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Pathology

NEVOCELLULAR NEVI MELANOMA

Learning objectives

- List types of Nevocellular Nevi (Congenital Nevus, blue nevus, Spitz's Nevus, halo nevus ,dysplastic nevus) along with their clinical significance.

- Describe the clinical and morphological features of dysplastic nevi
- Describe malignant melanoma with respect to frequent site of origin, clinical and morphological feature

Types of nevi

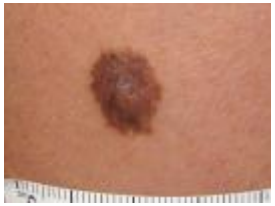
- Congenital nevus.
- Acquired nevus.
- Blue nevus.
- Spitz nevus.
- Halo nevus.
- Dysplastic nevus.

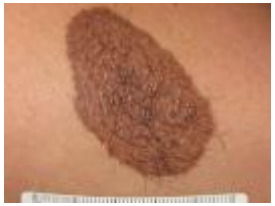
Melanocytic Nevus/Nevocellular Nevus

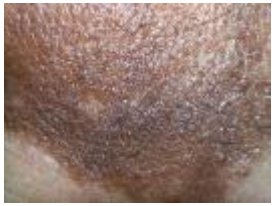
- Common benign neoplasm.
- Subtypes are distinguished on the basis of clinical and histological features.
- Acquired melanocytic nevi are the most common type.

Congenital melanocytic naevi

Small congenital naevus	Medium congenital naevus	Giant naevus	Hairy congenital naevus
Small congenital naevus is < 1.5 cm diameter.	Medium congenital naevi are 1.5–19.9 cm diameter.	A large or giant congenital melanocytic naevus is ≥ 20 cm	Hairy congenital naevi grow thick long hairs.

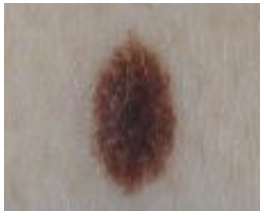


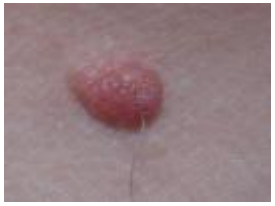


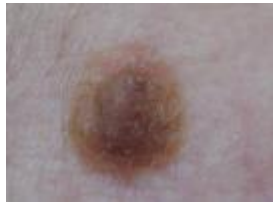


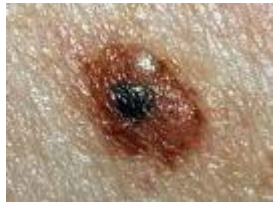
The Pathological classification of Melanocytic Naevi relates to where naevus cells are found in the skin.

Junctional nevus	Intradermal nevus	Compound nevus	Combined naevus
A junctional naevus has groups or nests of naevus cells at the junction of the epidermis and the dermis. A flat mole.	A dermal or intradermal naev us has naevus cell nests in the dermis. A papule, plaque or nodule with a pedunculated, pa pillomatous (Unna naevus) or smooth surface (Miescher naevus).	A compound naevus has nests of naevus cells at the epidermal-dermal junction as well as within the dermis. A central raised area surrounded by a flat patch.	A combined naevus has two distinct types of mole within the same lesion – usually blue naevus and compound naevus.

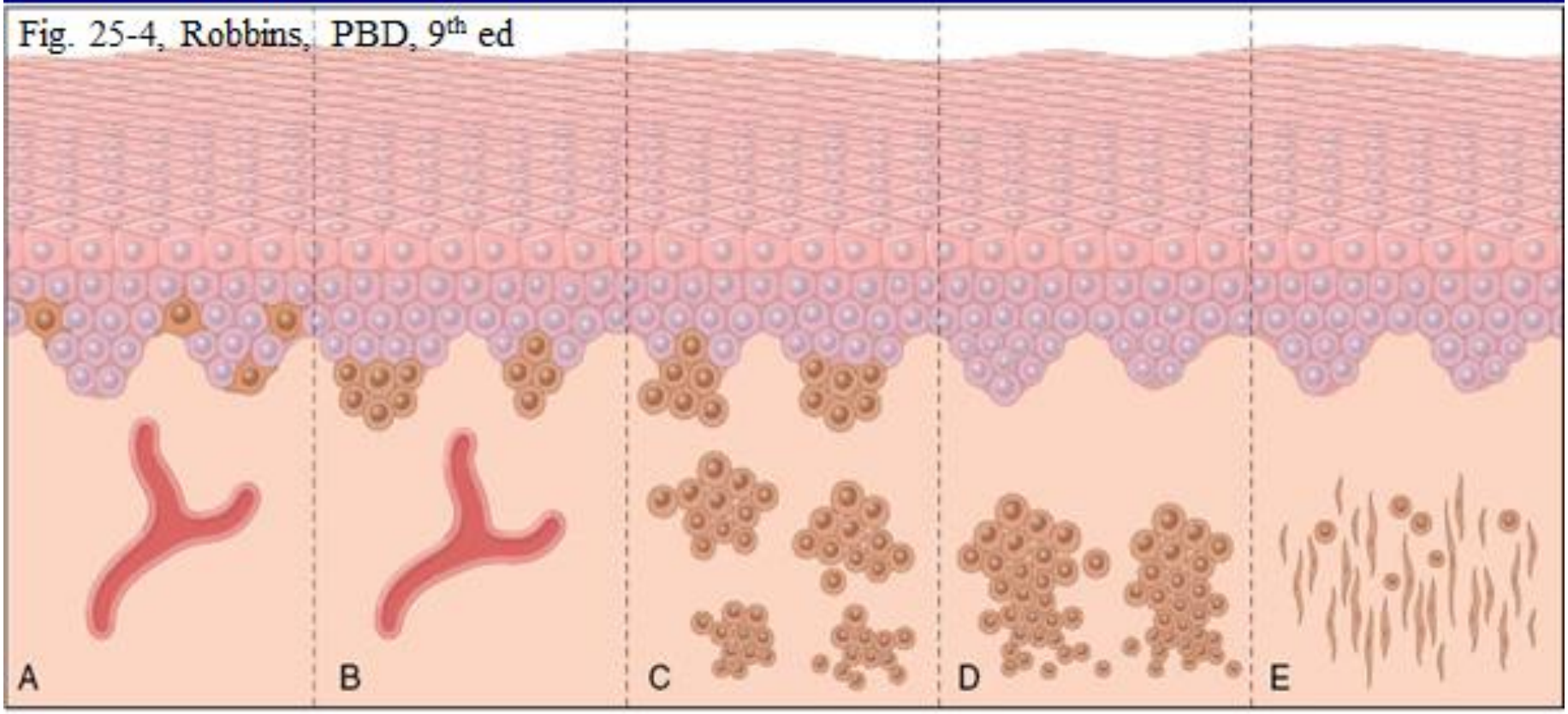








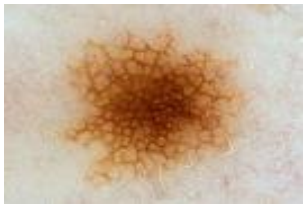
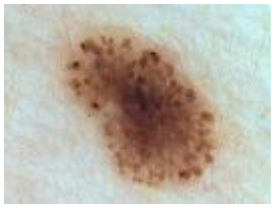
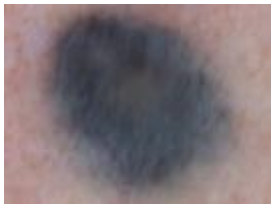
IIA2. Natural history of a melanocytic nevus (non-dysplastic)

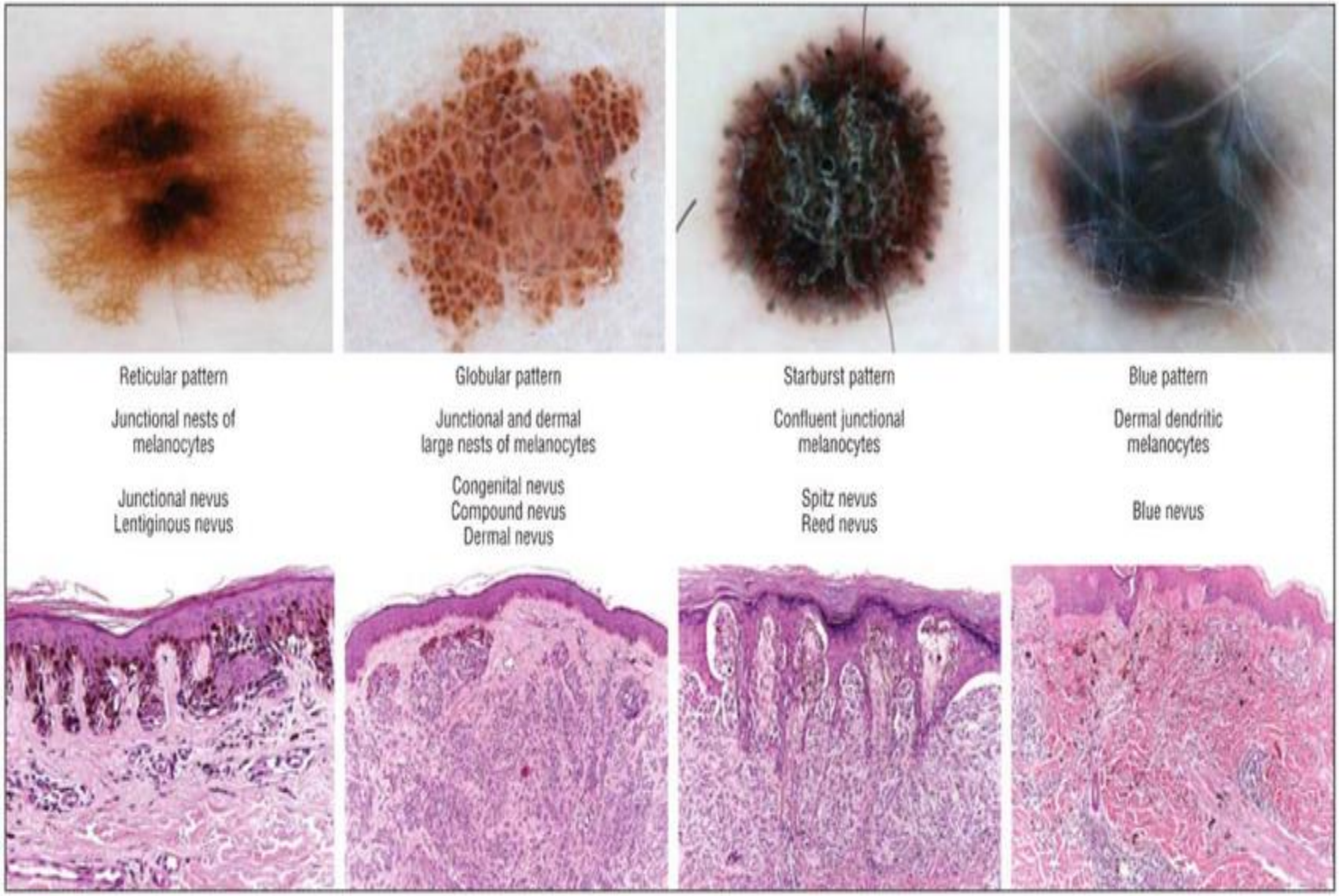


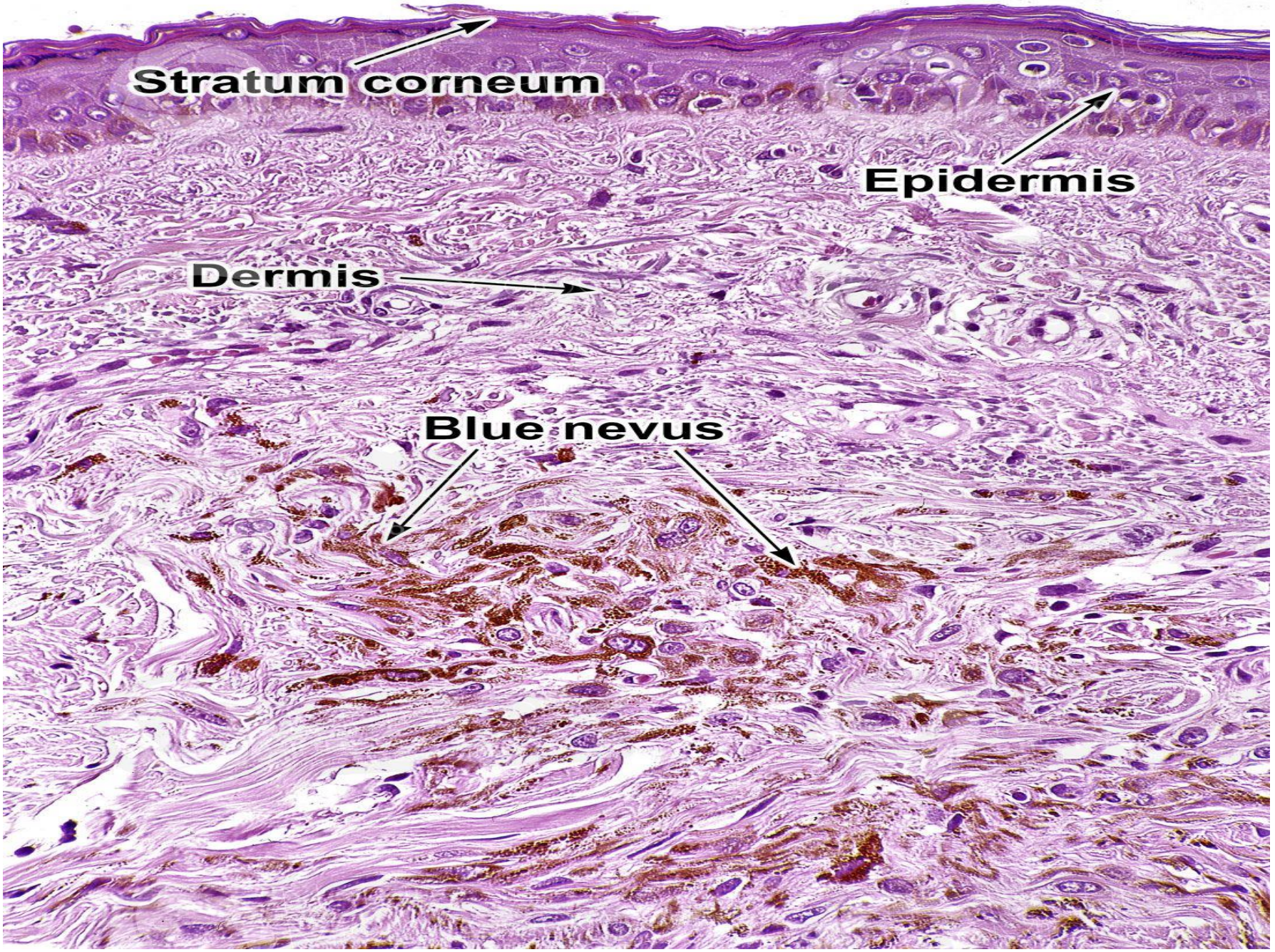
Normal: one melanocyte per 10 keratinocytes	Junctional nevus: basal epidermal nests	Compound nevus: nests in epidermis & dermis	Intradermal nevus: deeper melanocytes are smaller (D) or grow in cords/spindle cells (E)

Dermatoscopic patterns of melanocytic naevi

Reticular naevus	**Globular naevus**	Blue naevus	Starburst naevus
Reticular naevus reveals a lattice of intersecting brown lines.	Globular naevus characteristically shows aggregated brown oval structures.	The blue naevus is a uniform structure less lesion, steel blue in color.	Starburst naevus reveals radial lines around the periphery of the lesion.

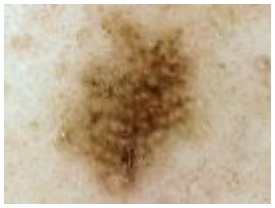




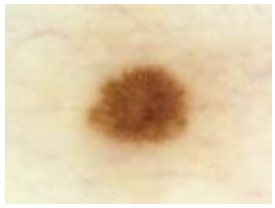
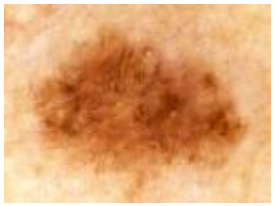


Reticular pattern
Junctional nests of melanocytes
Junctional nevus
Lentiginous nevus
Globular pattern
Junctional and dermal large nests of melanocytes
Congenital nevus
Compound nevus
Dermal nevus
Starburst pattern
Confluent junctional melanocytes
Spitz nevus
Reed nevus
Blue pattern
Dermal dendritic melanocytes
Blue nevus


Stratum corneum
Epidermis
Dermis
Blue nevus

Dermatoscopic patterns of melanocytic naevi cont

Site-related naevus: facial	Site-related naevus:acral	Naevus with special features	Unclassifiable naevus
Facial naevi reveal pseudo network around hair follicles	Acral naevi (these are on palms and soles) tend to be made up of parallel lines.	Naevi with special features include eczematised naevus , irritated naevi and halo naevi.	The unclassifiable naevus doesn't have any of the other patterns.

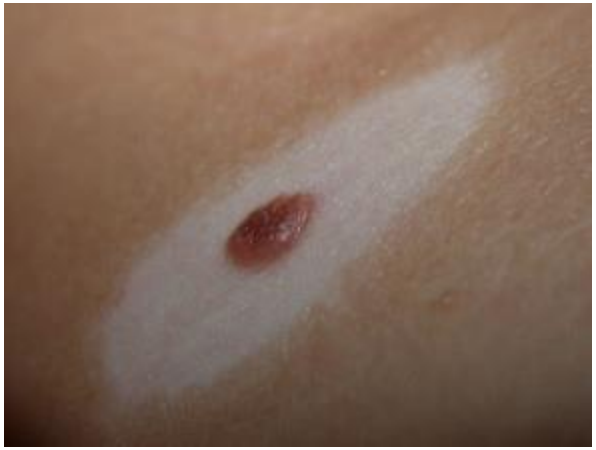


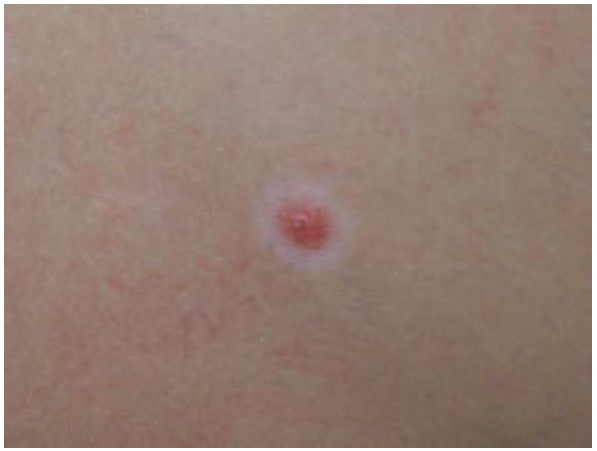



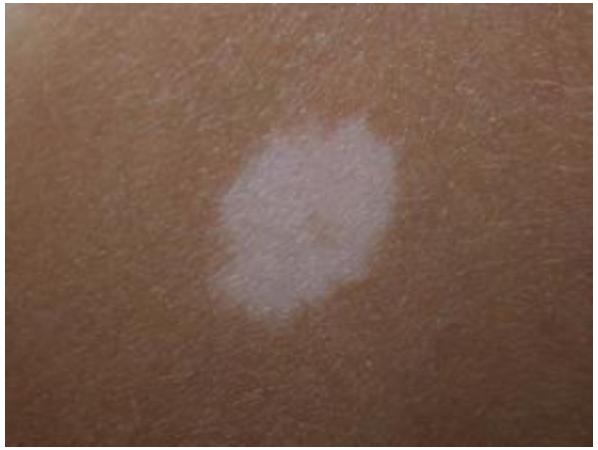
halo naevus

- A halo naevus is an otherwise normal mole with a white ring, or halo, around it. The central dark brown naevus fades from dark brown to light brown to pink, eventually disappearing completely.
- Halo naevus is also known as:
- Halo melanocytic naevus
- Halo mole
- Regressing naevus

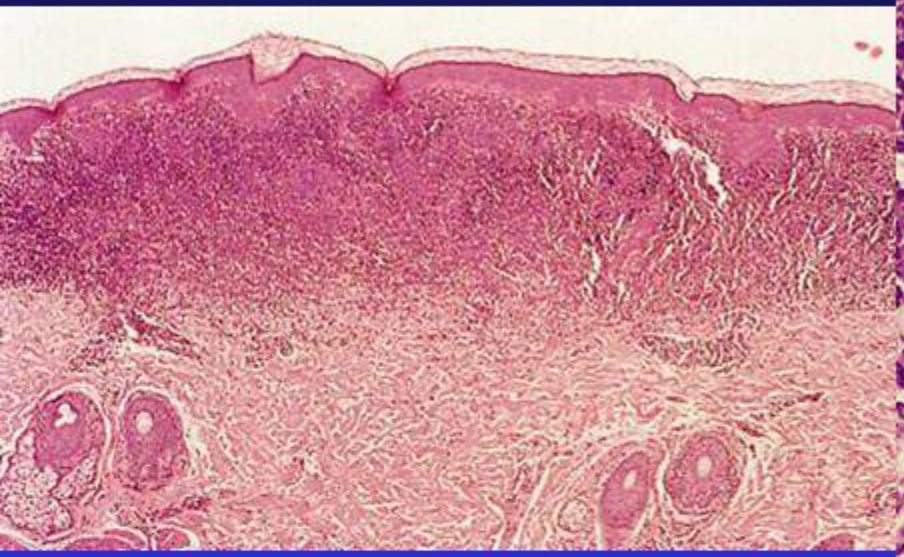
- The white halo is usually about 0.5–1.0 cm wide and is symmetrical (round or oval in shape). The halos develop at intervals around one or several moles, but not around all of them.
- There are four stages of a halo naevus. It may take several years to complete the cycle. Multiple halo naevi can be at different stages.
- Stage 1: A rim of pale skin surrounds a mole
- Stage 2: The mole may become pinker or less pigmented, and fades away
- Stage 3: A circular or oval area of depigmentation persists
- Stage 4: The affected skin gradually returns to its normal color

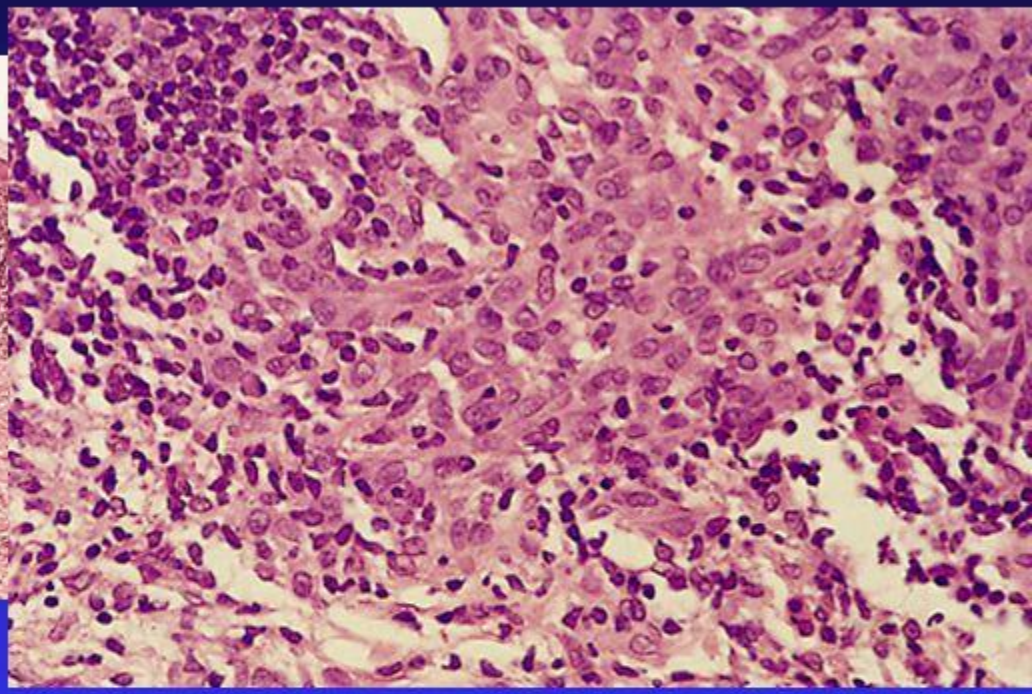






Halo Nevus



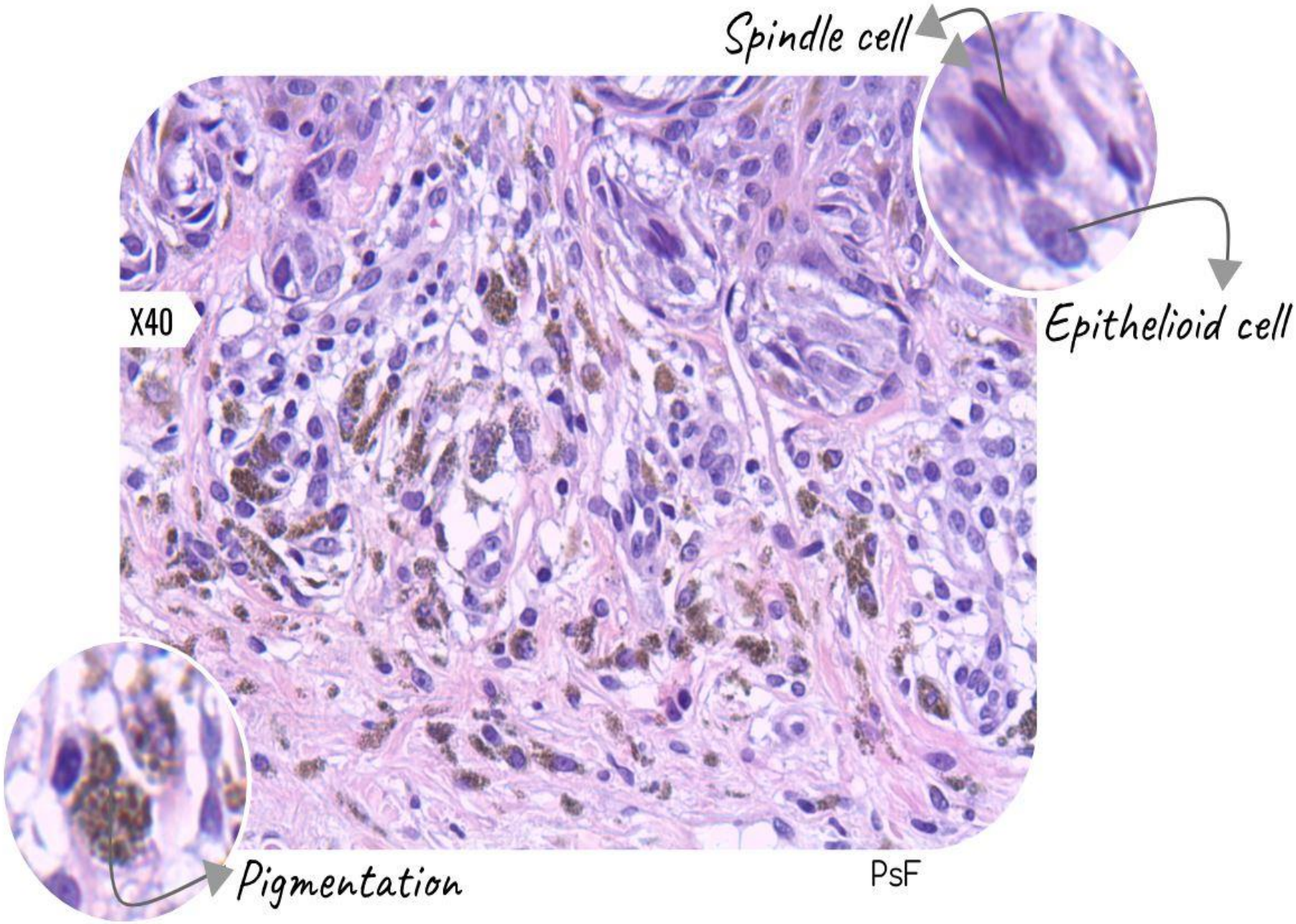


- The nevus architecture is obscured by a dense lymphocytic infiltrate

- Lymphocytes infiltrate among the dermal nevus cells, which eventually degenerate and disappear

Spitz nevus

- Spitz nevus, also known as Spitz tumor or spindle and epithelioid cell nevus, is an usually acquired, benign melanocytic lesion and one of the main differential diagnosis of melanoma.
- Most Spitz nevi are predominantly compound, although junctional and intradermal lesions are also observed.
- composed of large and/or spindle-shaped melanocytes, usually in nests. The nests are composed of an admixture of spindle cells and/or epithelioid cells, although frequently, the spindle-shaped cells predominate


Spindle cell
Epithelioid cell
X40
Pigmentation
PsF

Pathogenesis.

- Acquired mutations in NRAS and BRAF.
- Oncogene induced senescence prevents malignant transformation.
- RAS/BRAF causes limited period of proliferation followed by permanent growth arrest by p16/INK4a which is a potent inhibitor of several cyclin dependant kinases .
- This protective response is lost in melanomas and some precursor lesions.

Morphology

- Tan to brown and uniformly pigmented.
- Small <6mm upto 20 cm
- Flat macules or elevated papules with well defined , rounded borders.
- Become prominent during pregnancy.

Series of morphological changes are seen over time.

1) Junctional nevi
2) Compound nevi
3) Intradermal nevi

Clinical features

- Cosmetic concern.
- May cause irritation.
- May mimic melanoma requiring surgical removal.

Table 25-2 Representative Variant Forms of Melanocytic Nevi

Nevus Variant	Diagnostic Architectural Features	Cytologic Features	Clinical Significance
Congenital nevus	Deep dermal and sometimes subcutaneous growth around adnexa, neurovascular bundles, and blood vessel walls	Identical to ordinary acquired nevi	Present at birth; large variants have increased melanoma risk
Blue nevus	Non-nested dermal infiltration, often with associated fibrosis	Highly dendritic, heavily pigmented nevus cells	Black-blue nodule; often confused with melanoma clinically
Spindle and epithelioid cell nevus (Spitz nevus)	Fascicular growth	Large, plump cells with pink-blue cytoplasm; fusiform cells	Common in children; red-pink nodule; often confused with hemangioma clinically
Halo nevus	Lymphocytic infiltration surrounding nevus cells	Identical to ordinary acquired nevi	Host immune response against nevus cells and surrounding normal melanocytes
Dysplastic nevus	Coalescent intraepidermal nests	Cytologic atypia	Potential marker or precursor of melanoma

components of the Ras

Dysplastic Nevi

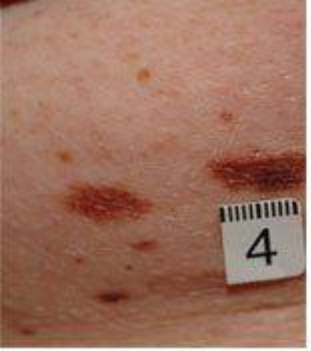
- May be sporadic or familial.
- Familial identify cases with increased risk of melanoma.
- Activating RAS or BRAF mutations are common.

Morphology

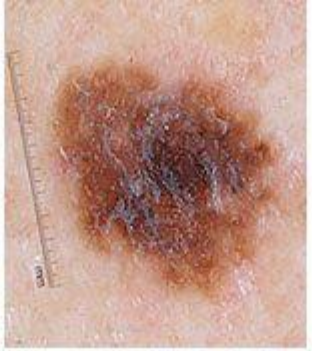
- Dysplastic nevi are larger than MN.
- More than 5mm across.
- Multiple often in hundreds.
- Flat macules to raised plaques with pebbly surface.
- Variable pigmentation and irregular borders.

Morphology cont

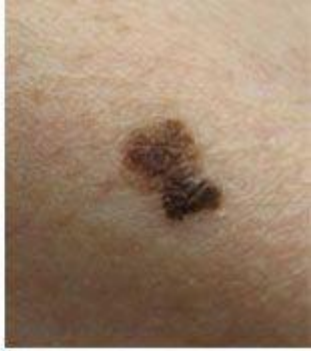
- Histologically compound nevi exhibiting cytological and architectural evidence of abnormal growth.
- Bridging.
- Lentiginous hyperplasia.
- Cytological atypia.
- Lymphocytic infiltrate.
- Melanin incontinence.
- Linear fibrosis



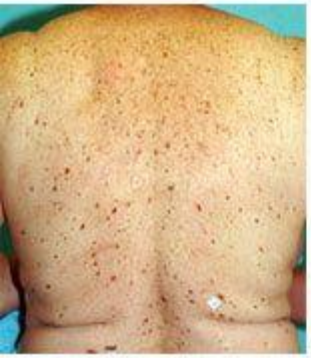
Dysplastic 1



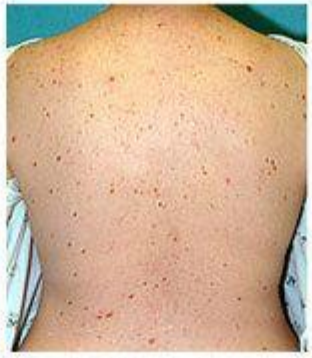
Dysplastic 2



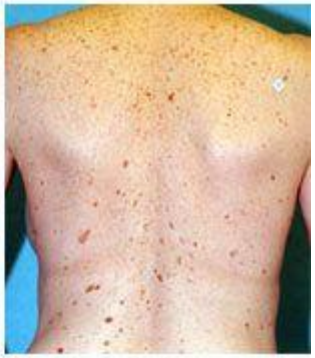
Dysplastic 3



Dysplastic Back 1



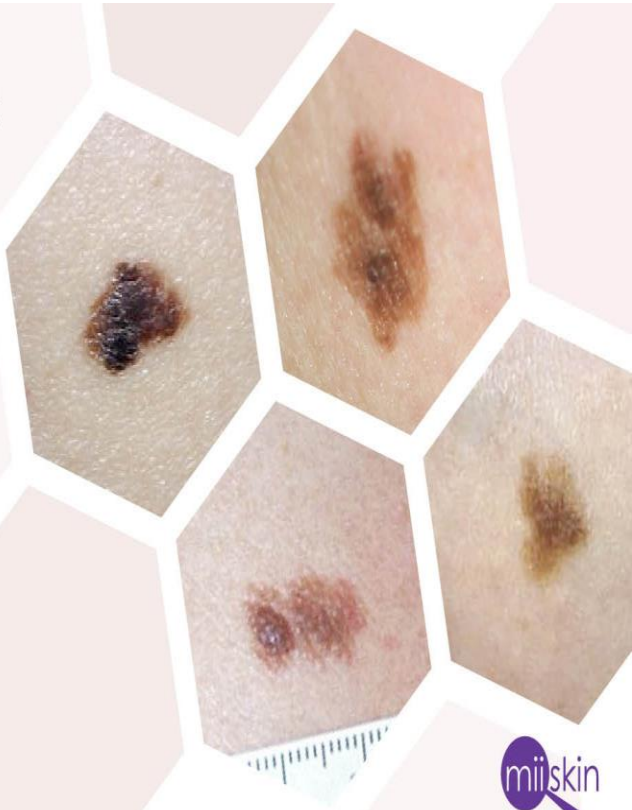
Dysplastic Back 2



Dysplastic Back 3

ATYPICAL MOLES

- Irregular borders or unusual shape
- > 6 mm diameter
- Asymmetry
- 2+ shades of colour
- Flat and bumpy surface



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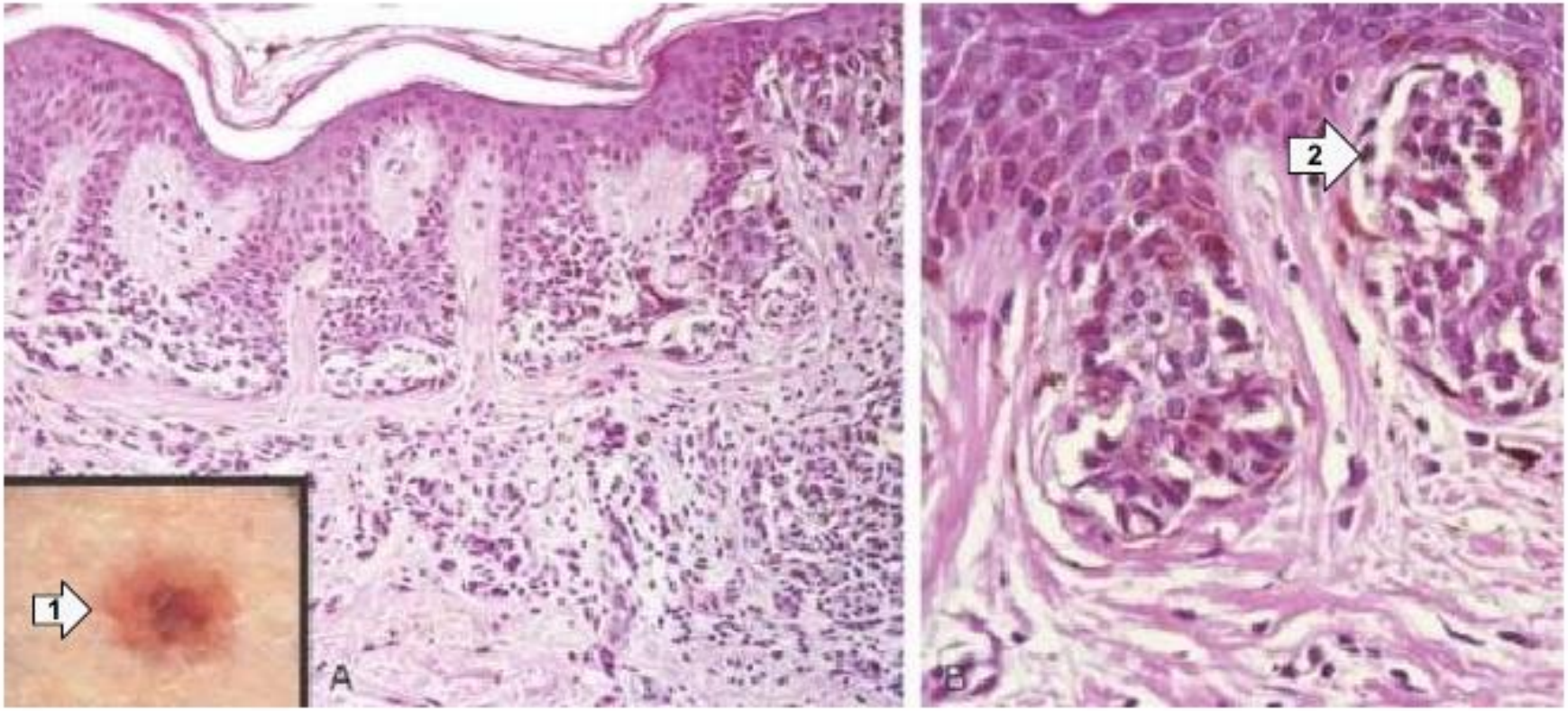
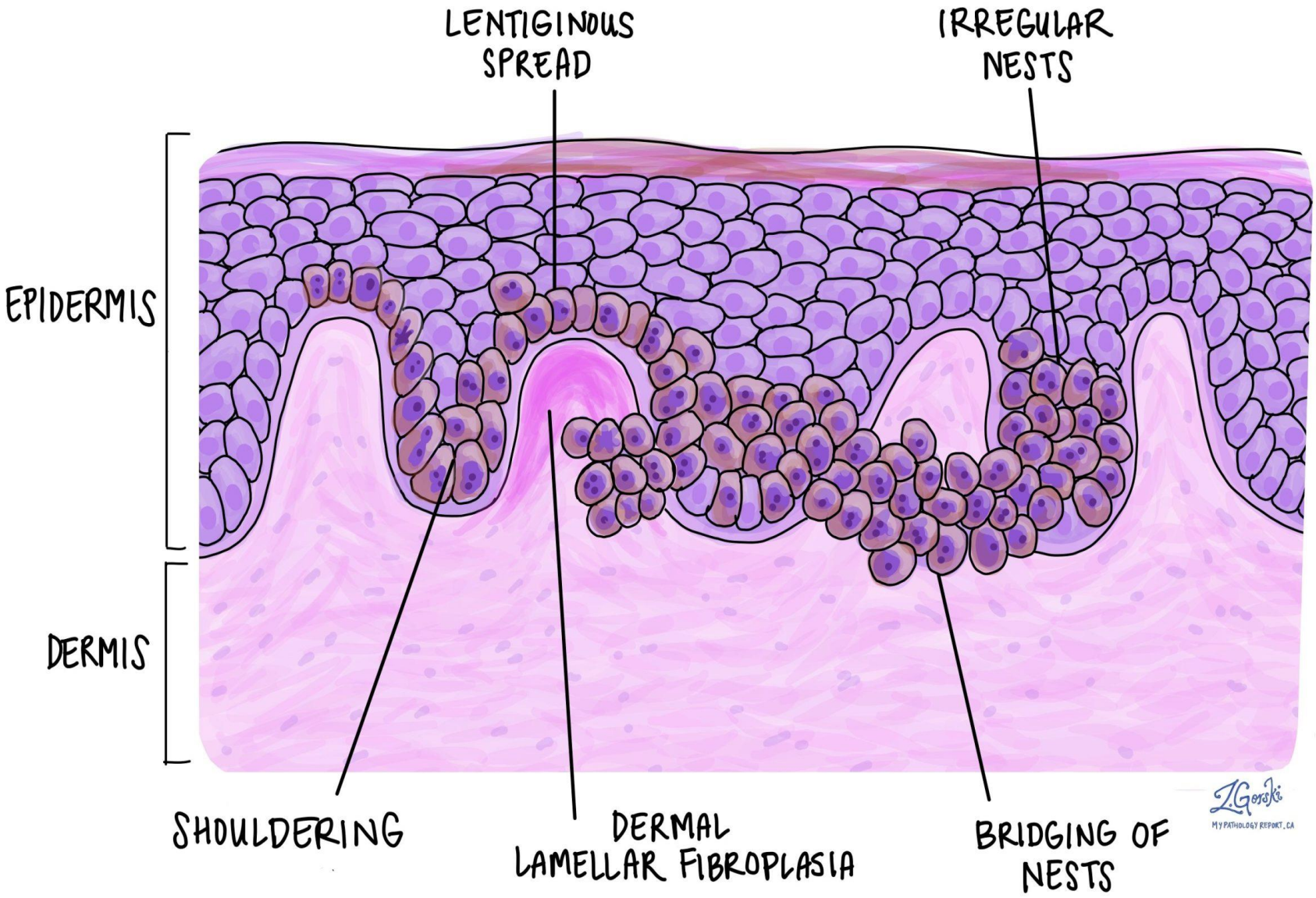
Dysplastic Nevus:

1. Pigmented raised lesion with central darker shade (arrow).
2. Junctional cluster of irregular melanocytes (arrow)



DYSPLASTIC NEVUS



Clinical features

- It occurs on areas not exposed to sun as well as on sun exposed areas.
- Familial dysplastic nevus syndrome is strongly associated with melanoma with lifetime risk of 100%.
- In sporadic cases individuals with 10 or more dysplastic nevi are at increase risk.

Melanoma.

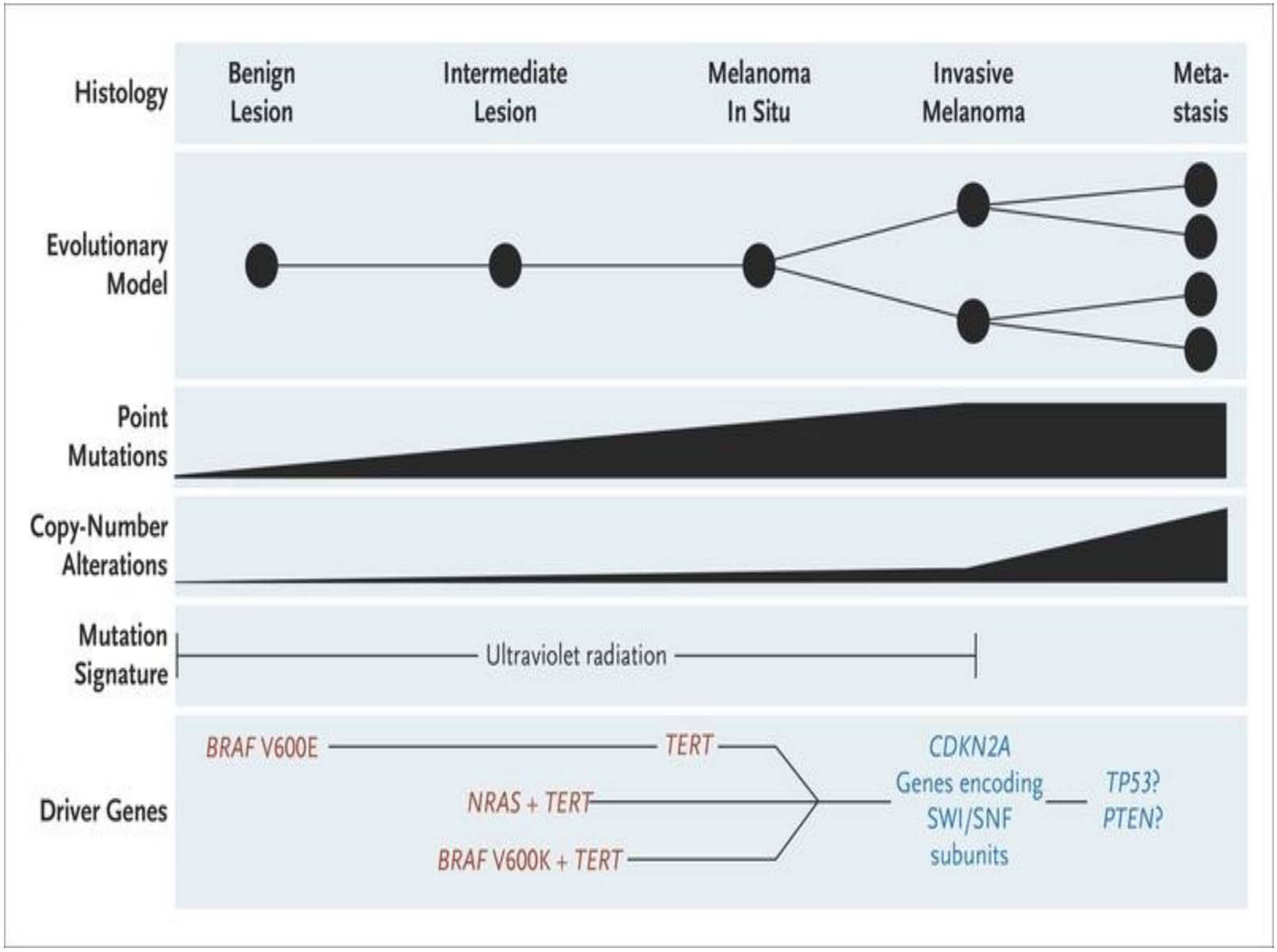
- Melanoma is less common but much more deadly than Basal or Squamous cell carcinoma.
- The incidence of these lesions has increased dramatically over the past several decades, at least in part as a result of increasing sun exposure and/or higher detection rates resulting from vigorous surveillance.

PATHOGENESIS

- sunlight plays an important role in the development of melanoma.
  - Intense intermittent exposure at an early age is particularly harmful.
  - Recent "deep sequencing" studies have confirmed that tumor genomes contain thousands of acquired mutations, most bearing a signature consistent with UV-induced DNA damage.
  - Sunlight, however, is not the only predisposing factor; hereditary predisposition also plays a role.

MUTATIONS in sun exposed

- CDKN2A locus on 9p21 present in 40% of familial cases.
- Encodes p16 and p14 & p15.
- Initiating event is activating mutation in BRAF or RAS.
- Mutations that activate expression of telomerase serve as an antidote to senescence.
- With additional mutations inCDKN2A and continuous exposure to UV light ----tumor progression.
- Additional mutation inTP53 and PTEN ---metastasis.
- Aneuploidy and genomic copy number alteration adds to genetic heterogeneity of tumor.


Histology
Benign Lesion
Intermediate Lesion
Melanoma In Situ
Invasive Melanoma
Meta-stasis
Evolutionary Model
Point Mutations
Copy-Number Alterations
Mutation Signature
Ultraviolet radiation
Driver Genes
BRAF V600E
TERT
NRAS + TERT
BRAF V600K + TERT
CDKN2A
Genes encoding SWI/SNF subunits
TP53?
PTEN?

Mutations in non sun exposed sites

- Initiating mutation is gain of function mutation in KIT.
- Melanoma in uvea of eye show mutations that activate GTP binding proteins GNAQ and GNA11.

To summarize

Mutations that disrupt cell cycle control genes	• CDKN2A • P16/p14
Mutations that activate progrowth signaling pathways	• RAS • BRAF • PTEN • NF1
Mutations that activate telomerase	• TERT encodes catalytic unit of telomerase

PHASES OF MELANOMA

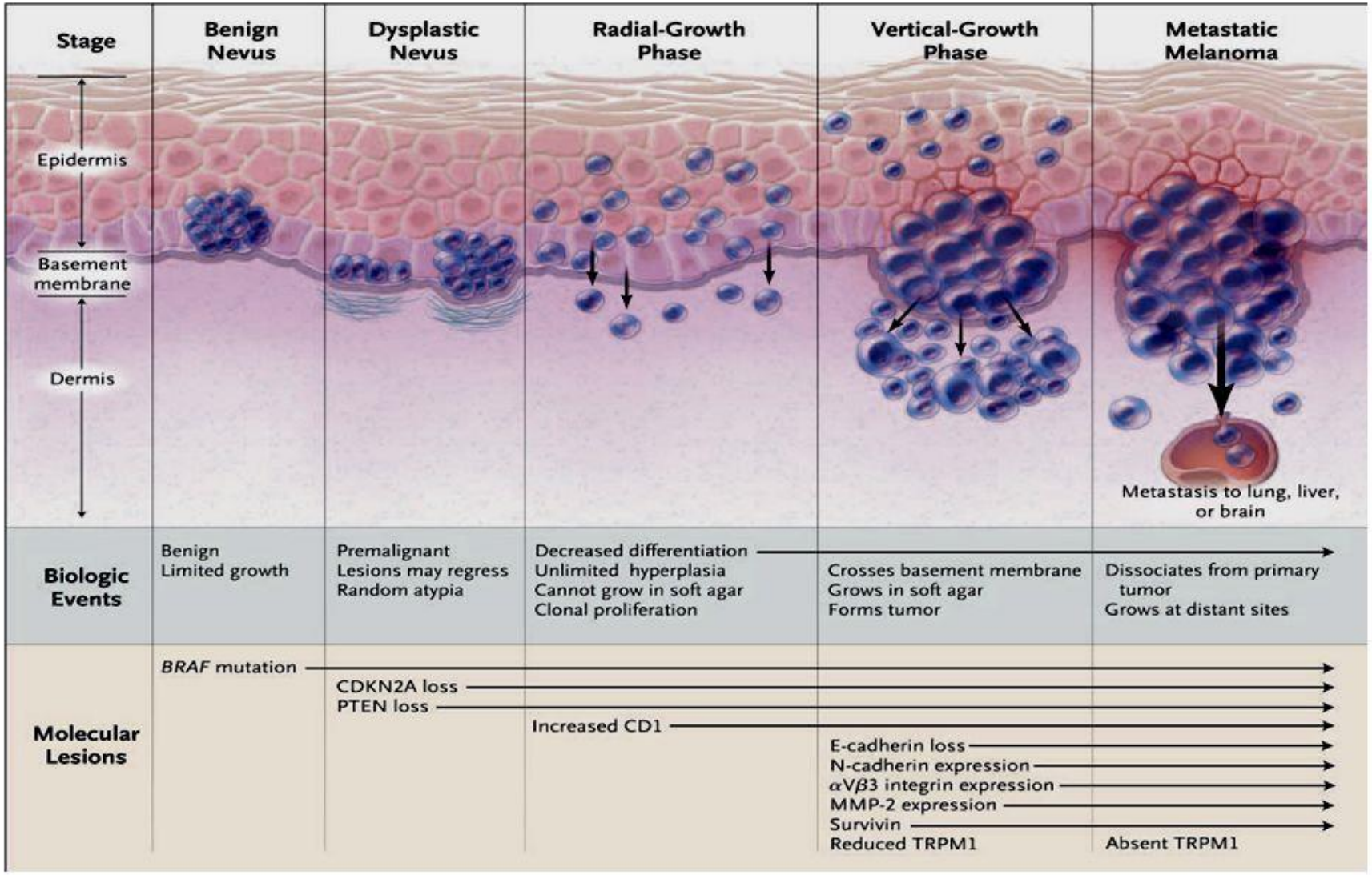
Radial growth

- Lateral expansion of melanocytes along the dermoepidermal junction.
- Progresses to phase of melanoma in situ marked by radial growth within the epidermis.
- No invasion or metastasis

Vertical growth

- Tumor grows downward in to deeper dermis as an expansile mass lacking maturation.
- Nodule appears in previously flat lesion.
- Metastatic potential develops.

Metastatic Melanoma – Molecular Evolution



Arlo et al., NEJM 2006

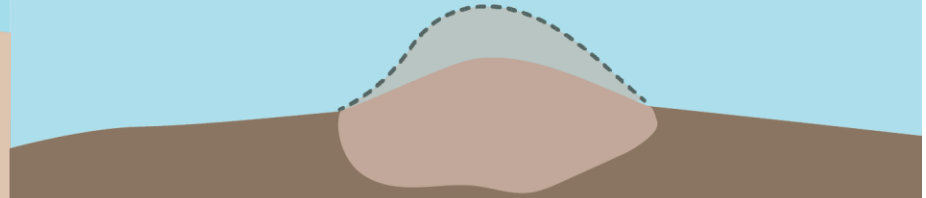
MORPHOLOGY

- Striking variations in pigmentation including shades of black, brown, red, dark blue, and gray.
- *The **borders are irregular*** and often "notched."
- Microscopically, malignant cells grow as poorly formed nests or as individual cells at all levels of the epidermis (pagetoid spread) and in expansile dermal nodules; these constitute the radial and vertical growth phases.
- *superficial spreading melanomas* are often associated with a brisk lymphocytic infiltrate *a feature that may reflect a host response to* tumor-specific antigens.

Four Types of Melanoma

Superficial spreading

Typically begins as dark spot that is asymmetric, has irregular borders, or changes color

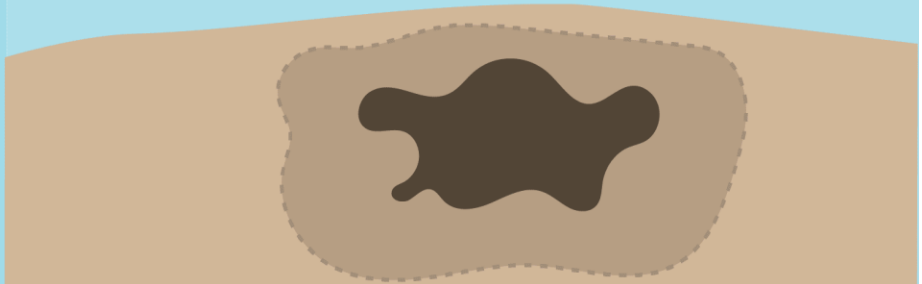


Nodular melanoma

Starts as a raised spot—dark or light—and grows vertically

Acral lentiginous

Appears as irregular growth or patch on palms of hands or soles of feet. Changes color and size



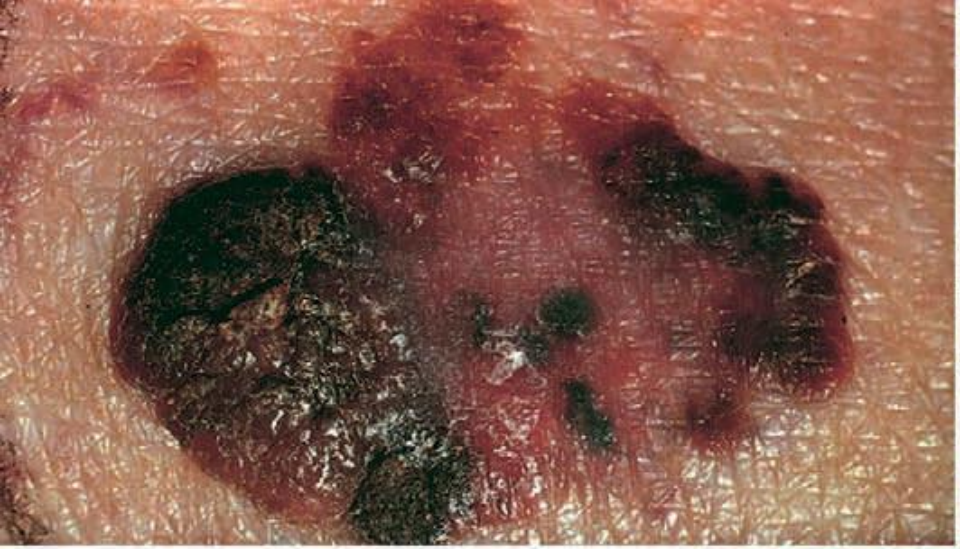
Lentigo maligna

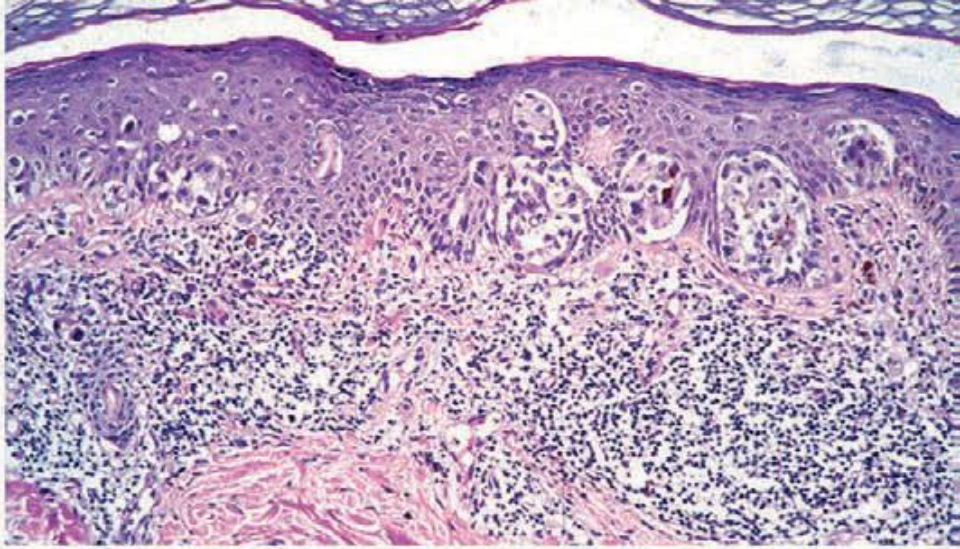
Starts as an irregularly-shaped tan or brown spot, growing slowly over years. It may become raised or change colors

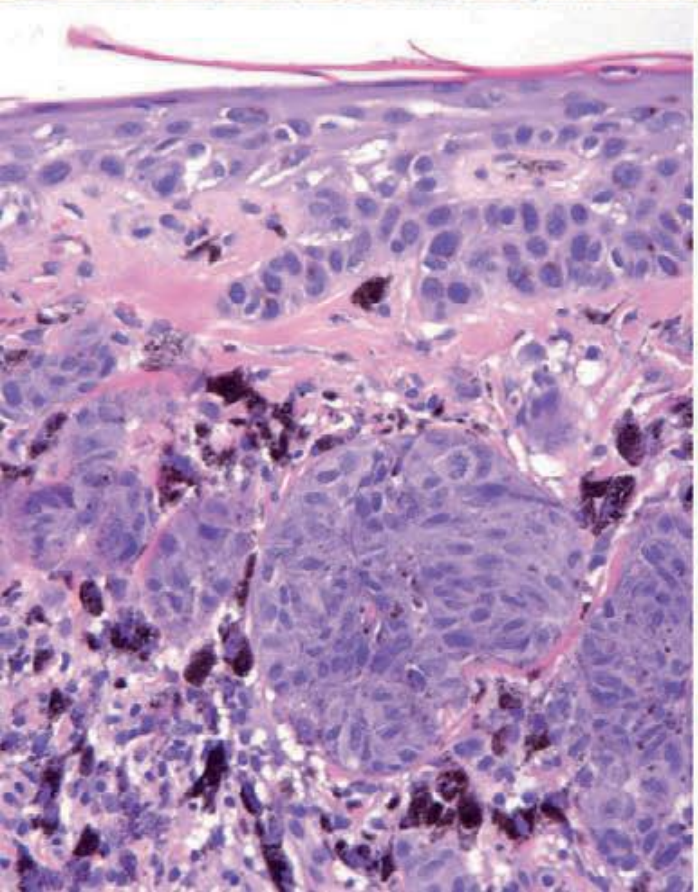
verywell

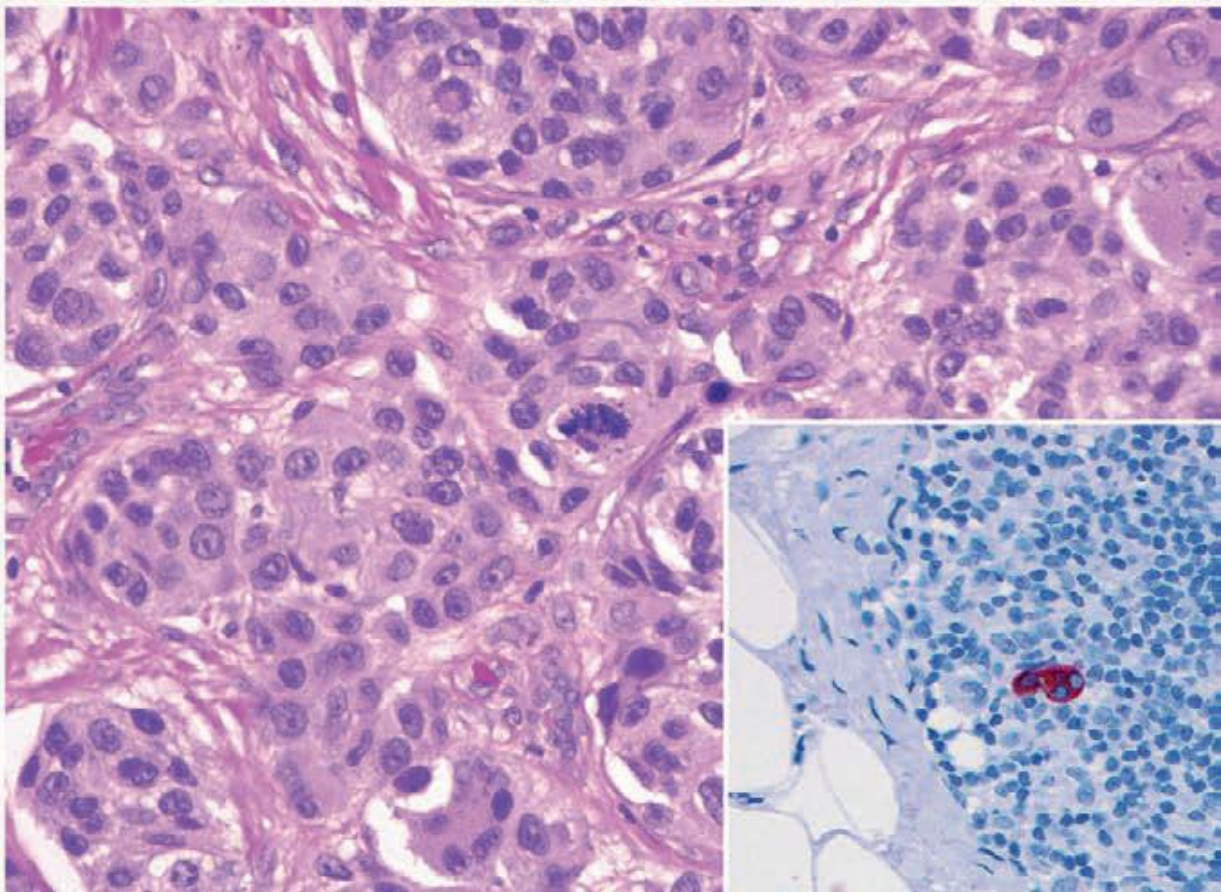
MORPHOLOGY

- **The nature and extent of the vertical growth phase determine the biologic behavior of melanomas.**
- Individual melanoma cells usually are considerably larger than nevus cells. They have large nuclei with irregular contours, chromatin that is characteristically clumped at the periphery of the nuclear membrane, and prominent "cherry red" eosinophilic nucleoli.
- *Immunohistochemical* stains (HMB-45) can be helpful in identifying metastatic deposits.









Clinical features

- most of these lesions arise in the skin, they also may involve the *oral and anogenital mucosal surfaces, the esophagus, the meninges, and the eye.*
- Melanoma of the skin usually is asymptomatic, although pruritus may be an early manifestation.
- *The most important clinical sign is a change in the color or size of a pigmented lesion.*

clinical warning signs

- 1. Rapid enlargement of a preexisting nevus
- 2. Itching or pain in a lesion
- 3. Development of a new pigmented lesion during adult life
- 4. Irregularity of the borders of a pigmented lesion
- 5. Variegation of color within a pigmented lesion

NORMAL		CANCEROUS
	**"A" IS FOR ASYMMETRY** • If you draw a line through the middle of the mole, the halves of a melanoma won't match in size.	
	**"B" IS FOR BORDER** • The edges of an early melanoma tend to be uneven, crusty or notched.	
	**"C" IS FOR COLOR** • Healthy moles are uniform in color. A variety of colors, especially white and/or blue, is bad.	
	**"D" IS FOR DIAMETER** • Melanomas are usually larger in diameter than a pencil eraser, although they can be smaller.	
	**"E" IS FOR EVOLVING** • When a mole changes in size, shape or color, or begins to bleed or scab, this points to danger.	

Clinical features cont

- The probability of metastasis is predicted by measuring the depth of invasion in millimeters of the vertical growth phase nodule from the top of the granular cell layer of the overlying epidermis (Breslow thickness).

  Metastasis risk also is increased in tumors with a high mitotic rate and in those that fail to induce a local immune response.

.

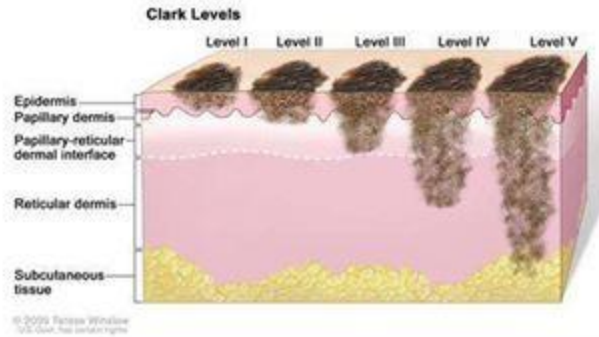
Thickness at excision	Probability of 5 year survival
<1mm	>95%
1-2mm	90%
2-4mm	63-67%%
>4mm	45%

Table 1. Five-year survival rates predicted by the Breslow thickness

Staging

- Breslow Staging:
  - Classifies tumor according to thickness in millimeters
  - Inverse correlation between thickness and survival
- Clark level of Invasion:
  - Classifies based on level of invasion into the histologic layer of the skin
  - I-V
- Independent Prognostic Factors:
  - Tumor stage, ulceration, nodal status, distant metastasis

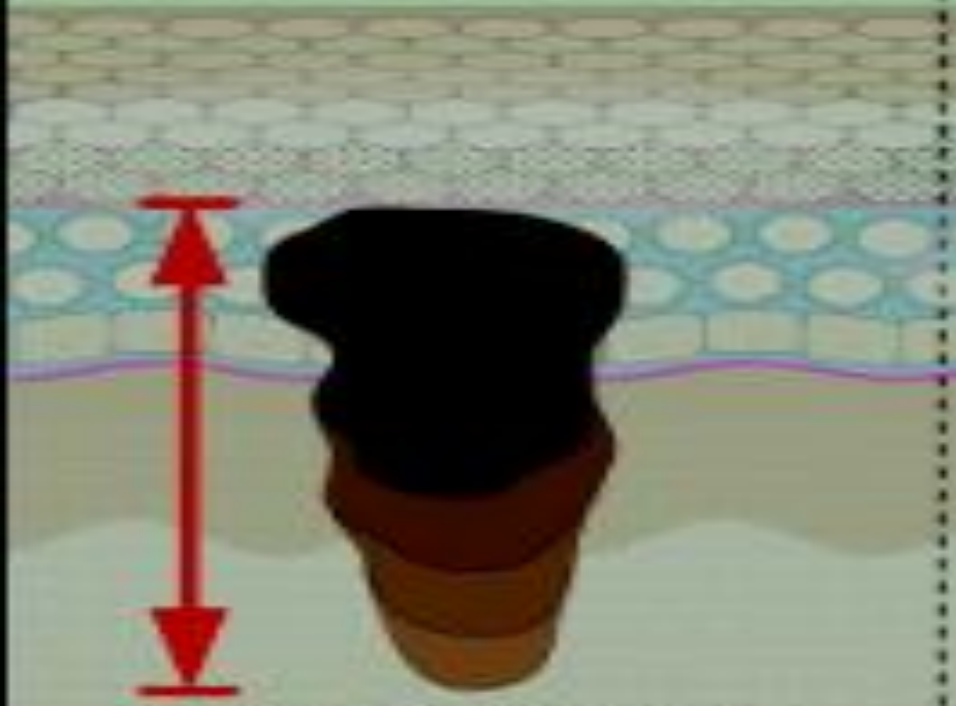
≤ 0.75 mm → 89%
0.76-1.49 mm → 75%
1.50-2.49 mm → 58%
2.50-3.99 mm → 46%
>4 mm → 25%



Level I: melanoma confined to the epidermis (melanoma in situ)
Level II: Invasion into the papillary dermis (through basement membrane)
Level III: Invasion to the junction of the papillary and reticular dermis
Level IV: Invasion into the reticular dermis
Level V: Invasion into the subcutaneous fat

Breslow Thickness

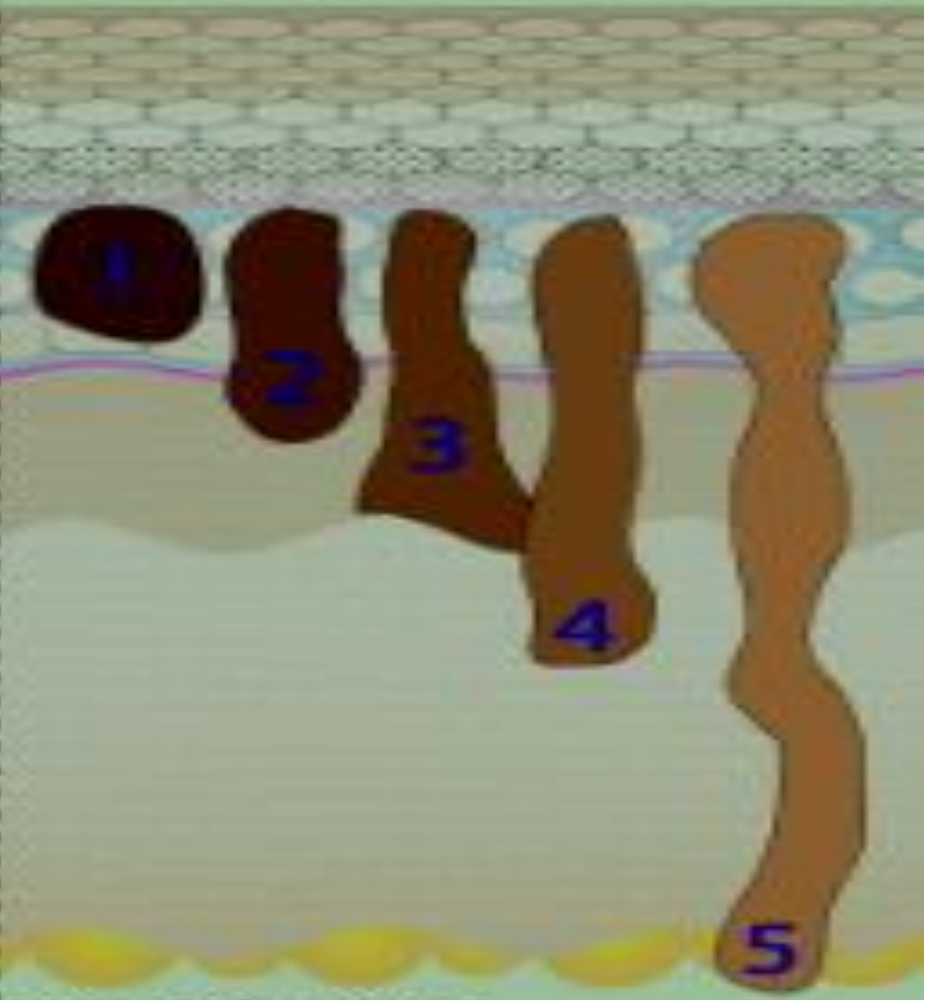
(measured in millimeters)
Widely used and regarded as a good indicator of outcome.



Measure from the granular layer of the epidermis (or the base of the superficial ulceration) **down to** the deepest point that the tumour has invaded in the tissues.

Clark Level

(indicates the anatomical level of invasion)



Level 1 **In situ** melanoma
(i.e. is remains with the epidermis)
Level 2 Invasion **INTO the papillary dermis**
Level 3 **THROUGHOUT the papillary dermis**
Level 4 Invasion **INTO the reticular dermis**
Level 5 Invasion into the subcutaneous tissues

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Clinical features cont

- When metastases occur, they involve not only regional lymph nodes but also liver, lungs, brain, and virtually any other site that can be seeded hematogenously.
- Sentinel lymph node biopsy (of the first draining node of a primary melanoma) at the time of surgery provides additional information on biologic aggressiveness

Clinical features cont

- In some cases, metastases may appear for the first time many years after complete surgical excision of the primary tumor, suggesting a long phase of dormancy, during which time the tumor may be held in check by the host immune response.
- Recognition of the likely role of the host immune response has led to therapeutic trials of immunomodulators.

- Some impressive responses in patients with advanced melanoma have been seen, especially to antibodies that block endogenous inhibitors of immune responses such as CTLA-4 and PD-1, and thus "release the brakes" on host antitumor immunity.

Classification	Thickness	Ulceration/Mitoses
T1	≤ 1.00 mm	a: no ulceration, mitoses $< 1/mm^2$
		b: ulceration and/or mitoses $\geq 1/mm^2$
T2	1.01—2.00 mm	a: without ulceration
		b: with ulceration
T3	2.01—4.00 mm	a: without ulceration
		b: with ulceration
T4	> 4.00 mm	a: without ulceration
		b: with ulceration

Classification	No. of Positive Nodes	Nodal Burden
N0	0	
N1	1	a: micrometastases
		b: macrometastases
N2	2—3	a: micrometastases
		b: macrometastases
		c: in-transit metastases or satellite lesions without metastatic nodes
N3	4+	Or in-transit metastases or satellite lesions with any number of metastatic nodes

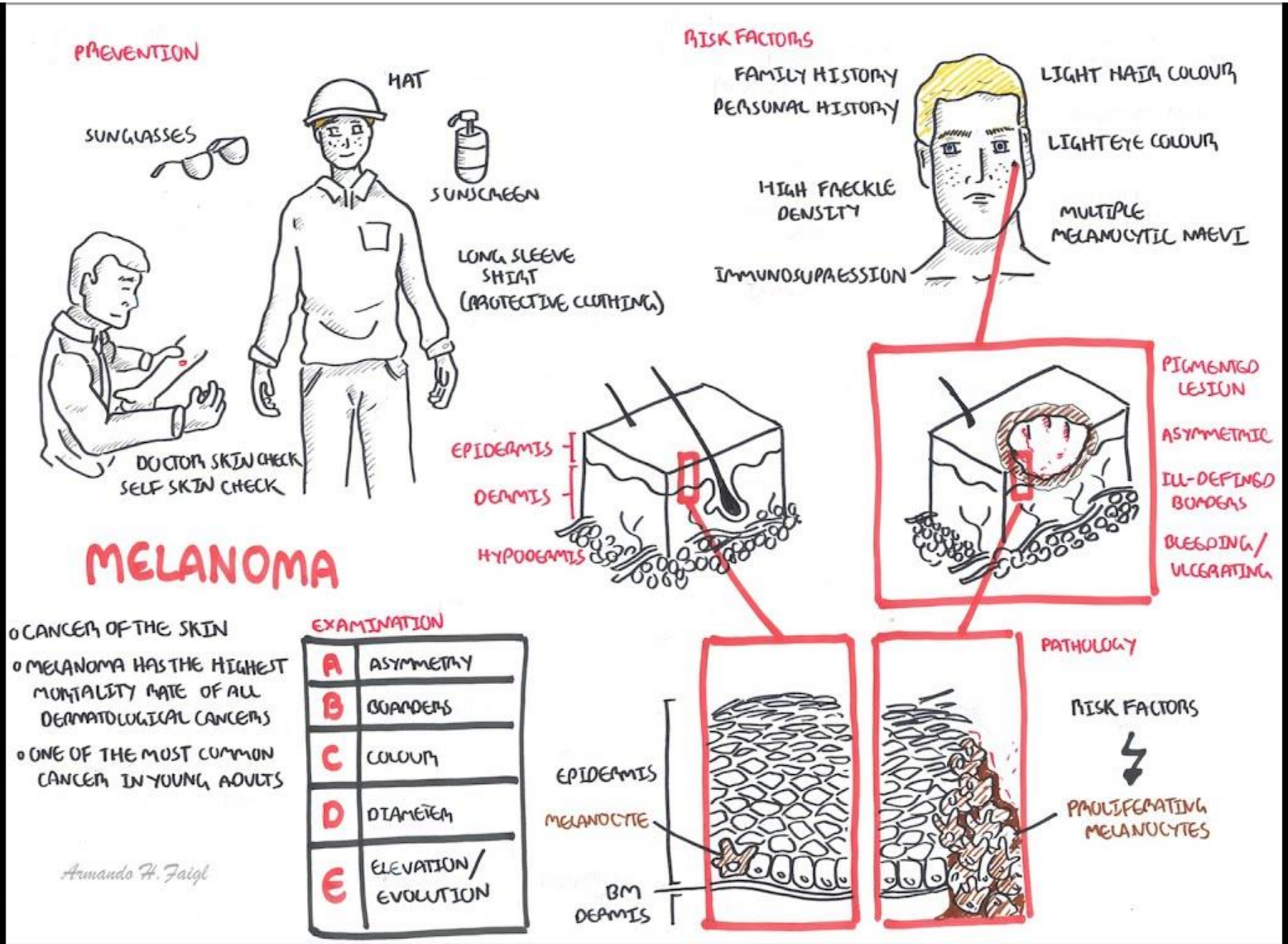
Classification	Site	Serum LDH
M0	None	NA
M1	Distant skin, subcutaneous, or nodes	Normal
M2	Lung	Normal
M3	All other visceral metastases	Elevated

Source: Ref. 6.

Prognostic factors

- Tumor depth.
- No of mitosis.
- Evidence of tumor regression.
- Ulceration of skin.
- Presence and number of tumor infiltrating lymphocytes.
- Gender.
- Location.

Summary


PREVENTION
HAT
SUNGLASSES
SUNSCREEN
LONG SLEEVE SHIRT (PROTECTIVE CLOTHING)
DOCTOR SKIN CHECK
SELF SKIN CHECK
RISK FACTORS
FAMILY HISTORY
PERSONAL HISTORY
LIGHT HAIR COLOUR
LIGHT EYE COLOUR
HIGH FRECKLE DENSITY
MULTIPLE MELANOCYTIC NAEVI
IMMUNOSUPPRESSION
EPIDERMIS
DERMIS
HYPODERMIS
PIGMENTED LESION
ASYMMETRIC
ILL-DEFINED BORDERS
BLEEDING/ ULCERATING
MELANOMA
CANCER OF THE SKIN
MELANOMA HAS THE HIGHEST MORTALITY RATE OF ALL DERMATOLOGICAL CANCERS
ONE OF THE MOST COMMON CANCER IN YOUNG ADULTS
EXAMINATION
A ASYMMETRY
B BORDERS
C COLOUR
D DIAMETER
E ELEVATION/ EVOLUTION
Armando H. Faigl
PATHOLOGY
RISK FACTORS
PROLIFERATING MELANOCYTES
EPIDERMIS
MELANOCYTE
BM
DERMIS

Melanoma: *Pathogenesis and clinical findings*

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*Habib A Kurwa
* *MD at time of publication*

Tanning beds
No sunscreen
Sun exposure

Ultraviolet (UV) light exposure
- Short wavelength UV worse due to higher photon energy; UVB (280–315nm) is worse than UVA (315–400nm).
- Short duration intense exposure (i.e. sunburns) worse than long duration low intensity exposure.

Genetics
- Fair skin and/or many nevi
- Other disease (e.g. Xeroderma pigmentosum)
- Most melanomas involve somatic mutations to BRAF (proto-oncogene), but germline mutations can occur such as CDKN2A (this has high penetrance but low incidence).

Keratinocyte damage and release of inflammatory cytokines

Energy applied to melanocytes

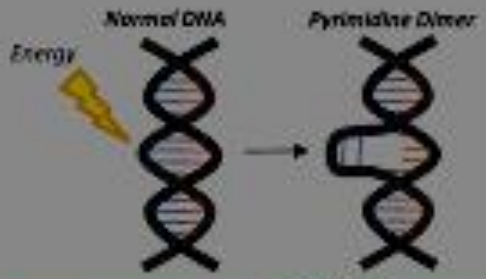
Extensive damage, non-recognition, or immunosuppression

Neutrophilic inflammatory response

Formation of DNA pyrimidine dimers

Failure of DNA repair mechanisms

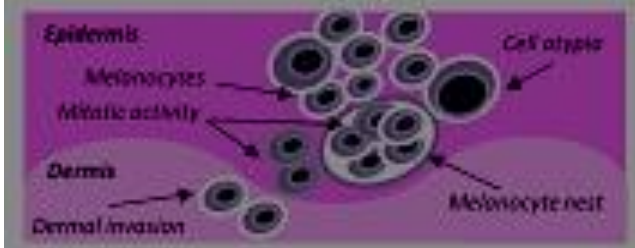
Notes:
- Usually, melanoma will undergo radial growth first, followed by vertical growth (exception is nodular melanoma).
- Breslow thickness most important prognostic factor.
- Mechanical loading may also be implicated in pathogenesis (plantar melanomas develop on regions of foot with highest pressures)
- Solar radiation is 95% UVA, 5% UVB.



Abnormal melanocyte DNA

Dysregulated cell transition from G1 phase (cell growth) to S phase (DNA replication)

Accelerated and uncontrolled melanocyte replication



Metastasis (e.g. brain, liver, lungs, bone)

Resistance to radiation therapy

Asymmetry: *One half of lesion does not look like the other*

Borders: *Irregular, poorly defined, or scalloped appearance*

Color: *Varied throughout lesion; e.g. can be black, blue, or red*

Diameter: *Usually greater than 5 mm*

Evolving: *Changing in shape, size, or color*

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Best Of Luck