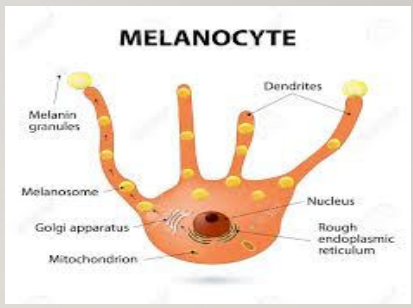
DISORDERS OF MELANOCYTES

DISORDERS OF MELANOCYTES

- **Stratum germinativum /basal layer.**
  - **Also contains melanocytes**
- **Stratum spinosum**
- **Stratum granulosum**
- **Stratum lucidum**
- **Stratum corneum**

DISORDERS OF MELANOCYTES

Melanocytes –



- **Derived from the neural crest.**
- **Spindle-shaped clear cells with dendritic processes and dark nucleus.**
- **Produce melanin packaged in melanosomes, delivered along dendrites to surrounding keratinocytes.**

DISORDERS OF MELANOCYTES

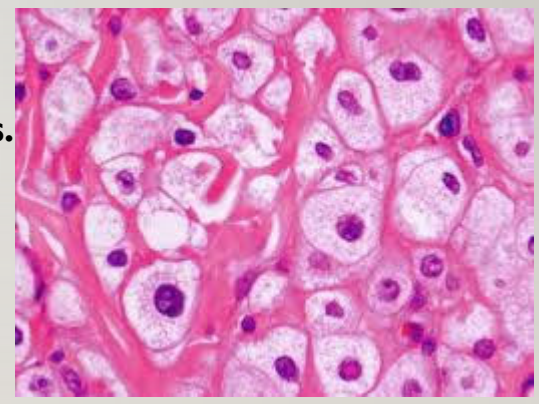
Melanin-

- **Synthesised within melanocytes from the amino acid tyrosine, via the intermediate Dopa.**
- **Accumulates in vesicles within melanocytes called melanosomes.**
- **Cells around melanocytes usually contain more melanin than the melanocytes.**
- **Increased pigmentation is due to increased basal production of melanin.**

DISORDERS OF MELANOCYTES

Naevus cells -

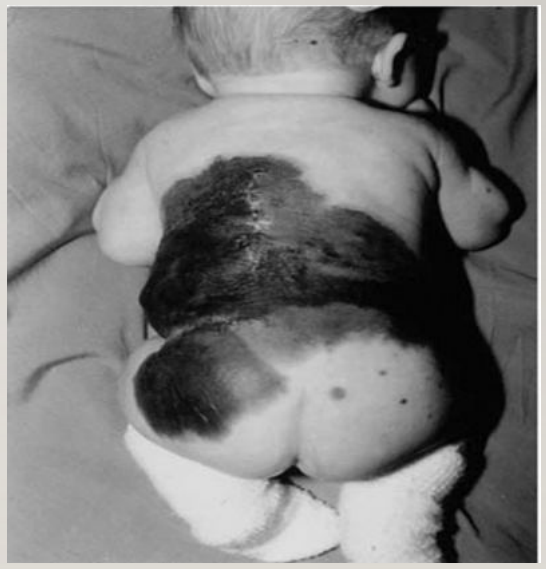
- **When melanocytes leave the epidermis and enter the dermis they become naevus cells.**
- **Naevus cells are round rather than spindle shaped and has no dendritic processes**
- **Tend to congregate in nests.**
- **Large with abundant cytoplasm**



DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Congenital Melanocytic Naevus (CMN)-

- **Brown or black lesions present at birth.**
- **'Giant' if >20cm diameter in adulthood.**
- **Sometimes called giant hairy naevi.**
- **Annual incidence of CMN is approximately 2%.**
- **Giant CMN is much rarer – annual incidence 1 in 20,000.**



DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Congenital Melanocytic Naevus (CMN)-

- **Significant risk of central nervous system (CNS) abnormalities with CMN :**
  - **Disorders of CNS development**
  - **Intracranial melanosis .**
  - **Nonmelanotic intracranial abnormalities**
- **More recent prospective reports show risk of melanoma is 0.7–2.4%**

DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Congenital Melanocytic Naevus (CMN)-

- **Excision of the nevus is the treatment of choice**

DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Acquired Nevus-

- **Classified as junctional, compound, or dermal**
- **Nevus cells**
  - **Accumulate in Epidermis (junctional),**
  - **Migrate partially into the dermis (compound)**
  - **Completely in the dermis (dermal).**
- **Eventually most lesions undergo involution.**

DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Acquired Nevus-

Junctional nevus-

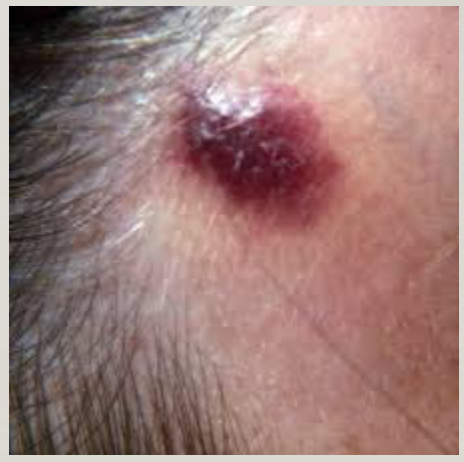
- **Flat, smooth, irregularly pigmented lesions.**
- **Usually found in the young.**
- **Nests of naevus cells clustered at the dermoepidermal junction**

DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Acquired Nevus-

Compound naevus-

- **Round, well-circumscribed, slightly raised lesions.**
- **Nests of naevus cells clustered at the dermoepidermal junction extending into dermis.**



DISORDERS OF MELANOCYTES- NAEVUS CELL NAEVI

Acquired Nevus-

Intradermal naevus-

- **Dome-shaped lesions; may be nonpigmented or hairy.**
- **Tend to occur more in adults. •**
- **Nests of naevus cells clustered solely within dermis.**

DISORDERS OF MELANOCYTES- MELANOCYTIC NAEVI

Epidermal melanocytic naevi -

Ephelis -

- **Commonly known as a freckle.**
- **Contains a normal number of melanocytes.**
- **Pigmentation is due to increased melanin production.**
- **Lesions are said to disappear in the absence of sunlight**

DISORDERS OF MELANOCYTES- MELANOCYTIC NAEVI

Epidermal melanocytic naevi -

Lentigo –

- **Contains an increased number of melanocytes.**
- **Persists in the absence of sunlight.**
- **Different types of Lentigo:-**
  - **Lentigo simplex – occurs in the young and middle aged**
  - **Lentigo senilis – occurs in the elderly**
  - **Solar lentigo – occurs after sun exposure.**

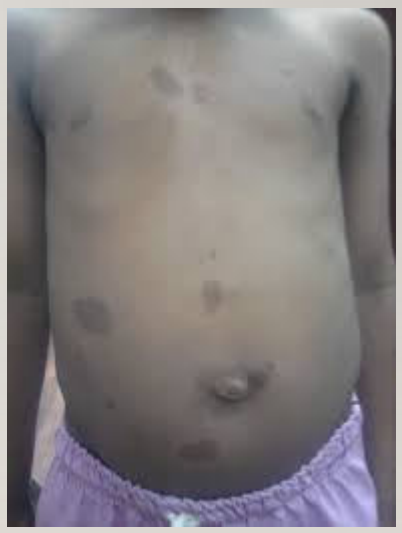
DISORDERS OF MELANOCYTES- MELANOCYTIC NAEVI

Epidermal melanocytic naevi -

Café-au-lait patch –

- **Pale brown macule.**
- **Histologically there are 'macromelanosomes' in basal melanocytes.**
- **Six or more >5mm in children (>15mm in adults)**

  required to support a diagnosis of NF1.



DISORDERS OF MELANOCYTES- MELANOCYTIC NAEVI

Dermal melanocytic naevi -

Mongolian blue spot –

- **Characterised by blue-grey pigmentation over the sacrum.**
- **Said to be present in 90% of Mongolian infants.**
- **Can be mistaken for bruising and attributed to non accidental injury of children.**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

- **A melanoma – or malignant melanoma (MM) – is a malignant tumour of melanocytes**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Epidemiology

- **Fifth most common cancer in the United Kingdom.**
- **4% of all new cancers.**
- **Annual incidence approximately 20 per 100,000 population.**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Etiology:

- **May develop de novo or arise within a pre-existing nevus**
- **Cumulative and prolonged UVB and/or UVA exposure**
- **UVA exposure from tanning beds increases risk for melanoma**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Heredity –

- **10 % of melanomas are familial and have a genetic basis**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Risk factors -

Premalignant lesions

- **Atypical naevi •**
- **FAMM syndrome (previously called atypical naevus syndrome) is defined as:**
  - **Patients with FAMM have a lifetime risk of melanoma close to 100%.**
- **Congenital melanocytic naevus has risk of 0.7–2.4%.**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Clinical Manifestations –

- **Usually asymptomatic**
- **May develop de novo or arise within a pre-existing nevus**
- **Majority located in sun-exposed areas, but also occur in non-sun-exposed areas**
- **Also occur on mucous membranes (mouth, genitalia)**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Clinical Manifestations –

- **Typically appears as a pigmented papule, plaque or nodule.**
- **Demonstrates any of the ABCDEs**
- **It may bleed, be eroded or crusted**
- **Patients may give history of change**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Suspicious moles may have any of the following features

ASYMMETRY
- With regard to shape or color

BORDER
- Irregular or notched

COLOR
- Very dark or variegated colors
- Blue, Black, Brown, Red, Pink, White

DIAMETER
- >6 mm, or "larger than a pencil eraser"
- Diameter that is rapidly changing

EVOLVING
- Evolution or change in any of the ABCD features

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Types of Malignant Malenoma –

- **Superficial spreading type-**
- **Nodular type-**
- **Lentigo maligna type-**
- **Acral lentiginous type-**
- **Amelanotic/Hypomelanotic type-**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

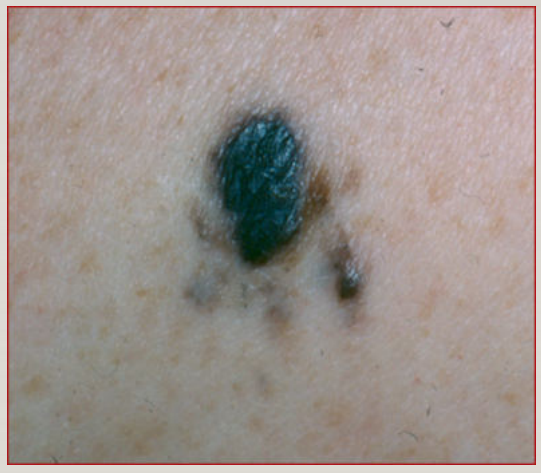
Superficial spreading type-

- **Most common type**
- **Involves back in men; back and legs in women**
- **Growth of tumour is primarily horizontal rather than down into the dermis**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Nodular type-

- **Rapid growth**
- **Growth is vertical, giving tumor an increased Breslow's depth**
- **Breslow's depth = thickness of the primary melanoma measured from the granular layer of the epidermis to the deepest part of the tumour**



DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

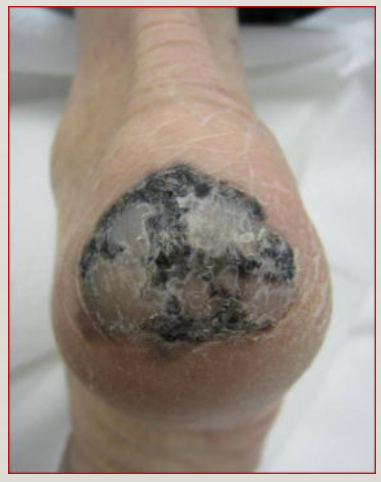
Lentigo maligna type-

- **Occurs on chronically sun-damaged skin, more common in elderly patients**
- **Slow progression**
- **Growth of tumor is primarily horizontal, and not vertical**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Acral lentiginous type-

- **More common in people with darker skin color (Asians and persons of African ancestry)**
- **Diagnosis is often delayed, so lesions tend to be many centimeters in diameter**



DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Diagnosis–

Biopsy-

- **Excision (Golden standard)**
- **Incision biopsy**
- **Punch biopsy**
- **Partial thickness or shaving biopsies are contraindicated**

- **All dermis layers should be included in the biopsy**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Staging (AJCC)–

TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)	
T0	No evidence of primary tumor	
Tis	Melanoma *in situ*	
T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Staging (AJCC)–

Regional Lymph Nodes (N)

NX	Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2–3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/ satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* meta-static node(s)	

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Staging (AJCC)–

Distant Metastasis (M)

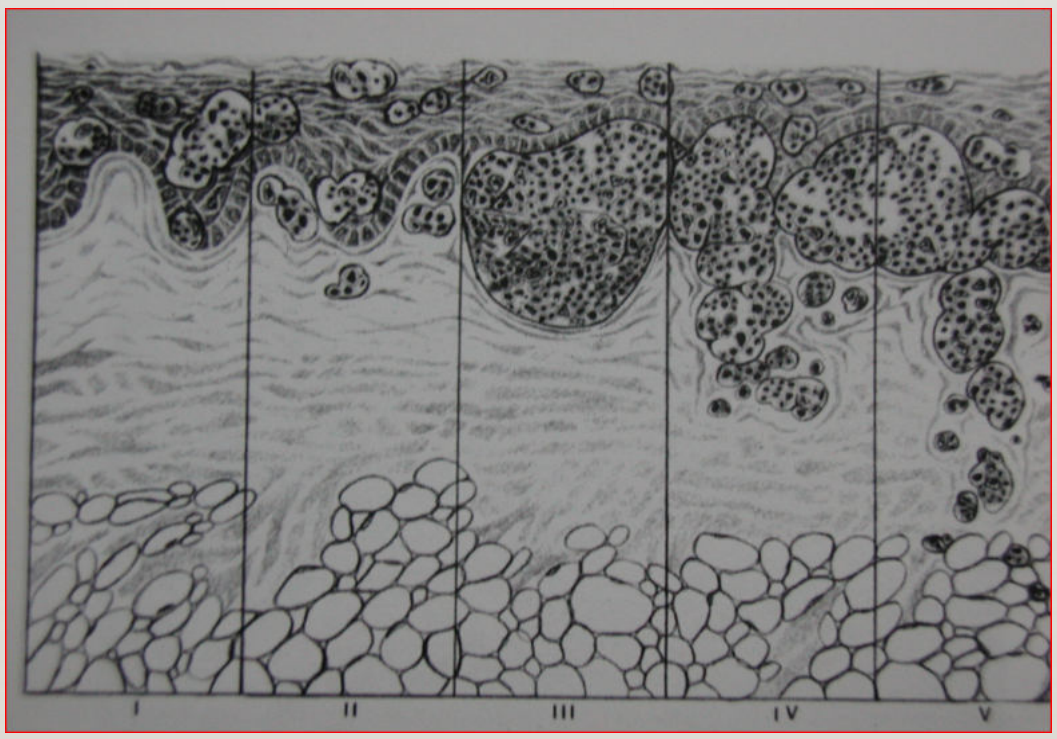
M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

The histopathologic classification by Clark-



DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Prognostic Factors

- Breslow thickness (most important)
- Clark invasion level
- Ulceration
- Age, sex, location
- Size and surgical margins
- Others (Mitotic index, growth phase, regression...)

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Surgical treatment-

- Biopsy
- Wide Local Excision
- Staging with Sentinel Lymph Node biopsy
- Therapeutic Lymph Node Dissection
- Treatment of Distant Metastasis

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Wide Surgical Excision

Suggested surgical margins: (according to Breslow thickness)

- **In-situ MM:** **0.5-1 cm**
- **Breslow thickness < 1mm :** **1 cm**
- **Breslow thickness 1-4 mm:** **2 cm**
- **Breslow thickness >4 mm:** **> 3 cm**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Sentinel Lymphadenectomy

- **Sentinel lymph node shows the regional node status**
- **If sentinel lymph node negative, others lymph nodes in the basin are also negative**
- **If sentinel lymph node contains tumour cells, It means disease spread to the regional nodal basin**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Management of metastatic disease

Distant Metastasis-

- **Skin**
- **Subcutaneous Tissue**
- **Distant Lymph Nodes**
- **Pulmonary**
- **Liver**
- **Brain**
- **Bone**
- **Intestine**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Management of Locoregional recurrent melanoma-

Treatment options are palliative:

- **Surgical excision for solitary lesions.**
- **CO2 laser for multiple small (<1mm) dermal lesions.**
- **Extensive limb disease may benefit from regional chemotherapy by isolated limb infusion/ perfusion.**
- **Consider radiotherapy.**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Management of Systemic metastatic disease

- **Signal transduction inhibitor Vemurafenib**
  - **Given orally.**
  - **Targets a mutated form of the BRAF gene present in about half of MMs.**
  - **Resected MM tissue is first tested to confirm presence of the BRAF V600 mutation.**
  - **Without a V600 mutation, vemurafenib stimulates growth of tumour cells.**
- **Immunotherapy**
  - **Monoclonal antibody(Ipilimumab)**
    - **Inhibits cytotoxic T-lymphocyte antigen 4 (CTLA-4).**
    - **CTLA-4 normally downregulates T-cell activation.**
    - **Inhibiting CTLA-4 therefore stimulates the immune system to attack the cancer.**
  - **Interleukin-2**
    - **Arrests growth of metastatic MM for prolonged periods.**

DISORDERS OF MELANOCYTES- MALIGNANT MELANOMA

Management of Systemic metastatic disease

- **Chemotherapy**
  - **The main drug for MM is dacarbazine, an alkylating agent.**
  - **Response rates are 10–20% and short-lived, usually <6 months.**
- **Metastases to distant lymph node basins can be palliated by lymphadenectomy.**
- **Single metastases can be palliated with resection.**
- **MM is classically radioresistant, but radiotherapy may alleviate symptoms.**