically said to look as if it has been 'stuck on' the skin. However, heavy pigmentation and the tendency to itching, inflammation and bleeding can result in the lesion sometimes being misdiagnosed as a nodular or advanced superficial spreading melanoma. On the face, the lesion may be large and macular, giving rise to diagnostic confusion with lentigo maligna. Histologically, the lesion is epidermal with an abundance of poorly differentiated basal cells. Keratin is often produced in large quantities and is arranged into spherical masses that are termed keratin cysts. Melanocytes are present amongst the basal cells that produce melanin in great amounts.

1.4 Malignant Melanoma

Introduction:

This section of the chapter will discuss the pathology and epidemiology of malignant melanoma. Melanoma can arise from tissues other than the skin, most notably the eye but also buccal and genital mucosa –comprehensive summaries of these lesions can be obtained elsewhere [Mooi & Krausz, 1992a; Rogers & Gibson, 1997]. However, these melanomas are beyond the discussion of this thesis and hereafter the term malignant melanoma (abbr. MM) refers to cutaneous malignant melanoma only, unless otherwise stated. Included within this section is lentigo maligna, which is not strictly a malignant melanoma but is regarded by most authorities as a premalignant condition [Mooi, 1992b].

1.4.1 Epidemiology:

1.4.1.1 Incidence & Mortality:

Malignant melanoma (MM) is a cancer of melanocytes and the overwhelming majority of the literature documents its relentless progress up the incidence league tables of all cancers in both incidence and mortality. Over several decades, the incidence of melanoma has been roughly doubling in most countries studied. The problem is not restricted to a few countries but is worldwide: even in those such as Japan with its low-risk population [Tanaka *et al.*, 1999]. In the USA, the incidence in the Caucasian population increases annually by 6% and the lifetime risk has risen from 1 in 1500 in 1935 to 1 in 75 at the present time [Rigel, 1996; Hall *et al.,* 1999a]. These statistical trends are mirrored in other countries such as Scotland [MacKie *et al.,* 1997], Sweden [Thorn *et al.*, 1998] & South Africa [Saxe *et al.*, 1998]. The most dangerous place to be for melanoma is the Antipodes where a recent report from New Zealand [Jones *et al.,* 1999] indicates that Auckland has overtaken Queensland, Australia [MacLennan *et al.,* 1992] with the highest incidence of melanoma in the world that stands at a staggering 78 per 100,000 (crude rate). The statistics in England and Wales are complicated by problems of centralised reporting to the Cancer Registry but one study corrected for this and found figures comparable to Scotland [Melia *et al.,* 1995a]. The overall incidence of melanoma in the UK in 1997 was reported at 5710 cases (written communication from Dept. Medical Statistics, Cancer Research Campaign, London) [CRC website].

Statistics such as these have led to the dramatic rise being termed as an ‘epidemic’ and ‘an emerging medical catastrophe’ [Creagan, 1997]. A review of the literature, however, shows that this may be an over-simplified analysis and that a dichotomy of opinion and trends is

apparent. Whilst it is true that the overall incidence of melanoma was rising quite dramatically throughout the world as reported in the papers of the early 1990's, the most recent papers show a new trend [Brochez & Naeyert, 2000]. It appears that there is now a plateauing in the incidence of melanoma in many countries [Gaudette & Gao, 1998; Mackie, 1998; Buillard *et al.,* 1999], most noticeably in the females and the younger population. It is also apparent that the mortality is rising less sharply than the incidence and that the trend is towards the diagnosis of 'thinner', less aggressive lesions, whilst the incidence of thicker lesions has risen minimally [Lipsker *et al.,* 1999]. This is difficult to explain simply and may be a combination of increased surveillance and reporting, better diagnostic techniques and technicians, better treatment and better education of the public and clinicians alike [Dennis, 1999]. One interesting proposition is that early melanoma may be a separate and benevolent clinical entity and that our earlier understanding of the natural history of melanoma may be flawed [Swerlick and Chen, 1996 & 1997; Burton & Armstrong, 1995].

Similarly, mortality statistics throughout the world show a changing trend. Crude mortality measurements show that this is still rising [Hall *et al.,* 1999a], though the rate of increase is trailing off and in certain groups this has plateaued or is starting to fall [MacKie *et al.,* 1997; Gaudette & Gao*,* 1998]. The mortality rate is consistently higher in males than females in most countries. The mortality rate in England & Wales is approximately 3 per 100,000 in men and 2.8 per 100,000 in women with an overall total of 1640 cases in 1999 [CRC website].

1.4.1.2 Age, Sex & Anatomical Location:

In Scotland, the incidence of invasive melanoma is higher in women than men in all age groups except the over 85's [MacKie *et al.,* 1997]. This is not the case in other studies where the incidence is equal or reversed [Gaudette & Gao, 1998; Hall *et al.,* 1999a]. In both sexes, for all subclasses of melanoma, the incidence increases steadily with age, though in the UK melanoma is the third most common cancer in the 20-34 year-old age group [CRC website]. The anatomical distribution statistics are consistent from study to study in that the face and neck overall are the most frequently affected sites but broken down into sexes the trunk is most common in males and the lower leg is most common in females. In Scotland and elsewhere, this sex-site variation is correlated with thickness of melanoma at initial diagnosis [MacKie *et al.,*1997; Thorn *et al.,* 1990].

1.4.1.3 Risk Factors:

Exposure to ultraviolet light is probably the strongest environmental risk factor for melanoma. This would explain the site-specific and sex-specific incidence rates discussed in the previous paragraph. One study showed that the risk of acquiring melanoma of the lower limb is five-fold in skirt-wearing women compared to trouser-wearing males [Osterlind *et al.,* 1988]. A large

case-control study attempted to quantify and qualify the risk of exposure to UV light and associate these with skin type [Walter *et al.,* 1999]. The results strongly suggested that intermittent exposure such as beach holidays, burning in childhood and the use of sun-beds were associated with greatly increased risk of melanoma and that a fair skin type compounds this risk. Interestingly, the risk for chronic exposure such as an outdoor job was significantly *reduced* and confirms the results of other studies [Gallagher *et al.,* 1987].

Assessing the genetic risks of individuals and their families in the development of melanoma has generated much research and Greene wrote an excellent review of the literature in 1997. Since 1983, when the first reports of a link between the dysplastic naevus syndrome inherited in an autosomal dominant fashion emerged, three possible gene loci have been proposed for these families and one (CMM2) has been confirmed, mapped to chromosome 9p21 [Greene, 1999]. Greene also discusses the risk factors collected from several studies of dysplastic naevi diagnosed on clinical grounds and found that they were a potent factor with the relative risk varying from 1.0 to 16.7 (median 5.2). In addition, data from several studies that prospectively followed up dysplastic naevus families was collated and it was found that the relative risk of melanoma ranged from 167 to 964 and the melanomas occurred exclusively in those family members that had dysplastic naevi. In addition to the dysplastic naevus syndrome, association with other hereditary disorders has been well documented – especially xeroderma pigmentosum, an autosomal recessive disorder that causes a defect in DNA repair after damage by UV light [Mooi & Krausz, 1992a].

A paper by Rigel (1995) summarised succinctly the key risk factors for the development for melanoma and these were: (1) red/blond hair, (2) family history of melanoma, (3) Actinic keratoses, (4) considerable freckling on the upper back area, (5) three or more blistering sunburns before 20 and (6) 3 or more years of outdoor summer jobs during teenage years. The presence of one or two factors produced a 3-4-fold increase risk of developing melanoma and this soars to 20-fold with three or more factors.

1.4.2 Macroscopic & Microscopic Appearance of Malignant Melanoma:

Classically, melanoma is divided into four separate diagnostic subclasses [Clark *et al.,* 1969] that are nominally superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. This arises from the observations that melanoma is not a single entity and has different behaviours, characteristics and probably natural history depending on site, race and age distributions. The four diagnostic categories have become widely accepted by many authors with the exception of a few notable dissenters [Ackerman,

1980; 1982; Weyers *et al.,* 1999]. Mooi & Krausz (1992a) outline some of the problems with this concept. The main problem is that there is no single logical system of histopathological criteria but a mixture of features from histology, cytology and clinical locality that, unfortunately, can occur across subtype boundaries. Second, tumour progression may mean that distinguishing characteristics can be obscured such as the nodular portion of a superficial spreading melanoma destroying the lateral superficial radial growth. Third, a melanoma may fit into more than one different subtype. This obviously can pose a diagnostic conundrum for the histopathologist in about 10% of melanomas and some may remain unclassifiable. However, Mooi & Krausz (1992a) point out that this problem is not unique to melanomas but to most tumours resulting in a minority of subtypes that cannot be compartmentalised. As a result of the wide acceptance of the subclasses initially proposed by Clark in 1969, they will be discussed and used in this thesis.

1.4.2.1 Clinical (Macroscopic) Appearance:

Much of the menace of melanoma that can prey on the paranoia of patients and clinicians alike can be attributed to the banal nature of their clinical presentation. Unlike other major cancers, melanomas are rarely painful except in a few advanced cases that display perineuronal spread or direct neuronal invasion. Similarly, bleeding is a sign of advanced local disease, where the rate of increase in tumour mass outstrips the ability of the blood supply to deliver oxygen and nutrition causing focal necrosis and ulceration. Most melanomas present as a lesion, arising *de novo* or from within an existing naevus, that is changing in size, shape or colour over a period of several months [Hall, 1992].

Like a cutaneous chameleon, melanomas can vary greatly in their colouration and appearance, often depending on the region of the body that they are located. Classically, these lesions are asymmetrical in shape, have a blurred, irregular and notched border, are variegated in colour, greater than 6mm in diameter (and can be several centimetres across) and have an elevated, papular or nodular component within the lesion. This description has been termed the 'ABCDE' of melanoma [Friedman *et al.,* 1985; Hazen *et al.,* 1999]. In addition, melanomas often have a pinkish, hyperaemic rim, colours ranging from blue to black and whitish areas of depigmentation, termed regression, within the lesion [MacKie, 1992]. The surface may be ulcerated and there may be separate nodules a few centimetres from the lesion and these are called satellite nodules.

1.4.2.2 Microscopic Appearance:

The process of diagnosing a melanoma is a function of all the information presented from the clinical, macroscopic and microscopic details of the lesion [Mooi & Krausz, 1992a]. In assessing the lesion microscopically, both the architectural and cytological qualities are of

importance. As with the macroscopic appearance, there is a broad spectrum of features that occur within the umbrella of melanoma: one lesion may demonstrate severe architectural disturbances and yet have small, uniform cells and another may have quite regular architecture.

In describing the architecture, there is a constellation of features that are used to exclude the diagnosis of benign naevus, though no single feature is invariably present and diagnostic of melanoma. The most common and probably the most important feature to assess is asymmetry. Benign naevi are usually symmetrical at the mid-point. In contrast, melanomas display asymmetry in most of their architecture -lateral extension, dermal descent, components & fibrosis- as well as their cytology - pleomorphism, atypia and distribution.

It is also worth noting that nearly all melanomas have an epidermal component, where it is thought that malignant transformation occurs [Mooi & Krausz, 1992a]. In the epidermis, Pagetoid spread is a major indicator of melanoma. This describes the upward ascent of *atypical* melanocytes from the stratum Malpighii to the granular layer and above in the lateral margins of the tumour. Upward spread is usually seen throughout the lesion but Pagetoid spread specifically refers to the lateral margins of the tumour. Atypical ascent or Pagetoid spread is highly specific for melanoma but melanocytic ascent may be present in benign lesions, most notably Spitz naevus and congenital naevus in infants. With the exception of nodular melanoma, the lateral borders of melanomas are poorly demarcated described as a 'gradual petering out' by Mooi & Krausz (1992b). They contrast this to the situation of the benign naevus where both lateral borders are sharply demarcated by naevus cell nests in most cases. In addition, there may be epidermal hyperplasia but this is seen in many benign lesions and is not considered a useful diagnostic feature [Mooi & Krausz, 1992b].

The intradermal growth pattern is irregular in melanoma with combinations of nodules, sheets of tumour and single cells in a mixture of fibrosis and inflammatory exudate. In contrast to compound naevi, there is no maturation with increasing depth of the melanocytes. Once invading into the dermis, melanomas tend to instigate an inflammatory reaction that is usually seen in a band-like region at the base of the tumour, often with an abundance of melanophages [Lever & Schaumburg-Lever, 1986]. As a result of the inflammation, there is usually a vascular proliferation with the vessels appearing quite ectatic in places. Regression of melanomas is seen in many cases [Barnhill & Mihm, 1993] and is a significant observation. It is thought to be an immune-mediated process and may be categorised into three stages. Early regression is characterised by a dense immunocytic reaction disrupting nests of melanoma cells in the papillary dermis without fibrosis whilst the intermediate stage demonstrates patchy loss of tumour in the papillary dermis, fibrosis, melanophages and

telangectasia. Late fibrosis is characterised by absence of tumour, marked thickening of the papillary dermis by fibrosis and flattening of the normally sinusoidal dermo-epidermal contour. The collagen bundles in the papillary dermis are thick and arranged parallel to the skin surface. There may be extensive telangectasia and angioneogenesis.

In keeping with the general trends of melanoma, the morphology of the cells varies widely [Mooi & Krausz, 1992a]. The cells come in a variety of shapes and can be very small or gigantic. The cytoplasm can be granular or clear and can contain fine, powdery melanin, giant melanosomes or no melanin whatsoever - the amelanotic melanoma. The nucleus (or, indeed, nuclei) can vary in both size and shape and mitoses, often abnormal, are usually present at the base of the invading tumour in large numbers.

1.4.2.3 Carcinogenesis and the Horizontal & Vertical Growth Phases

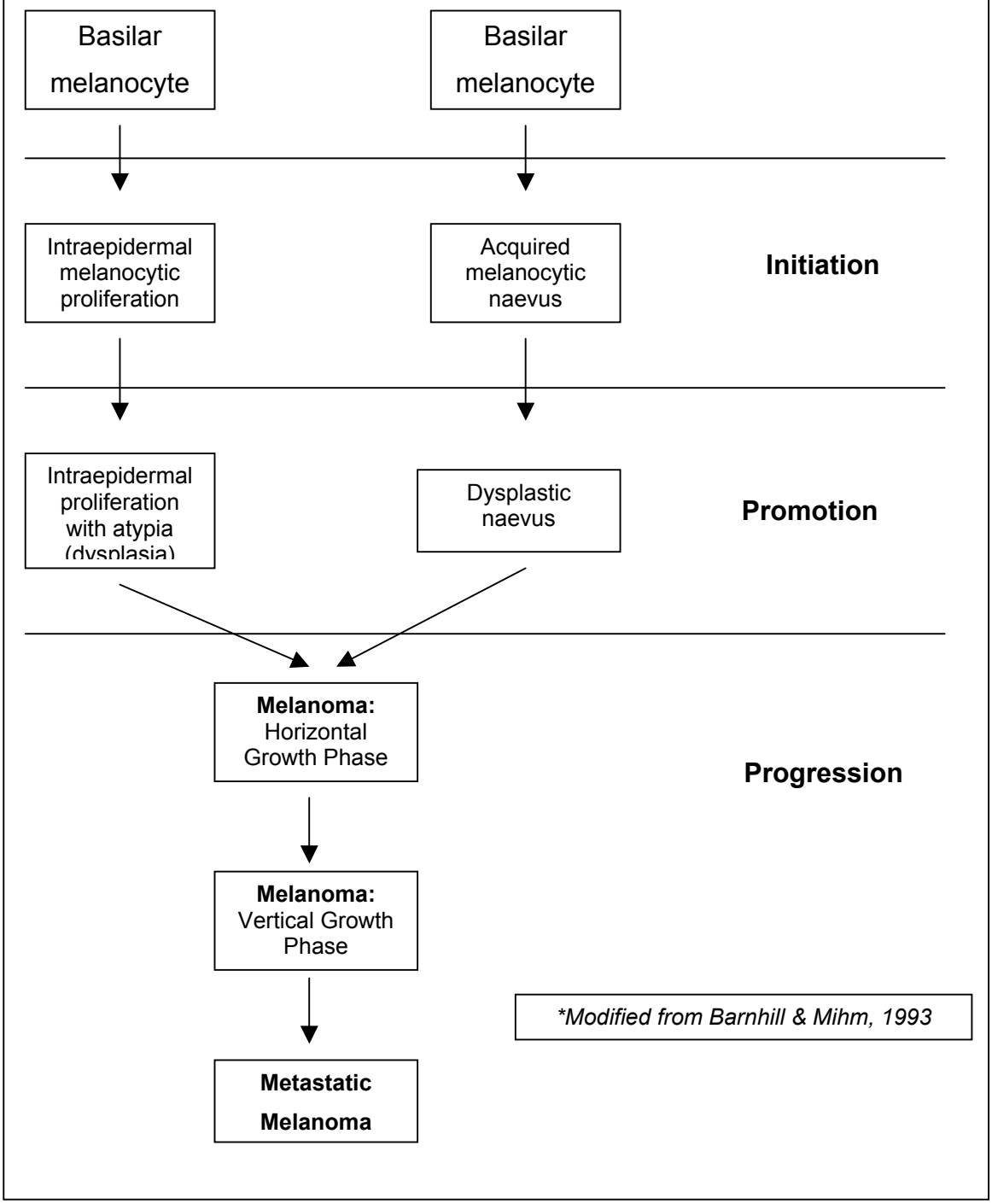
Carcinogenesis can be thought of as a three-step process that starts at initiation through to promotion and on to progression [Brodland, 1997]. A cell is *initiated* when it undergoes an irreversible genetic mutation and this most commonly occurs in the skin by exposure to ultraviolet light (UV B) [Streilein *et al.,* 1994]. If the cell continues to divide, then this genetic mutation is passed onto the cell's progeny. Second, *promotion* of the initiated cell expands the colony by a factor of millions and is thought to be a reversible receptor-mediated process. With such a large expansion, the likelihood of an initiated cell acquiring a second, irreversible genetic mutation is increased. When this occurs the cell is said to have *progressed* and can be seen as cellular atypia under the light microscope. Now that the cell has progressed, there is progressive genetic instability with each mitosis and the various clones of the original progressed cell show pleomorphism with different rates of growth. Progressive malignancy of the cells confers increasing invasive potential and resistance to cytotoxic influences. Therefore as time progresses one colony of malignant cells will have a growth advantage over all the others, will rapidly spread and may eventually metastasise. Brodland (1997) applied this theory to the dysplastic naevus syndrome. As discussed earlier, certain genetic deletions have been found in these patients and so they are born with initiated melanocytes. Clinically the promoted melanocytes are apparent as large, atypical or dysplastic moles and a second, malignant mutation is increasingly likely compared to a person with normal melanocytes.

The current accepted classification of melanoma attempts to underpin this basic science concept of the stepwise progression of cancer. It describes two phases of melanoma tumorigenesis - the horizontal (radial) growth and the vertical (tumefactive) growth phases [Barnhill & Mihm, 1993]. These phases represent two categories in the continuous cascade of increasing malignancy that occurs after progression and the boundaries between the two are sometimes not easy to distinguish. The horizontal growth phase represents the *in situ* and

microinvasive stage of the disease. Most authorities agree that this begins in the epidermis. Initially there is singular basilar proliferation of melanocytes that show marked cellular atypia. There is also the characteristic Pagetoid spread. After the initial epidermal proliferation there comes the microinvasive stage with individual or small clusters of melanoma cells present in the papillary dermis. As a result, the host often mounts a striking immune response that can be seen under the light microscope that includes lymphocytic infiltrate, macrophages and fibrosis. Macroscopically, this appears as regression - a scar-like depigmentation within the tumour. The vertical growth phase is characterised by the presence of cohesive units of melanoma cells in the dermis. This is thought to represent a qualitative change in the phenotype of the melanoma cells, the most important being the potential to metastasise [Elder *et al.,* 1996]. Under the microscope there is at least one dermal nest larger than the epidermal nests, a decrease in immunocytic activity around these nodules and the presence of mitoses in the dermis. It is thought that the vertical growth phase is a natural progression from the horizontal growth phase in 90% of cases and arises *de novo* in the remaining 10% (see below) [Barnhill & Mihm, 1993].

The conventional subtypes of melanoma can be divided according to the presence of horizontal/vertical growth phases and the qualities of the horizontal growth phase. This subtyping follows clinical, pathological and epidemiological observations. Superficial spreading, acral lentiginous, and lentigo maligna melanomas belong to the horizontal group and nodular belongs to the vertical group.

Figure 1.10: Summary of Carcinogenesis in Cutaneous Melanoma*



Modified from Barnhill & Mihm, 1993

1.4.3 Clinical Subtypes of Melanoma:

1.4.3.1 Superficial Spreading Melanoma (SSM):

This is the most common melanoma of Caucasians and about 70% of all melanomas are of this subtype [Mooi & Krausz, 1992a]. It occurs in most age-ranges but typically peaks at the fourth decade and can arise *de novo* or from a pre-existing naevus. They are most common on the lower limbs of females and the backs of males. Clinically the lesion is flat, variegated, notched and irregular and can produce itching or burning sensations. The presence of a blue-grey or pink nodule heralds the start of the vertical growth phase and this may bleed and ulcerate in later stages. Later still, satellite lesions may develop near the original tumour. A history of intermittent sunburn, especially in childhood is a risk factor and this the usual subtype of hereditary melanoma.

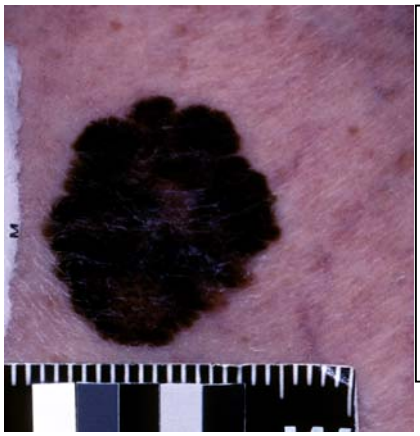


Figure 1.11

Superficial Spreading Melanoma. This lesion has a large diameter, irregular edges, a blurred border at 4 o'clock and demonstrates several colours

Under the light microscope, the classic feature of SSM is the presence of Pagetoid spread at least three rete ridges from the dermal component [Clark *et al.,* 1969]. The epidermis may be thickened with hyperkeratosis and irregular rete ridges. The dermis usually displays thickening and fibrosis, immunocytic reaction and vascular proliferation. The vertical growth phase has been described in the previous section.

1.4.3.2 Nodular Melanoma (NM):

This form represents 10% of melanomas and is separated from the superficial melanoma by the absence of significant intraepidermal lateral spread [Mooi & Krausz, 1992a]. However, according to these authors, the separation is often arbitrary and it is believed by some to represent a superficial spreading melanoma where the melanoma cells have, after a brief intraepidermal proliferation, progressed rapidly to a vertical growth phase and engulfing the horizontal component along the way [Ackerman, 1982]. It is claimed that this hypothesis is supported by evidence from epidemiological studies demonstrating the same age/sex/location attributes between the two subtypes. Clinically, the lesion presents as a rapidly enlarging blue-black nodule that often ulcerates and bleeds. An infamous subtype is the amelanotic nodular

melanoma that presents the clinician with a diagnostic challenge. Histologically the vertical growth phase is often deeply invasive at the time of diagnosis with little epidermal involvement.

1.4.3.3 Lentigo Maligna & Lentigo Maligna Melanoma (LMM):

Lentigo maligna (syn. Hutchison's Freckle) is a lesion that arises as a result damage to the skin brought about by chronic exposure to the sun [Mooi & Krausz, 1992a]. As one would expect, therefore, it presents most commonly on the faces of elderly subjects. It is irregular, macular lesion with various shades of brown and often some depigmentation and can grow to a considerable size. It can resemble other lesions such as macular seborrheic keratosis and solar keratosis, but the distinction clinically is that these lesions are usually palpable whereas the lentigo maligna is not. Lentigo maligna is thought to be the precursor of lentigo maligna melanoma, but the incidence of malignant transformation is small and the lifetime risk has been estimated at between 2 and 5 per cent [Weinstock & Sober, 1987]. Under the light microscope, the skin shows signs of solar (actinic) damage - dyselastosis, flattening of rete ridges, epidermal atrophy, degeneration of collagen and telangectasiae. Within the picture there is a proliferation of atypical melanocytes with multiple dendritic processes that spread along the dermo-epidermal junction - termed lentiginous spread. This lateral spread often extends into the skin appendages and there may be small nests of pleomorphic melanocytes distributed in the epidermis. In the dermis there may be melanophages present.

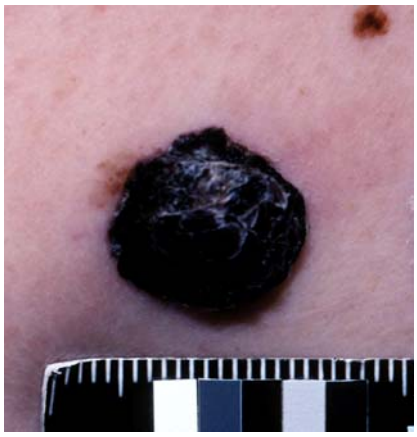


Figure 1.12

Nodular Melanoma. This lesion demonstrated rapid growth, pain, ulceration and bleeding.

Lentigo maligna melanoma (LMM) is often heralded by the presence of a dark blue/black palpable nodule within the margins of a lentigo maligna. It usually presents on the face of elderly white subjects and represents 10-15% of melanomas. Histologically, the LMM shows intraepidermal progression with lentiginous spread and microinvasion to the papillary dermis - the horizontal growth phase - and there may be fibrosis, melanophages and lymphocytes as a reaction to this. Progression from the horizontal to the vertical growth phase is a slow and indolent process [Barnhill & Mihm,1993] and is thought to be reason why this is considered to be a relatively benign disease. However, studies have shown that the prognosis is similar to other melanoma types [Koh *et al.,* 1984].

1.4.3.4 Acral Lentiginous Melanoma (ALM):

This accounts for less than 5% of melanomas but is the most common subtype in patients with Afro-Caribbean and Asian skin types. It is site-specific and occurs only on the hands and feet including the nailbeds and digits. It occurs throughout adulthood and peaks in the 7th decade. On the palmar or plantar skin, the lesion may appear as a linear streak or a large pigmented macule or papule. Subungual melanoma can be thought of as a separate clinical entity and occurs with equal frequency on the hallux and thumb [Levit *et al.,* 2000] and usually presents with nail destruction and ulceration of the nailbed. It has a variable appearance and is often misdiagnosed as a fungal infection or subungual haematoma and treated accordingly. There may be a pigmented streak continuous with the nailbed and this is known as Hutchison's sign.

Histologically, the lesion demonstrates lentiginous spread of dendritic melanocytes along the basement membrane and extension into sweat glands. Some cells may ascend into the upper epidermis that may in turn be hyperkeratotic and advanced tumours may eventually ulcerate the stratum corneum. However, the rete ridges pattern tends to be preserved [Su, 1997]. Early dermal invasion is often associated with a marked host response including fibrosis, vascular proliferation and immunocytic infiltration [Barnhill & Mihm, 1993] but with the onset of the vertical growth phase massive invasion may be present. Subungual melanomas are similar in appearance to ALM but more often have a vertical growth phase that may even extend into bone.

1.4.3.5 Rare Cutaneous Melanomas:

Desmoplastic melanoma including the neurotropic type is diagnosed histologically by its distinctive vertical growth phase [Barnhill & Mihm, 1993]. It arises in association with lentiginous melanoma, especially LMM and therefore appears in the elderly white population on the sun-exposed head and neck, presenting as a firm, colourless nodule. Histopathologically, there are large spindle cells with large quantities of collagen between them. The vertical growth phase may extend from the dermis into the subcutis and the neurotropic variety has a sinister predilection for cranial nerves that may spread far beyond the clinically apparent margins. Poor prognosis and localised recurrence are the rule with these tumours.

Other melanomas include malignant blue naevus, minimal deviation melanoma, balloon cell naevus and verrucous naevoid melanoma. They are all exceedingly rare and a good account of them can be found in Mooi & Krausz (1992a).

1.4.4 Spread and Staging:

Clinical and microscopic staging of melanoma is important in order for the physician to explain the treatment and prognosis to the patient and also to allow comparison of treatment and research. Cutaneous melanoma metastasises by several well-recognised routes. Locally, there may be satellite nodules that are metastases within 5cm of, but discontinuous with the primary tumour. This is more likely to occur with superficial spreading and nodular melanomas [Breuninger *et al.,* 1999] and is important when planning the surgery of these lesions as localised spread may be subclinical at the time and local recurrence may be more likely. Along the lymphatics, the metastases may impact in the regional lymphatic basin or in the intermediate skin between there and the primary site. The latter are termed as *in transit* metastases. The lymphatic spread of melanoma has been the focus of much research and debate recently. Melanoma, has been shown to metastasise in an orderly fashion through the regional nodal basin [Reintgen *et al.,* 1994] and has led to the theory that biopsy of the first node encountered by potential melanoma, the 'Sentinel Node' may accurately stage the region as a whole [Morton *et al.,* 1992]. However, there remains some controversy regarding this technique and is not widely practised in the UK [Hall & de Takats, 1998]. Finally, melanoma may spread haematogenously to involve distant sites. In order, starting with the most common, these sites are lung, subcutis, bone, brain and liver [Nambisan *et al.,* 1987].

The natural progression of melanoma can be thought of as occurring in three predictable and orderly stages. In general, stage I disease is localised to the primary tumour, stage II represents regional cutaneous (*in transit*) and lymphatic involvement and stage III represents distant metastasis [Mooi & Krausz, 1992a]. However as Mooi & Krausz explain, there are large differences in prognosis within these groups that has resulted in the development of other classification systems with more sophisticated stratification of the stages. Until recently, there was not a universally accepted system that the potential to lead to confusion and misinterpretation of the research literature. However, the latest TNM classification system aims to address this issue [Clememte *et al.,* 2001].This thesis will concentrate on localised disease and the primary tumour, termed Stage I. However, this stage may also represent satellite metastases and localised recurrence located within 5cm of the original lesion that are not the concern of this thesis.

1.4.5 Microscopic Staging - Tumour Thickness:

It has long been known that the depth of invasion of the primary tumour is directly related to the prognosis of the patient [Allen & Spitz, 1953] and a proposal by Mehnert & Heard to stage these lesions microscopically was published in 1965. However, there are two microscopic staging systems that are widely used today - nominally the eponymous Clark's level (1969) and

Breslow thickness (1970). Like Mehnert & Heard (1965) before them, Clark and colleagues relate tumour depth to the microarchitecture of the skin and the Clark's level is divided into 5 stages:

Stage I - melanoma *in situ*, confined to the epidermis
Stage II - melanoma invades the papillary dermis or adnexal adventitial dermis (even if in the vicinity of the reticular dermis)
Stage III - melanoma fills the papillary dermis
Stage IV - melanoma invades the reticular dermis
Stage V - melanoma invades the subcutis

Mooi & Krausz (1992a) point out the shortcomings of this system. Whilst they point out that survival correlates well with level, there are wide variations between studies and probably due to inter-observer variation in distinguishing levels. Often the papillary and reticular dermis is indistinguishable, the difference between levels II & III is not always apparent and tumour may bypass the papillary dermis and invade the reticular dermis in discontinuity.

Breslow described the universally accepted staging system for microstaging of melanomas in his classic paper in 1970. The system measures the maximal depth of tumour invasion along a line perpendicular to the top of the stratum granulosum and is expressed in millimetres. The measurement is made under the microscope by the histopathologist and is reproducible [Mooi & Krausz, 1992a]. There are some caveats with this technique: if the stratum granulosum is absent due to ulcer then the measurement is taken from the ulcer base; adnexal invasion is not counted but discontinuous microsatellites are; epidermal melanoma (*in situ*) does not have a Breslow thickness. Mooi & Krausz (1992a) discuss the advantages of this system over Clark's level. First the system has good inter/intra-observer reproducibility. Second, as was stated earlier in this chapter, there is wide variation in the microarchitecture of the skin from region to region so that the correlation between a level III lesion on the calf and the scapular region is markedly reduced. Thus, a study by Balch *et al.* (1992) found that Clark's level IV melanomas varied in Breslow thickness from 0.6mm to 12.6mm.

1.4.6 Prognosis:

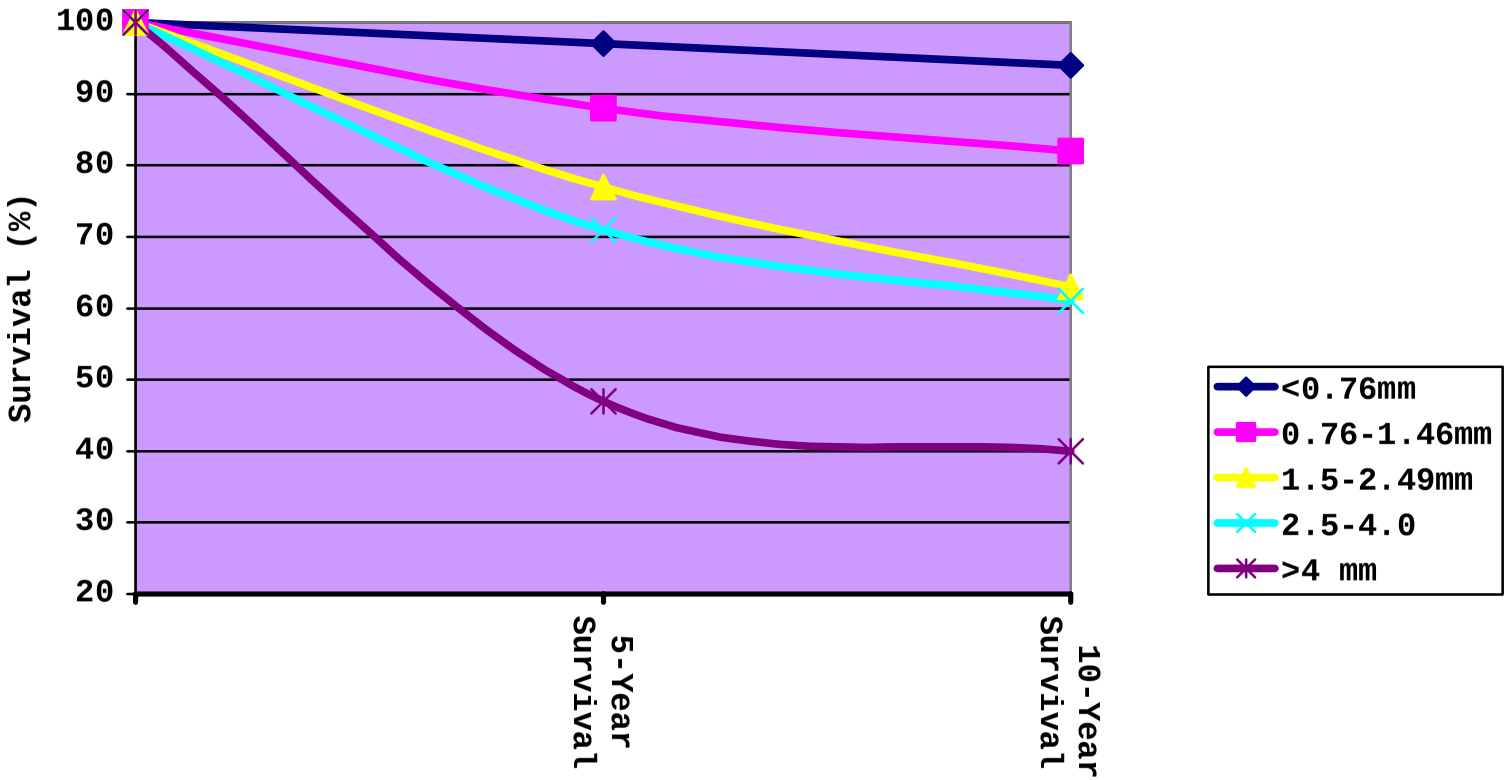
Prognostic factors can be divided into two sets - histopathological and clinical [Ahmed, 1997]. Clinically the three major factors that appear to influence prognosis are age, sex and anatomical location. Older age is associated with more aggressive tumours [Cohen *et al.,*1987] and stage I melanoma is associated with better prognosis in females [Balch *et al.,*1992], though they are likely to get recurrences after a much longer period of latency than their male counterparts. Tumours located on the limbs have a better prognosis than the trunk and head &

neck [Balch *et al.,*1992]. Part of the reason may be due to the patient being able to see limb lesions more easily than, say, those on their scalp.

Of all the prognostic factors, both clinical and histopathological, Breslow thickness of the primary lesion is by far the most important [Mooi & Krausz, 1992a]. Prognosis is so intrinsically linked with this measurement that apparent differences in survival between patient groups is often negated or greatly reduced when they are stratified for tumour thickness. According to the latest TNM classification [Clemente *et al.,* 2001], tumour thickness is subdivided into 4 categories: less than or equal to 1.0mm, 1.01mm – 2.0mm, 2.01mm – 4.0mm and greater than 4.0mm. Descriptively, this stratification of melanoma can be condensed to 'thin' (< 1mm), 'intermediate' (1-4mm) and 'thick'(>4mm) melanomas and these have their basis in the surgical treatment resulting from studies by Veronesi & Cascinelli (1991) and by Balch *et al.* (1993). However, Mooi & Krausz (1992a) discuss the artificial and arbitrary nature of these cut-offs and explain that metastatic potential and survival is a continuous function of tumour thickness. Figure 1.13 displays the patient survival trends with increasing thickness of primary tumour. From this data it can be clearly seen that it is the goal of the physician to diagnose melanoma when it is thin.

Ulceration greater than 3mm is a strong predictor of nodal metastatic involvement [Balch *et al.,* 1992; Clemente *et al.,* 2001]. Even after correction for tumour thickness, 5-year survival rates drop by 25%. Men are most likely to have thick, ulcerated tumours and these are usually situated on the trunk. The presence of microscopic satellites is also a poor prognostic sign [Harrist *et al.,* 1984]. 5-Year *disease-free* survival rates for patients with microsatellites were 36% compared with 90% of those without. Radial growth phase melanomas have an excellent prognosis, irrespective of tumour depth whereas vertical growth phase melanomas have a worse prognosis that is dependent on other factors [Elder *et al.,* 1996]. Other, less significant or reproducible, histopathological prognostic indicators include inflammatory infiltrate, vascular invasion, regression, mitotic count and cell type [Mooi & Krausz, 1992a]. The variety of prognostic indicators and the variability of their reporting has produced calls for a standardisation of histopathology reports for cutaneous melanoma [Cochran *et al.*,1998].

Figure1.13 Survival(%) with increasing primary tumour thickness *



* Data from Mooi & Krausz (1992a) p.311

1.4.7 Treatment & Survival Trends:

Detailed descriptions of treatment modalities for melanoma are beyond the remit of this thesis and the reader is directed elsewhere for a concise and up-to-date article [Hall *et al*., 1999b]. In summary, surgery remains the cornerstone in the treatment of cutaneous melanoma and offers the only realistic chance of a cure. Excision biopsy is initially performed and the lesion is excised with a 2mm margin with a cuff of subdermal fat. If the lesion is diagnosed as a melanoma, then the definitive surgical treatment - wider local excision - depends on Breslow thickness and anatomical site, and thicker melanomas may involve reconstructive surgery or skin grafting to repair the defect. Therefore, for the reasons of cosmesis and post-operative morbidity, the aim of the physician is to diagnose melanoma at an earlier, thinner stage. For regional lymph node involvement, lymph node dissection is usually performed. Surgeons in the USA are more likely to perform elective lymph node dissection for intermediate thickness though the benefit to the patient in increased survival is of great debate and doubtful value [Anderson, 1995; Balch *et al.* 1993]. For advanced disease, the treatments involve chemotherapy and palliative measures. The prognosis for these patients is uniformly dismal with the average life expectancy of six months [Balch *et al*.,1992].

Mortality from melanoma continues to rise worldwide (section 1.4.1.1) reflecting the rise in incidence of the disease. However the survival of patients diagnosed with melanoma continues to fall in this country [CRC Statistics, personal communication], in Scotland [MacKie *et al.,* 1997], in Europe as a whole [Smith *et al.,* 1998] and across the Atlantic, too [Anderson*,* 1995]. In each paper, the authors suggest that this is down to earlier and more accurate diagnosis by clinicians. A recent paper estimated that 1098 deaths were avoided in England and Wales between 1986 and 1990 representing a drop in mortality of 22.6% [Richards *et al.,* 2000].

Discussion:

This chapter explained the basic science behind human skin including its anatomy and microstructure. This is important information for the next chapter in the understanding and qualitative assessment of imaging techniques applied to the skin. Second, this chapter discussed the epidemiology, clinical presentation and histopathology of cutaneous congenital and acquired naevi and then the clinical presentation and the histopathology of cutaneous malignant melanoma. This information forms the basis of understanding imaging techniques used for the differential diagnosis of pigmented skin lesions that will be discussed in the next chapter. Finally, the epidemiology, survival and treatment of melanoma was discussed in detail. The reader will now be able to appreciate the increasing menace of cutaneous melanoma, the difficult task that clinicians face in achieving an early diagnosis of a multifarious disease entity

and the need for a system that can improve the diagnostic accuracy of the doctor assessing these patients.