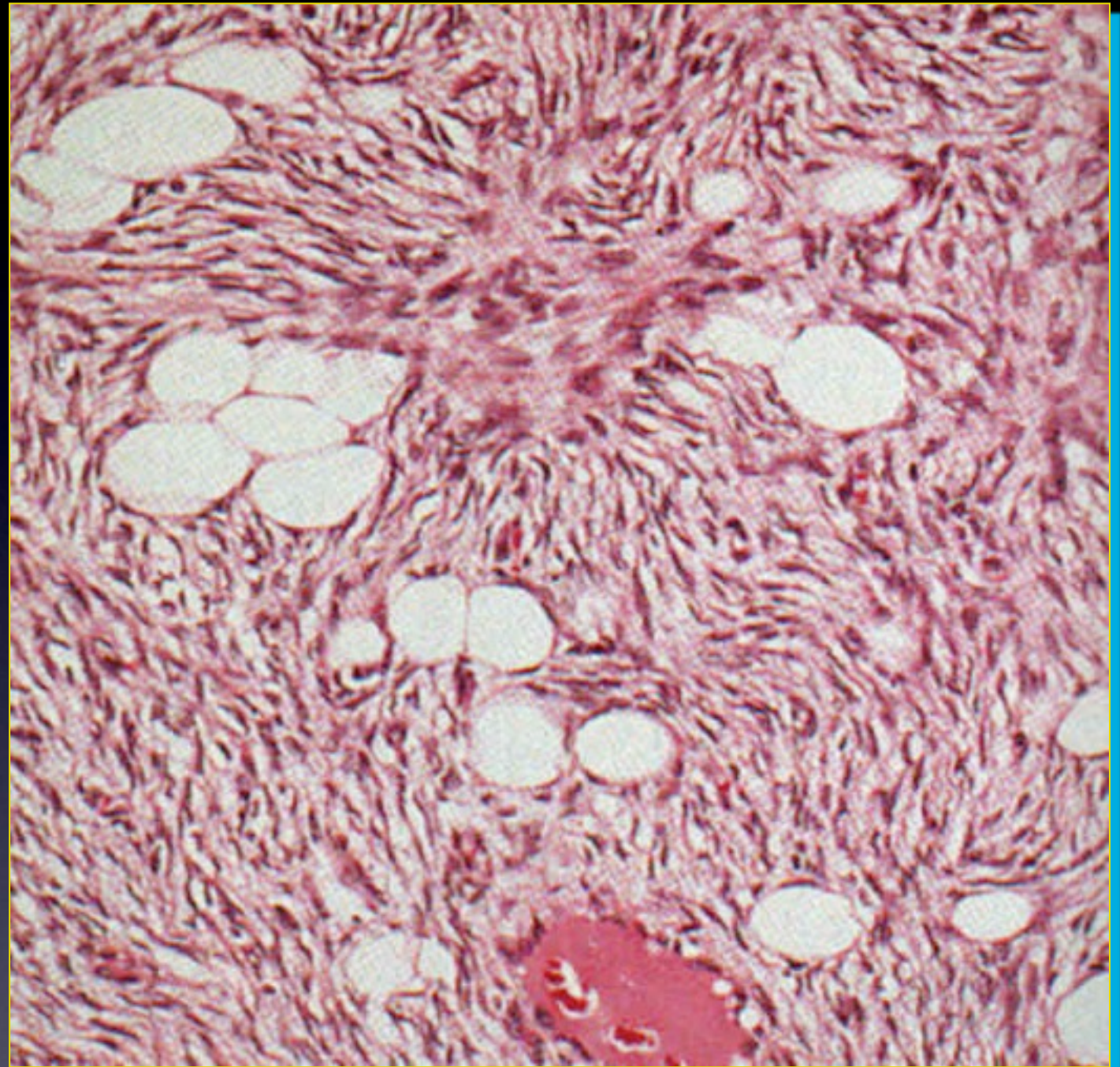
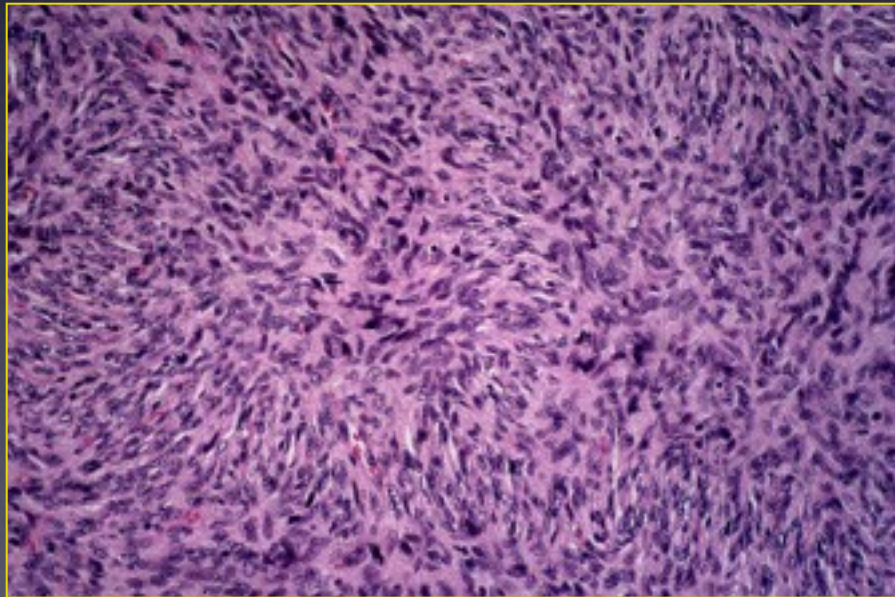
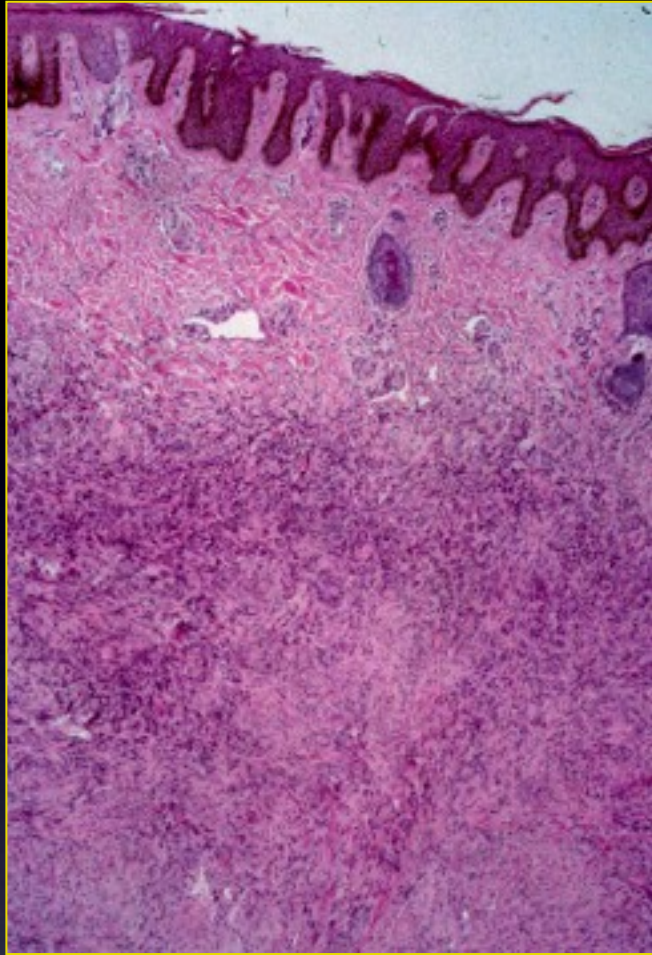


Primer of Immunohistochemistry (DFSP and Melanoma)

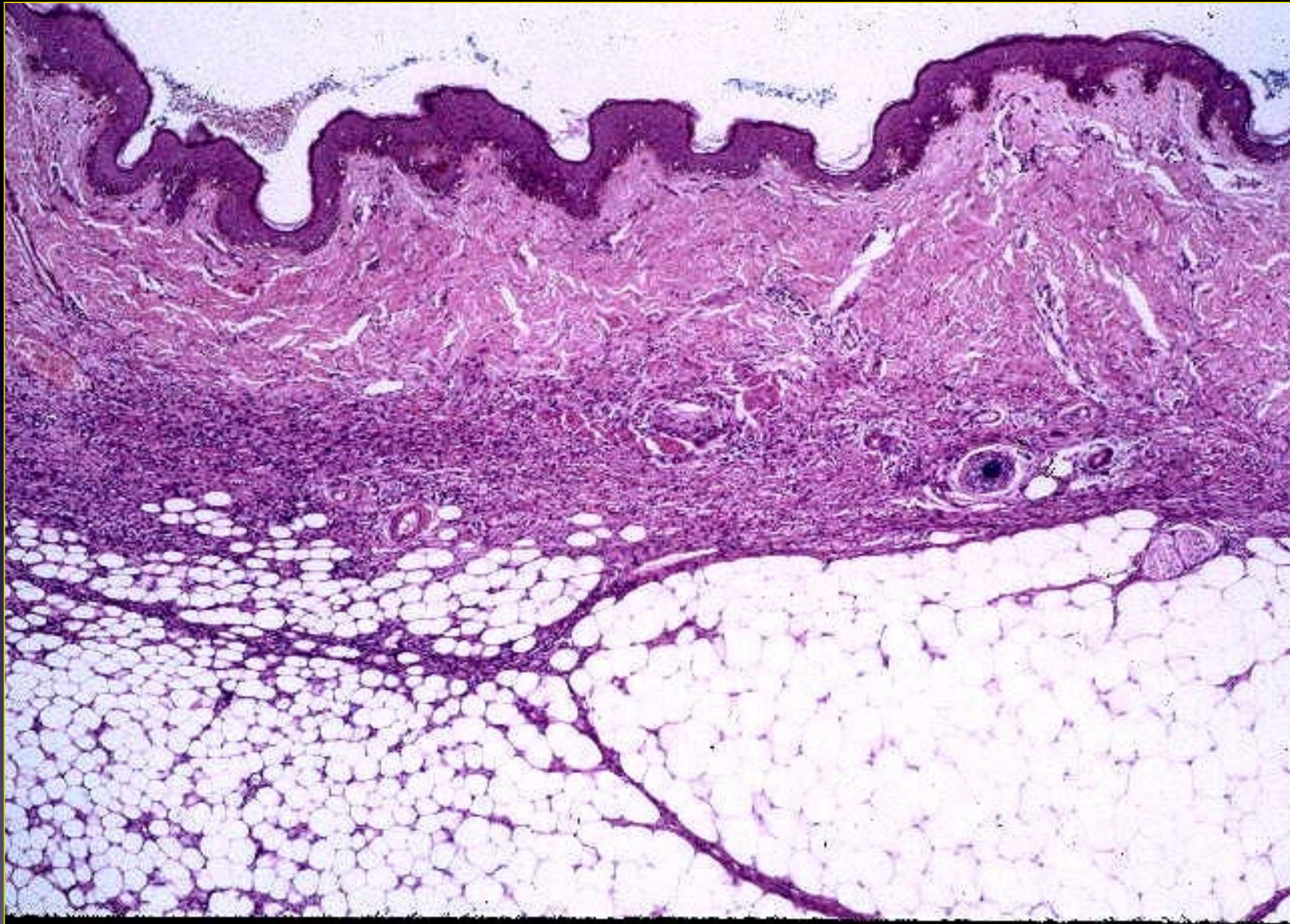
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Dermatofibrosarcoma protuberans

DERMATOFIBROSARCOMA PROTUBERANS: Microscopic Variants

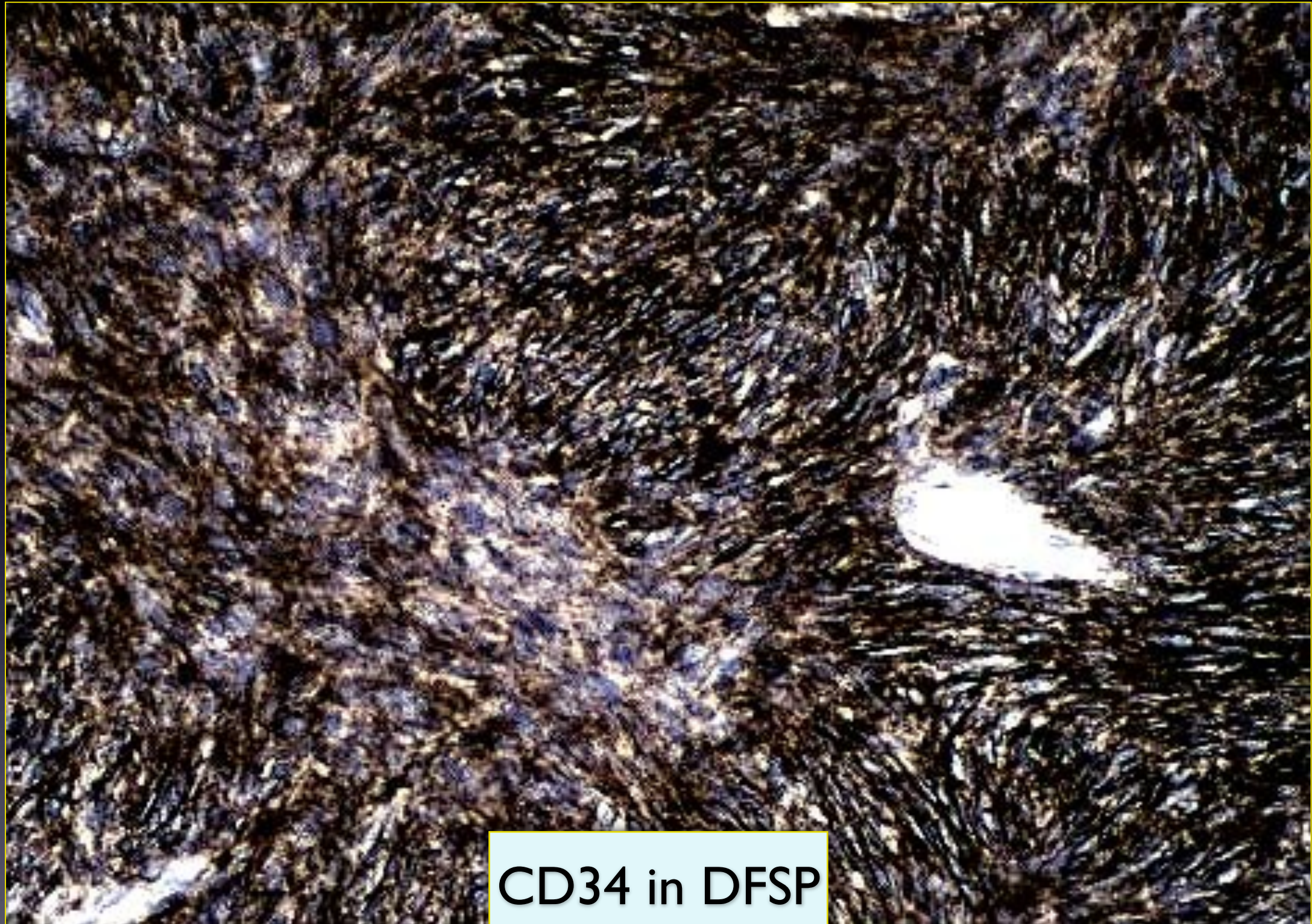
- Myxoid
- “Dedifferentiated”
- DFSP with giant-cell fibroblastoma-like differentiation
- Pigmented (Bednar tumor)
- Myoid



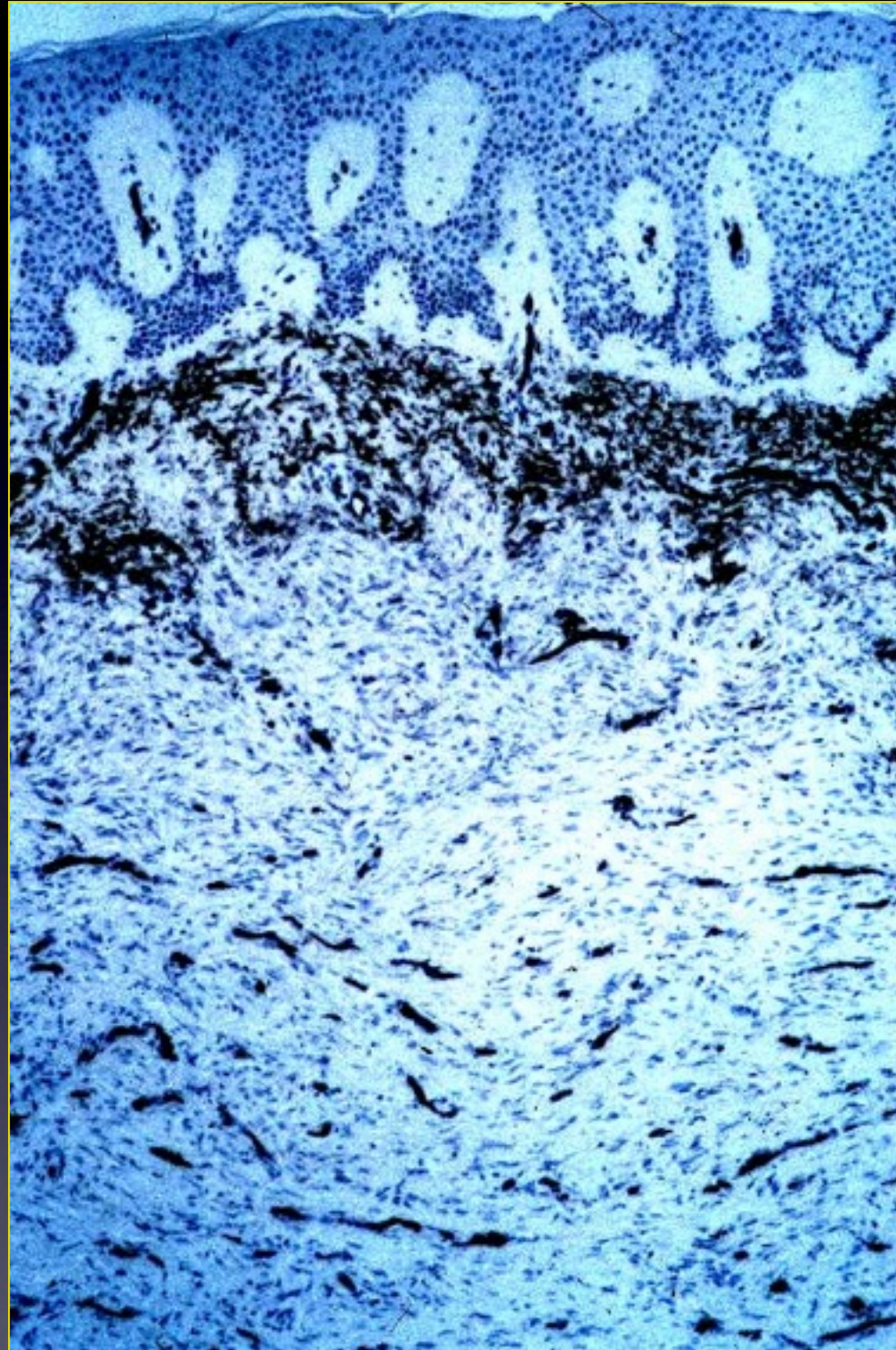
Atrophic Dermatofibrosarcoma protuberans

**DERMATOFIBROSARCOMA PROTUBERANS vs.
“DEEP” DERMATOFIBROMA:
An Immunohistological Approach**

- **Immunostains for CD34 (human hematopoietic progenitor cell antigen-1) and factor XIIIa are said to be discriminatory between DFSP and deep DF (DDF) in most cases**
- **DFSP is diffusely CD34 (+) & FXIIIa (-); DDF is CD34 (-) or only focally (+) & diffusely FXIIIa (+)**



CD34 in DFSP



CD34 in Dermatofibroma



Factor XIIIa in Dermatofibroma

CD 34 Distribution

- *In the skin and soft tissues, antibodies to CD34 have the ability to label:*
 - Selected perineurial mesenchymal cells (*not* so-called “dermal dendrocytes” as described by Nickoloff et al.
 - Selected perifollicular stromal cells
 - Endothelial cells of arterioles, venules, & capillaries
- *Neoplasms* of the skin that are CD34+ include DFSP, selected nerve sheath tumors, endothelial tumors, giant cell fibroblastoma, and hemangiopericytomas

CD34 Positive Tumors

- Dermatofibrosarcoma protuberans & variants
- Giant cell fibroblastoma
- Selected nerve sheath tumors
- Solitary fibrous tumors
- Giant cell angiofibroma
- Hemangiopericytoma
- Selected leiomyosarcomas
- Epithelioid sarcoma
- Clear cell sarcoma
- Spindle cell lipoma

DERMATOFIBROSARCOMA PROTUBERANS (DFSP): Cytogenetics

Synovial sarcoma	t(X;18)(p11.2; q11.2)
Liposarcoma, myxoid	t(12;16)
Rhabdomyosarcoma, alveolar	t(2,13)(q37; q14); del(13q14)
Rhabdomyosarcoma, embryonal	t(8;11)(q12;q21); +11(trisomy); del(11)
Ewing's sarcoma	t(11,22)(q24; q12), & i(11)
Neuroepithelioma (PNET)	t(11,22); +1q
Desmoplastic small cell tumor	t(11,22)(p13;q12)
Clear cell sarcoma	t(12;22)(q13;q12)
Epithelioid sarcoma	t(8;22)(q22;q11); +2
Chondrosarcoma, myxoid	t(9;22)(q31; q12.2)
Fibrosarcoma, infantile	+8, +11, +17 (trisomies)
MPNST in neurofibromatosis	t(17;22)(q21;q13.1;?)
Malignant fibrous histiocytoma	del(1, q11); others, complex
Leiomyosarcoma	t(12;14); others
Alveolar soft part sarcoma	+8, +12 (trisomy); del(17)
Pigmented villonodular synovitis	+7 (trisomy)
Fibromatosis (desmoid)	del(5)(q13-q31); +8; +20 (trisomies)
Neurofibroma	t(1,22)
Atypical lipoma	r(?3)(ring)
Lipoma	t(3,12)(q28; q14); 3 groups
Leiomyoma, uterus	del(7)(q21); t(12,14)(q14-15;q23-24)
Plexiform fibrohistiocytic tumor	-6, -8; deletions
Dermatofibrosarcoma	t(17;22)(q22;q13)
Hemangiopericytoma	t(12;19); t(13;22)

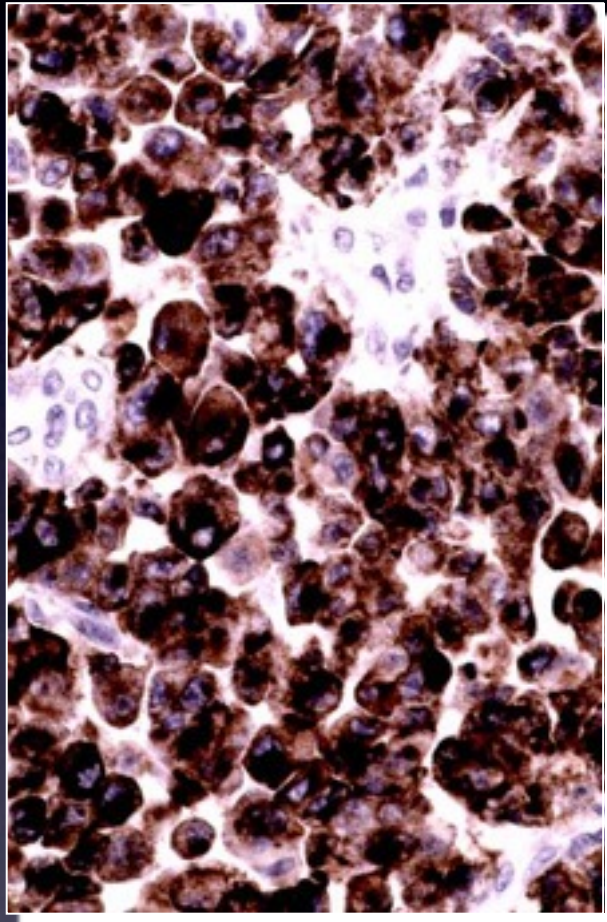
DERMATOFIBROSARCOMA PROTUBERANS (DFSP):

Relationship to Giant Cell Fibroblastoma

- Giant cell fibroblastoma (GCF) is a biologically-similar tumor to DFSP that occurs almost exclusively in children & adolescents
- Several cases have now been reported in which recurrences of GCF assumed the microscopic appearance of typical DFSP variants
- Examples of DFSP also exist that contain foci with GCF-like images
- Immunophenotypes of DFSP and GCF are closely similar
- *It is now generally accepted that GCF and DFSP are part of a single tumor spectrum*

Melanoma Markers

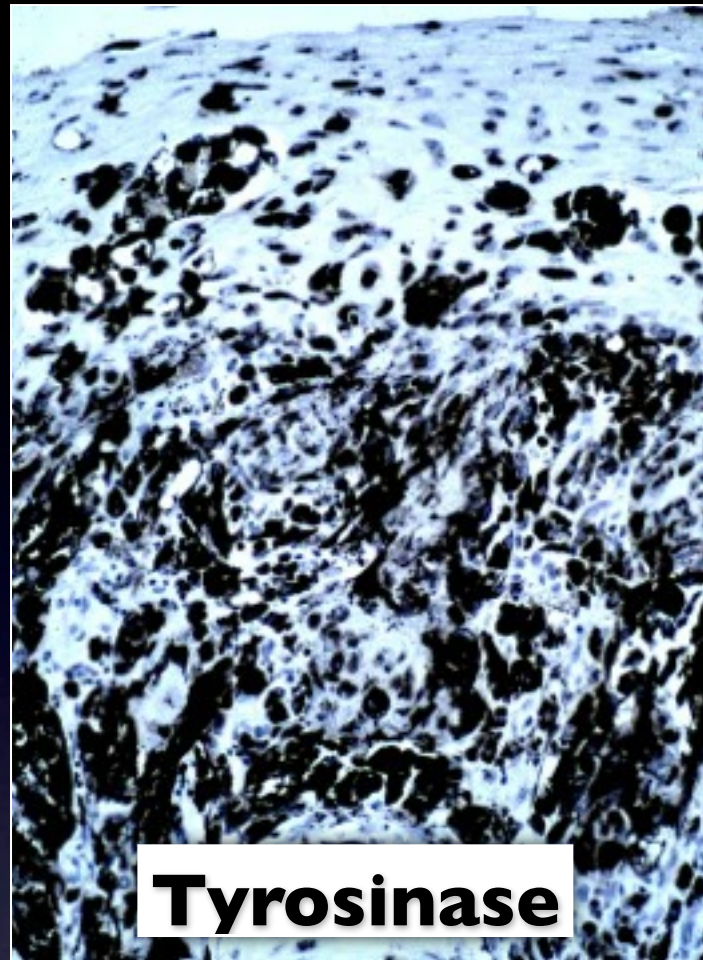
HMB-45: Useful or Useless?



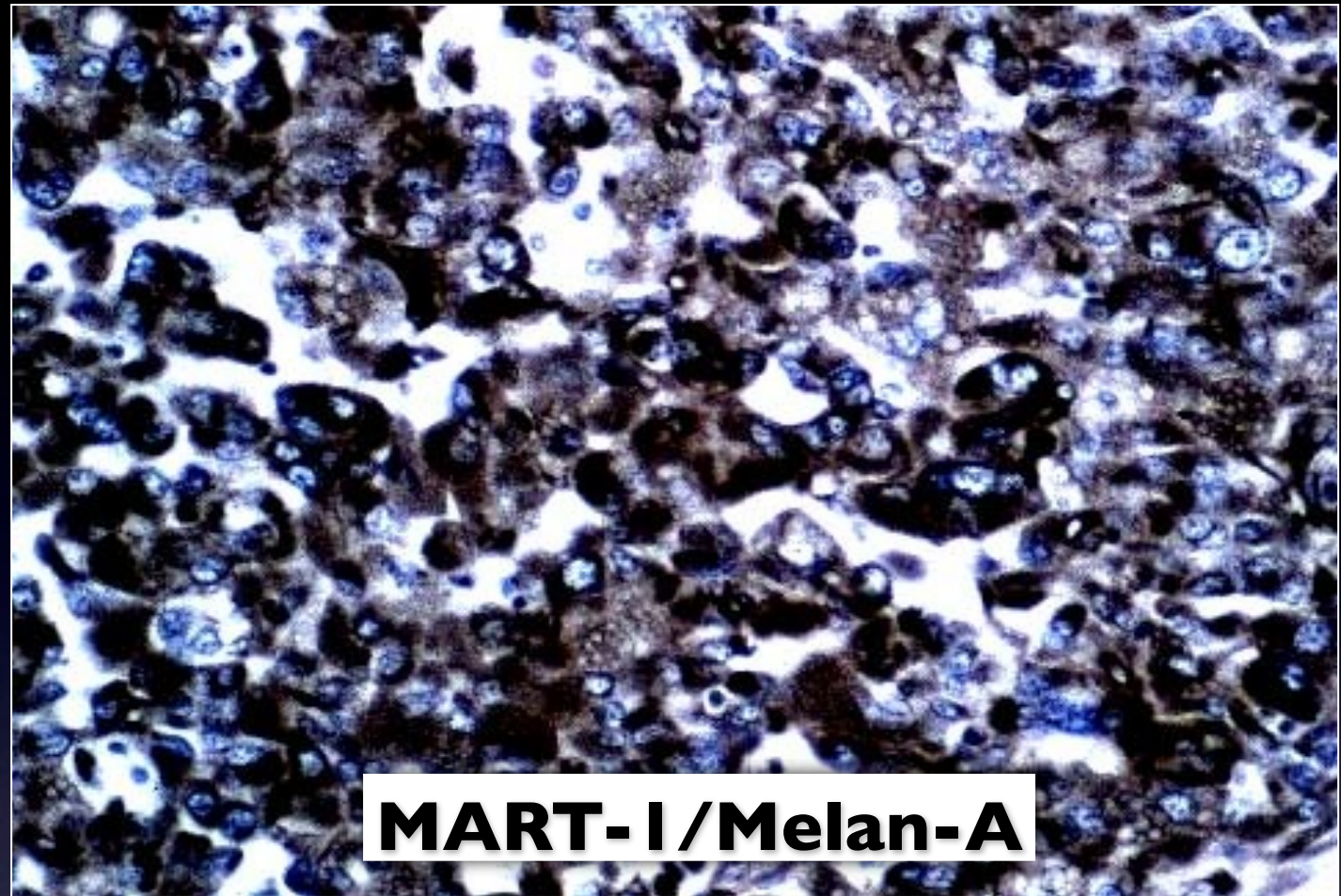
- **Several papers since 1986 have impugned the specificity of HMB-45 for melanoma; papers between 1988 and 1993 were based on unpurified supernatant marketed by Enzo Co., and were valid reports of spurious reactivity**
- **Since 1993, other vendors have returned to purified Ig preparation and regained specificity; however, sensitivity has dropped from an original figure of 93% to approximately 50% because of commercial manipulation**

“New” Immunohistologic Markers for Melanoma

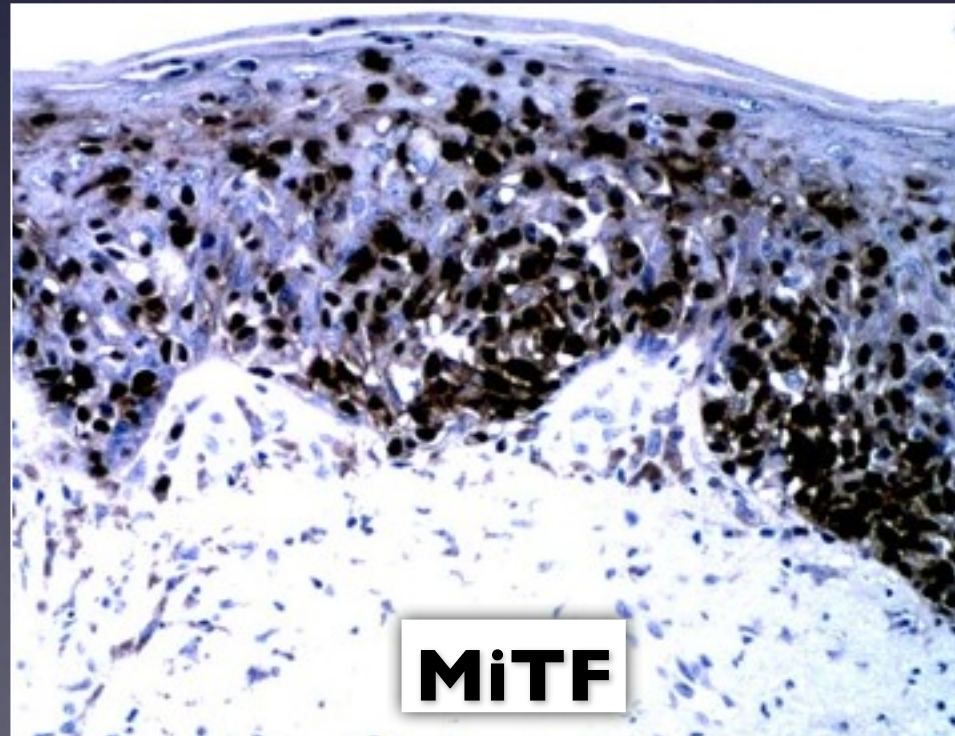
- **Anti-tyrosinase**: Excellent specificity; labels approximately 80% of small-cell, epithelioid, and large-cell pleomorphic melanomas, but consistently fails to recognize spindle-cell tumors
- **Melan-A/MART-1**: Similar comments to the above; also labels steroid-producing tumors of the adrenals, liver, and genitals
- **Microphthalmia transcription factor**: A nuclear protein that is seen in the majority of morphologically-“conventional” melanomas, but not in spindle-cell tumors; also labels a proportion of non-melanocytic malignancies



Tyrosinase



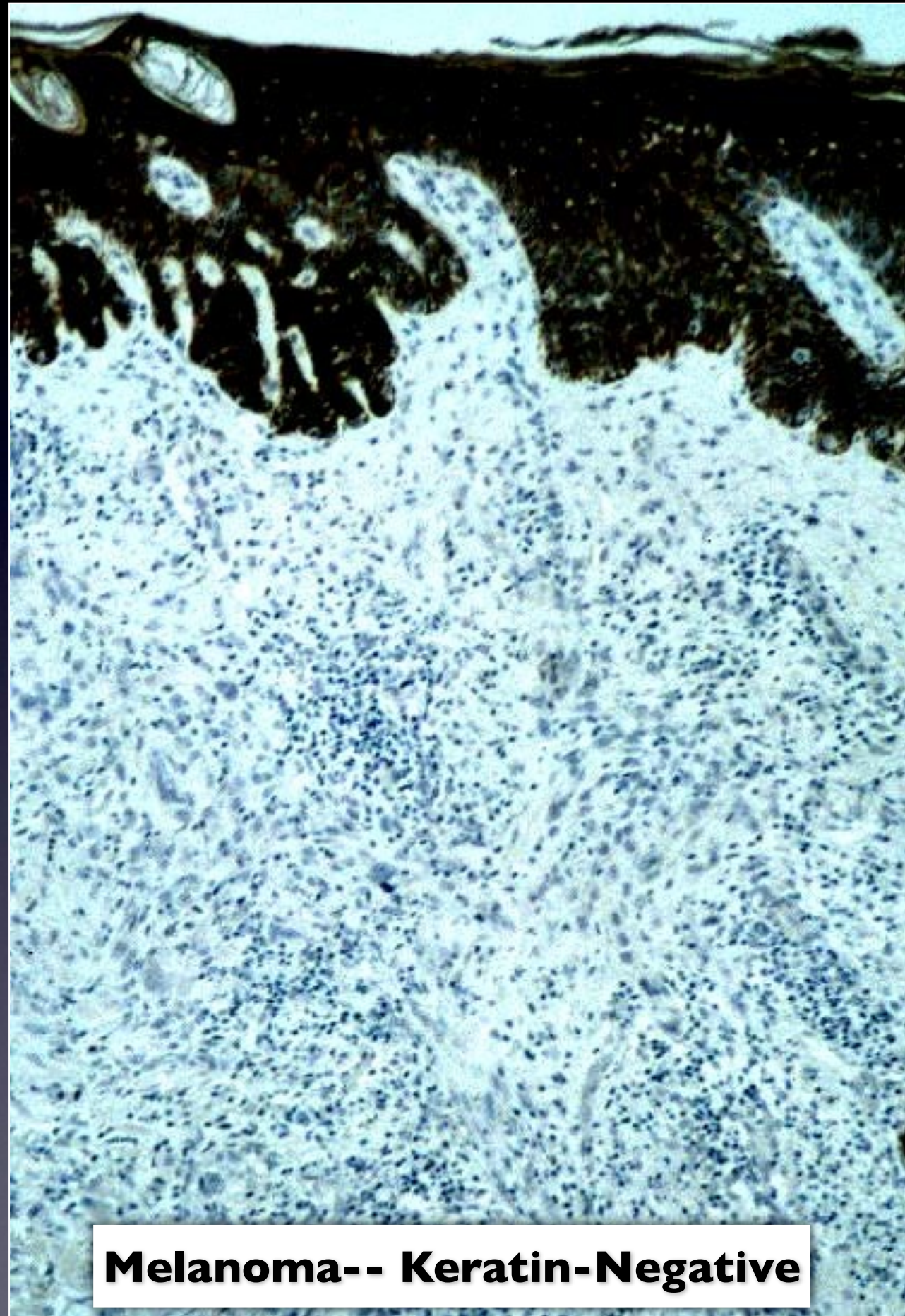
MART-1/Melan-A



MiTF

KERATIN IN MELANOMA: Overall Incidence

- **Consensus data obtained in a cooperative multi-institutional study showed an overall incidence of keratin-positivity of 3 in 300 formalin-fixed, paraffin-embedded melanomas**
- **Institution reporting the greatest incidence of keratin-positivity (6 tumors) used automated immunodetection methods and high concentration of anti-keratin antibodies**
- **Conclusion--- *keratin immunoreactivity in melanoma is probably real in part, but is largely a byproduct of methodological bias***

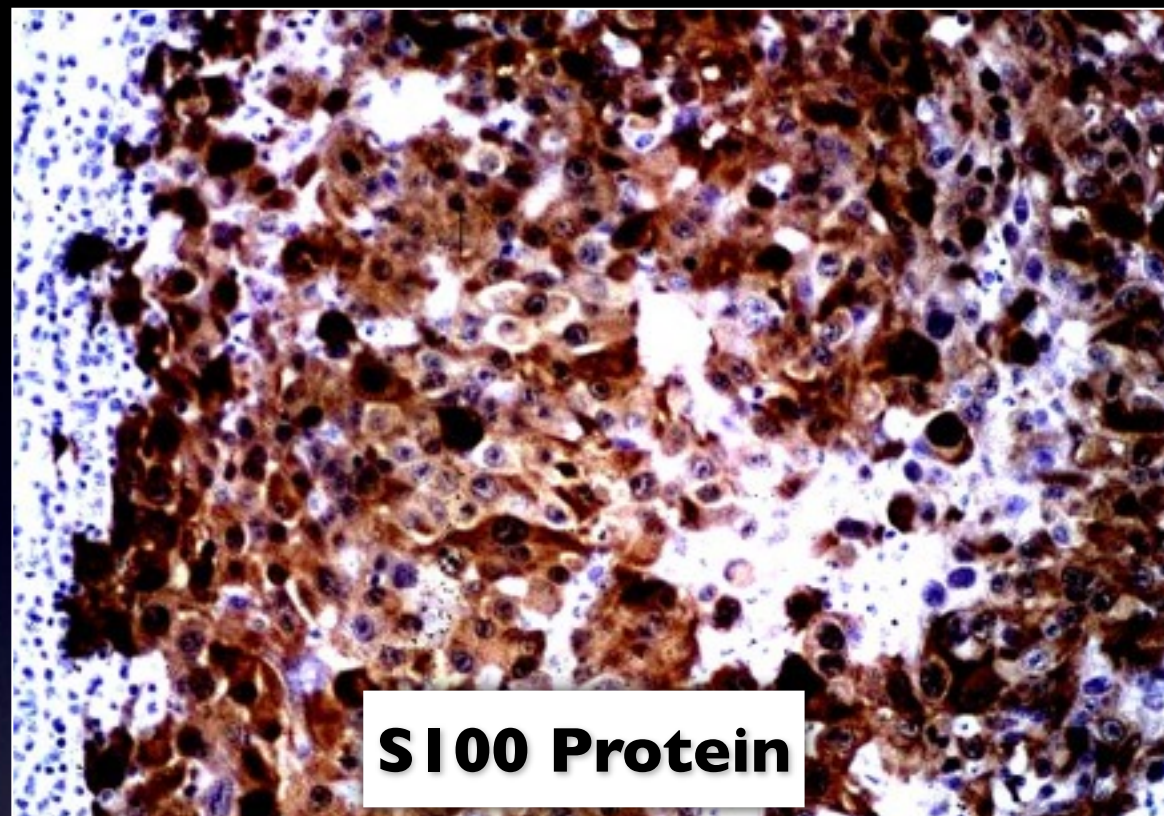


Melanoma-- Keratin-Negative

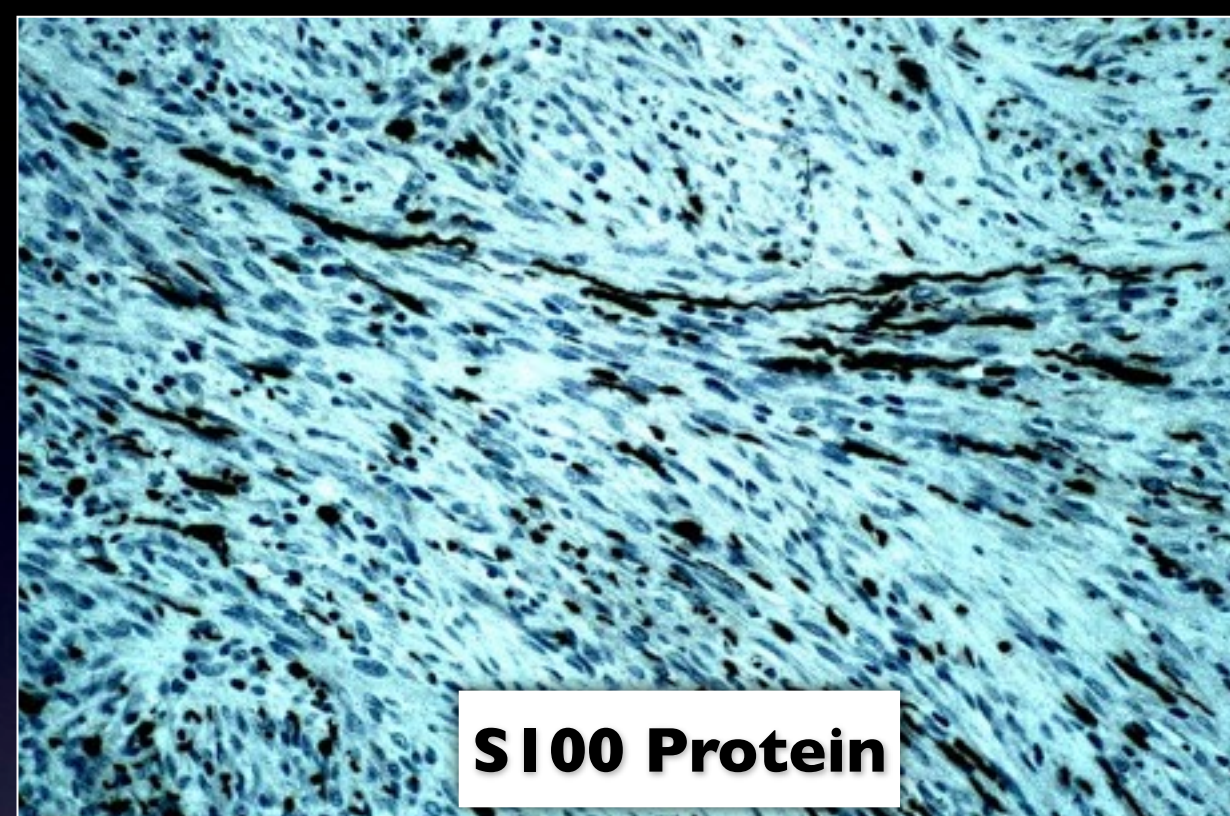
Working Immunohistologic Panel for Diagnosis of Melanoma

- **Keratin**
- **EMA**
- **Muscle-specific actin (for spindle-cell tumors only)**
- **S100 protein**
- **Tyrosinase**
- **MART-1**
- **HMB-45**

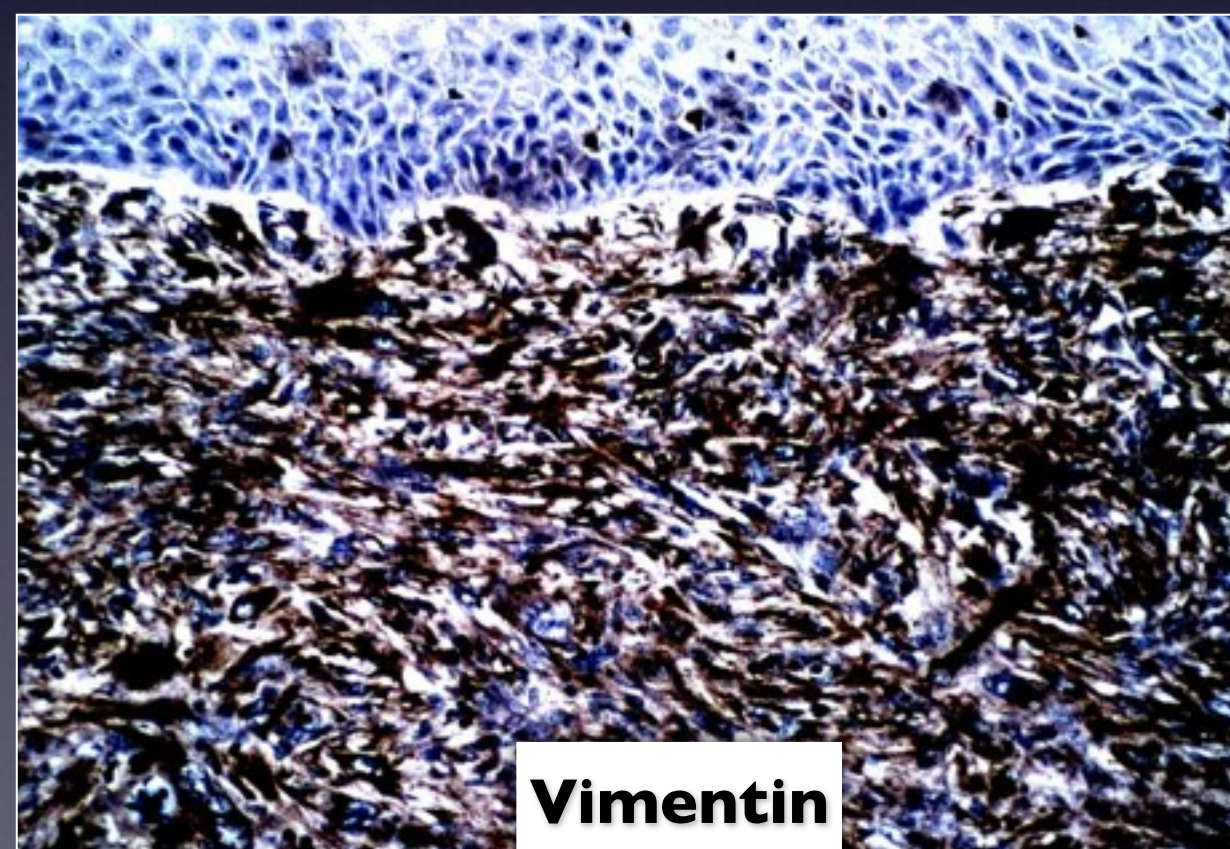
Reactivity for S100 protein and negativity for keratin and EMA (or MSA) is actually sufficient to make the diagnosis in the vast majority of cases



S100 Protein



S100 Protein



Vimentin

p53 Immunostaining in Melanocytic Lesions: Background

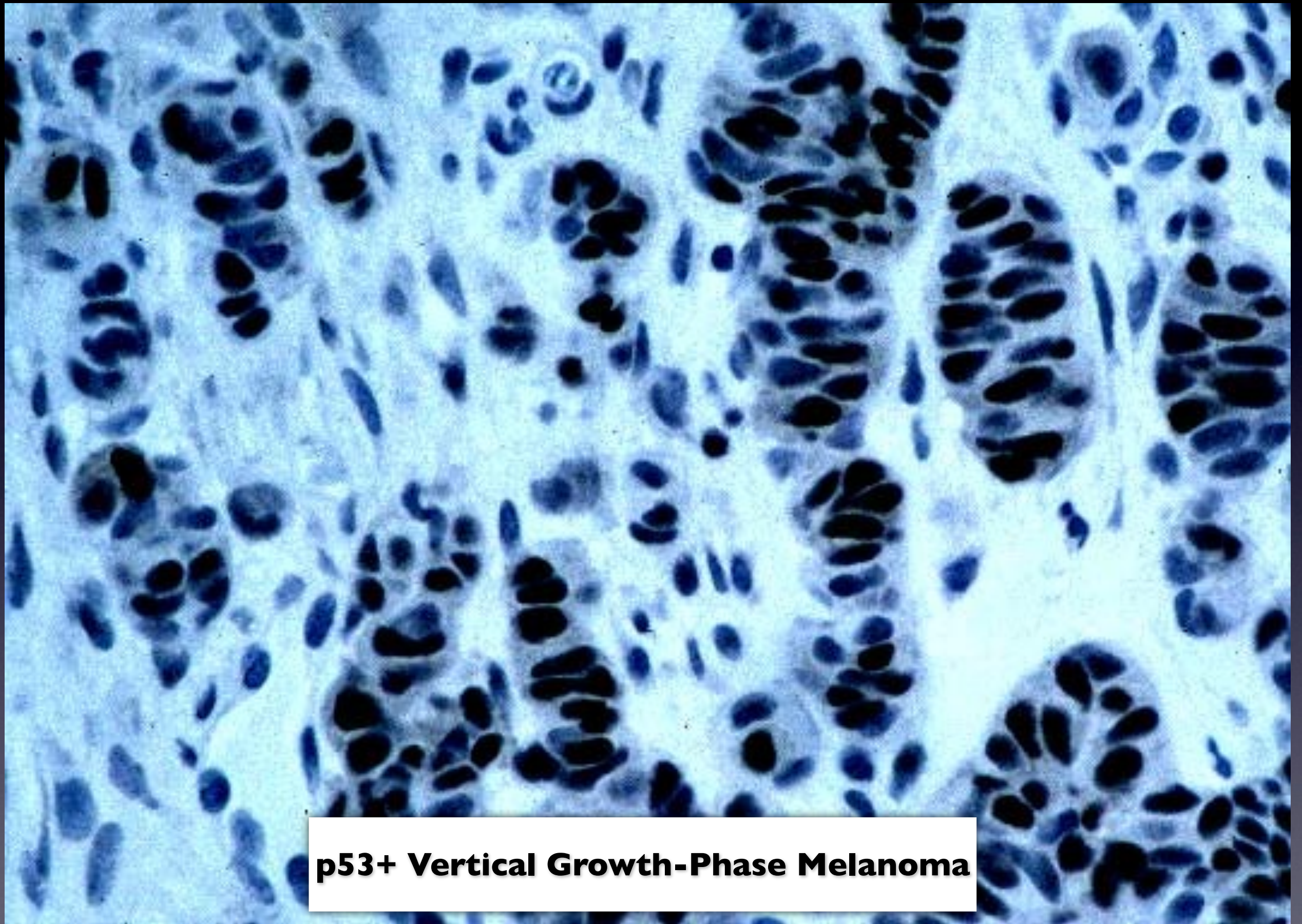
- **Mutations in the p53 suppressor gene, located on chromosome 17 at locus p13, are the most common genetic alterations found in human malignancies**
- **The current understanding of mutant p53 protein in the biology of melanoma is incomplete, but this moiety may play a role in the progression of melanocytic lesions as a general group**

p53 Immunostaining in Melanocytic Lesions

- **A total of 256 well-characterized cutaneous melanocytic neoplasms was studied, including 113 nevi (including 40 Spitz nevi), 23 melanomas arising in preexisting nevi, and 120 melanomas of other histologic types**
- **Paraffin sections of each tumor were studied immunohistologically using the ABC method with prior antigen retrieval and a mixture of 2 monoclonal antibodies (P1801 and D07)**

p53 Immunostaining in Cutaneous Melanocytic Lesions: Summary of Results

- **No nevi-- regardless of type-- showed any p53-immunoreactivity whatsoever,**
- **73% of melanomas were p53-positive overall, but only 29% showed >5% labeling**
- **p53 labeling was most common in nodular melanoma, followed respectively by superficial spreading and lentigo maligna melanomas; melanomas arising in nevi were negative in 70% of cases**



p53+ Vertical Growth-Phase Melanoma

p53 Immunostaining in Cutaneous Melanocytic Lesions: Summary of Results (Continued)

- **The prototypical vertical-growth-phase melanoma (nodular type) showed a median labeling index of 8%, as compared with 2% labeling in radial-growth-phase superficial spreading melanomas**
- **The number of p53-positive cases among malignant melanomas (73%) was statistically highly-significant ($p < 0.000001$) vis-a-vis the number of p53-reactive melanocytic nevi (0%)**

p53 Immunostaining in Cutaneous Melanocytic Lesions: Conclusions

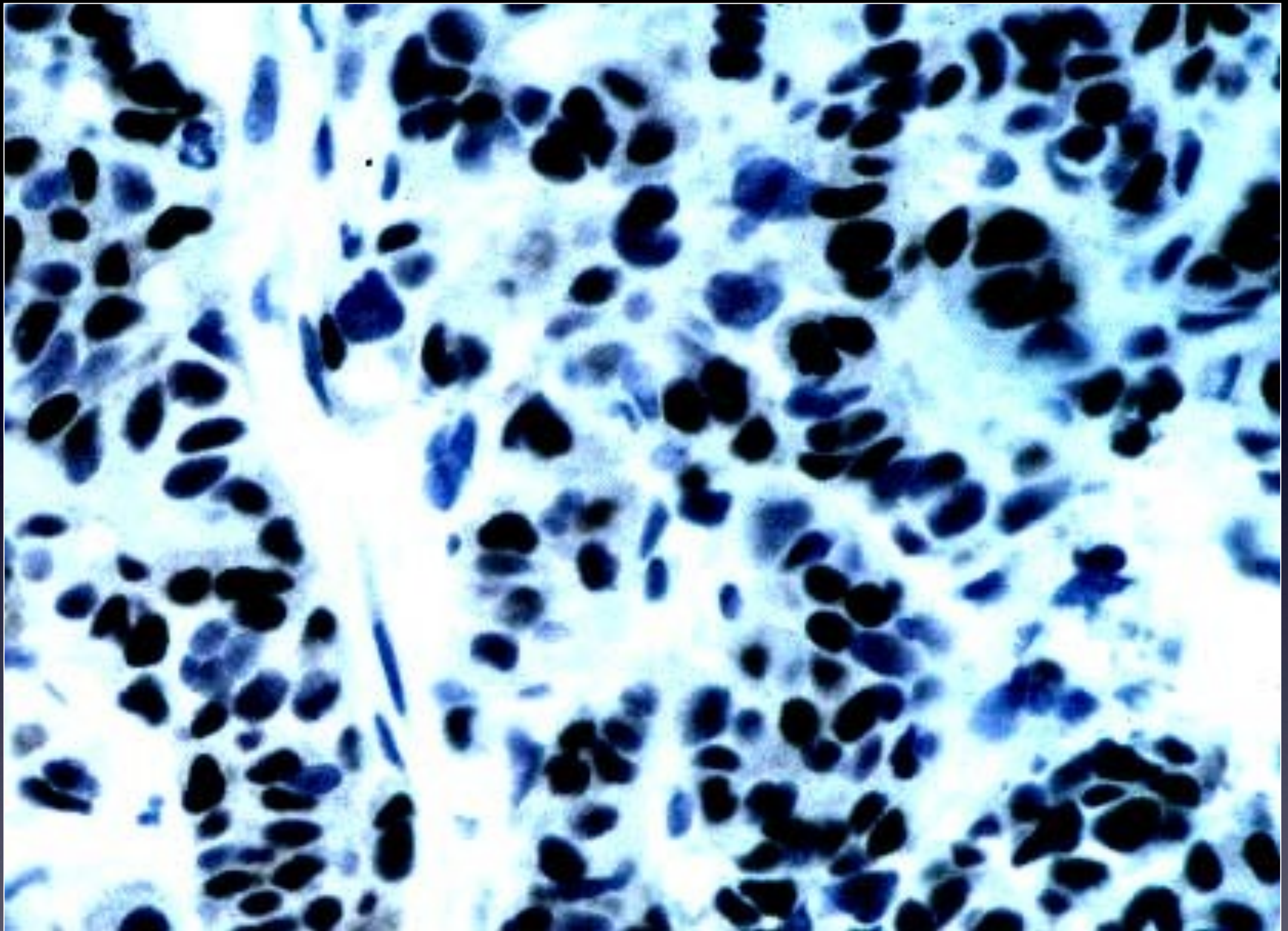
- **1. Immunopositivity for p53 protein is one factor favoring a pathologic interpretation of malignant melanoma, and may be helpful diagnostically in selected cases;**
- **2. *Negative* p53 immunostaining results cannot , however, be equated with a diagnosis of benignancy in melanocytic lesions, because nearly 30% of melanomas are *also* negative;**

p53 Immunostaining in Cutaneous Melanocytic Lesions: Conclusions ***(Continued)***

- **3. The problem of Spitz nevus versus “Spitzoid” melanoma lends itself most readily to application of p53 immunostains in a diagnostic context;**
- **4. Because of the differences in p53 indices in vertical and radial growth phase malignant melanomas, it would appear that an arbitrary immunolabeling cutoff of 10% could be of aid in the separation of these two biological entities**

Ki-67 in Melanocytic Lesions

- **Ki-67 indices of >10% in dermal melanocytic proliferations favor a diagnosis of malignancy; indeed, they are seen predominantly in *vertical growth phase* melanomas. It is in the recognition of the latter, and their separation from radial growth phase tumors, that Ki-67 has the most merit**



Ki-67+ Vertical Growth-Phase Melanoma

Primer of Immunohistochemistry (DFSP and Melanoma)

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