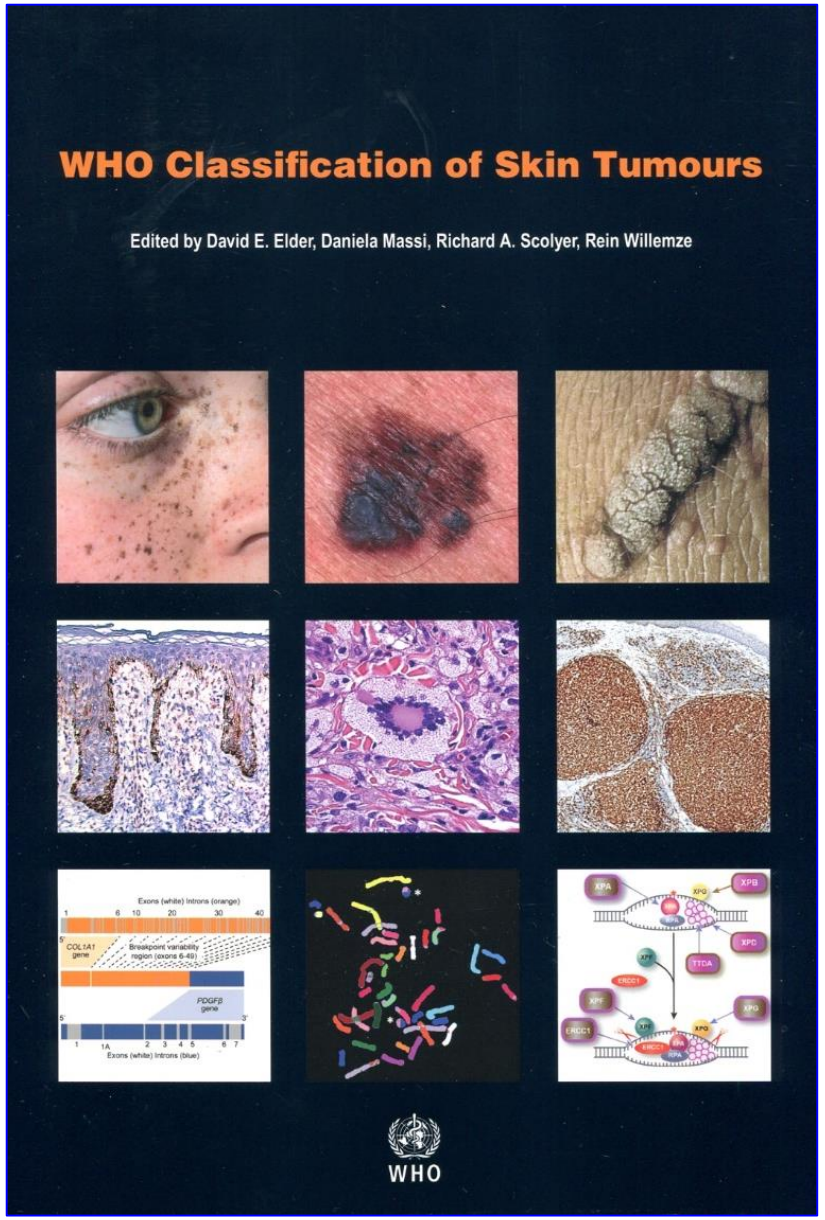
Die aktuelle WHO-Klassifikation melanozytärer Läsionen

W. Weyers
Zentrum für Dermatopathologie Freiburg



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28. Jahrestagung der Arbeitsgemeinschaft Dermatologische Histologie (ADH),
Duisburg, 24.-26.9.2021

Rund anderthalb Jahre sind vergangen, seit ich gebeten wurde, auf der ADH-Tagung in Duisburg die damals noch recht neue WHO-Klassifikation des Melanoms einer kritischen Betrachtung zu unterziehen. Inzwischen ist das geschehen,

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Abstract: The World Health Organization's classification of skin tumors of 2018 presents melanoma as a loose assembly of independent biologic entities, each of which is characterized by a distinctive constellation of clinical, histopathologic, and molecular findings that evolve through different pathways of lesional progression from a benign to an intermediate and, ultimately, malignant tumor. The alleged pathways, however, are based on vague correlations and fail to take into account the common occurrence of lesions that cannot be assigned to either of them. Moreover, there is no such thing as a lesional progression. The evolvement of neoplasms is always a clonal and, therefore, initially focal event. In the majority of melanomas, there is no evidence of a juxtaposition of a benign, intermediate, and malignant portion. Occasionally, a melanoma may develop within the confines of a melanocytic nevus, but a nevus cannot transform into melanoma. The concept of lesional progression merely serves to handle problems of differential diagnosis because it obscures and, in fact, denies the difference between benign and malignant neoplasms. In the current classification of the World Health Organization, every lesion is said to bear some risk of malignant progression, intermediate categories are recognized for all alleged pathways, and no distinction is made between "high-grade dysplasia" and melanoma in situ. Differentiation between benign and malignant neoplasms of melanocytes may be difficult, but the concept of lesional progression does not address those problems; it merely offers evasions under the disguise of diagnoses.

Key Words: WHO classification, melanoma, dysplastic nevus, Spitz nevus

(*Am J Dermatopathol* 2020;42:989–1002)

As we know from Andersen's fairy tales, there was once an emperor who attached great importance to his attire. Hence, it was no surprise that he became highly interested when being offered a very special garment, one so light that one could hardly feel it on one's body and with the magic quality of being invisible to anyone either unfit for his position or hopelessly stupid. To check the intriguing offer, the emperor sent forth his most trusted ministers who could not see anything at all on the weaving loom, but out of fear of appearing unfit for their positions, they asked the weavers to explain every detail of the alleged clothes and went on to repeat those fanciful descriptions before the emperor. When informed that the garment was finished, the latter went to the weavers, noticed with shock that he could not see the garment described so enthusiastically by his ministers but pretended utmost delight. He awarded the fraudulent weavers high decorations, asked them to dress him up, and then marched in procession before his subjects. The townsfolk uncomfortably went along with the pretense until, finally, a child in the crowd blurted out that the emperor was wearing nothing at all. When that cry was taken up by others, the emperor realized the assertion was true, but he kept his head high and continued the procession.

This fairy tale has been told times and again for nearly 200 years and has been the theme of movies, songs, and operas. Its popularity results from the exaggerated depiction of attitudes that are common in many areas of life, including medicine. As in the fairy tale, there are emperors in medicine whose old clothes have become a bit shabby and who obtain new clothes from witty weavers, which they wear with great pride, although the fabric is flimsy. As in the fairy tail, it is a common attitude in medicine to repeat the fanciful descriptions provided by others, even though there is little to see. Also, as in the fairy tail, new garments in medicine are often considered to be visible only to prudential folk, whereas those unable to appreciate them are at risk of being regarded as unfit for their position, if not hopelessly stupid. One of those emperors in new clothes is malignant melanoma in the garment of the new World Health Organization's (WHO's) classification of skin tumors.

The new garment has been upgraded by the luxurious drapery of molecular findings. Because of differences in the spectrum of mutations, the existence of "*multiple biologically distinct categories*" of melanoma has been postulated that differ in regard to "*cell of origin, age at onset, clinical and histologic presentation, pattern of metastases, ethnic distribution, causative role of UV radiation, predisposing germ line alterations, mutational processes, and patterns of somatic mutations.*" [3] The view has become widely accepted that "*malignant melanoma is in fact not a single entity but a group of different neoplasms with variable etiopathogenesis, biologic behavior and prognosis.*"

To tailor a made-to-measure suit for melanoma in the light of molecular findings was the aim and claim of the new WHO classification. The latter was published in 2018 and recognized 9 "*alternative pathways in the development of melanoma,*" ranging from rare uveal melanomas and melanomas arising in blue nevi to the "*2 major pathways, which account for the majority of melanomas in populations with*

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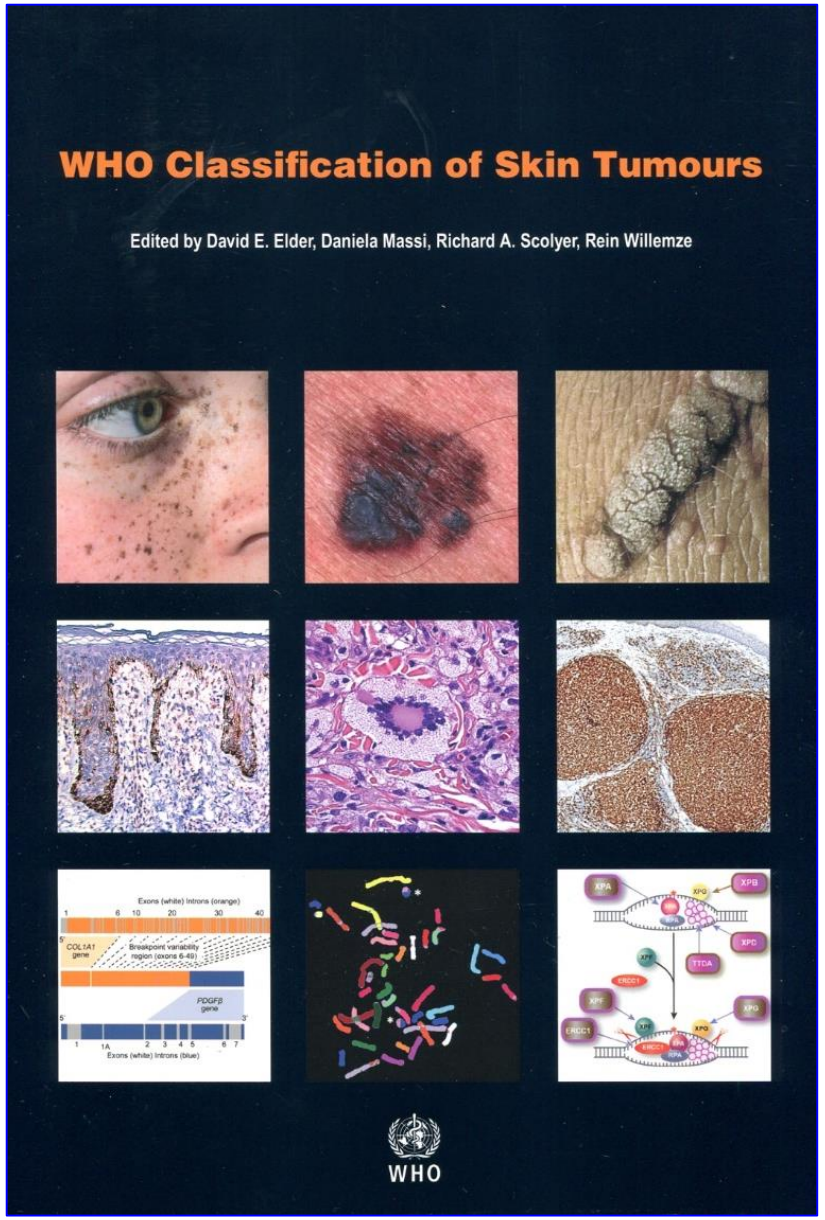

und in diesem Artikel im American Journal of Dermatopathology habe ich die Klassifikation mit des Kaisers neuen Kleidern verglichen.

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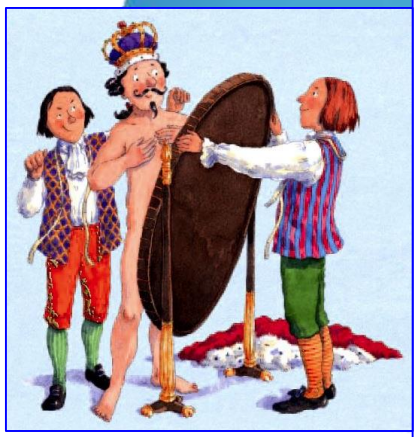

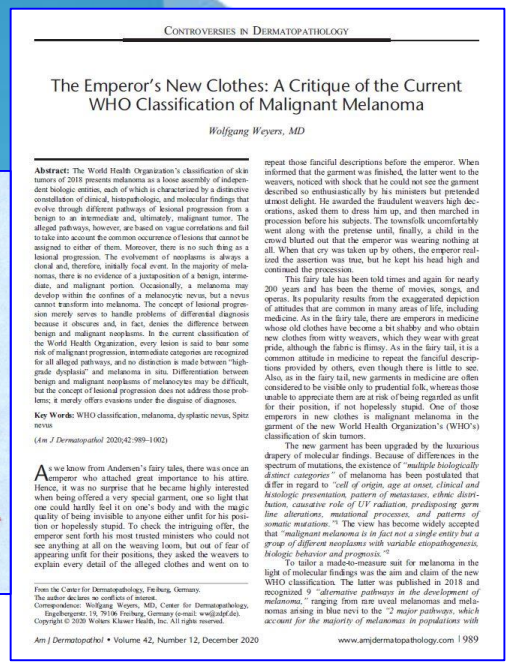

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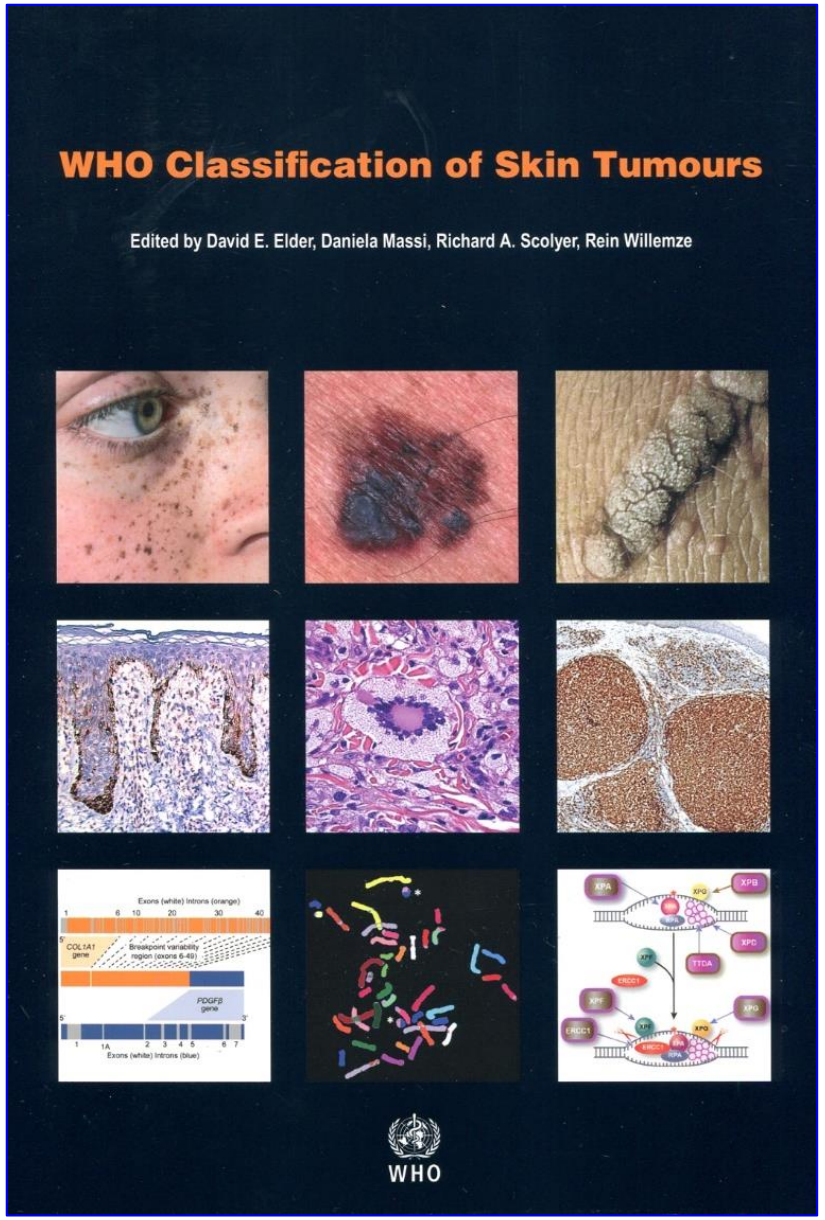

In dem Märchen von Hans Christian Andersen wird dem Kaiser weisgemacht, er habe wunderschöne neue Kleider an, doch in Wirklichkeit ist er nackt.

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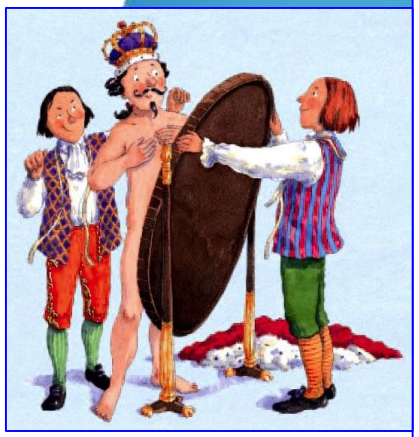

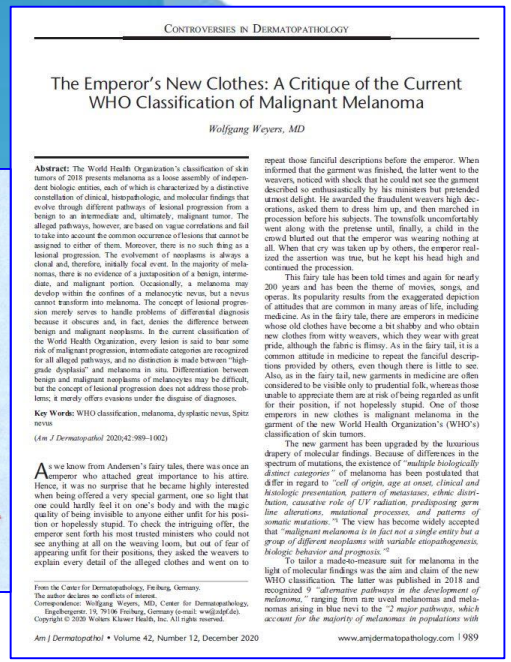

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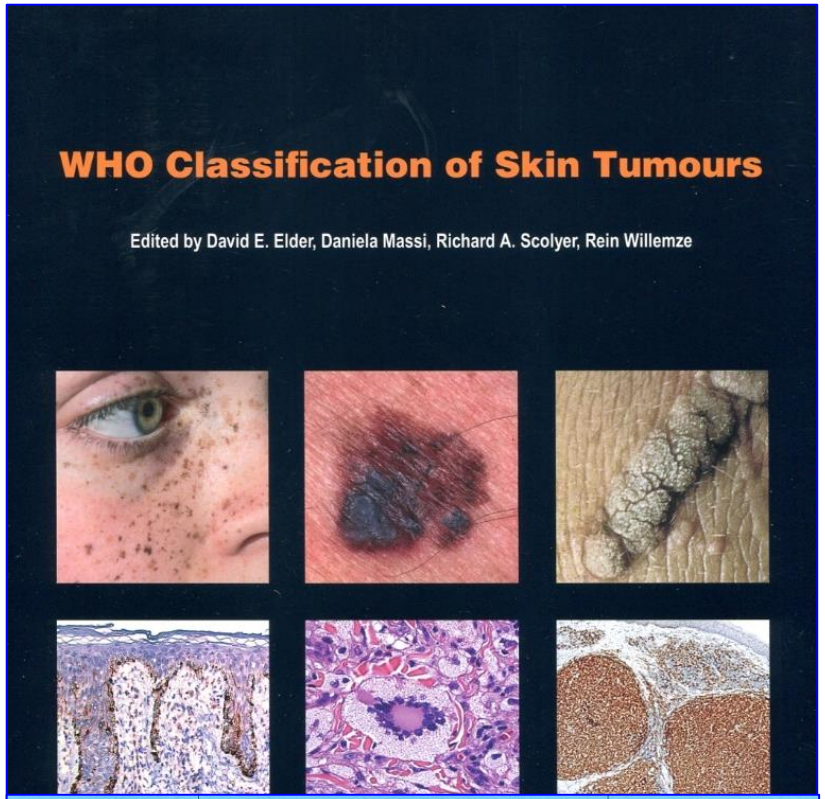

	Low UV radiation exposure/CSD				High UV radiation exposure/CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/MELTUMP	Deep penetrating melanocytoma/MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

Die neuen Kleider der Melanom-Klassifikation sind die Befunde der Molekulargenetik, die aber viel zu dünn sind, um die Nacktheit alter Konzepte zu überdecken, an denen in der WHO-KLassifiaktion weiter festgehalten wird. Dies alles in zwanzig Minuten darzustellen, ist nicht leicht, denn im Grunde geht es nicht um eine Klassifikation, sondern um mehrere fadenscheinige Klassifikationen, die miteinander verknüpft wurden und die weder einzeln noch in Kombination haltbar sind.

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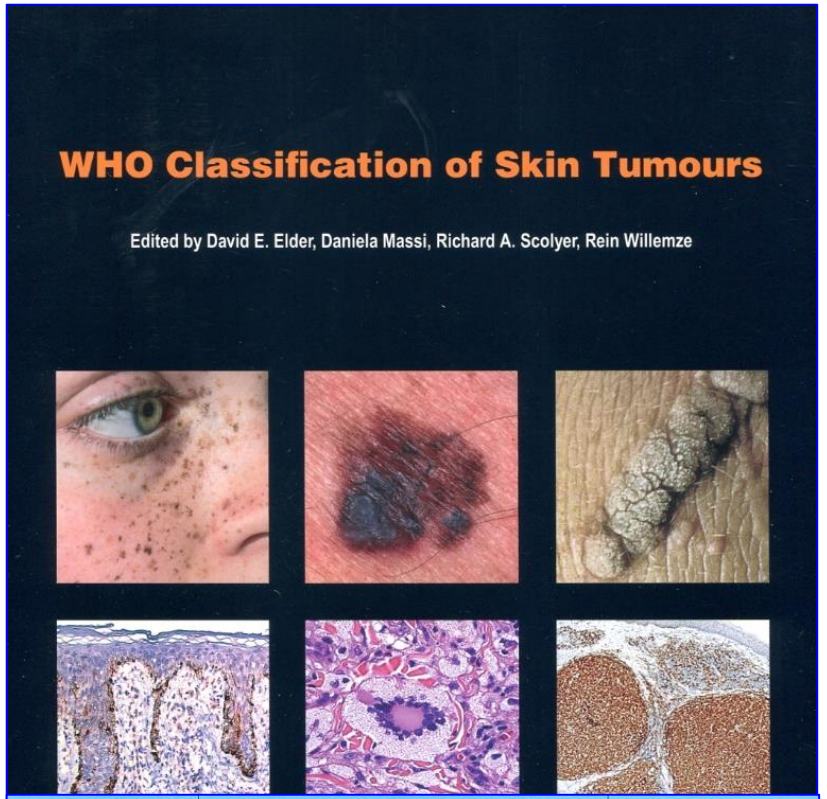

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Die Schwierigkeit der Klassifikation des Melanoms besteht darin, dass es im breiten Spektrum der Melanome zwar gewisse Korrelationen gibt, die eine Gruppeneinteilung nahelegen, gleichzeitig jedoch viele Ausnahmen von der Regel und Übergangsformen. Letztlich sind keine zwei Melanome gleich, so dass man sich an die Aussage

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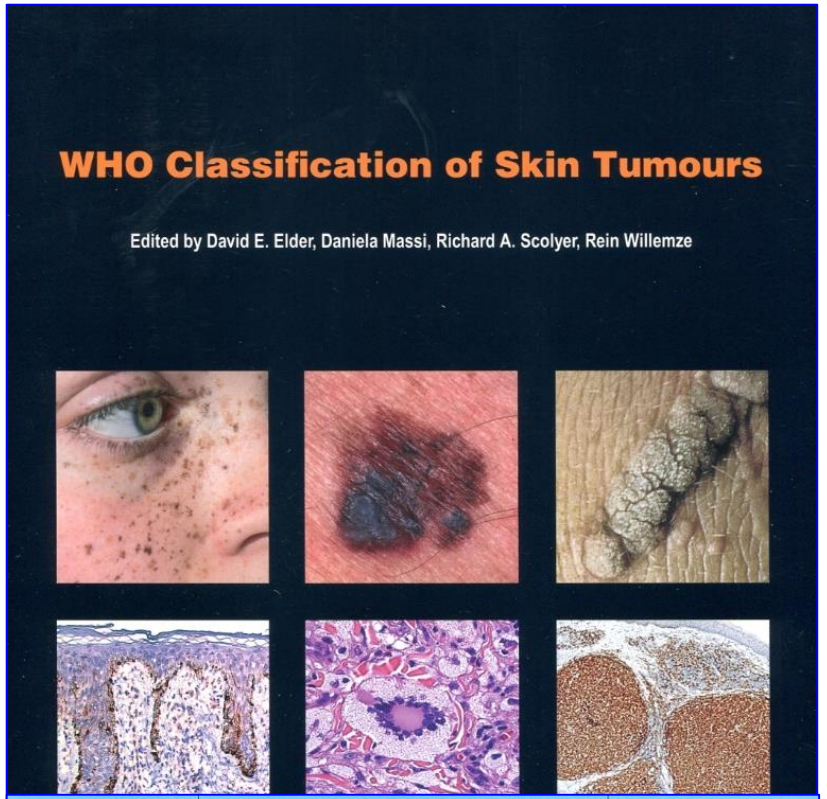
Georges-Louis Leclerc de Buffon, 1749



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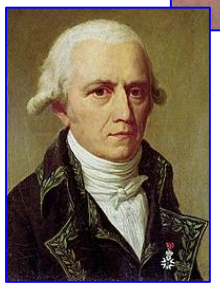
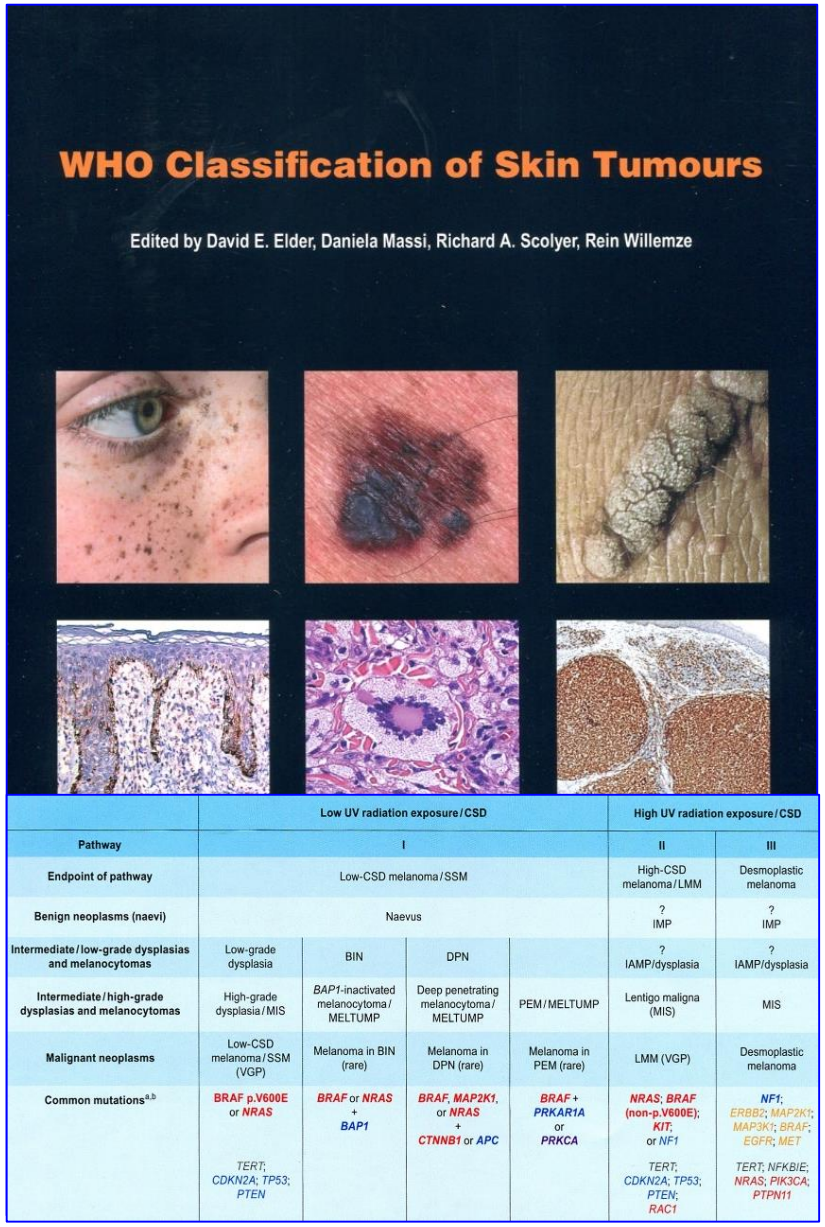


Alle Klassifikationen sind gedankliche Kunstprodukte.

Jean-Baptiste de Lamarck, 1809



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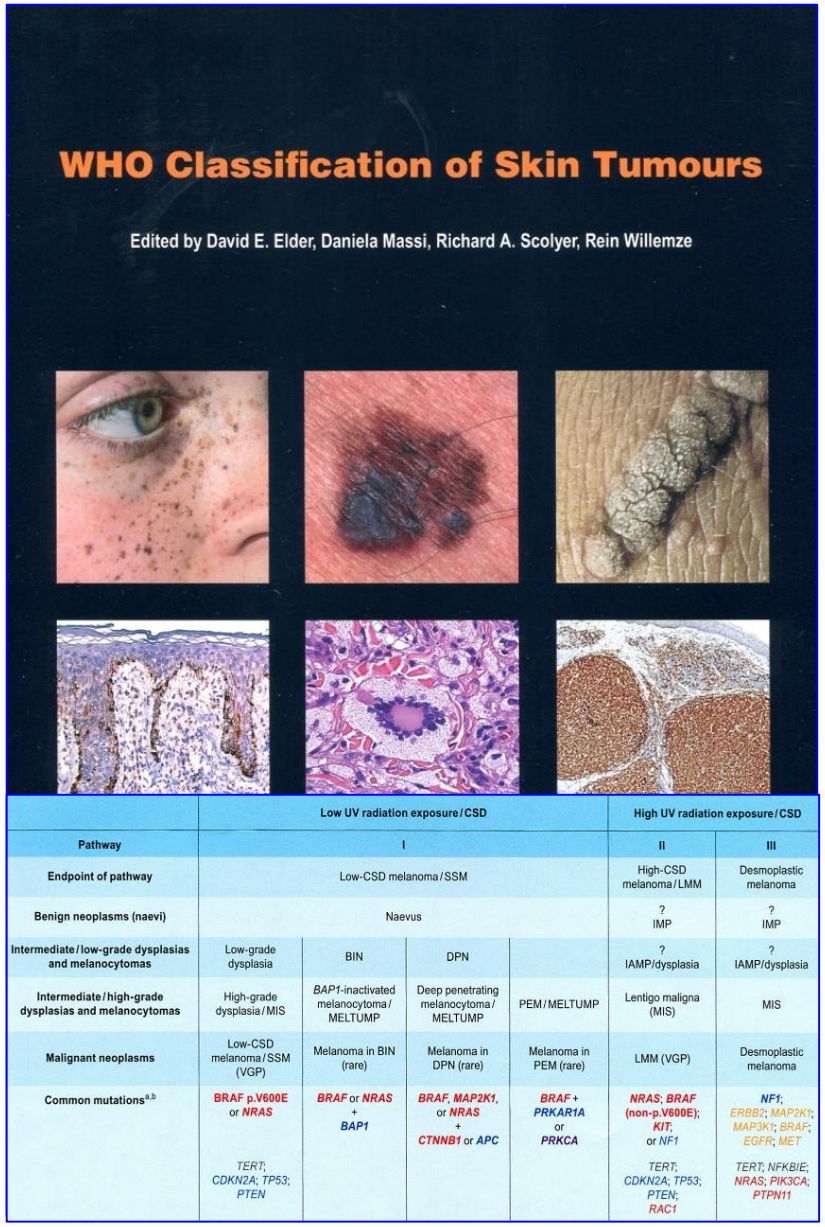
Georges-Louis Leclerc de Buffon, 1749

Alle Klassifikationen sind gedankliche Kunstprodukte.

Jean-Baptiste de Lamarck, 1809



	Low UV radiation exposure/CSD				High UV radiation exposure/CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/MELTUMP	Deep penetrating melanocytoma/MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

Diese Auffassung wurde seit langem verlassen, denn natürlich gibt es biologische Spezies, die relativ konstant sind und sich durch zahlreiche Kriterien voneinander abgrenzen lassen. Die Schwierigkeit liegt in der Unterscheidung zwischen einer natürlichen Klassifikation und einem gedanklichen Kunstprodukt, das immer dann entsteht, wenn Einzelbeobachtungen in unzulässiger Form generalisiert und Beobachtungen, die nicht dazu passen, mit Gewalt in vorgefertigte Schemata gepresst werden. Dies gilt auch für die WHO-Klassifikation melanozytärer Tumore.

Melanocytic tumours in intermittently sun-exposed skin

Low-CSD melanoma (superficial spreading melanoma)

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Bastian B.C.
Elder D.E.
Mihm M.C. Jr

Definition
Low-CSD melanoma – melanoma in skin with a low degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis – is characterized by pagetoid and/or lentiginous intraepidermal components [492,493]; both of these major patterns are encompassed by the term "superficial spreading melanoma (SSM)". Melanomas arising via other pathways (e.g. melanoma arising in blue naevus) can occasionally also occur in low-CSD skin and should be interpreted accordingly.

ICD-O code 8743/3

Synonyms
Superficial spreading melanoma; non-CSD melanoma

Epidemiology
Low-CSD melanomas/SSMs account for nearly two thirds of cases occurring in lighter-skinned people (Fitzpatrick skin type I–III), and they are significantly less common in darker-skinned people. Males and females are affected similarly.

Etiology
Low-CSD melanoma/SSM is epidemiologically linked to sun exposure, and genomic analyses have revealed a high mutation burden with an ultraviolet (UV) radiation mutation signature [1094]. Repeated sunburns in childhood and intermittent sun exposure throughout life are associated with an increased risk of developing SSM. Tanning bed use has been linked to an increased rate of melanoma in young women [1508].

Localization
Low-CSD melanoma/SSM can occur at any cutaneous site, but is most common in locations with intermittent sun exposure, including women's legs and men's backs and shoulders.

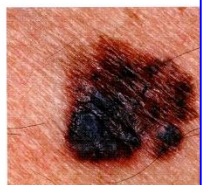

Fig. 2.04 Superficial spreading melanon
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Clinical features
In situ, low-CSD melanoma/S
as a pigmented macule with
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a papule or plaque develop
ders of SSM are usually sha
ited from the surrounding
may be poorly defined. The
tion is quite variable; multi
of brown are often seen, ra
tan to nearly black. There m
areas corresponding to regr

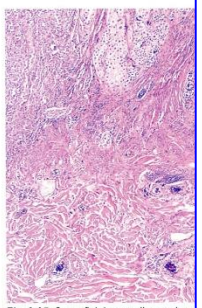

Fig. 2.05 Superficial spreading melanc
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[CANCER RESEARCH 29, 705–726, March 1969]

The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin[1]

Wallace H. Clark, Jr.,[2] Lynn From, Evelina A. Bernardino, and Martin C. Mihm
Departments of Pathology and Dermatology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

SUMMARY

This paper describes the histogenesis of 3 forms of human malignant melanoma: superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma. A comparative analysis by computer of the biologic behavior and clinical characteristics of the different neoplasms has been done. An additional 60 tumors have been studied by serial block sectioning. Evidence is presented suggesting that superficial spreading melanoma and lentigo maligna melanoma (Hutchinson's melanotic freckle), though evolving at different rates, show a long period of superficial growth, followed by the relatively rapid appearance of nodules or deeper invasion within the primary lesion. This change in the nature of the primary lesion may be due to the appearance of one or more strains of cells of aggressive biologic potential. Thus the primary melanoma may exist for a relatively long period of time during which host selectional forces act to permit the growth of quite malignant strains of cells. It is these cells that seem to be capable of deeper growth. The subdivision of each of the forms of melanoma into 5 anatomic levels of invasion permits the accurate assignment of prognosis to each case. It is suggested that melanomas are tumors of the epidermal melanocytes and are not necessarily derived from melanocytic nevi. Each melanoma has a distinctive clinical appearance, even in its superficial and curable phases, and this appearance is the same whether or not the process arose in association with a melanocytic nevus.

INTRODUCTION

This paper describes 3 different malignant tumors affecting the human epidermal melanocytic system. These neoplastic processes are described under the terms superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma (Hutchinson's melanotic freckle or circumscribed precancerous melanosis of Dubreuilh). Each of these tumors has a recognizable appearance in the patient, distinctive microscopic characteristics, and to a certain extent unique fine structural features. The history of the evolution of each of the primary neoplasms is different, and each has a predictable biologic behavior. Furthermore, within each kind of tumor, behavior may be accurately predicted by the depth of invasion of the neoplastic cells. Finally, various clinical characteristics such as location and age also serve in distinguishing the various melanomas.

We shall also discuss the relationship of the junction nevus to malignant melanoma. It is our opinion that the junction nevus has no formal histogenetic relationship to malignant melanoma. Only in the bathing trunk nevus is there a high incidence of malignant melanoma and the tumors arising in these lesions are of no statistical importance in the overall problem of melanoma. We regard the majority of melanomas as malignant neoplasms of epidermal melanocytes. This pigment-synthesizing system has a specific distribution throughout the normal epidermis (27, 39, 40), and the cells of the system may be found in a variety of cutaneous lesions including the intraepidermal component of various nevi. Regardless of where melanocytes are located, in normal skin, in freckles, in pigmented nevi, or in other benign lesions, the etiologic factors, as yet largely unknown, that cause melanoma can act upon these melanocytes. The concept of the junction nevus as a premalignant lesion seems to have obscured the fact that most malignant melanomas pass through a long phase of superficial growth during which the process differs in appearance from junctional nevi and is easily recognized on clinical examination.

MATERIALS AND METHODS

This report is based upon the study of 3 series of malignant melanomas observed at the Massachusetts General Hospital. The first series consisted of 96 cases observed prior to Jan. 1, 1958. These cases were selected solely on the basis of the availability of technically satisfactory histologic material of the primary neoplasm and on adequate followup information. The histogenetic concepts underlying much of the present report were formulated through the investigation of the first series of 96 melanomas and have been previously reported in detail (5). These 96 cases have been incorporated with the second series of 113 cases observed between January 1958 and October 1965, and subjected to statistical analysis by computer. The third series of melanomas consists of 60 cases observed from October 1965 through May 1968, which have been studied in detail, clinically and morphologically, but not incorporated into the statistical study because of short follow-

[1]Supported by grants from the National Cancer Institute CA-06221, the Massachusetts Division of the American Cancer Society, and the Damon Runyon Fund.
[2]Present address: Temple University School of Medicine, Dept. of Pathology, 3420 N. Broad St., Philadelphia, Pennsylvania 19140.
Received July 8, 1968; accepted November 4, 1968.

Melanocytic tumours in chronically sun-exposed skin

Lentigo maligna melanoma

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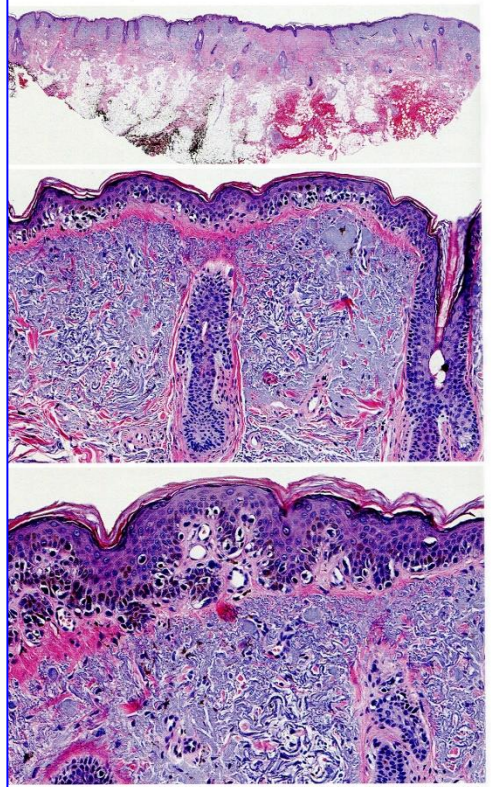

go maligna. **A** Broad resection specimen with a pink biopsy site scar, extensive solar elastosis, es of the epidermal contour including patchy rete ridge effacement. **B** This field shows the so- pattern, with continuous basal (lentiginous) proliferation of uniformly atypical naevoid to epithelioid **C** Another field shows the dysplastic naevus-like (or naevoid lentigo maligna) pattern. Although this ot diagnostic of lentigo maligna, it is part of the larger lesion illustrated in panels A and B.

Um die aktuelle Klassifikation zu beleuchten, kommt man nicht umhin, auf einige alte Konzepte einzugehen, wie die Unterscheidung zwischen superfiziell spreitendem und Lentigo maligna Melanom, die ursprünglich von Clark eingeführt wurde und an der in der neuen Klassifikation festgehalten wird.

Diese beiden Typen wurden anhand verschiedener Kriterien definiert, die tatsächlich miteinander korrelieren, wie etwa Dominanz epitheloider Melanozyten, pagetoides Wachstum und Fehlen von solarer Elastose beim SSM.

Melanocytic tumours in intermittently sun-exposed skin

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(superficial spreading melanoma)

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ICD-O code 8743/3

Synonyms
Superficial spreading melanoma; non-CSD melanoma

Epidemiology

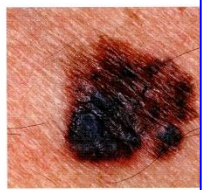

Fig. 2.04 Superficial spreading melanoma has a radial-growth-phase component (p dominantly tan, at the upper-right of the l morigenic vertical growth phase (raised black in this example).

Clinical features
In situ, low-CSD melanoma/S as a pigmented macule with lar outline; with the onset a papule or plaque develop

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Fig. 2.05 Superficial spreading melanoma extend as a shoulder beyond the invas (lower right).

76 Melanocytic tumours

- v.a. epitheloide Melanozyten
- pagetoides Wachstum
- geringe Kernatypien
- kaum Regression
- relativ scharfe Begrenzung
- Hyperplasie der Epidermis
- keine solare Elastose

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Melanocytic tumours in chronically sun-exposed skin

Lentigo maligna melanoma

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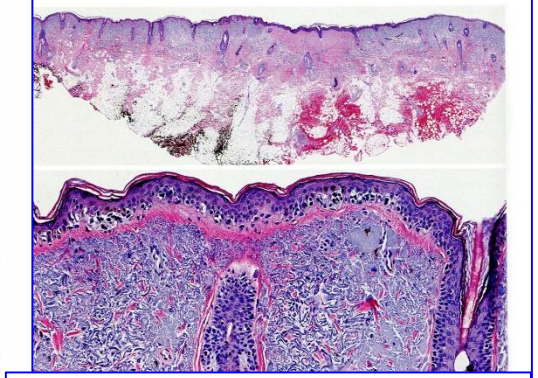

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- v.a. spindelige Melanozyten
- kaum pagetoides Wachstum
- ausgeprägte Kernatypien
- Regression
- unscharfe Begrenzung
- Atrophie der Epidermis
- solare Elastose

Melanocytic tumours in intermittently sun-exposed skin

Low-CSD melanoma (superficial spreading melanoma)

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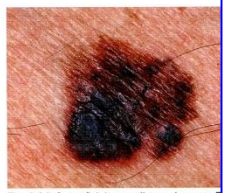
ICD-O code 8743/3

Synonyms
Superficial spreading melanoma; non-CSD melanoma



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Clinical features
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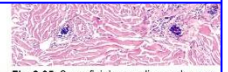

Fig. 2.05 Superficial spreading melanoma.
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- v.a. epitheloide Melanozyten
- pagetoides Wachstum
- Hyperplasie der Epidermis
- keine solare Elastose

26/830 (3,1%)

Classification of Cutaneous Malignant Melanoma

A Reassessment of Histopathologic Criteria for the Distinction of Different Types

Wolfgang Weyers, M.D.[1]
Matthias Euler, M.D.[2]
Carlos Diaz-Cascajo, M.D.[1]
Wolf-Bernhard Schill, M.D.[2]
Matthias Bonczkowitz, M.D.[2]

[1] Center for Dermatopathology, Freiburg, Germany.

[2] Center of Dermatology and Andrology, Justus-Liebig University, Giessen, Germany.

BACKGROUND. Human cutaneous malignant melanoma currently is classified into four principle types: nodular, superficial spreading, lentigo maligna, and acral lentiginous. The criteria for the histopathologic diagnosis of these types are not applied consistently. Nevertheless, the classification has become the foundation of many clinical, histopathologic, epidemiologic, and molecular studies. The results of those studies can have validity only if the classification itself is valid. For this reason, the authors reassessed histopathologic criteria advocated for the distinction of the different types of melanoma and searched for other repeatable constellations of findings that may serve to define distinct subsets of the neoplasm.

METHODS. Nine hundred fifteen melanomas were examined with regard to 72 parameters that are considered to be important for histopathologic diagnosis. The results were analyzed statistically with special attention to findings that have been reported to be characteristic of the four principle types of melanoma.

RESULTS. The histopathologic criteria advocated for the distinction of different types of melanoma were found not to correlate with one another. A logistic regression analysis did not detect any other repeatable constellation of morphologic findings that may reflect a distinct biologic subgroup.

CONCLUSIONS. The validity of the current classification of cutaneous malignant melanoma into four principle types could not be substantiated. Malignant melanoma may present with many different forms, but these forms appear to be part of a continuous spectrum rather than examples of distinct biologic entities. *Cancer* 1999;86:288–99. © *1999 American Cancer Society.*

KEYWORDS: malignant melanoma, classification, nodular melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral-lentiginous melanoma.

Primary cutaneous malignant melanoma is currently classified into four principle types: nodular melanoma (NM), superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), and acral-lentiginous melanoma (ALM). These four types are considered by some authors to be distinct clinicopathologic entities that differ from one another with regard to etiology, biologic properties, and prognosis. For example, LMM has been claimed to originate from spindle-shaped junctional melanocytes, thus representing "melanocytic malignant melanoma," and SSM has been claimed to originate from round junctional nevus cells, representing "nevocytic malignant melanoma."[1] The risk for developing LMM has been said to be determined mostly by skin type, whereas the major risk factor for the development of SSM has been said to be the total number of melanocytic nevi.[2] LMM is thought to differ from SSM, in that it is related to chronic cumulative solar damage, has a longer period of intraepidermal growth, has slower growth of nodules, has migration of the neoplasm ("as the lesion spreads into one area, it seems to leave a

Address for reprints: Wolfgang Weyers, M.D., Center for Dermatopathology, Rosastrasse 9, 79098 Freiburg, Germany.

Received June 22, 1998; revisions received December 21, 1998 and March 1, 1999; accepted March 1, 1999.

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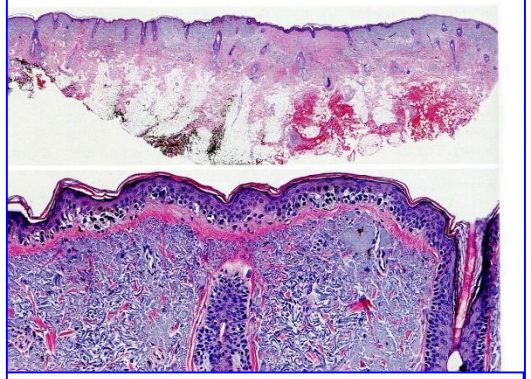

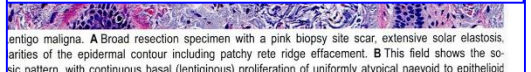

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- v.a. spindelige Melanozyten
- kaum pagetoides Wachstum
- Atrophie der Epidermis
- solare Elastose

7/830 (0,7%)

Allerdings sind die Korrelationen schwach, und die vier am häufigsten genannten Kriterien für das SSM und LMM sind nur selten gemeinsam erfüllt, nach einer eigenen Studie in 3,1% der Melanome für das SSM und in nur 0,7% der Melanome für das LMM. Mit anderen Worten lässt sich die große Mehrzahl der Melanome anhand der publizierten Kriterien keiner der beiden Gruppen zuordnen,

und Clark selbst erklärte 1984, dass bei strikter Anwendung der Kriterien das LMM „eine Rarität“ ist.

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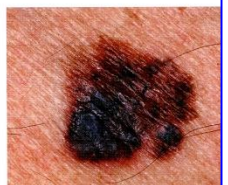
Epidemiology



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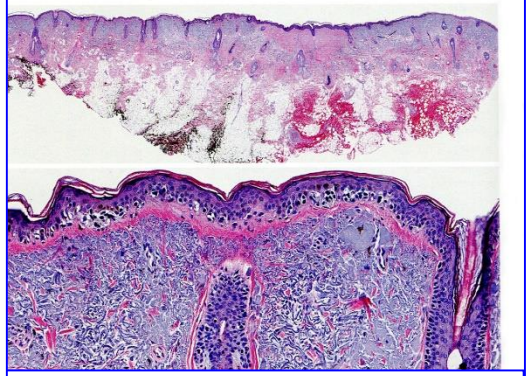
Wood B.A.



- v.a. spindelige Melanozyten
- kaum pagetoides Wachstum
- Atrophie der Epidermis
- solare Elastose

7/830 (0,7%)

any cutaneous site, but is most common in locations with intermittent sun exposure, including women's legs and men's backs and shoulders.

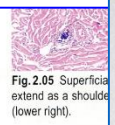
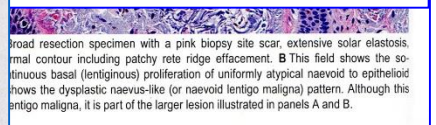


Fig. 2.05 Superficia
extend as a shoulde
(lower right).



road resection specimen with a pink biopsy site scar, extensive solar elastosis. rmal contour including patchy rete ridge effacement. **B** This field shows the so- tinuous basal (lentiginous) proliferation of uniformly atypical naevoid to epithelioid hows the dysplastic naevus-like (or naevoid lentigo maligna) pattern. Although this entigo maligna, it is part of the larger lesion illustrated in panels A and B.

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Classification of Cutaneous Malignant Melanoma

A Reassessment of Histopathologic Criteria for the Distinction of Different Types

Wolfgang Weyers, M.D.[1]
Matthias Euler, M.D.[2]
Carlos Diaz-Cascajo, M.D.[1]
Wolf-Bernhard Schill, M.D.[2]
Matthias Bonczkowitz, M.D.[2]

[1] Center for Dermatopathology, Freiburg, Germany.
[2] Center of Dermatology and Andrology, Justus-Liebig University, Giessen, Germany.

BACKGROUND. Human cutaneous malignant melanoma currently is classified into four principle types: nodular, superficial spreading, lentigo maligna, and acral lentiginous. The criteria for the histopathologic diagnosis of these types are not applied consistently. Nevertheless, the classification has become the foundation of many clinical, histopathologic, epidemiologic, and molecular studies. The results of those studies can have validity only if the classification itself is valid. For this reason, the authors reassessed histopathologic criteria advocated for the distinction of the different types of melanoma and searched for other repeatable constellations of findings that may serve to define distinct subsets of the neoplasm.
METHODS. Nine hundred fifteen melanomas were examined with regard to 72 parameters that are considered to be important for histopathologic diagnosis. The results were analyzed statistically with special attention to findings that have been reported to be characteristic of the four principle types of melanoma.
RESULTS. The histopathologic criteria advocated for the distinction of different types of melanoma were found not to correlate with one another. A logistic regression analysis did not detect any other repeatable constellation of morphologic findings that may reflect a distinct biologic subgroup.
CONCLUSIONS. The validity of the current classification of cutaneous malignant melanoma into four principle types could not be substantiated. Malignant melanoma may present with many different forms, but these forms appear to be part of a continuous spectrum rather than examples of distinct biologic entities. *Cancer* 1999;86:288–99. © *1999 American Cancer Society.*

KEYWORDS: malignant melanoma, classification, nodular melanoma, superficial

Lentigo Maligna Melanoma Has No Better Prognosis Than Other Types of Melanoma

J Clin Oncol 1984; 2: 994

By Howard K. Koh, Edna Michalik, Arthur J. Sober, Robert A. Lew, Calvin L. Day, Wallace Clark, Martin C. Mihm, Alfred W. Kopf, M. Scott Blois, and Thomas B. Fitzpatrick

We studied 48 patients with lentigo maligna melanoma (LMM) and compared the clinical stage I patients with non-LMM melanoma p… and thickness) to see if prog… no significant difference in n… between the two groups (*P* … low-up time of five years (67… months for non-LMM). In addition, a Cox multivariate analysis of the entire matched group showed that only thickness was significantly associated with death from melanoma ($P = .0007$) while histology …nake a significant contribu… …ggest that after accounting …ss and site, LMM and non- …osis and biologic behavior, …held belief that LMM has a better prognosis than other forms of melanoma.

LMM is a rarity.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS***	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*
	TERT; *CDKN2A*; *TP53*; *PTEN*				*TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

In der neuen Klassifikation mutieren diese Raritäten zu den zwei wichtigsten „Pathways“ der Melanomentstehung. Dabei wird von allen Kriterien für das SSM und LMM nur eines berücksichtigt: die solare Elastose. Das SSM wird mit Melanomen in gering lichtgeschädigter und das LMM mit Melanomen in stark lichtgeschädigter Haut gleichgesetzt.

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ORIGINAL ARTICLE

N Engl J Med 2005; 353: 2135

Distinct Sets of Genetic Alterations in Melanoma

John A. Curtin, Ph.D., Jane Fridlyand, Ph.D., Toshiro Kageshita, M.D., Hetal N. Patel, M.S., Klaus J. Busam, M.D., Heinz Kutzner, M.D., Kwang-Hyun Cho, M.D., Setsuya Aiba, M.D., Ph.D., Eva-Bettina Bröcker, M.D., Philip E. LeBoit, M.D., Dan Pinkel, Ph.D., and Boris C. Bastian, M.D.

ABSTRACT

BACKGROUND

Exposure to ultraviolet light is a major causative factor in melanoma, although the relationship between risk and exposure is complex. We hypothesized that the clinical heterogeneity is explained by genetically distinct types of melanoma with different susceptibility to ultraviolet light.

From the Comprehensive Cancer Center (J.A.C., J.F., H.N.P., D.P., B.C.B.) and the Departments of Epidemiology and Biostatistics (J.F.) and Dermatology and Pathology (P.E.L., B.C.B.), University of California, San Francisco, San Francisco; the Depart-

Ursprünglich wurde in den Untersuchungen zur Beziehung zwischen genetischen Veränderungen und dem Grad der Lichtschädigung wegen der unscharfen Definition von „SSM“ und „LMM“ bewusst auf diese Begriffe verzichtet. Ausgehend von der Hypothese, dass beim Melanom *„die klinische Heterogenität durch genetisch eigenständige Melanomtypen mit unterschiedlicher Empfindlichkeit gegenüber ultraviolettem Licht“* erklärt werden kann, untersuchte die Arbeitsgruppe von Boris Bastian 2005 Melanome mit starker und fehlender solarer Elastose

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
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Intermediate / high-grade dysplasias and melanocytomas						MIS
Malignant neoplasms						Desmoplastic melanoma
Common mutations[a,b]	**BRAF p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF*** **(non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

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Mutant BRAF
78% vs. 10%

ABSTRACT

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Exposure to ultraviolet light is a major causative factor in melanoma, although the relationship between risk and exposure is complex. We hypothesized that the clinical heterogeneity is explained by genetically distinct types of melanoma with different susceptibility to ultraviolet light.

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und fand bei letzteren viel häufiger BRAF-Mutationen: in 78 vs. 10% der Fälle.

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N Engl J Med 2005; 353: 2135

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PLoS MEDICINE

2008; 5: e120

Improving Melanoma Classification by Integrating Genetic and Morphologic Features

Amaya Viros[1], **Jane Fridlyand**[2,3], **Juergen Bauer**[1], **Konstantin Lasithiotakis**[4], **Claus Garbe**[4], **Daniel Pinkel**[2,5], **Boris C. Bastian**[1,2,6*]

1 Department of Dermatology, University of California San Francisco, San Francisco, California, United States of America, **2** University of California San Francisco (UCSF) Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, United States of America, **3** Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, United States of America, **4** Department of Dermatology, University of Tübingen, Tübingen, Germany, **5** Department of Laboratory Medicine, University of California San Francisco, San Francisco, California, United States of America, **6** Department of Pathology, University of California San Francisco, San Francisco, California, United States of America

Funding: Supported by grants from the National Cancer Institute (P01 CA025874, R01 CA094963). The funding agency did not have a role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Jonathan Rees, University of Edinburgh, United Kingdom

ABSTRACT

Background

In melanoma, morphology-based classification systems have not been able to provide relevant information for selecting treatments for patients whose tumors have metastasized. The recent identification of causative genetic alterations has revealed mutations in signaling pathways that offer targets for therapy. Identifying morphologic surrogates that can identify patients whose tumors express such alterations (or functionally equivalent alterations) would be clinically useful for therapy stratification and for retrospective analysis of clinical trial data.

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Daraufhin wurden weitere Kriterien im Hinblick auf den BRAF-Status überprüft, und auch dabei fanden sich Korrelationen,

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1 Department of Dermatology, University of California San Francisco, San Francisco, California, United States of America, 2 University of California San Francisco (UCSF) Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, United States of America, 3 Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, United States of America, 4 Department of Dermatology, University of Tübingen, Tübingen, Germany, 5 Department of Lab
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Academic Editor: Jo
University of Edinbur
Kingdom

- increased upward migration and nest formation of intraepidermal melanocytes
- thickening of the involved epidermis
- sharper demarcation to the surrounding skin
- larger, rounder, and more pigmented tumor cells

nämlich eine „*increased upward migration and nest formation of intraepidermal melanocytes, thickening of the involved epidermis, … sharper demarcation to the surrounding skin,"* und *"larger, rounder, and more pigmented tumor cells."*
Trotz statistisch messbarer Unterschiede korrelierten die morphologischen Parameter

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

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Competing Interests
have declared that n
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Academic Editor: Jo
University of Edinbur
Kingdom

- We identified age < 55 y as the single most predictive factor of BRAF mutation
- The WHO categories [SSM, LMM] were not independently associated with BRAF mutation status

aber schlechter mit dem BRAF-Status als das Alter unter 55 Jahren, und die WHO-Kategorien „SSM“ und „LMM“ waren nicht unabhängig mit dem BRAF-Mutationsstatus assoziiert.

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Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
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Die Gleichsetzung des SSM und LMM mit dem Grad der kumulativen Lichtschädigung in der neuen WHO-Klassifikation ist also nicht haltbar – oder nur dann haltbar, wenn man allein die solare Elastose berücksichtigt.

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	Low UV radiation exposure / CSD	High UV radiation exposure / CSD	
Pathway	**I**	**II**	**III**
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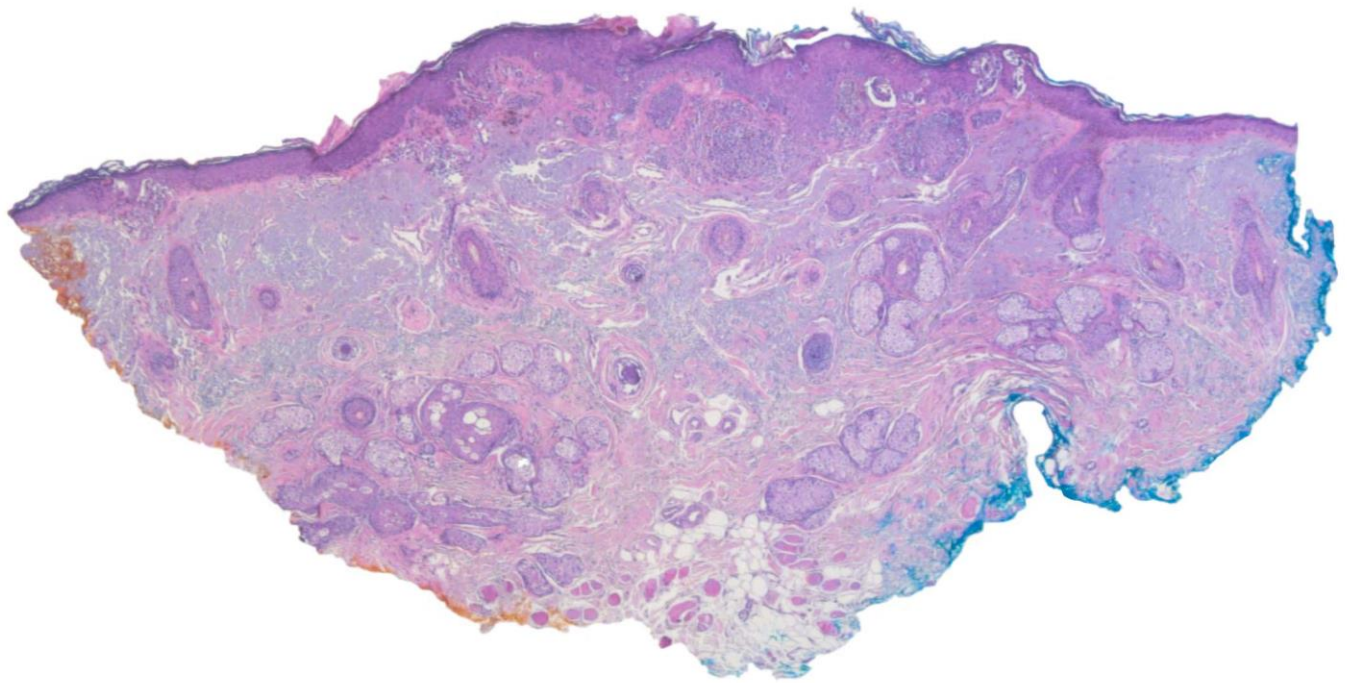
Benign neoplasms (naevi)	Naevus	? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas			
Intermediate / high-grade dysplasias and melanocytomas			
Malignant neoplasms			
Common mutations[a,b]			



BIN, *BAP1*-inactivated naevus; **BN**, blue
IAMP, intraepidermal atypical melanocy
cytic proliferation without atypia; **LMM**, l
MELTUMP, melanocytic tumour of uncer
STUMP, spitzoid tumour of uncertain ma

Dann müsste man zum Beispiel dieses Melanom wegen der knotigen solaren Elastose als „LMM“ klassifizieren,

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD	High UV radiation exposure / CSD	
Pathway	**I**	**II**	**III**
Endpoint of pathway	Low-CSD melanoma / SSM	High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus	? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas			
Intermediate / high-grade dysplasias and melanocytomas			
Malignant neoplasms			
Common mutations[a,b]			

BIN, *BAP1*-inactivated naevus; **BN**, blue
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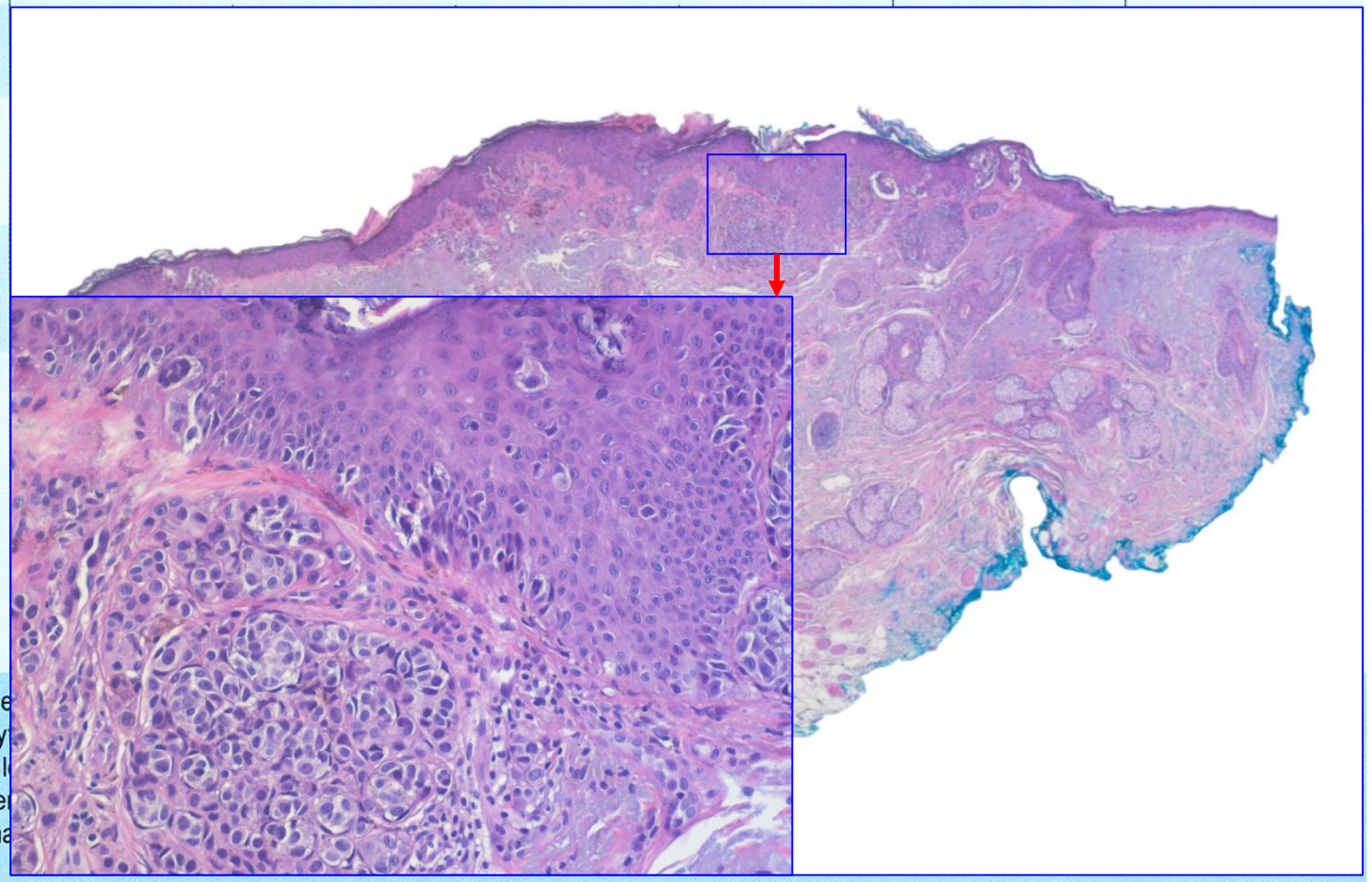


obwohl alle anderen Kriterien dagegensprechen, nämlich die Epithelhyperplasie, die Dominanz epitheloider Melanozyten und das pagetoide Wachstumsmuster.

Dies ist nur ein Beispiel für die sehr häufigen Ausnahmen von der Regel, die es schwermachen, innerhalb des Spektrums der Melanome distinkte „Pathways“ oder gar eigenständige biologische Entitäten anzugrenzen.

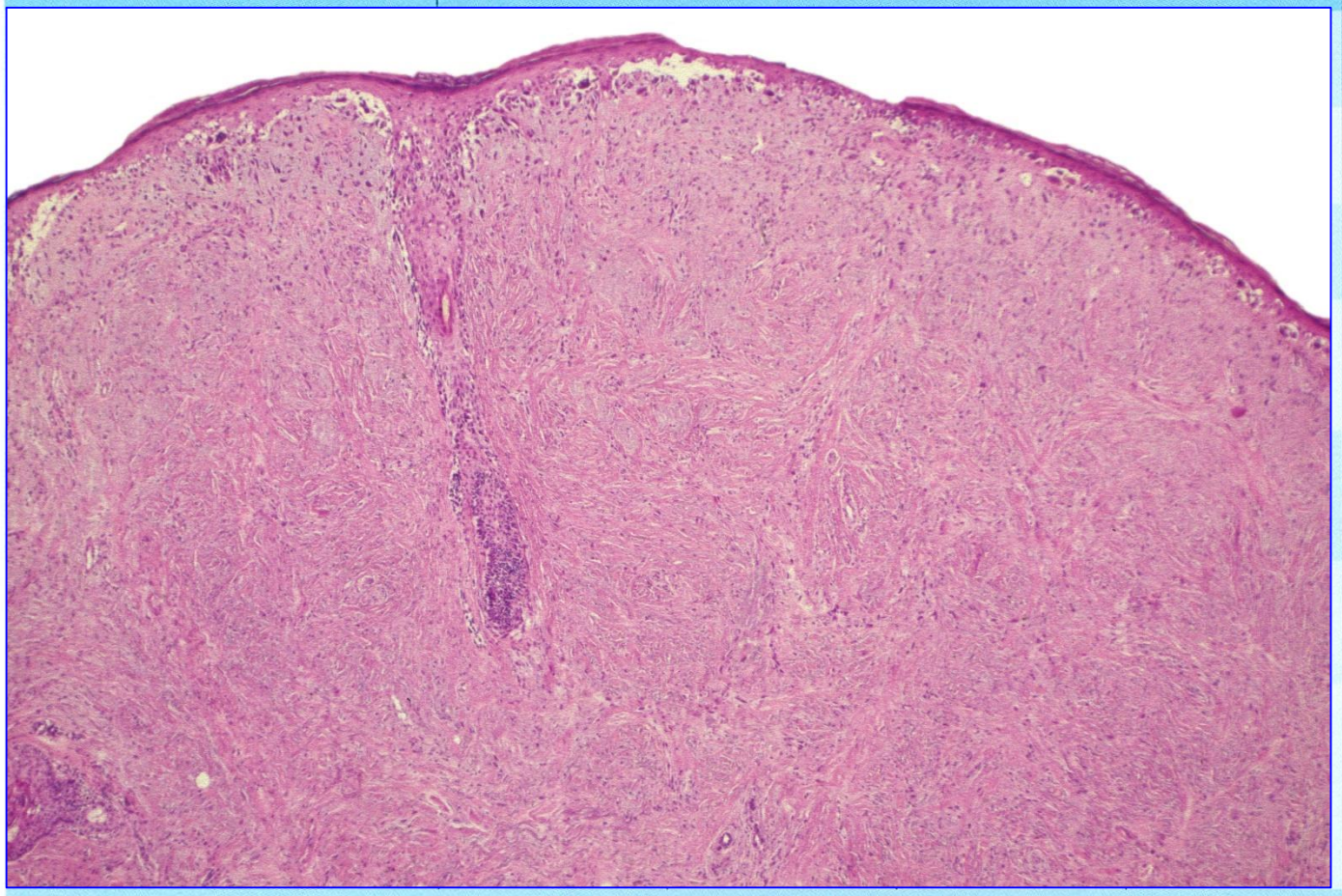
Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	**BRAF p.V600E** or ***NRAS***	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF (non-p.V600E)***; ***KIT***; or *NF1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*
	TERT; *CDKN2A*; *TP53*; *PTEN*				*TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Dies gilt in gleicher Form für die angeblich charakteristischen molekularen Befunde. Zum Beispiel werden bei den Melanomen mit starker Lichtschädigung zwei molekulare Pathways voneinander abgegrenzt, das LMM und das desmoplastische Melanom.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

Pathway	Low UV radiation exposure / CSD	High UV radiation exposure / CSD	
	I	II	III
		High-CSD melanoma / LMM	Desmoplastic melanoma
		? IMP	? IMP
		? IAMP/dysplasia	? IAMP/dysplasia
		Lentigo maligna (MIS)	MIS
		LMM (VGP)	Desmoplastic melanoma
		NRAS; ***BRAF*** **(non-p.V600E)**; ***KIT***; or *NF1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*
		TERT; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Beide kommen aber oft kombiniert vor, und der desmoplastische Anteil stellt dann nur eine Modifikation des LMM dar. Wie spezifisch kann dann das angeblich charakteristische molekularen Markerprofil sein?

Melanome in Haut mit solarer Elastose

- BRAF-Mutationen selten (~10%, BRAF V600K > BRAF V600E)
- inaktivierende NF1 mutations (~30%)
- aktivierende KIT mutations (~10%)

Das angeblich typische genetische Profil des LMM besteht in der Seltenheit von BRAF-Mutationen und dem relativ häufigen Vorkommen inaktivierender NF1-Mutationen und aktivierender Kit-Mutationen. Allerdings ist deren Vorkommen insgesamt gering und keine dieser Veränderungen ist für Melanome in Lichthaut spezifisch. Allein anhand molekularer Befunde lassen sich keine distinkten Melanomtypen abgrenzen.

Melanome in Haut mit solarer Elastose

High-CSD melanoma / LMM
? IMP
? IAMP/dysplasia
Lentigo maligna (MIS)
LMM (VGP)
NRAS; ***BRAF (non-p.V600E)***; ***KIT***; or *NF1*
TERT; *CDKN2A*; *TP53*; *PTEN*; *RAC1*

Pathway I:	Low-CSD melanoma/superficial spreading melanoma
Pathway II:	High-CSD melanoma/lentigo maligna melanoma

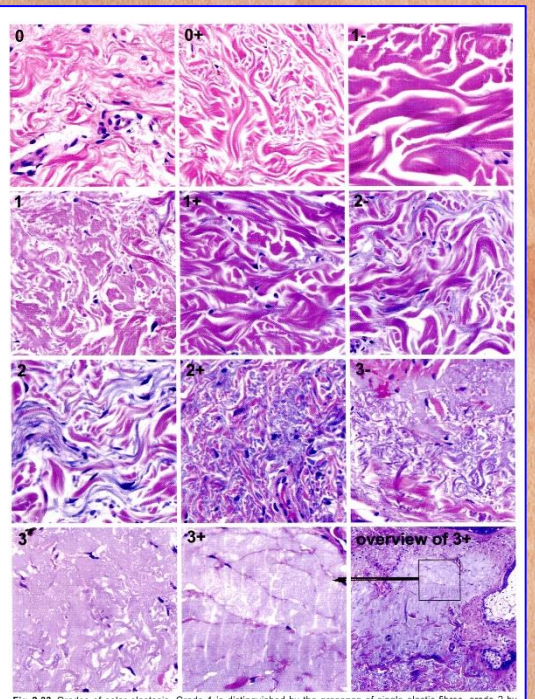
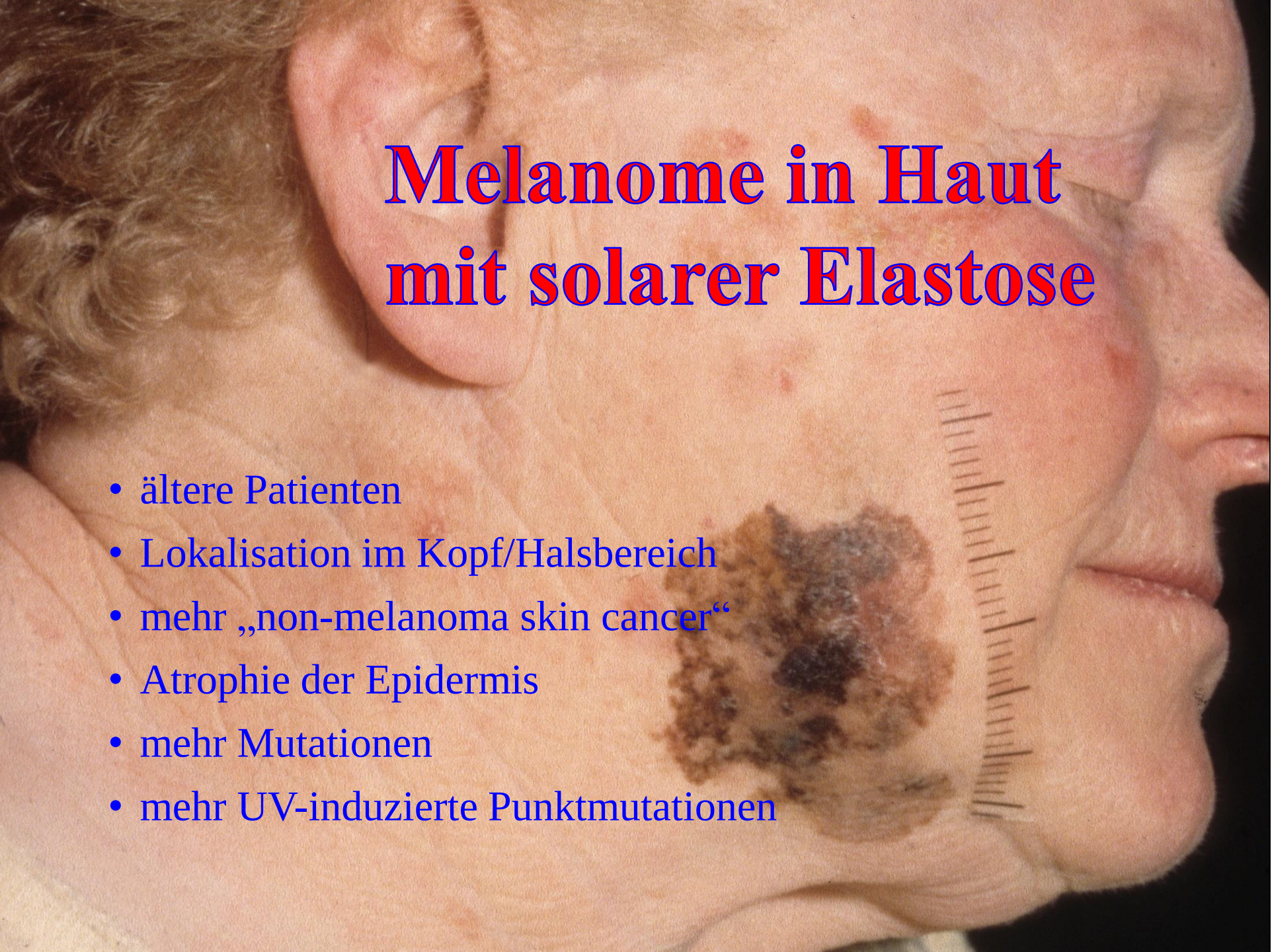


Fig. 2.03 Grades of solar elastosis. Grade 1 is distinguished by the presence of single elastic fibres, grade 2 by bunches of fibres, and grade 3 by basophilic material that has lost its fibrillary texture.

Deshalb wurde ja als zusätzlicher Parameter die solare Elastose herangezogen, doch diese ist ein gradueller Parameter und eignet sich schon deshalb nicht für eine dichotome Klassifikation.

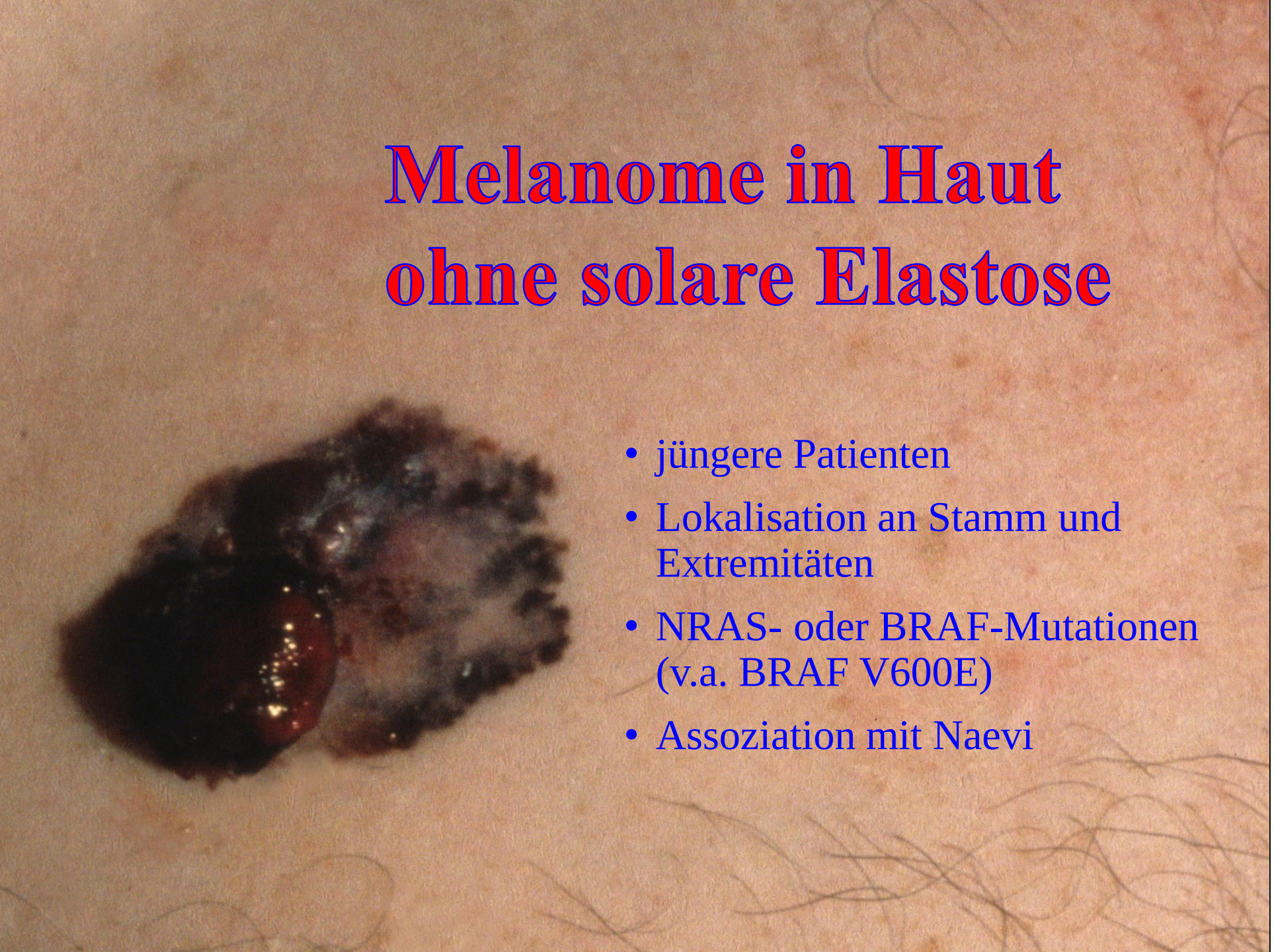
Um an der These distinkter biologischer Subtypen des Melanoms festzuhalten, wurden daher weitere Unterschiede angeführt:



Melanome in Haut mit solarer Elastose

- ältere Patienten
- Lokalisation im Kopf/Halsbereich
- mehr „non-melanoma skin cancer“
- Atrophie der Epidermis
- mehr Mutationen
- mehr UV-induzierte Punktmutationen

Melanome in stark lichtgeschädigter Haut treten bei älteren Personen auf, sind vor allem an Kopf und Hals lokalisiert und häufiger mit nicht-melanozytären Tumoren assoziiert; sie zeigen häufiger eine Atrophie der Epidermis, mehr Mutationen und vor allem UV-induzierte Punktmutationen – kein Wunder, denn sie liegen ja definitionsgemäß in chronisch lichtbelasteter Haut. All dies sind keine unabhängigen Variablen, sondern sie ergeben sich direkt aus der Definition.

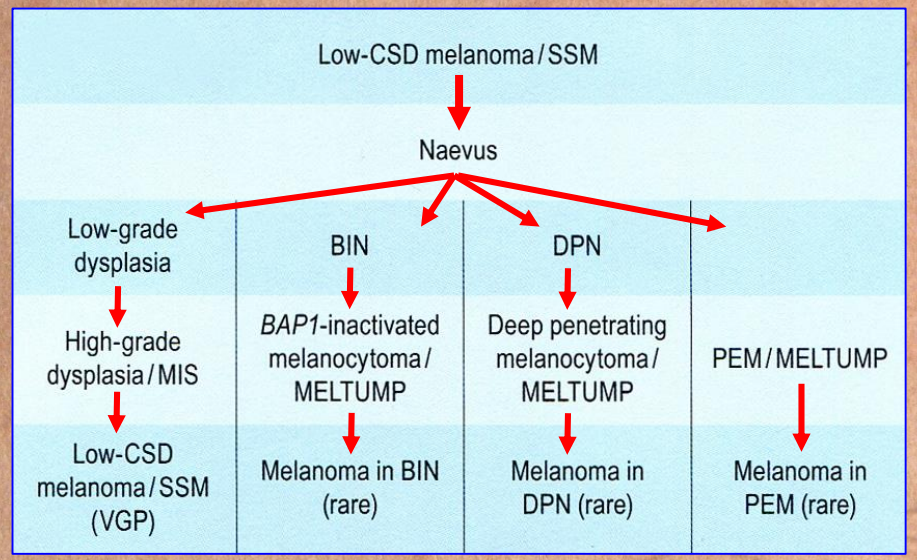


Melanome in Haut ohne solare Elastose

- jüngere Patienten
- Lokalisation an Stamm und Extremitäten
- NRAS- oder BRAF-Mutationen (v.a. BRAF V600E)
- Assoziation mit Naevi

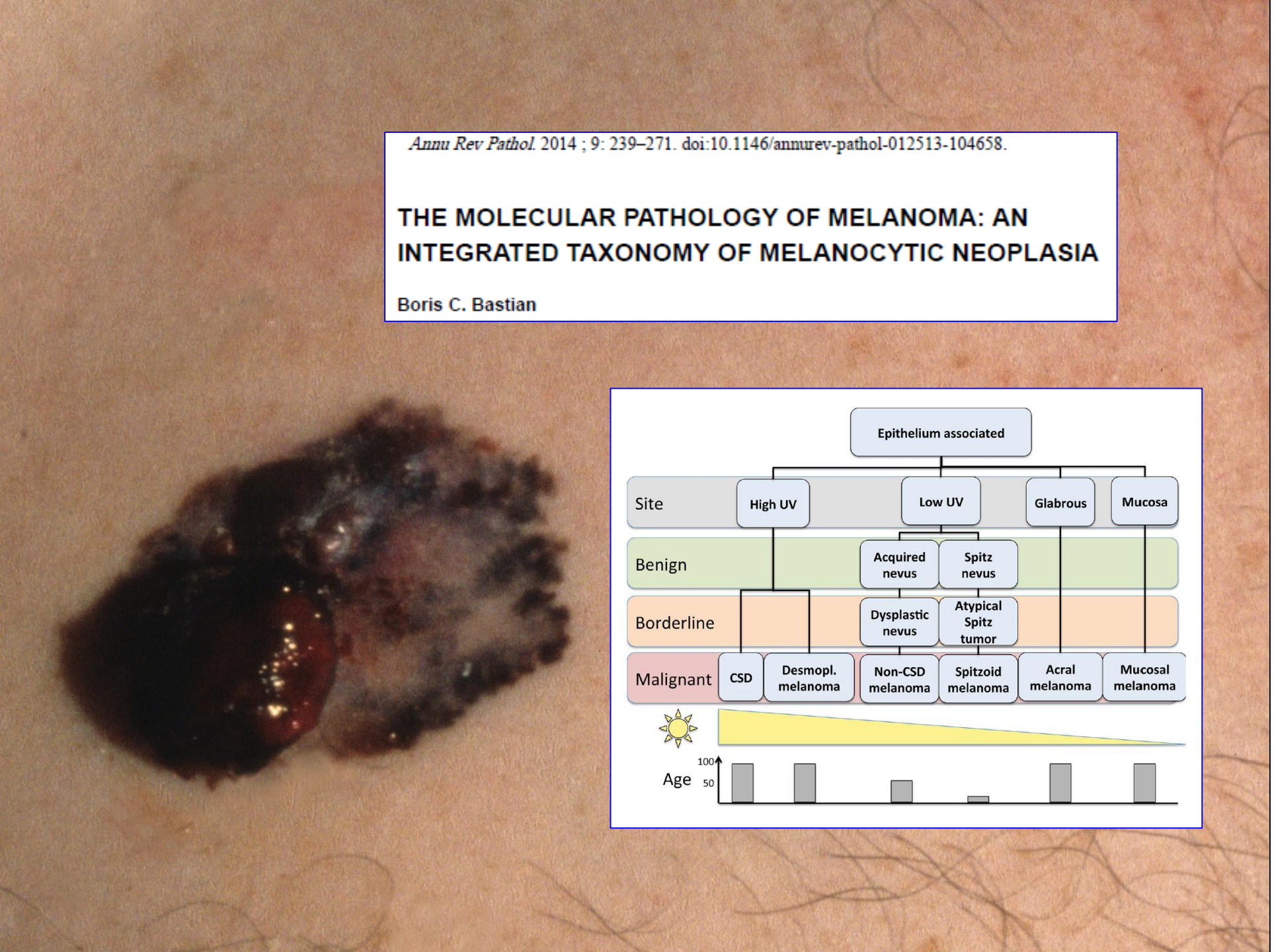
Auch Melanome in wenig lichtgeschädigter Haut sollen Besonderheiten aufweisen, die teils durch die Definition bedingt sind, wie das gehäufte Vorkommen bei jüngeren Patienten an Stamm und Extremitäten, zum Teil aber auch unabhängige Parameter darstellen, wie die Häufigkeit von NRAS- und BRAF-Mutationen und die Assoziation mit melanozytären Naevi, die ja ebenfalls oft die BRAF V600E-Mutation aufweisen.

Melanome in Haut ohne solare Elastose



Der neuen WHO-Klassifikation zufolge entstehen Melanome in stark lichtgeschädigter Haut de novo, während Melanome in nicht lichtgeschädigter Haut durch eine schrittweise Malignisierung aus Naevi hervorgehen.

In der WHO-Klassifikation wurde damit ein Konzept eins zu eins übernommen,

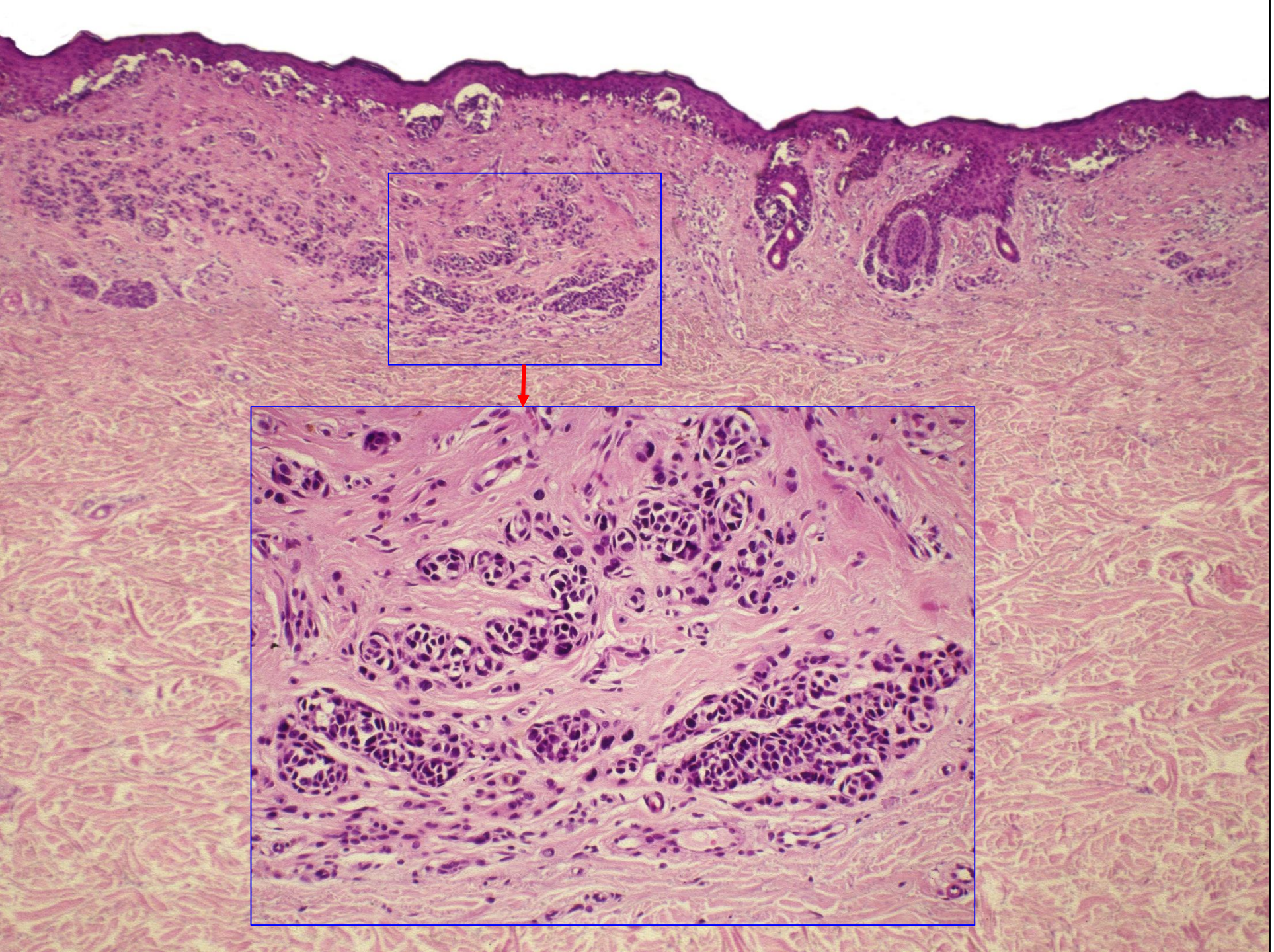


Annu Rev Pathol. 2014 ; 9: 239–271. doi:10.1146/annurev-pathol-012513-104658.

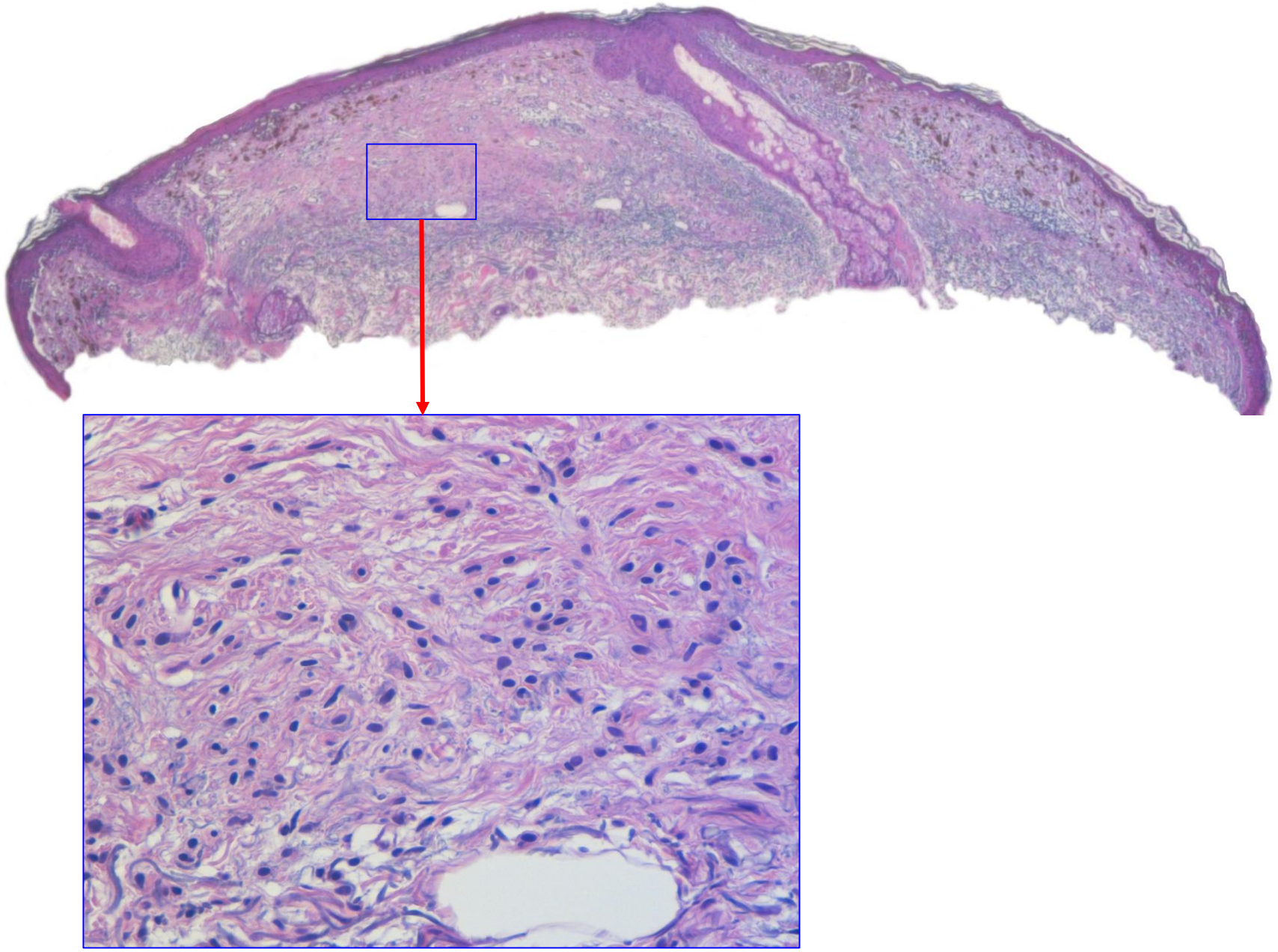
THE MOLECULAR PATHOLOGY OF MELANOMA: AN INTEGRATED TAXONOMY OF MELANOCYTIC NEOPLASIA

Boris C. Bastian

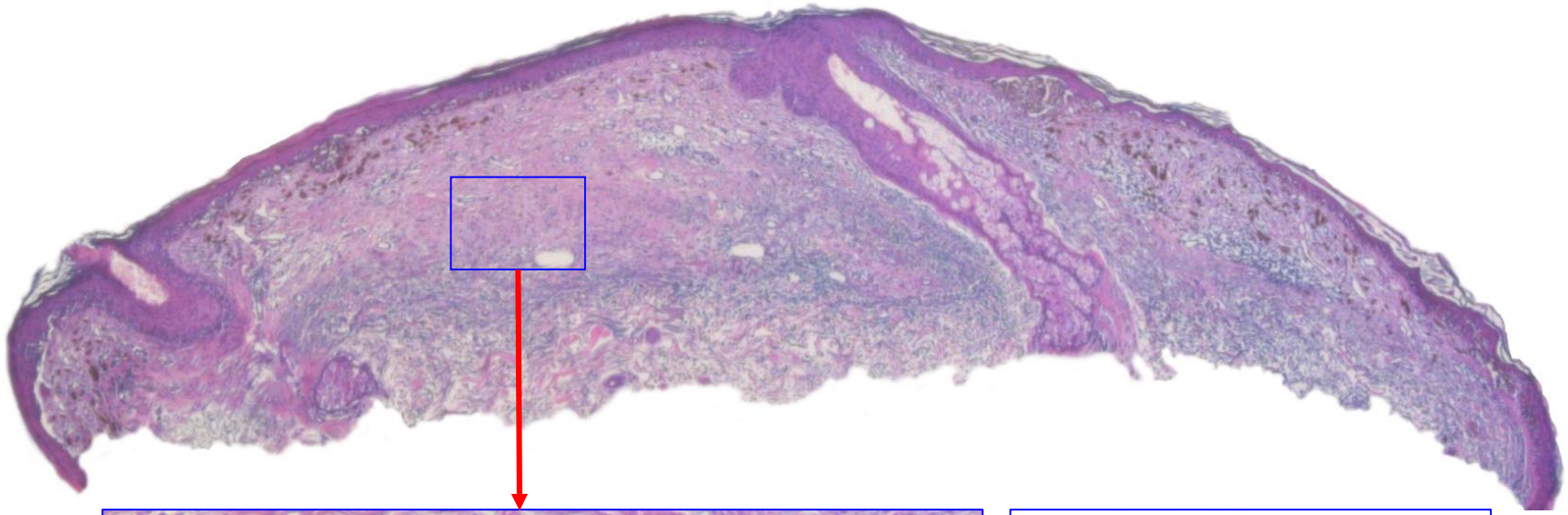
das von Boris Bastian 2014 als „integrierte Taxonomie melanozytärer Neoplasien“ vorgestellt wurde: eine de-novo-Entwicklung von Schleimhaut- und akralen Melanomen sowie Melanomen in stark lichtgeschädigter Haut, eine schrittweise Malignisierung anfangs gutartiger Naevi bei Melanomen in gering lichtbelasteter Haut, schön korreliert mit Sonnenscheindauer und Alter der Patienten. Allerdings wurde in diesem Schema die Tatsache ausgeblendet, dass assoziierte Naevi auch bei Melanomen in gering lichtbelasteter Haut nicht die Regel, sondern die Ausnahme sind.

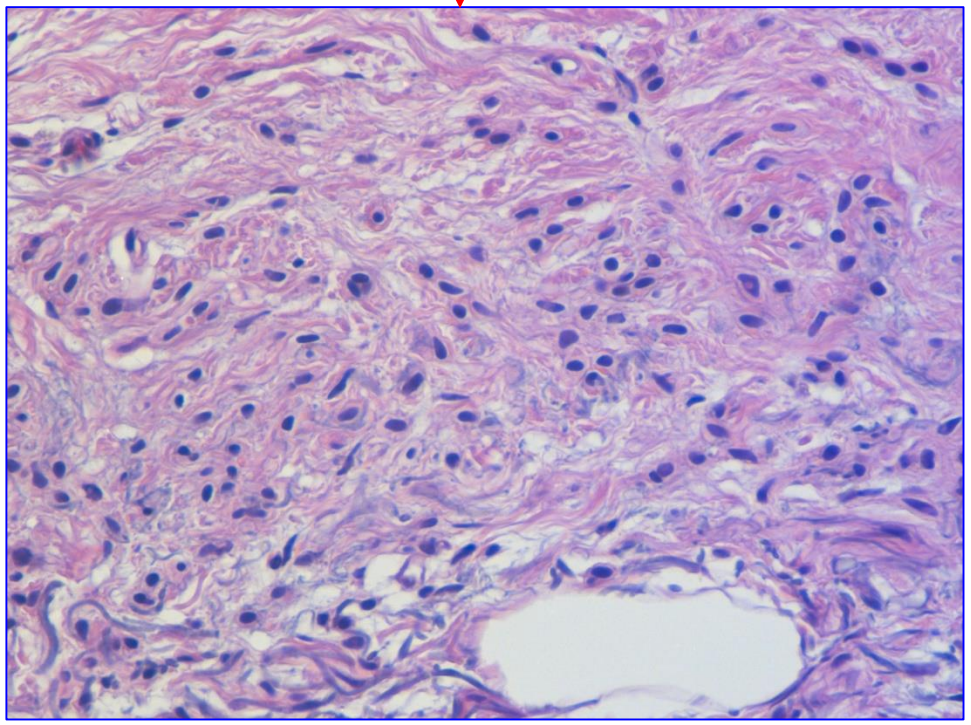


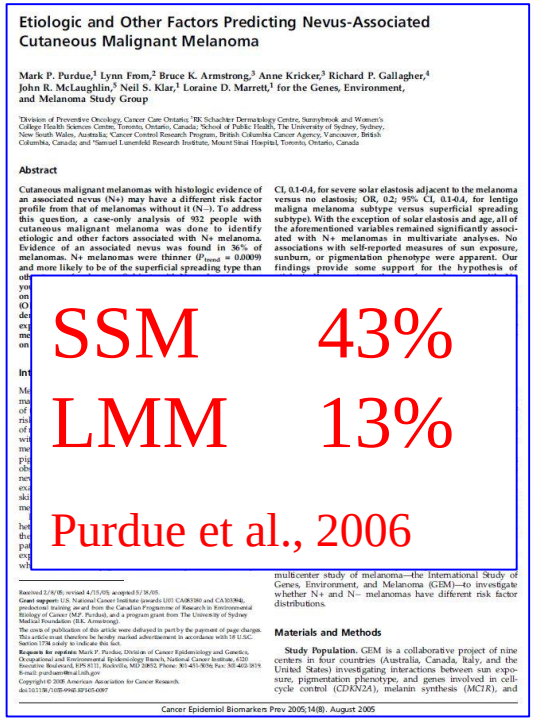
Die Literaturangaben dazu gehen weit auseinander, weil oftmals schwer zu entscheiden ist, ob Naevus-ähnliche Anteile eines Melanoms dem Melanom zuzurechnen sind oder einen assoziierten Naevus darstellen. Im Allgemeinen wird davon ausgegangen, dass bei Stamm- und Extremitätenmelanomen assoziierte Naevi in allenfalls 20% der Fälle vorkommen.



Bei Melanomen in Lichthaut sind sie etwas seltener, kommen aber ebenfalls vor. Hier ist ein Beispiel.







Etiologic and Other Factors Predicting Nevus-Associated Cutaneous Malignant Melanoma

Mark P. Purdue,[1] Lynn From,[2] Bruce K. Armstrong,[3] Anne Kricker,[3] Richard P. Gallagher,[4] John R. McLaughlin,[5] Neil S. Klar,[1] Loraine D. Marrett,[1] for the Genes, Environment, and Melanoma Study Group

Abstract

Cutaneous malignant melanomas with histologic evidence of an associated nevus (N+) may have a different risk factor profile from that of melanomas without it (N−). To address this question, a case-only analysis of 932 people with cutaneous malignant melanoma was done to identify etiologic and other factors associated with N+ melanoma. Evidence of an associated nevus was found in 36% of melanomas. N+ melanomas were thinner (P_{trend} = 0.0009) and more likely to be of the superficial spreading type than

CI, 0.1-0.4, for severe solar elastosis adjacent to the melanoma versus no elastosis; OR, 0.2; 95% CI, 0.1-0.4, for lentigo maligna melanoma subtype versus superficial spreading subtype). With the exception of solar elastosis and age, all of the aforementioned variables remained significantly associated with N+ melanomas in multivariate analyses. No associations with self-reported measures of sun exposure, sunburn, or pigmentation phenotype were apparent. Our findings provide some support for the hypothesis of

multicenter study of melanoma—the International Study of Genes, Environment, and Melanoma (GEM)—to investigate whether N+ and N− melanomas have different risk factor distributions.

Materials and Methods

Study Population. GEM is a collaborative project of nine centers in four countries (Australia, Canada, Italy, and the United States) investigating interactions between sun exposure, pigmentation phenotype, and genes involved in cell-cycle control (*CDKN2A*), melanin synthesis (*MC1R*), and

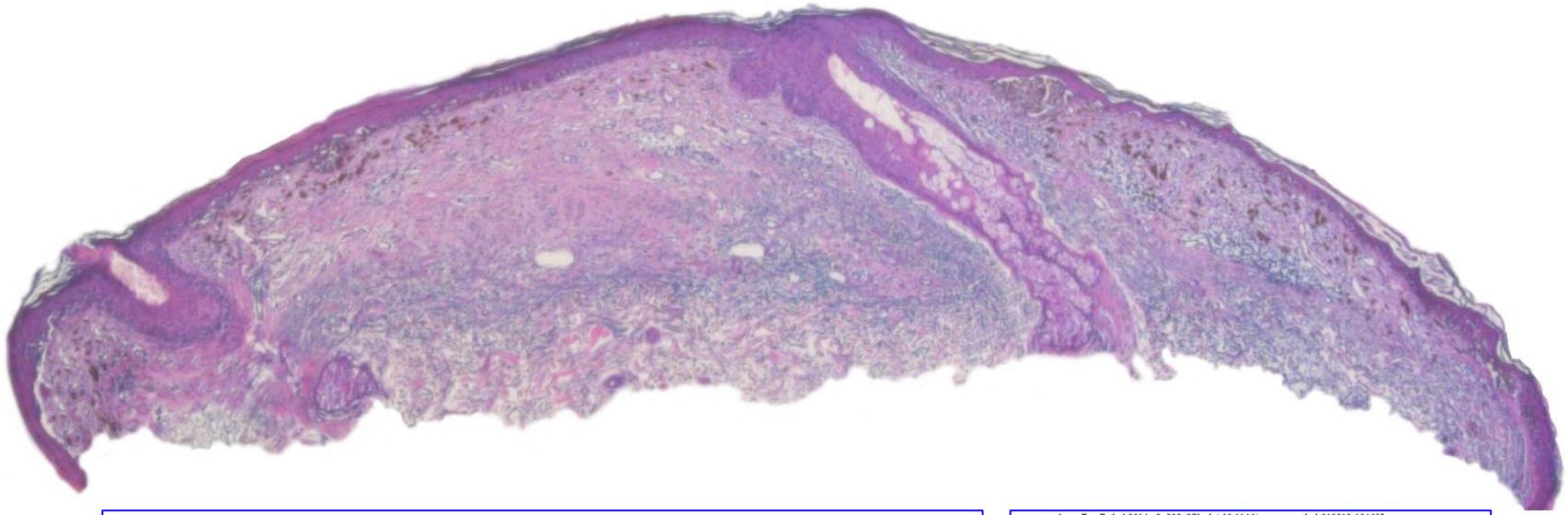
Cancer Epidemiol Biomarkers Prev 2005;14(8). August 2005

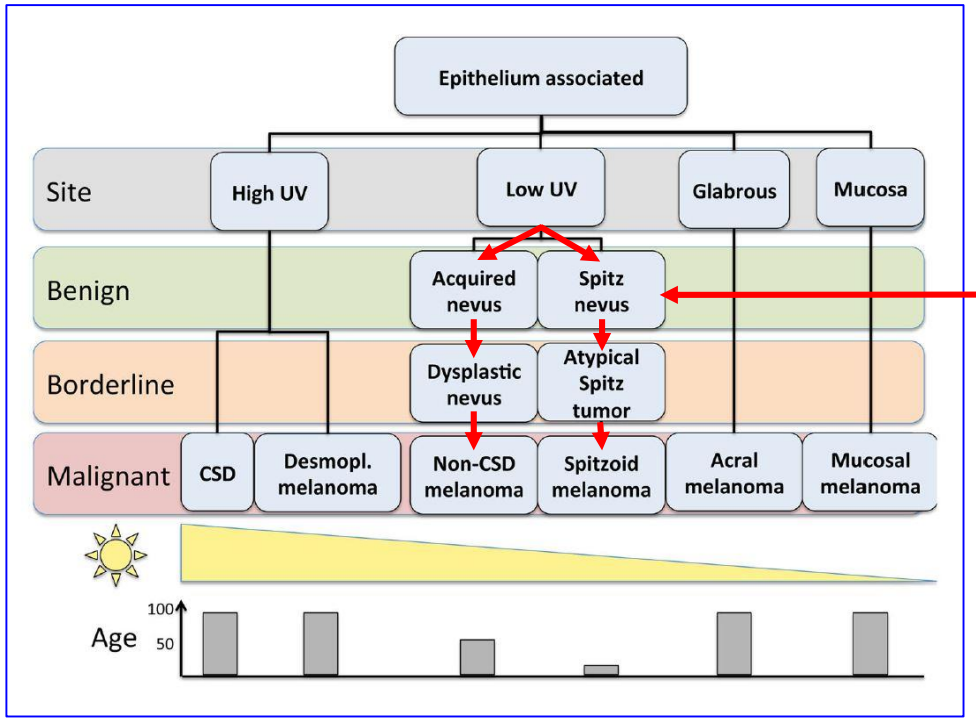
SSM 43%

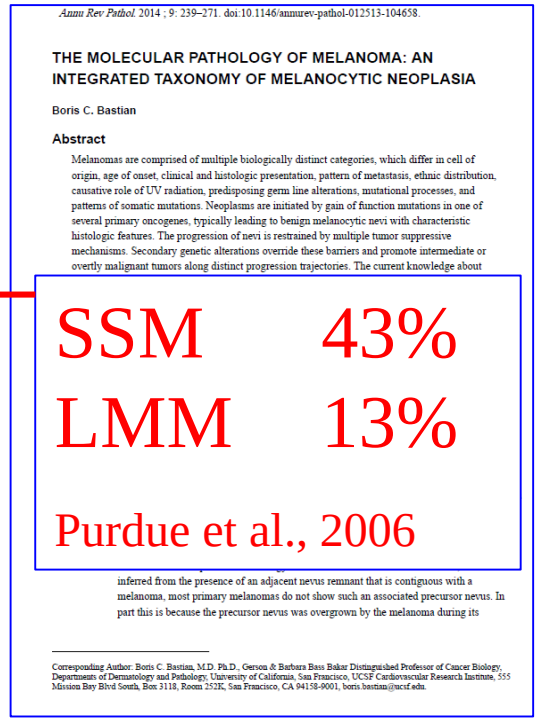
LMM 13%

Purdue et al., 2006

In der meistzitierten Studie zu diesem Thema wurde die Naevusassoziation beim SSM mit 43% und beim LMM mit 13% angegeben. Das ist ein Unterschied, ein Trend, doch dieser erlaubt keine klare Abgrenzung.







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THE MOLECULAR PATHOLOGY OF MELANOMA: AN INTEGRATED TAXONOMY OF MELANOCYTIC NEOPLASIA

Boris C. Bastian

Abstract

Melanomas are comprised of multiple biologically distinct categories, which differ in cell of origin, age of onset, clinical and histologic presentation, pattern of metastasis, ethnic distribution, causative role of UV radiation, predisposing germ line alterations, mutational processes, and patterns of somatic mutations. Neoplasms are initiated by gain of function mutations in one of several primary oncogenes, typically leading to benign melanocytic nevi with characteristic histologic features. The progression of nevi is restrained by multiple tumor suppressive mechanisms. Secondary genetic alterations override these barriers and promote intermediate or overtly malignant tumors along distinct progression trajectories. The current knowledge about

SSM 43%

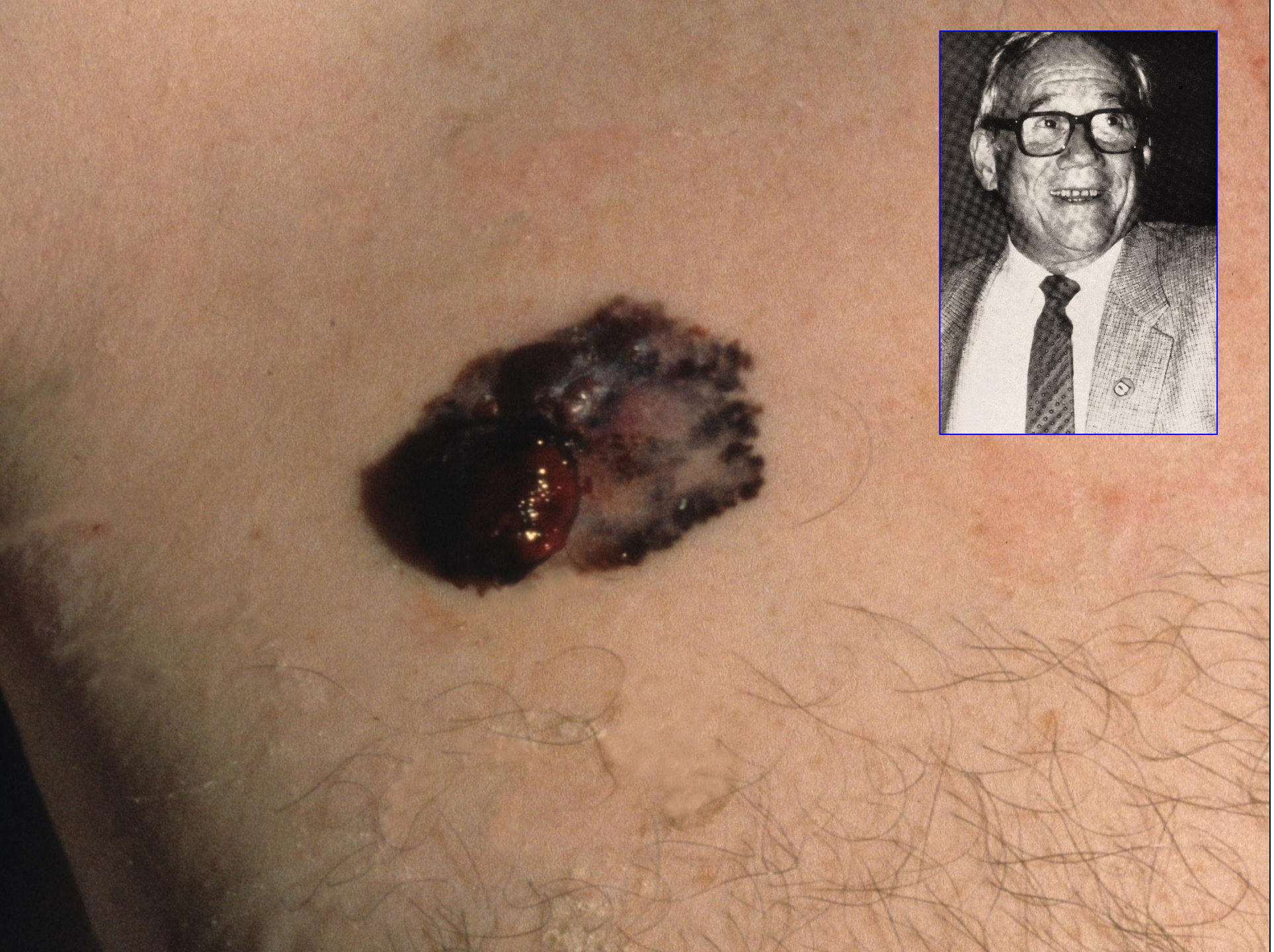
LMM 13%

Purdue et al., 2006

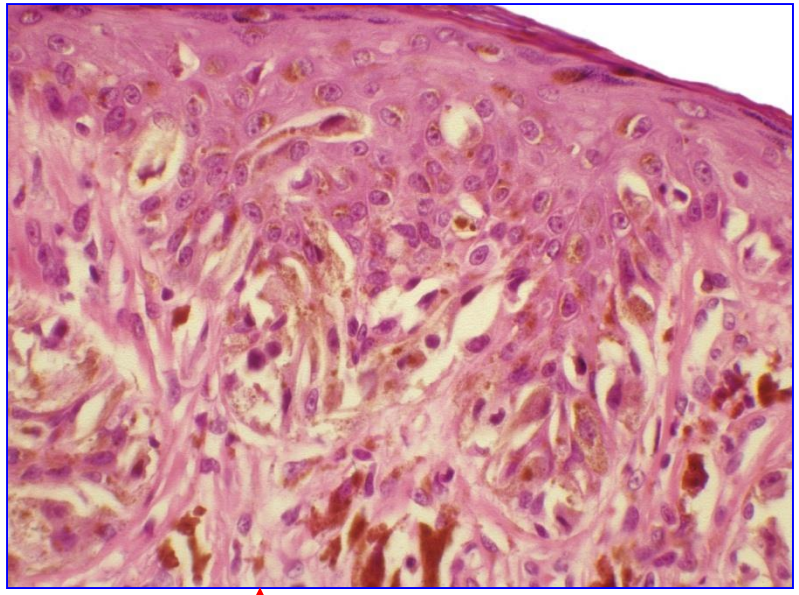
inferred from the presence of an adjacent nevus remnant that is contiguous with a melanoma, most primary melanomas do not show such an associated precursor nevus. In part this is because the precursor nevus was overgrown by the melanoma during its

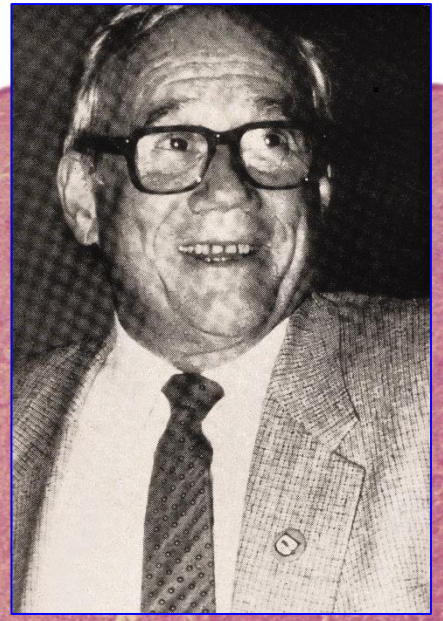
Corresponding Author: Boris C. Bastian, M.D. Ph.D., Gerson & Barbara Bass Bakar Distinguished Professor of Cancer Biology, Departments of Dermatology and Pathology, University of California, San Francisco, UCSF Cardiovascular Research Institute, 555 Mission Bay Blvd South, Box 3118, Room 252K, San Francisco, CA 94158-9001, boris.bastian@ucsf.edu.

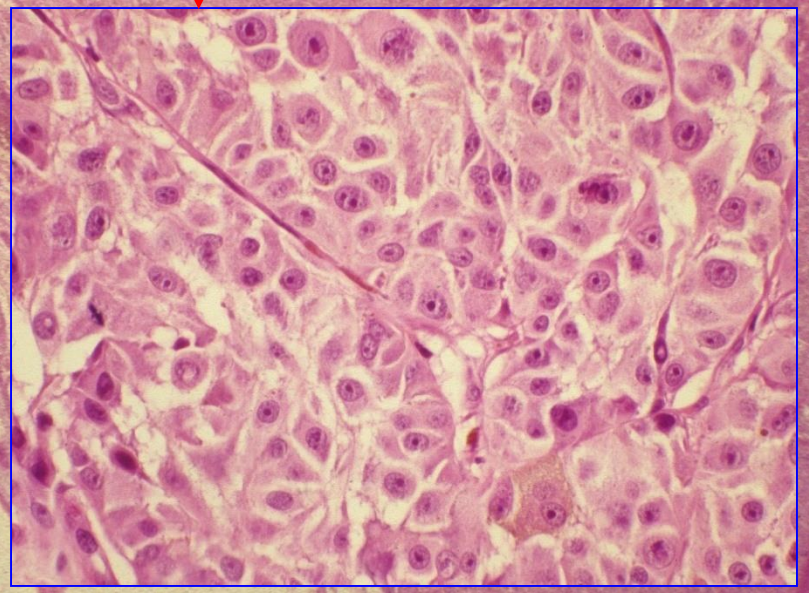
Daraus abzuleiten, dass es grundsätzliche Unterschiede zwischen Melanomen mit hoher und niedriger UV-Exposition gibt und dass letztere grundsätzlich aus Naevi hervorgehen, die schrittweise maligne entarten, ist mehr als gewagt. In der sogenannten „integrierten Taxonomie melanozytärer Neoplasien“, die der aktuellen WHO-Klassifikation zugrunde liegt, werden aber nicht nur eigenständige biologische Entitäten postuliert, die sich nicht reliabel voneinander abgrenzen lassen, sondern es werden Neoplasien in einen Topf geworfen, die völlig unterschiedlich sind, nämlich melanozytäre Naevi und maligne Melanome.



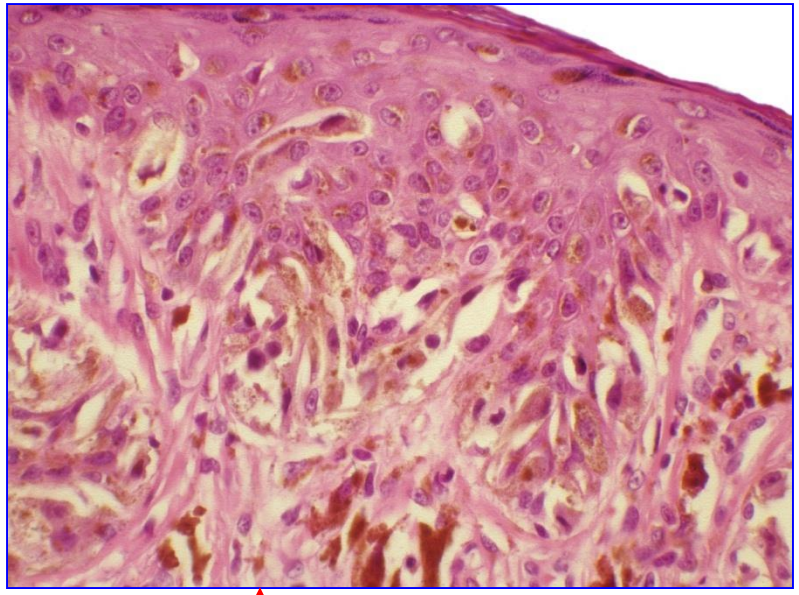
Der Grund dafür liegt in der unzulässigen Gleichsetzung der molekularen Mehrstufen-Kanzerogenese mit der histopathologischen Entwicklung von Läsionen. Der Ursprung dieses Fehlers liegt bei Clark, der wegen der häufigen Entwickung von Tumorknoten auf dem Boden eines flachen Anteils glaubte, im Melanom einen Modelltumor für Mehrstufen-Kanzerogenese gefunden zu haben,

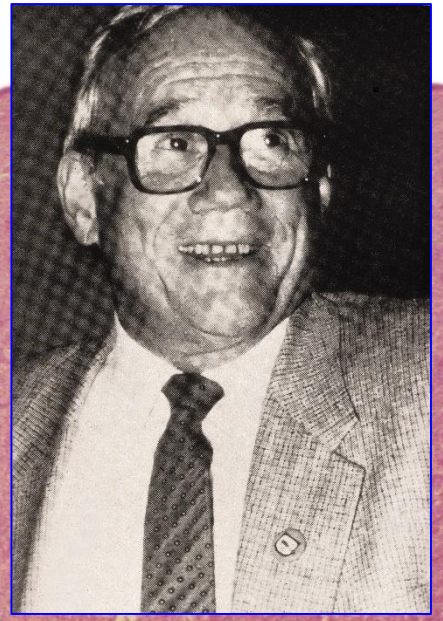




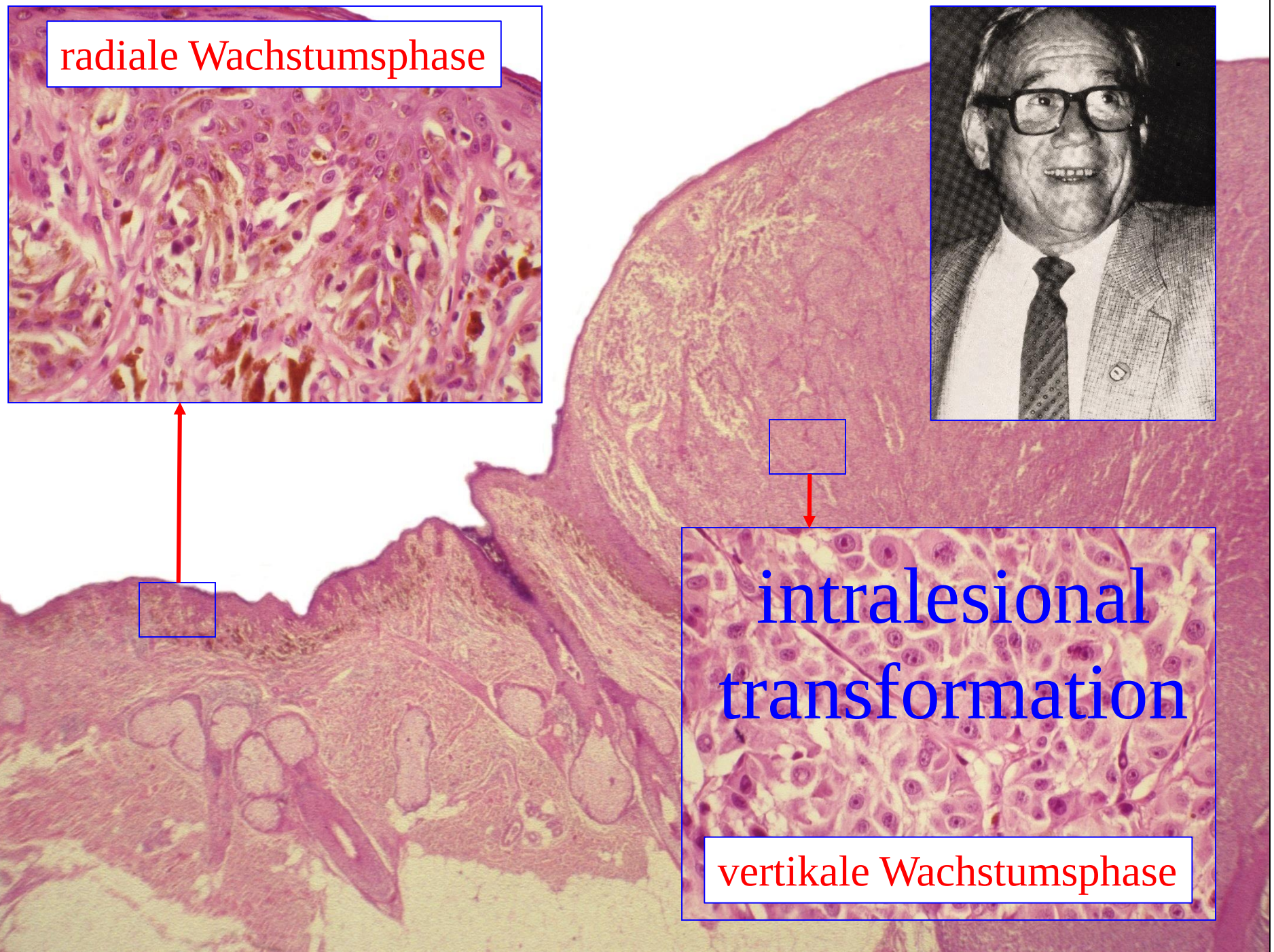


zumal sich die Zellen im flachen und im knotigen Anteil oft deutlich unterscheiden.





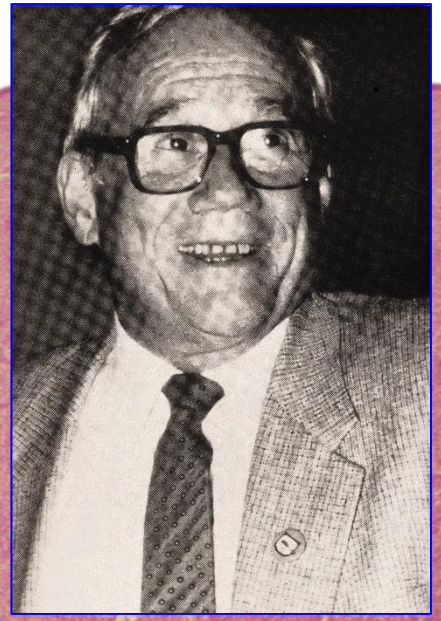
Clark bezeichnete dies als „intralesional transformation“



und leitete daraus das Konzept der radialen und der vertikalen Wachstumsphase ab: Er behauptete,

Die radiale Wachstumsphase ... ist nicht mit Metastasen assoziiert, und nach unserer Hypothese sind solche Tumoren nicht zur Metastasierung befähigt. Um diese Fähigkeit zu erwerben, müssen sie die nächste Stufe der Tumorprogression erreichen – …

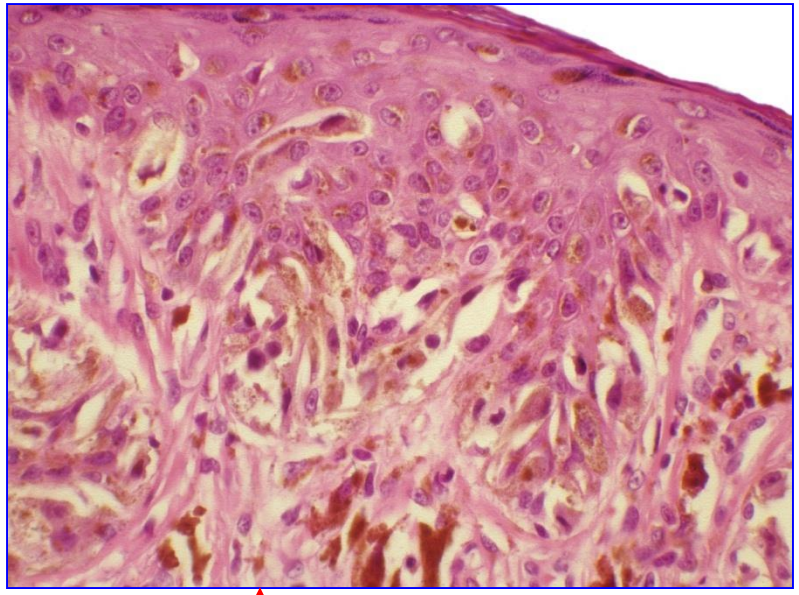
Clark WH Jr. et al., 1984

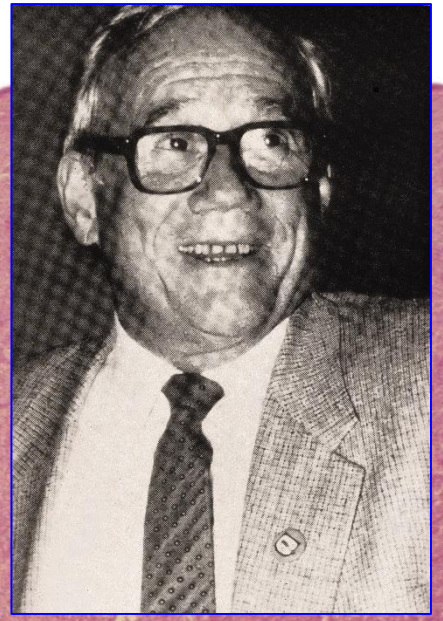


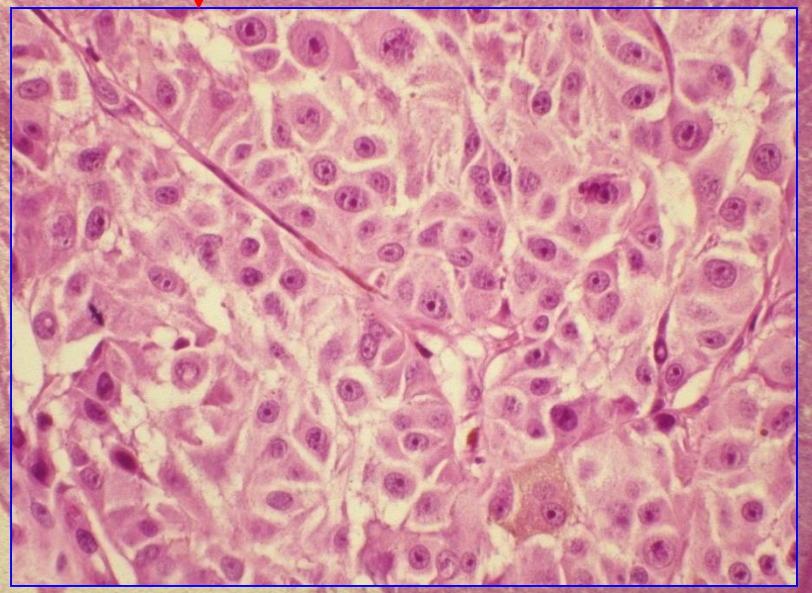
… die vertikale Wachtumsphase. Diese Stufe ist charakterisiert durch das Auftreten einer neuen Zellpopulation innerhalb des Melanoms und nicht durch Ausdehnung der Zellen der präexistenten radialen Wachstumsphase.

Clark WH Jr. et al., 1984

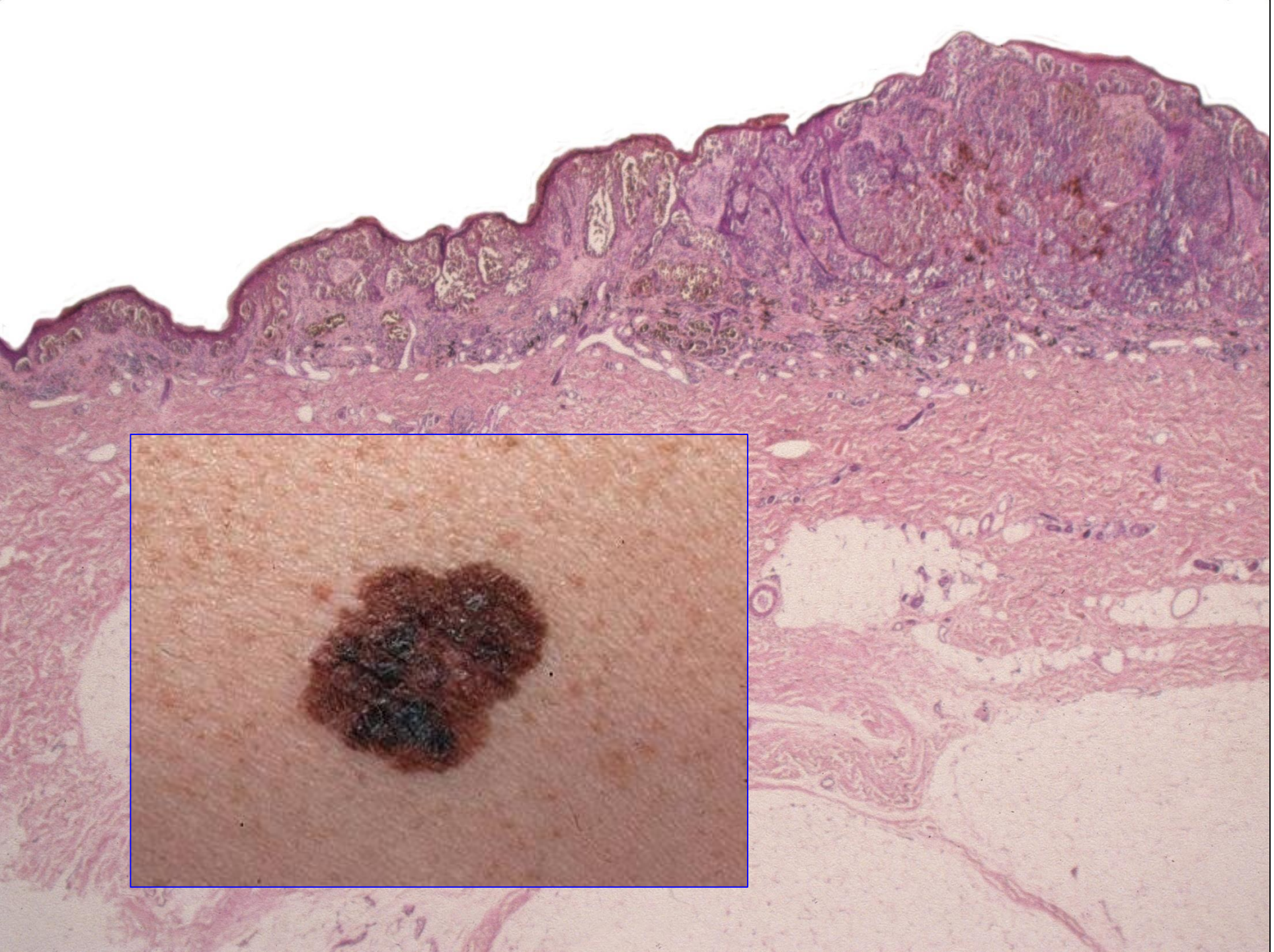
„die radiale Wachstumsphase ... ist nicht mit Metastasen assoziiert und nach unserer Hypothese sind solche Tumoren nicht zur Metastasierung befähigt. Um diese Fähigkeit zu erwerben, müssen sie die nächste Stufe der Tumorprogression erreichen – die vertikale Wachtumsphase. Diese Stufe ist charakterisiert durch das Auftreten einer neuen Zellpopulation innerhalb des Melanoms und nicht durch Ausdehnung der Zellen der präexistenten radialen Wachstumsphase.“



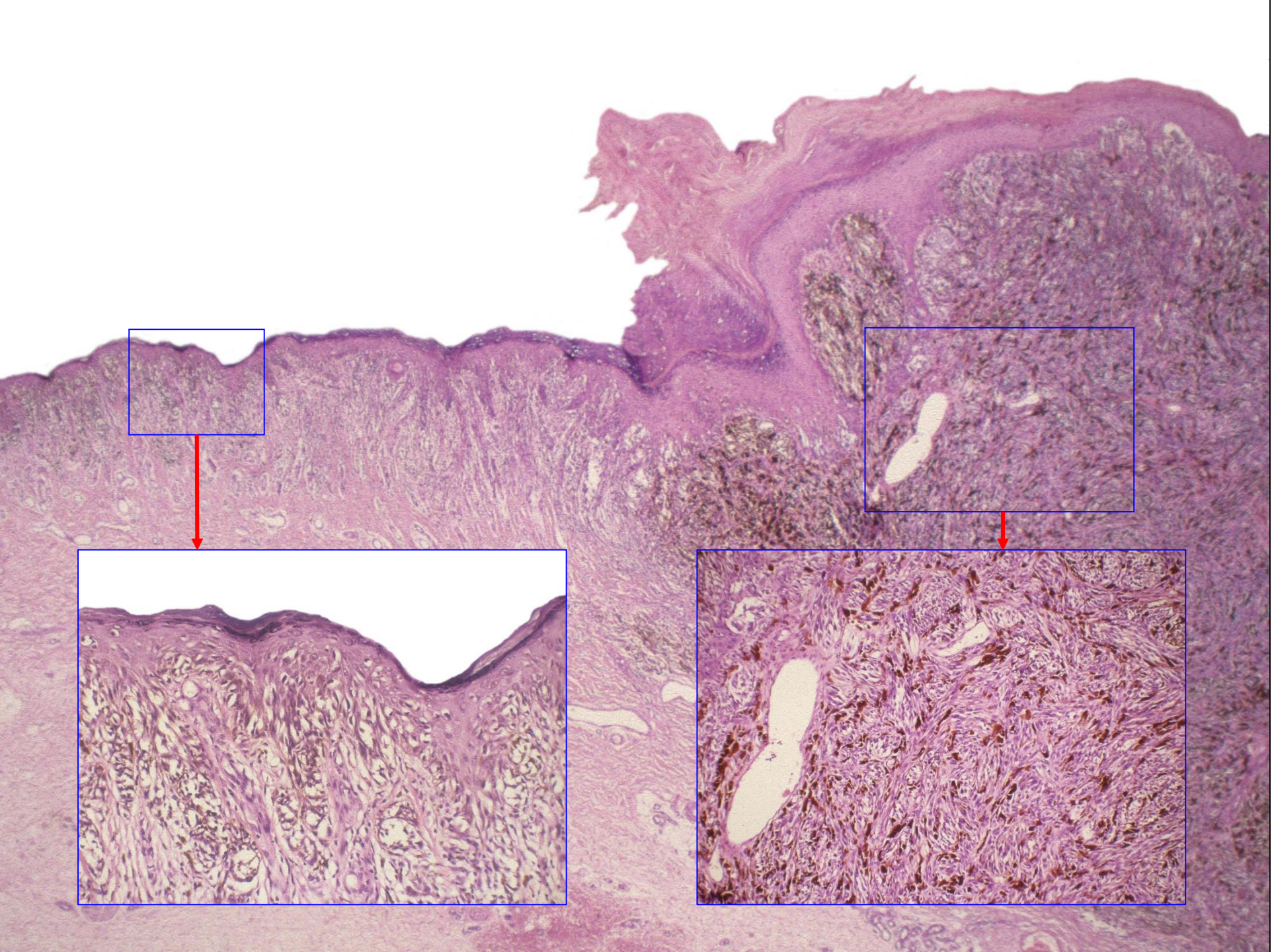




Zutreffend an dieser These war, dass Melanome in fortgeschrittenen Stadien häufig morphologisch abgrenzbare neue Zellpopulationen ausbilden. Dass dies für die Metastasierungsfähigkeit erforderlich ist, war jedoch reine Spekulation und im Grunde von vornherein abwegig,



denn viele Melanome zeigen auch in fortgeschrittenen Stadien eine gleichmäßige Vergrößerung,



und selbst wenn auf einem flachen Anteil umschriebene Knoten entstehen, weisen die beiden Anteile oft keine erkennbaren zytologischen Unterschiede auf. Aber selbstverständlich können auch solche Melanome metastasieren.

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Volume 6 Supplement 1
Summer 1984

Invasion to levels III, IV or V is, by definition, the vertical growth phase.

Clark WH Jr. et al., 1975

mass of contiguous melanomatous cells in the dermis … larger than the small nests … in the epidermis.

Elder et al., 1984

D.E. Elder **E. Lusk**

D. Guerry, IV **M. Van Horn**

M.N. Epstein* **W.H. Clark, Jr.**

L. Zehngebot

Invasive malignant melanomas lacking competence for metastasis

ABSTRACT Two stages of progression have been described in malignant melanomas, namely, the so-called "radial" and "vertical" phases of growth. We sought the presence or absence of vertical growth in 211 invasive cutaneous malignant melanomas. Disease-free survival in 146 patients with vertical growth was 63.7%, whereas 100% of 65 patients whose neoplasms lacked this feature survived 5 years or more after ablation of their lesions without evidence of recurrence or metastasis. Microstaging of patients with malignant melanoma by tradi-

In about 90% of cases, cutaneous malignant melanomas evolve through at least two stages of progression that have been termed the "radial" (plaque) and "vertical" (nodule) phases of growth.(1) The remaining 10% of cases progress directly to the vertical phase. Histologically, a plaque of malignant melanoma in the so-called radial phase may stay confined to the epidermis (*in situ*) or extend into the dermis in single or small groups of cells ("invasive").

Um am Konzept der läsionalen Mehrstufen-Kanzerogenese mit Existenz *„invasiver Melanome ohne Kompetenz zur Metastasierung"* festhalten zu können, mussten daherdie Definitionen geändert werden: 1975 wurde für die vertikale Wachstumsphase noch eine Invasion bis mindestens Level III verlangt, 1984 lediglich eine *„mass of contiguous melanomatous cells in the dermis … larger than the small nests … in the epidermis,"*,

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Radial growth phase (RGP)
An atypical melanocytic proliferation confined to the epidermis and superficial dermis, meeting the criteria for melanoma (in situ or invasive), but lacking a VGP.

Vertical growth phase (VGP)
A melanocytic proliferation in the dermis characterized by expansile growth (tumorigenic proliferation) and/or mitotic activity, meeting the criteria for melanoma. In the limiting case, there is a nest in the dermis larger than the largest intraepidermal nest. In a lentiginous melanoma with no nests, this criterion is necessarily more subjective.

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was sich auch in der aktuellen WHO-Definition wiederfindet. Heute reicht aber schon der Nachweis einer einzigen dermalen Mitose für die vertikale Wachstumsphase aus.

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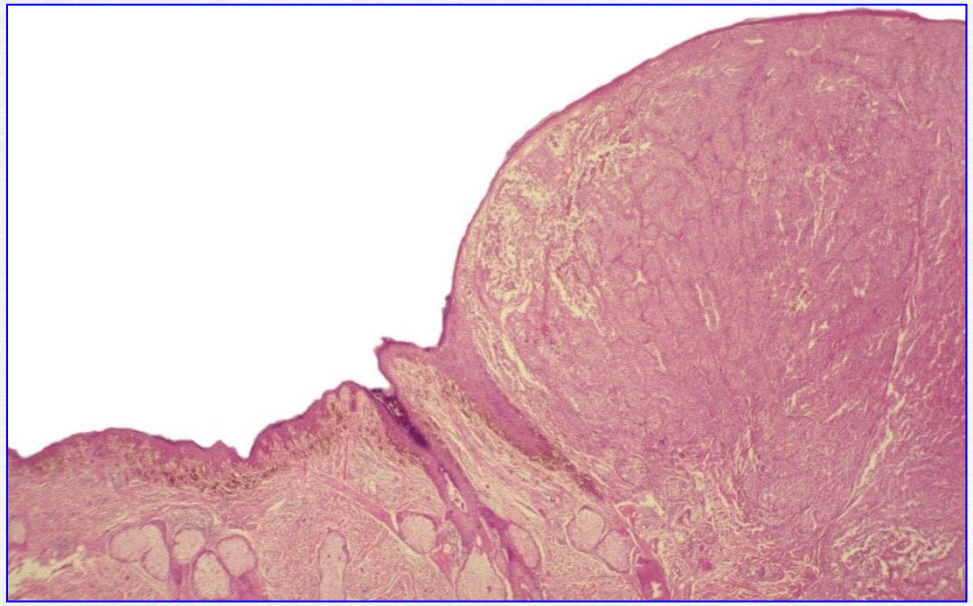

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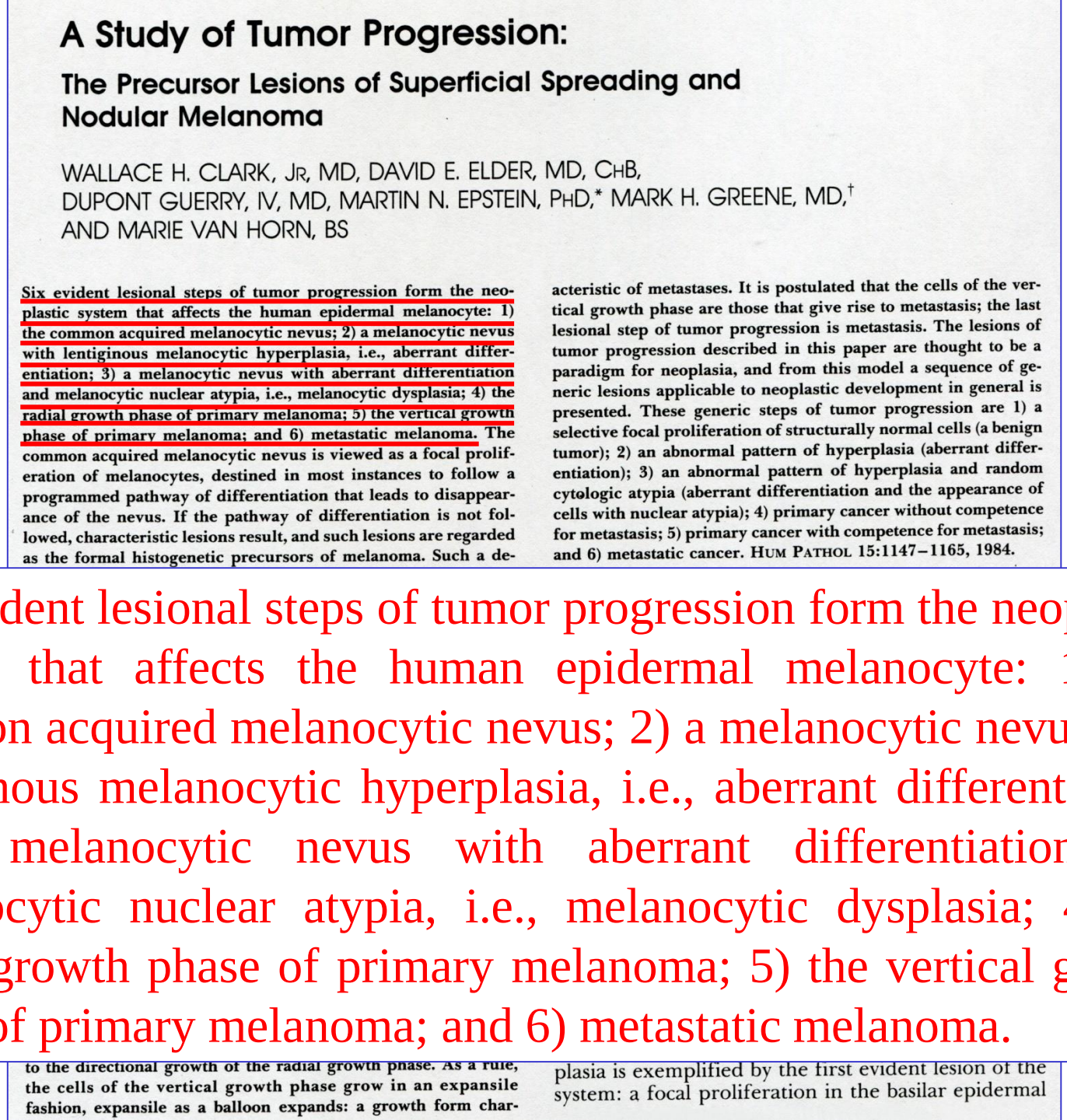
Mit der ursprünglichen authentischen Beobachtung einer „intralesional transformation“ hat dies nichts mehr zu tun.

War das Konzept der läsionalen Mehrstufen-Kanzerogenese zunächst auf Melanome begrenzt,



A Study of Tumor Progression:

The Precursor Lesions of Superficial Spreading and Nodular Melanoma

WALLACE H. CLARK, JR, MD, DAVID E. ELDER, MD, CHB,
DUPONT GUERRY, IV, MD, MARTIN N. EPSTEIN, PHD,* MARK H. GREENE, MD,†
AND MARIE VAN HORN, BS

Six evident lesional steps of tumor progression form the neoplastic system that affects the human epidermal melanocyte: 1) the common acquired melanocytic nevus; 2) a melanocytic nevus with lentiginous melanocytic hyperplasia, i.e., aberrant differentiation; 3) a melanocytic nevus with aberrant differentiation and melanocytic nuclear atypia, i.e., melanocytic dysplasia; 4) the radial growth phase of primary melanoma; 5) the vertical growth phase of primary melanoma; and 6) metastatic melanoma. The common acquired melanocytic nevus is viewed as a focal proliferation of melanocytes, destined in most instances to follow a programmed pathway of differentiation that leads to disappearance of the nevus. If the pathway of differentiation is not followed, characteristic lesions result, and such lesions are regarded as the formal histogenetic precursors of melanoma. Such a deacteristic of metastases. It is postulated that the cells of the vertical growth phase are those that give rise to metastasis; the last lesional step of tumor progression is metastasis. The lesions of tumor progression described in this paper are thought to be a paradigm for neoplasia, and from this model a sequence of generic lesions applicable to neoplastic development in general is presented. These generic steps of tumor progression are 1) a selective focal proliferation of structurally normal cells (a benign tumor); 2) an abnormal pattern of hyperplasia (aberrant differentiation); 3) an abnormal pattern of hyperplasia and random cytologic atypia (aberrant differentiation and the appearance of cells with nuclear atypia); 4) primary cancer without competence for metastasis; 5) primary cancer with competence for metastasis; and 6) metastatic cancer. HUM PATHOL 15:1147–1165, 1984.

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plasia is exemplified by the first evident lesion of the system: a focal proliferation in the basilar epidermal

wurde es mit der Beschreibung des „dysplastischen Naevus“ stark erweitert. 1984 behaupteten Clark und Mitarbeiter in einer „Study of Tumor Progression“, es gäbe *„six evident lesional steps of tumor progression“*, vom „common acquired melanocytic nevus“ über verschiedene Stadien zunehmender „Dysplasie“ bis hin zur radialen und vertikalen Wachstumsphase des Melanoms und zu Melanommetastasen. Obwohl keinerlei Evidenz für diese stufenweise Progression offeriert wurde, fand das Konzept insbesondere in den USA große Resonanz, weniger wegen seiner inhaltlichen Überzeugungskraft

A Study of Tumor Progression:

The Precursor Lesions of Superficial Spreading and Nodular Melanoma

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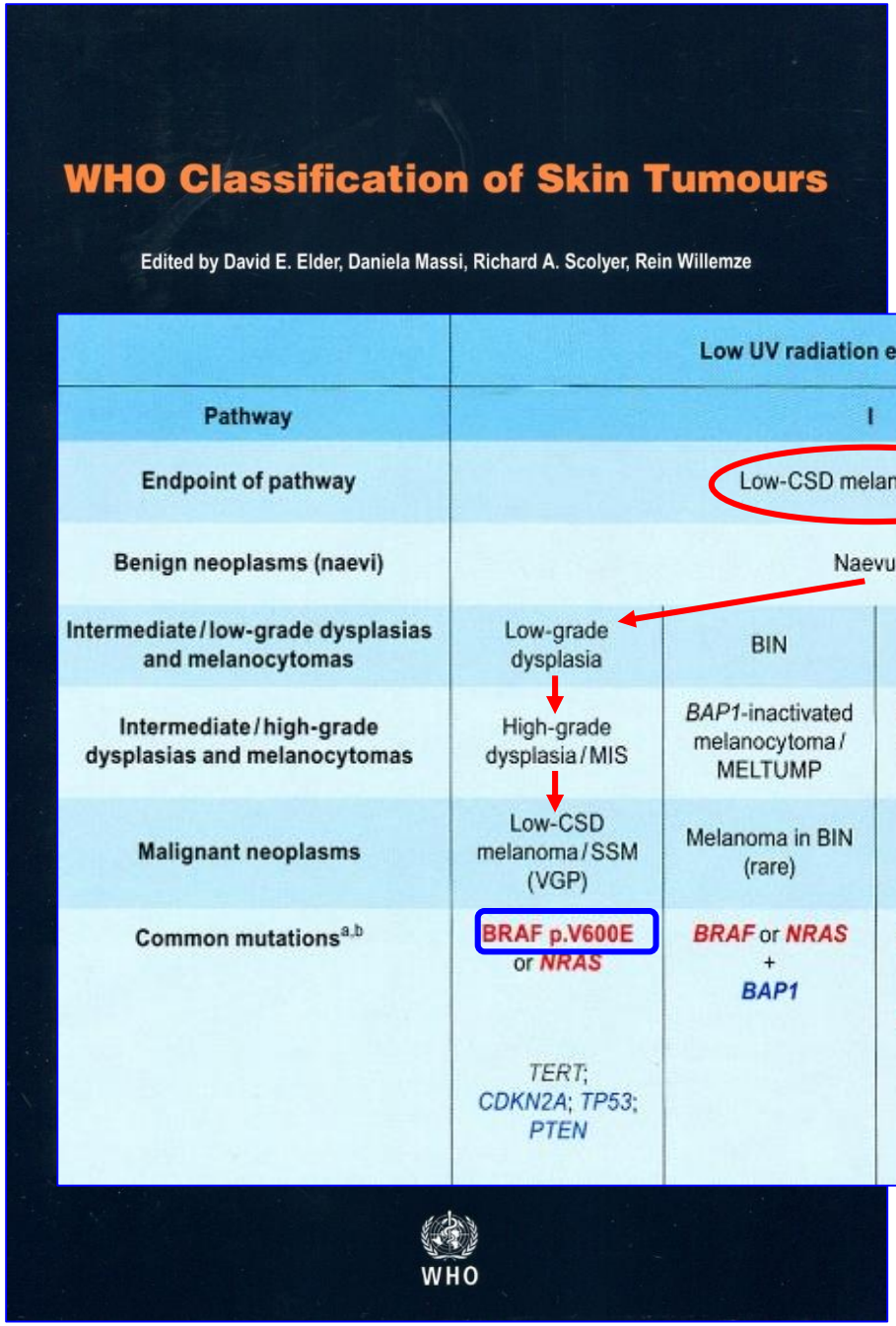
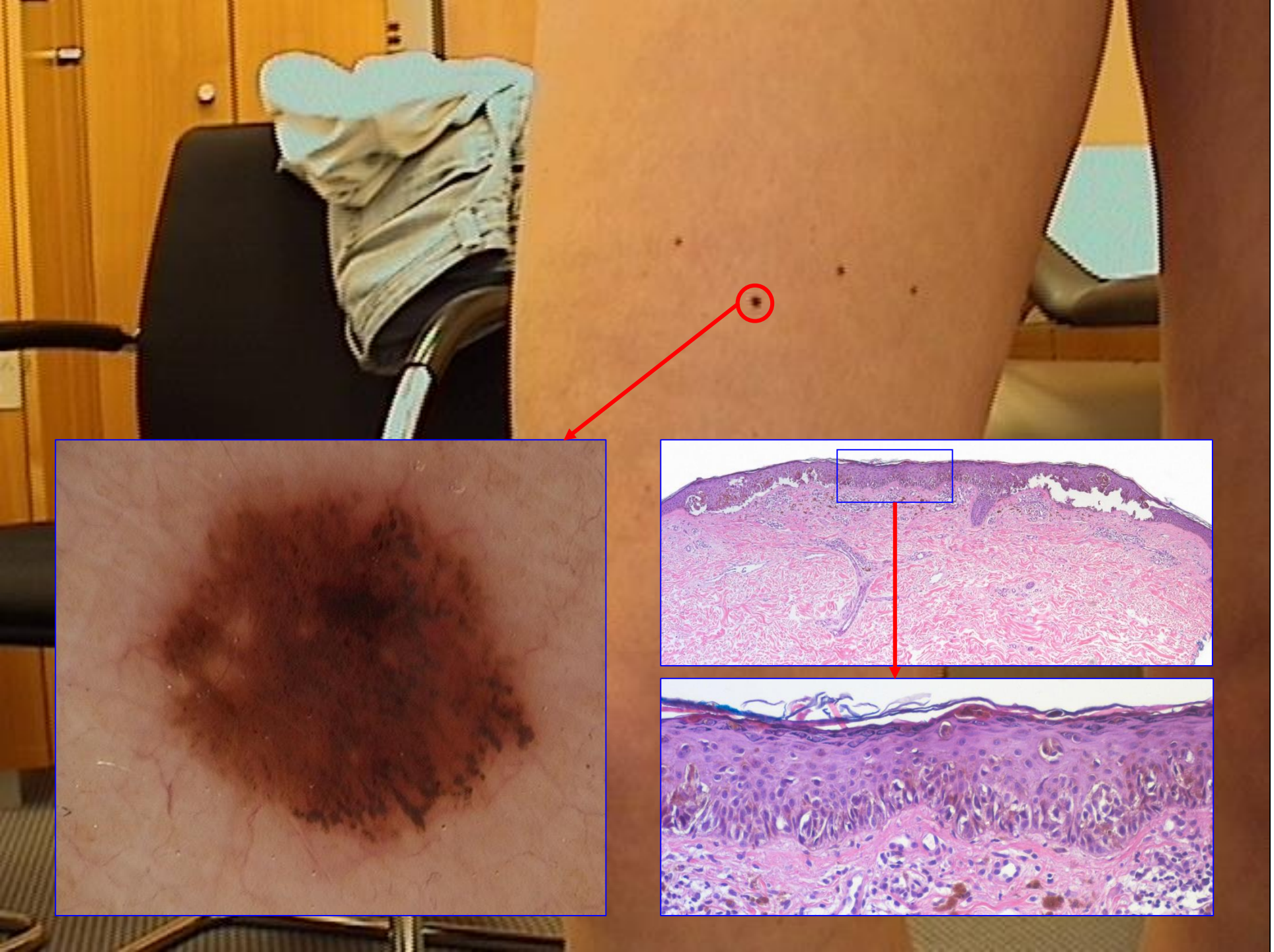
als wegen der juristischen Implikationen, denn wenn gutartige und bösartige Tumoren als unterschiedliche Entwicklungsstadien desselben Prozesses gelten, sinkt das Risiko, wegen einer Fehldiagnose verklagt zu werden.



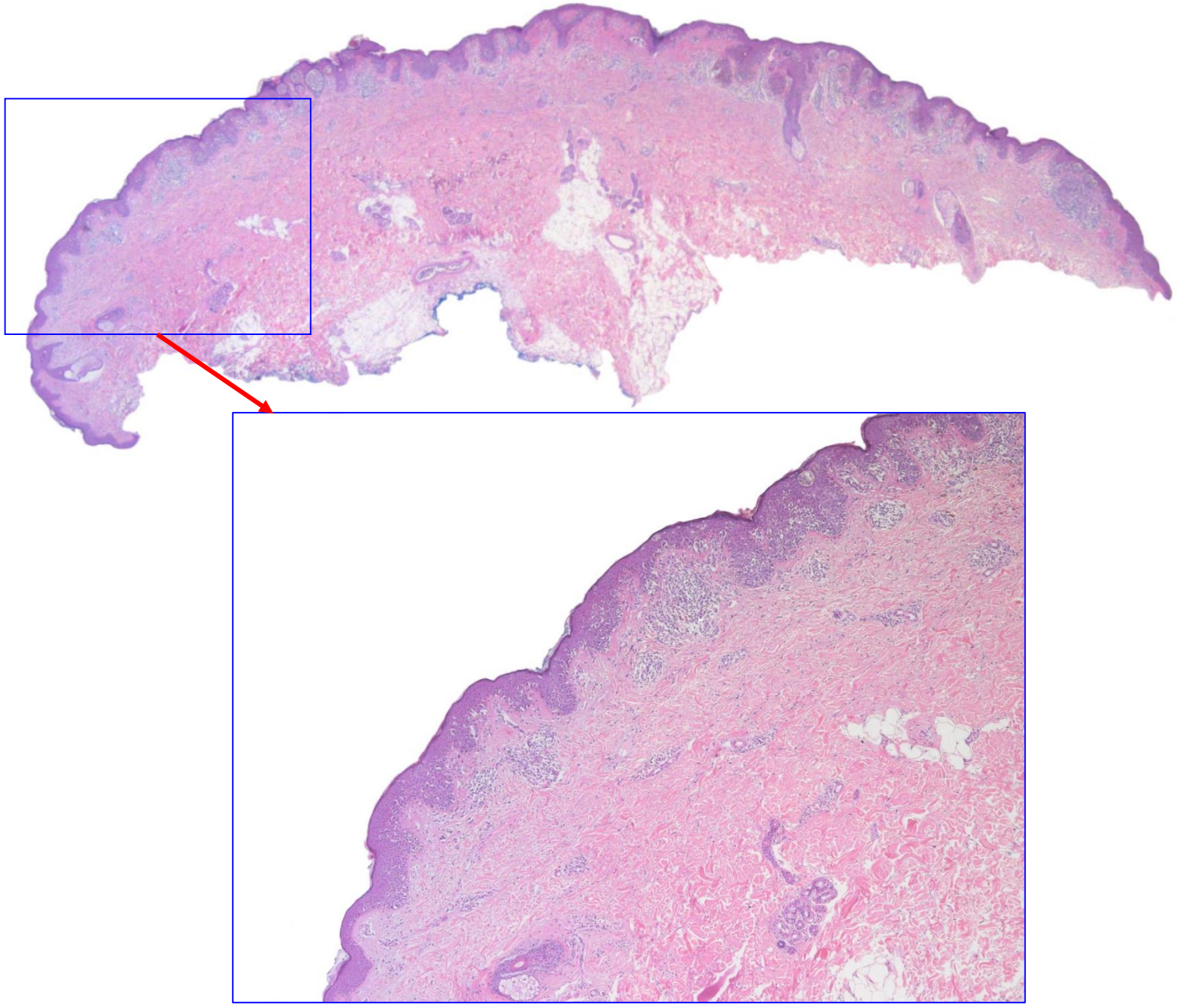
	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS***	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*
	TERT; *CDKN2A*; *TP53*; *PTEN*				*TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

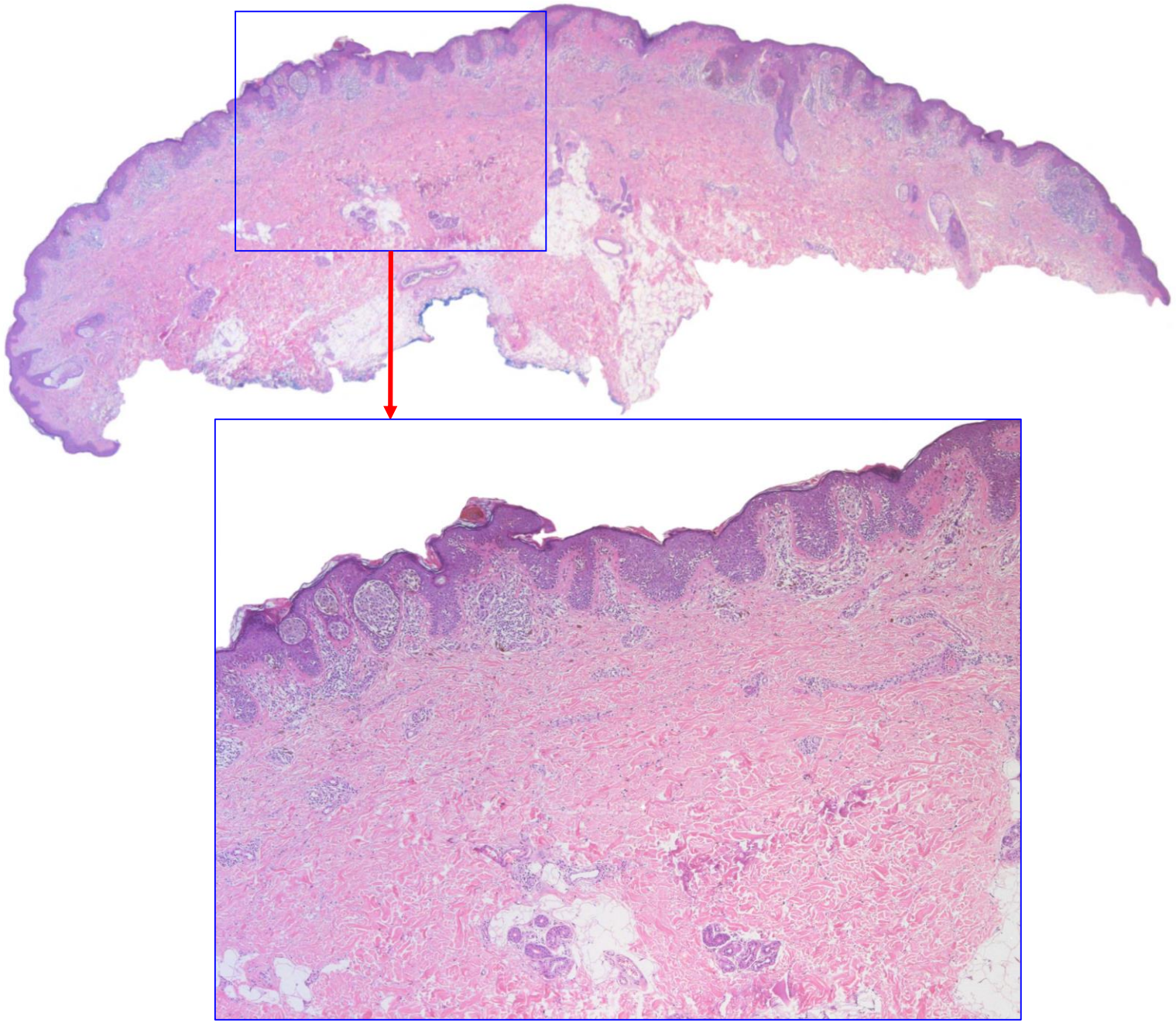
Deshalb erfreut sich Clarks altes Konzept großer Beliebtheit und gelangt in der aktuellen WHO-Klassifikation zu einer neuen Blüte, aufgefrischt durch molekulare Befunde, insbesondere das häufige Vorkommen von BRAF-V600E-Mutationen bei melanozytären Naevi und Melanomen. Offenbar sind BRAF-Mutationen ein erster Schritt in der Entstehung vieler Naevi und Melanome, aber man darf die molekulare Grundlage nicht verwechseln mit der Entwicklung von Läsionen. Ein Naevus ist keine Mutation,



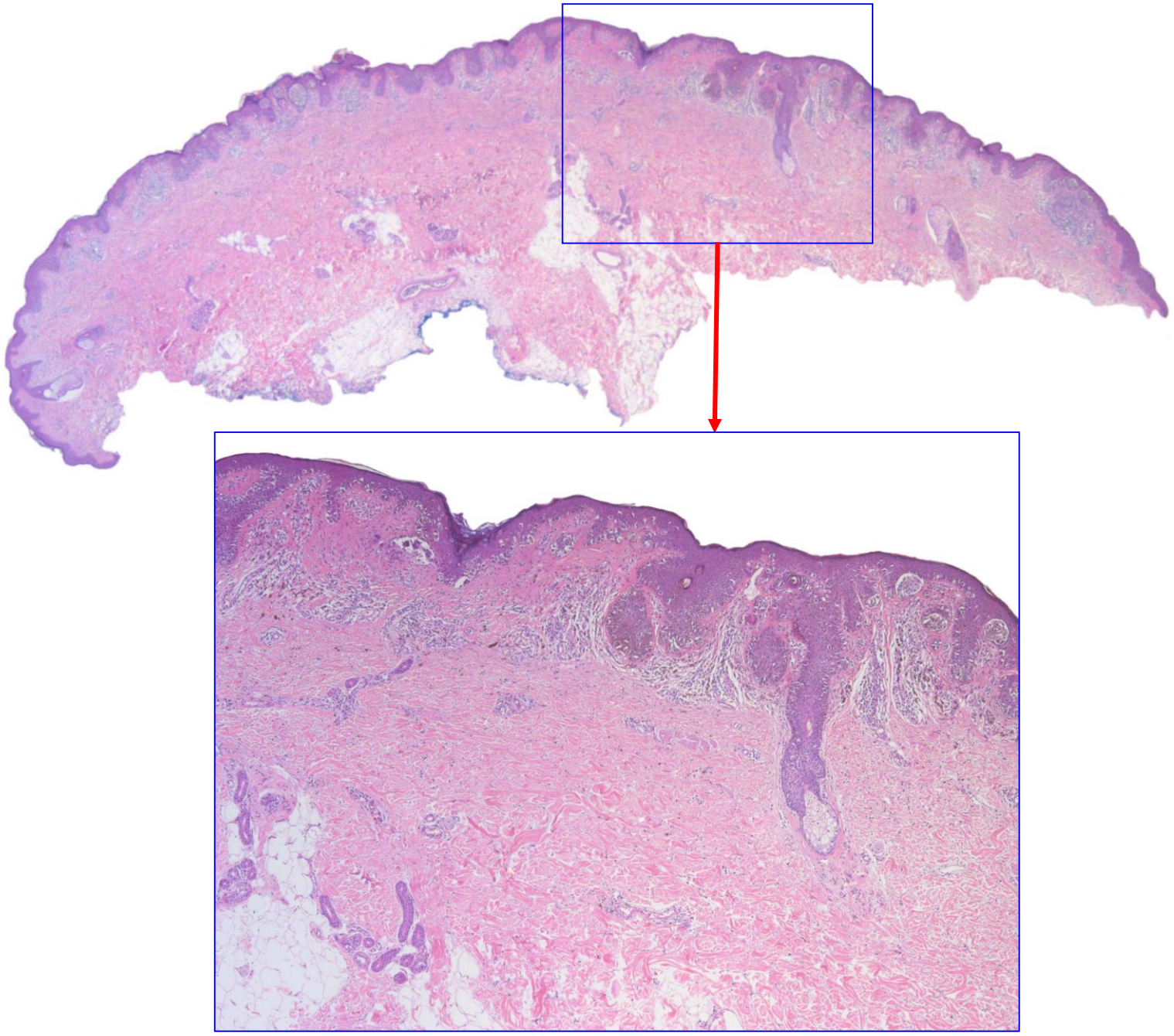
sondern ein Tumor, und dieser Tumor – ein assoziierter Naevus – ist bei Melanomen in der Regel nicht nachweisbar. Die meisten Melanome entstehen auf zuvor unveränderter Haut. Sie sind schon in den Frühstadien als solche erkennbar und zeigen von Beginn an ein anderes Wachstumsverhalten als Naevi; die entscheidende Phase der Kanzerogenese muss also schon stattgefunden haben.

Dann vergrößeren sie sich,

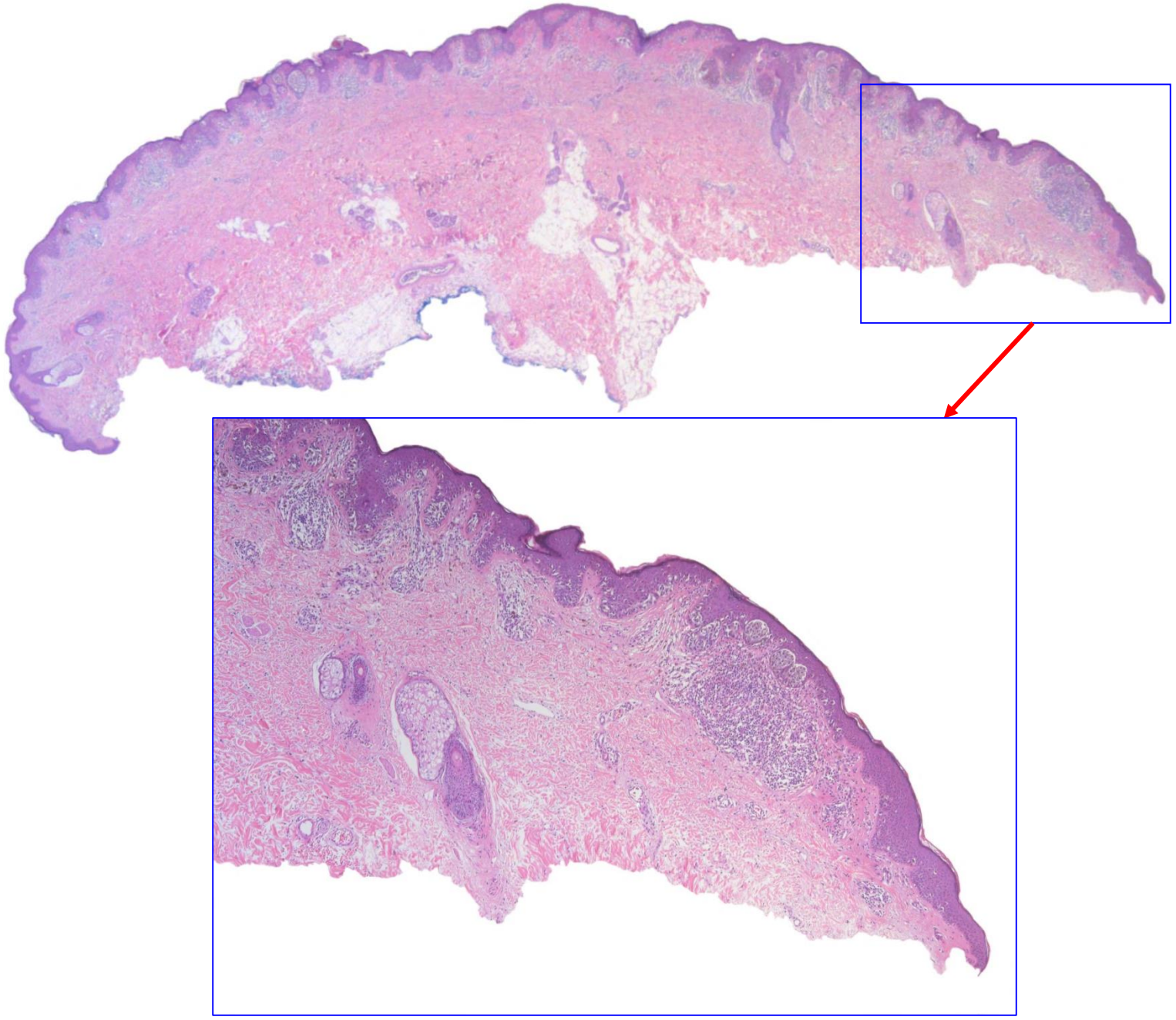




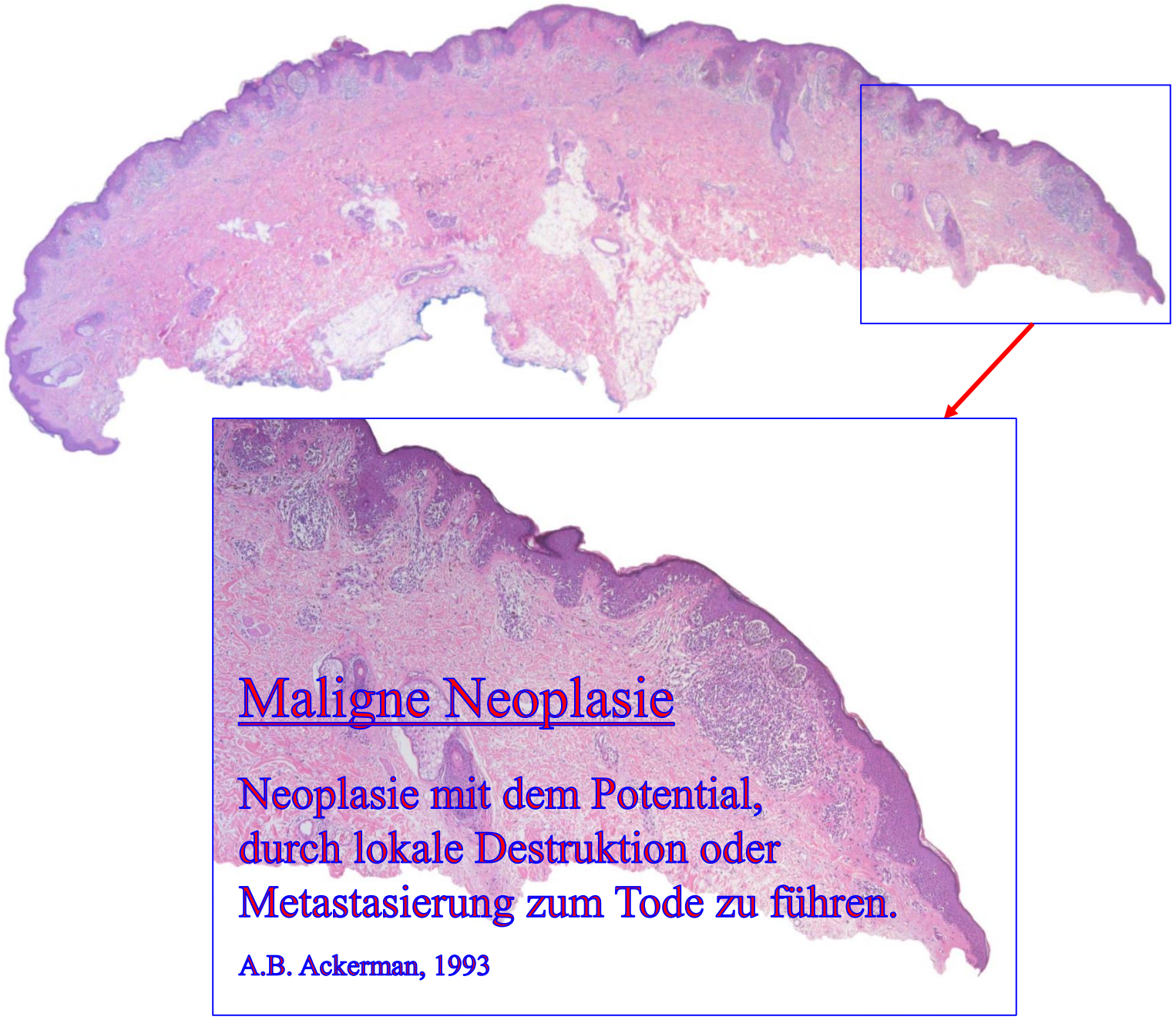
und die Unregelmäßigkeit des Wachstums als direktes Abbild ihres biologischen Verhaltens im Gewebe tritt deutlicher hervor,



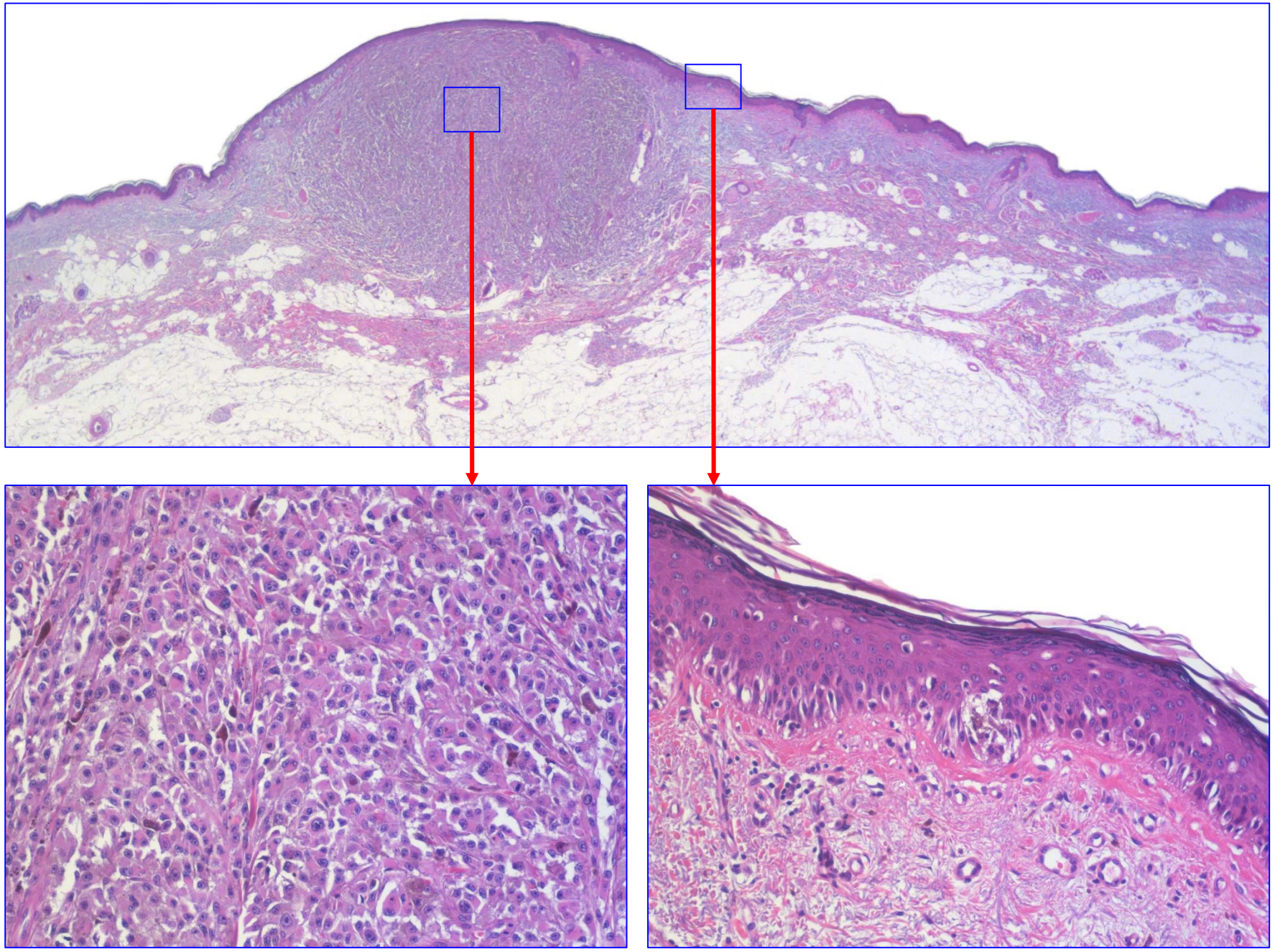
aber wo man hinschaut,
sind es dieselben Zellen,



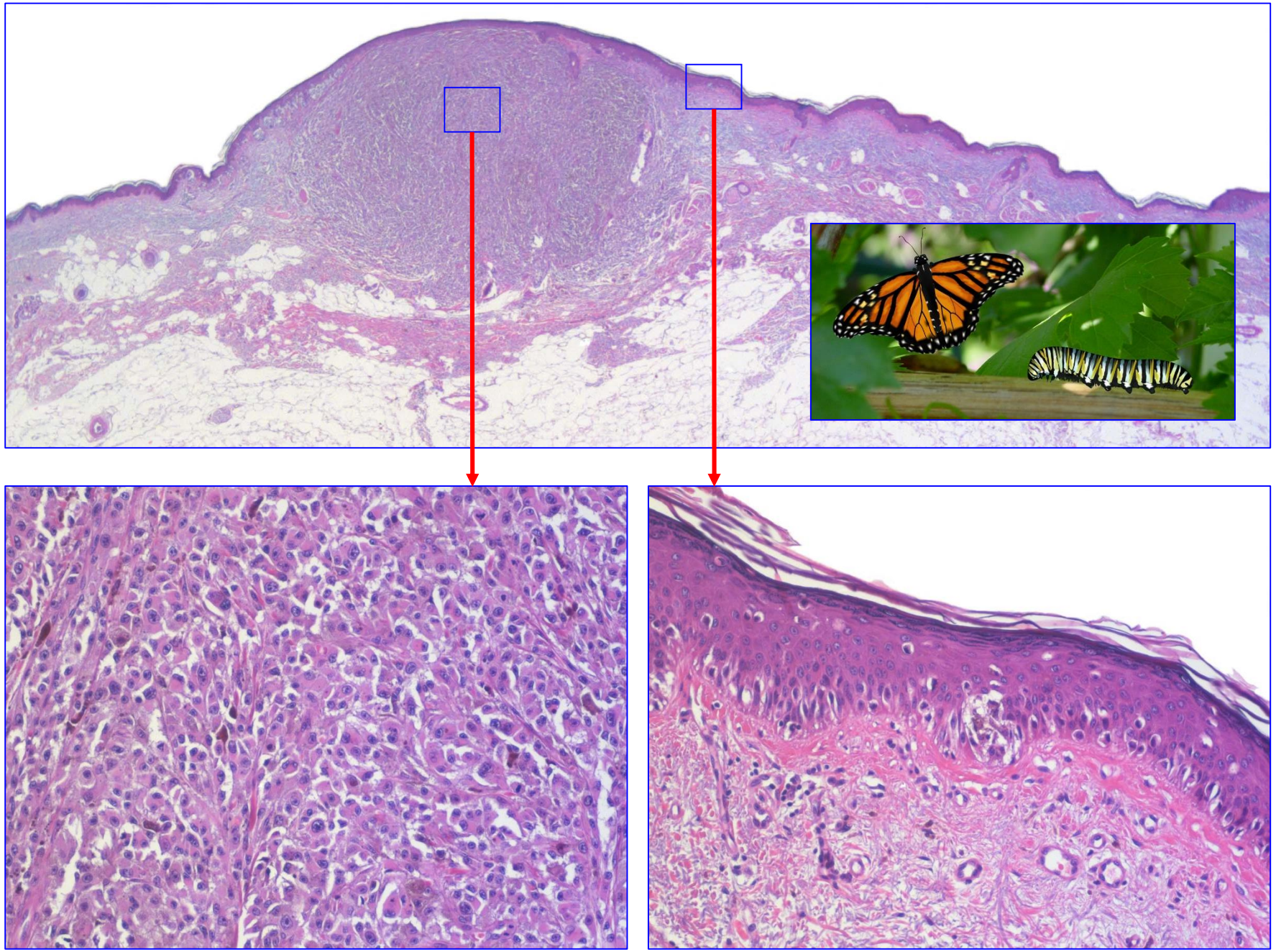
ein- und derselbe pathologische Prozess, und er erfüllt die Definition einer malignen Neoplasie,



nämlich einer Neoplasie mit dem *„Potential, durch lokale Destruktion oder Metastasierung zum Tode zu führen,“* sofern man ihr dazu Gelegenheit gibt.



Wenn man dies tut, wächst das Melanom, und durch weitere Mutationen entstehen neue Zellpopulationen. Mit anderen Worten kommt es nicht nur zu quantitativen, sondern auch zu qualitativen Veränderungen. Das ist in der Natur aber immer der Fall



und oftmals viel dramatischer. Es reicht nicht aus, um von einer neuen Entität zu sprechen.

Follow-up of melanocytic skin lesions with digital epiluminescence microscopy: Patterns of modifications observed in early melanoma, atypical nevi, and common nevi

Harold Kittler, MD,[a] Hubert Pehamberger,
and Michael Binder, MD[a] V

Background: Digital epiluminescence microscopy (DELM)
the follow-up of melanocytic nevi. One of the promises of t
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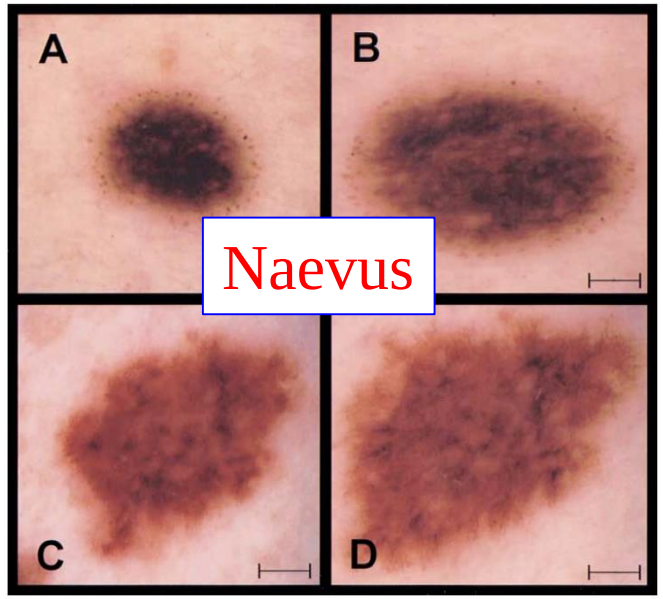
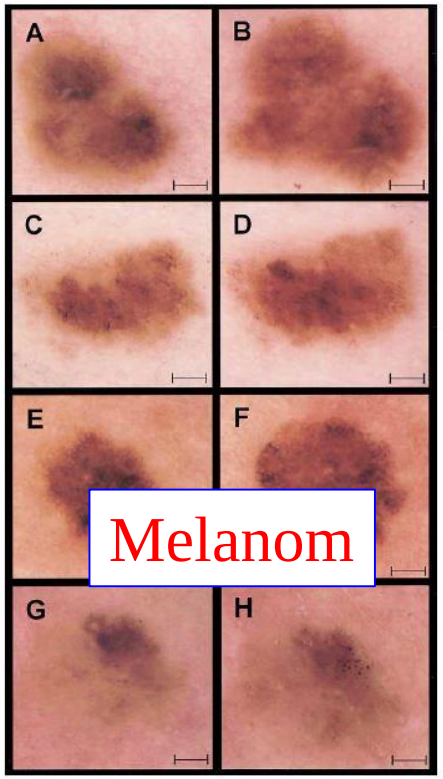
of morphologic modifications typical for early melanoma. DELM may therefore serve as a useful tool to improve the surveillance of patients with multiple atypical nevi. (J Am Acad Dermatol 2000;43:467-76.)



Naevus

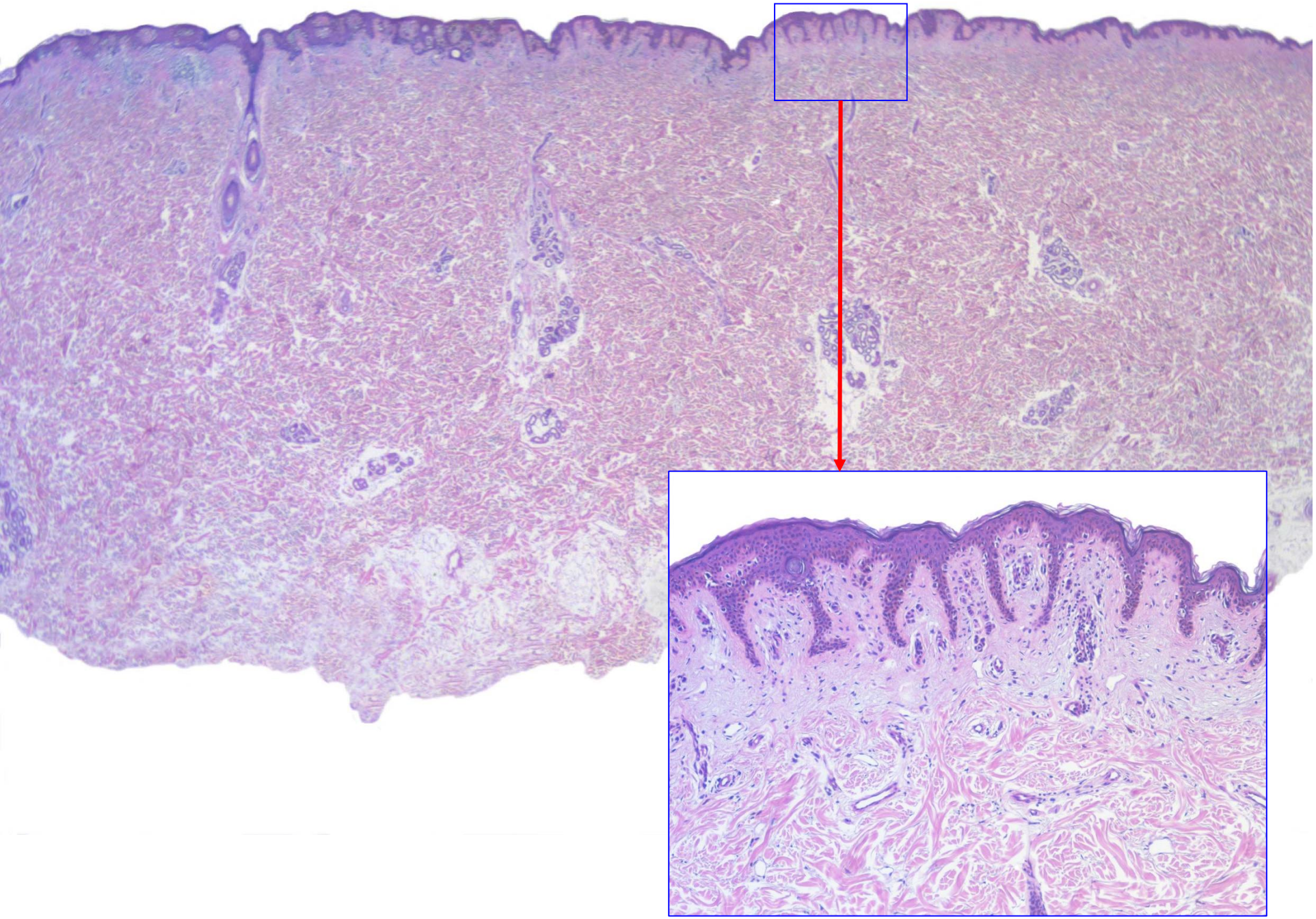
Fig 1. DELM images of two benign melanocytic skin lesions. **A** and **B,** Common nevus with symmetric enlargement without substantial structural modifications. *Right image* **(B)** was obtained 6 months after *left image*. Peripheral rim of brown globules **(A)** is a highly characteristic feature of symmetrically enlarging common nevi. **C** and **D,** Atypical nevus with symmetric enlargement. Substantial structural modifications are not observed. This lesion can also be identified on the photographic overview of the patient shown in Fig 5 *(white arrow)*. All magnifications are identical. *Bar* = 1 mm.



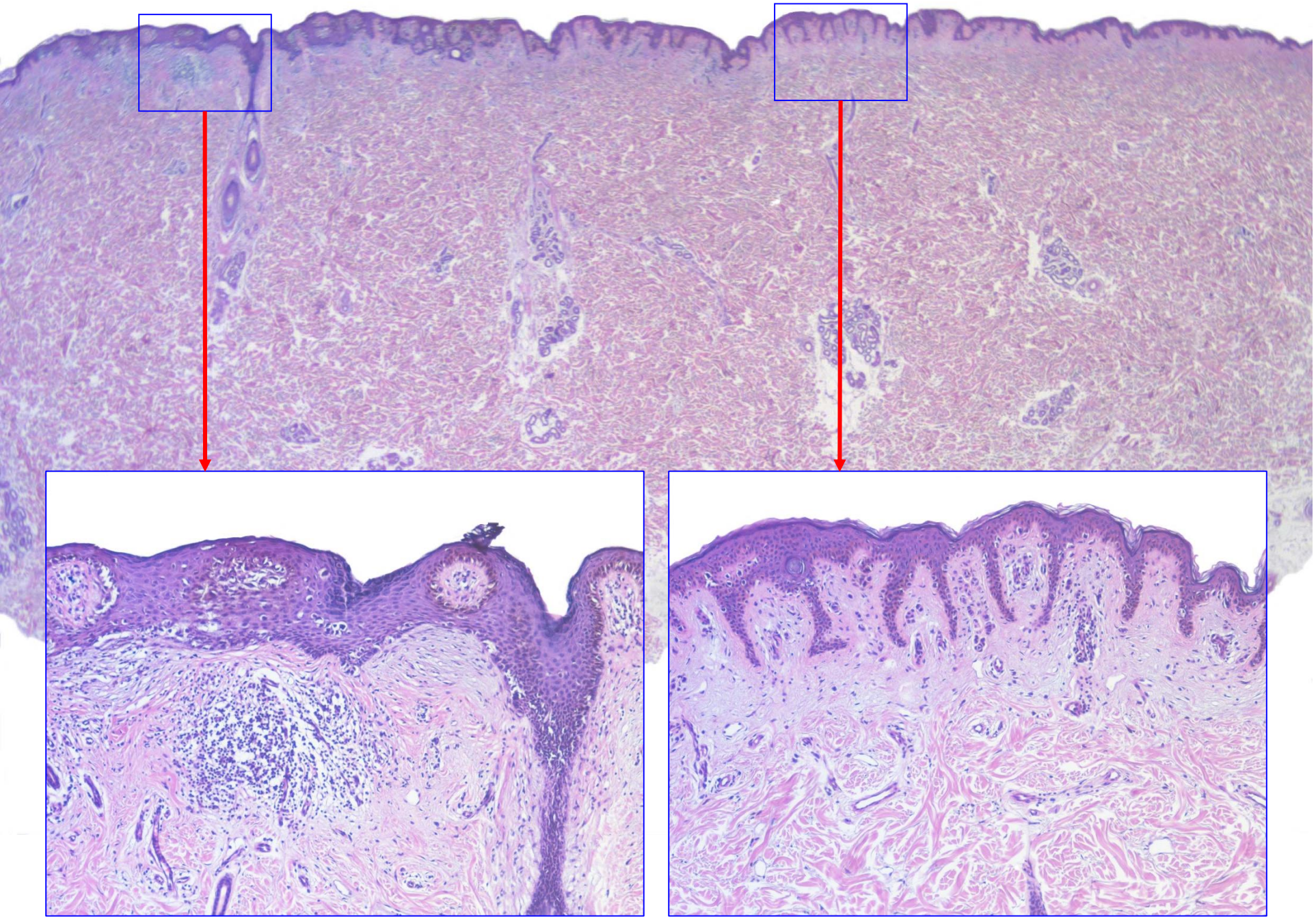
Melanom

Fig 4. Four early melanomas with substantial morphologic modifications over time identified by follow-up with DELM. **A** and **B,** Superficial spreading melanoma (Breslow thickness, 0.55 mm; Clark level, II). **B,** This image was obtained 14 months after image shown in **A**. Melanoma shows focal enlargement associated with a change in shape. **C** and **D,** Superficial spreading melanoma in situ. **D,** This image was obtained 7 months after image shown in **C**. This melanoma shows multifocal nonsymmetric enlargement and a change in the prominent and irregular pigment network (it appeared in areas where it had not been present previously or regressed where previously present). **E** and **F,** Superficial spreading melanoma (Breslow thickness, 0.3 mm; Clark level, II). This melanoma also shows multifocal nonsymmetric enlargement associated with a change in shape as well as the appearance of a highly irregular and prominent pigment network. **F,** This image was obtained 11 months after image shown in **E**. **G** and **H,** Superficial spreading melanoma in situ. **H,** This image was obtained 7 months after image shown in **G**. This melanoma did not enlarge but showed focal appearance of black dots in irregular distribution with varying size. All magnifications are identical. *Bar* = 1 mm.

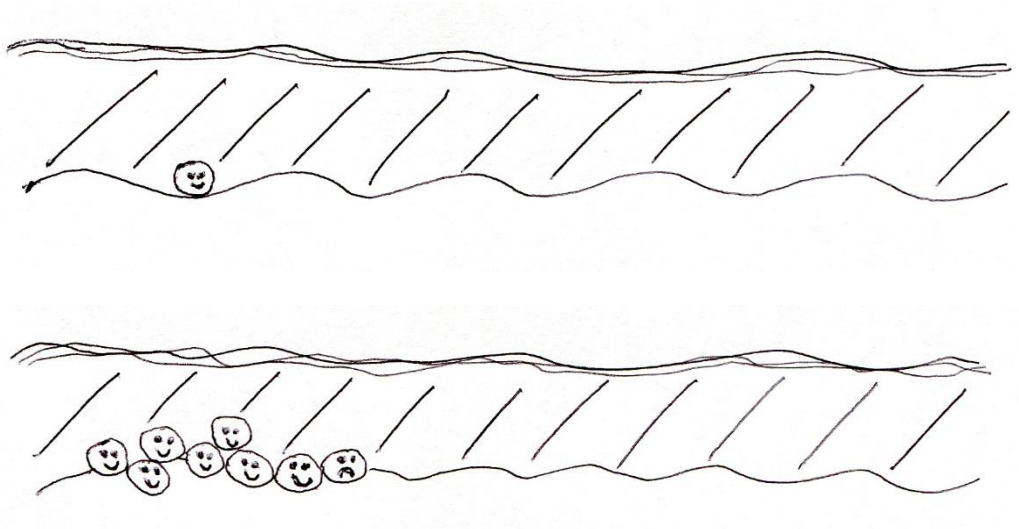
Ein gutartiger melanozytärer Tumor ohne Potential zu töten, also ein Naevus, zeigt von vornherein ein anderes Wachstumsverhalten. Das haben schon vor Jahren dermatoskopische Verlaufsstudien gezeigt. Morphologisch ist er viel gleichmäßiger aufgebaut und dadurch in der Regel erkennbar.

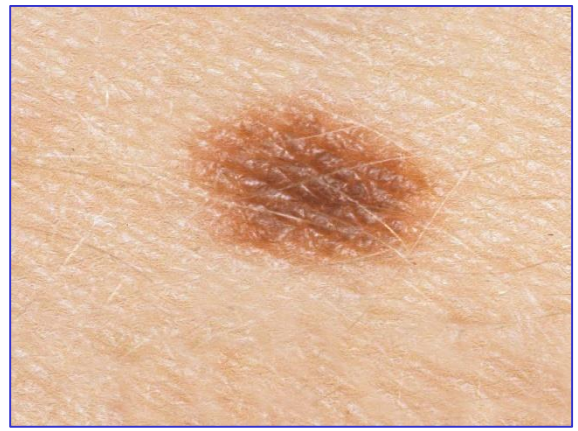


Auf einem solchen Naevus kann sich ein Melanom entwickeln.

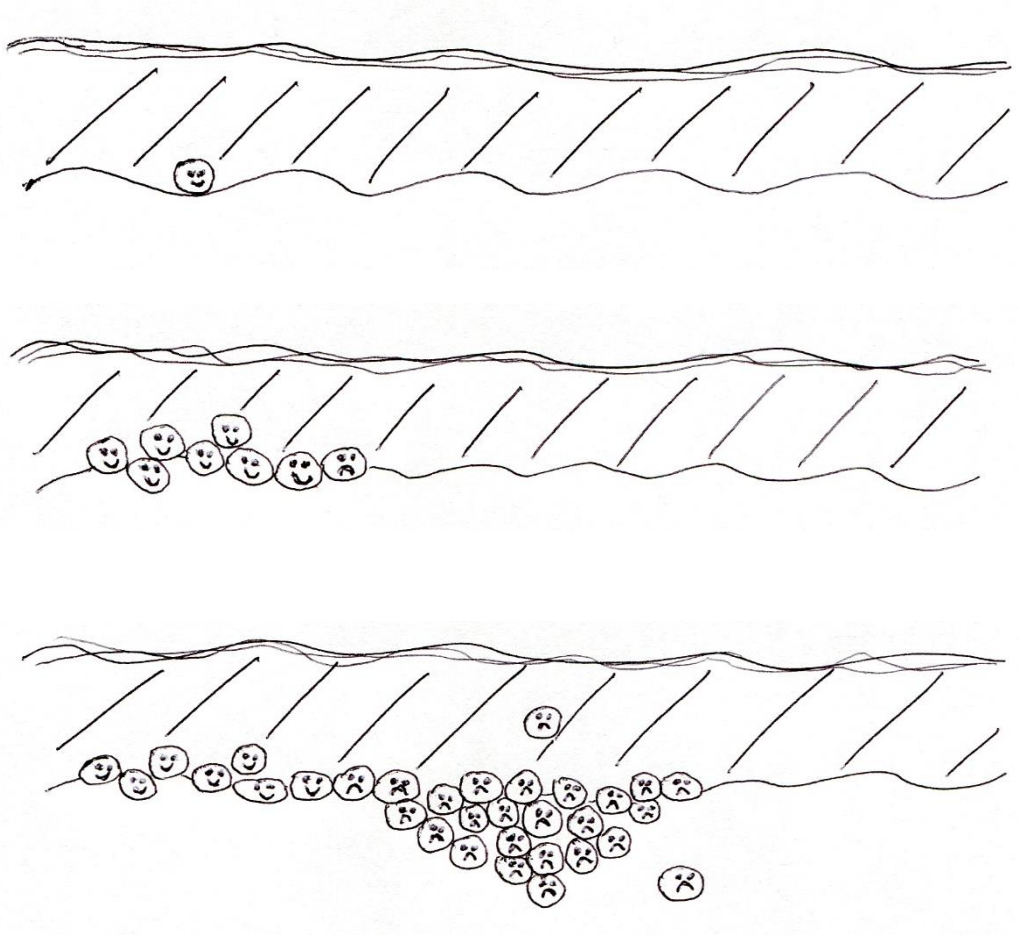


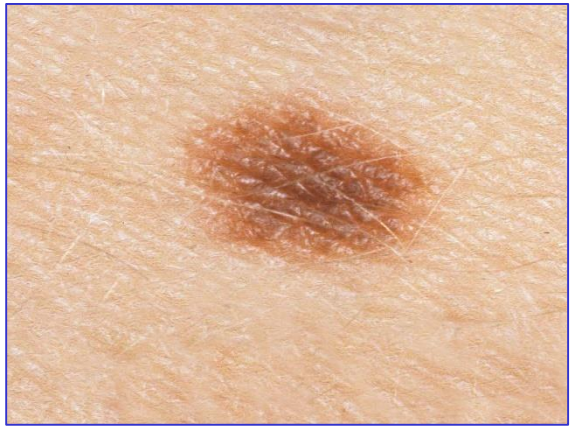
Dann gibt es eine andere Zellpopulation, die auch ein anderes Wachstumsmuster zeigt. Nicht immer sind in solchen Fällen die Zellpopulationen leicht voneinander abzugrenzen, aber es handelt sich immer um ein klonales Geschehen.

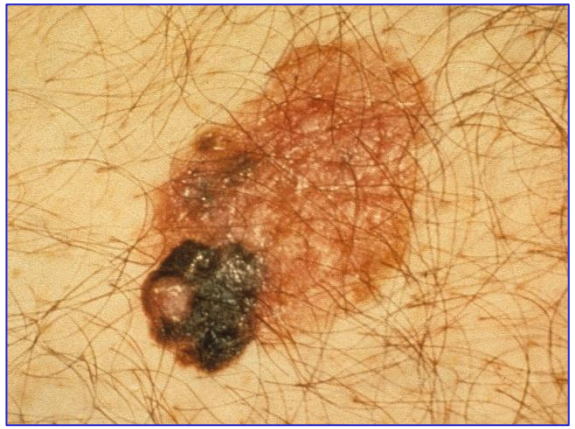




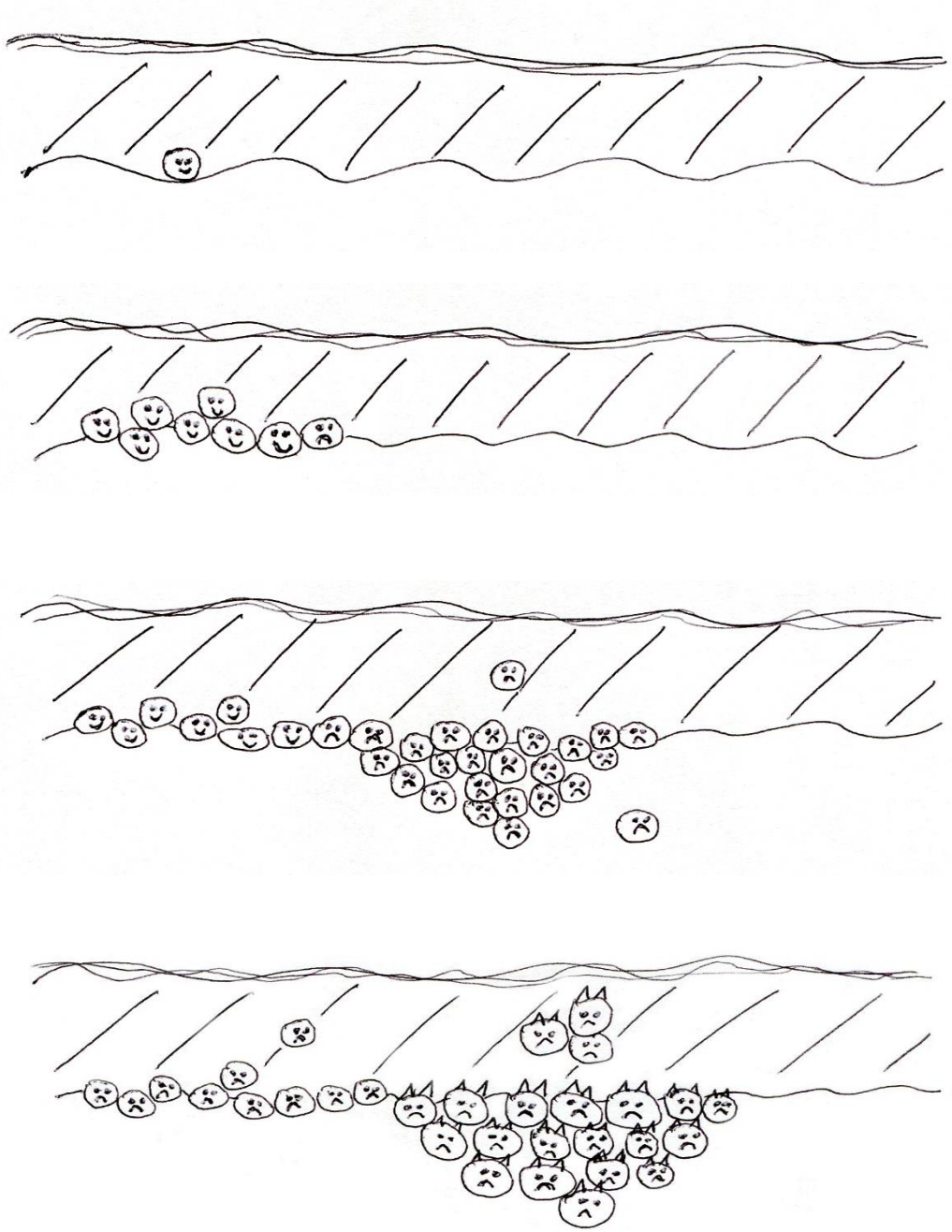
Eine gutartige Zelle innerhalb eines Naevus wird böse

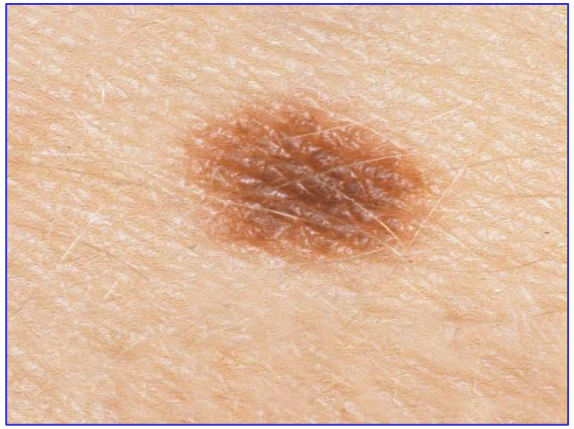


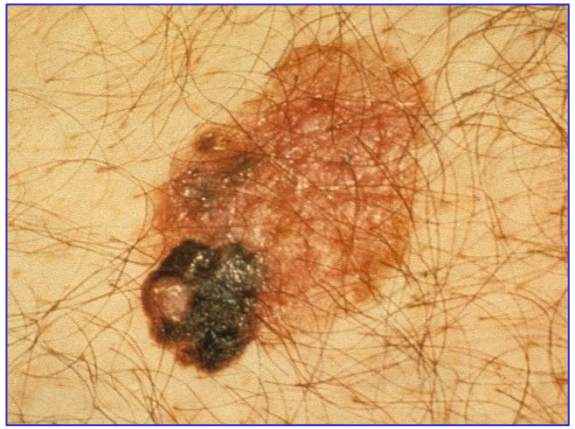


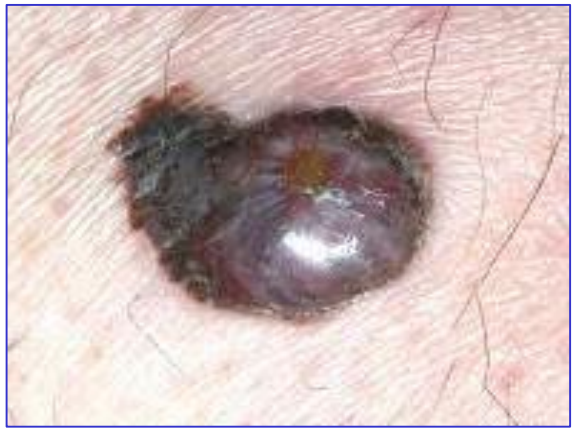


und beginnt zu proliferieren, ein Melanom entsteht auf dem Naevus. So etwas gibt es.

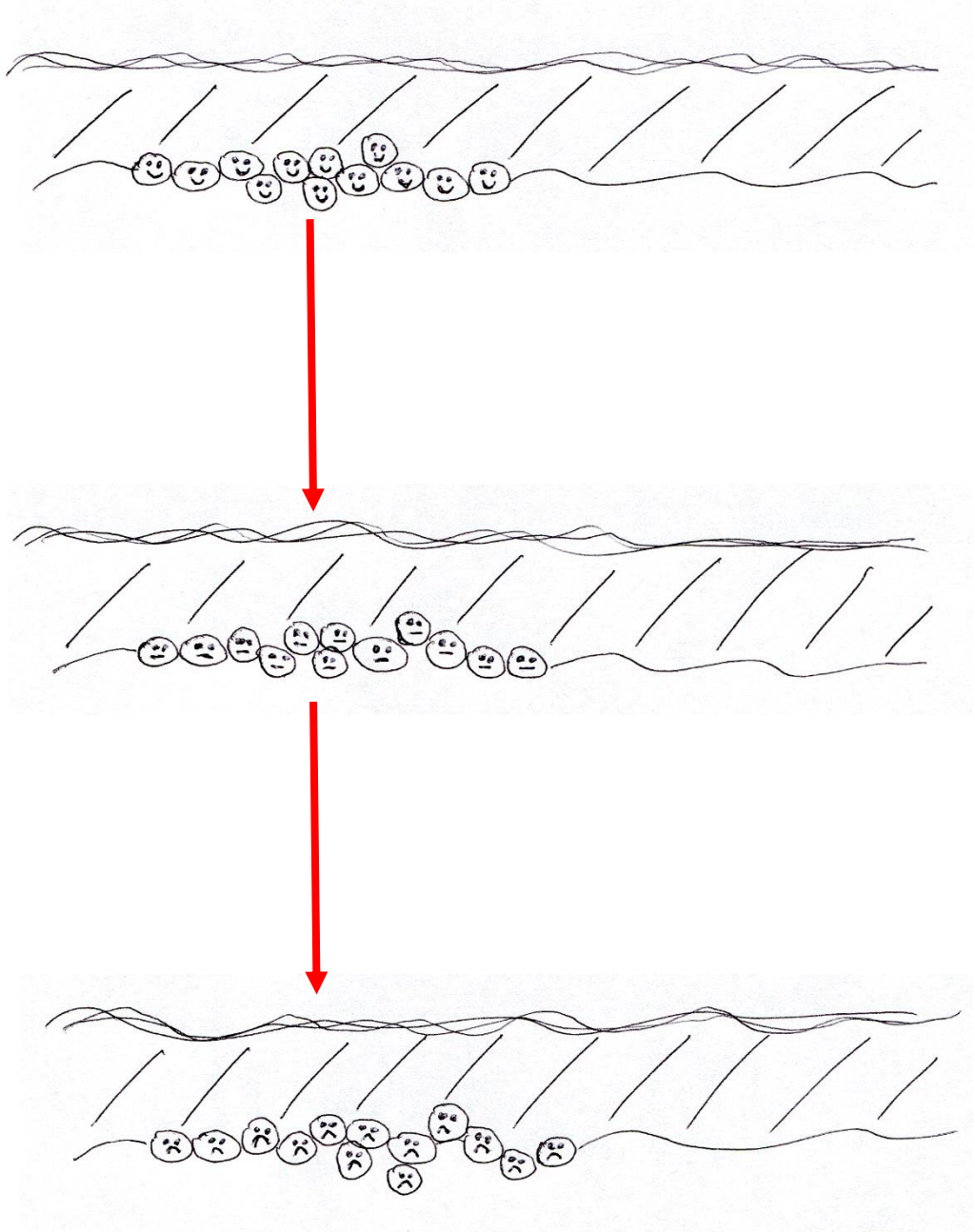


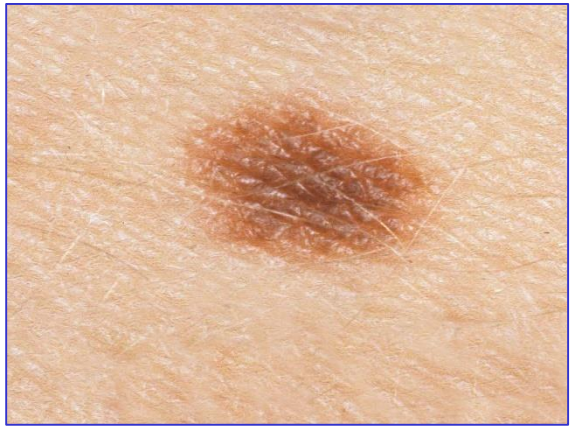


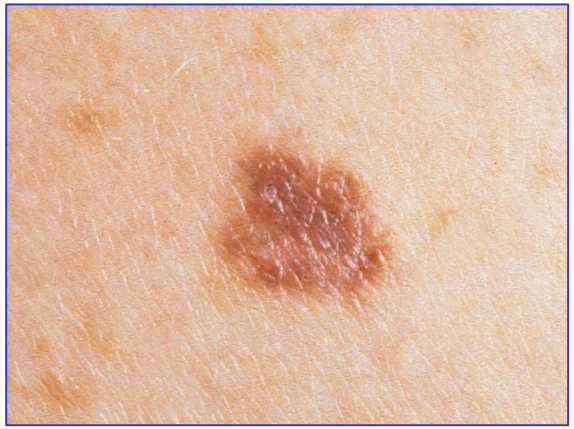


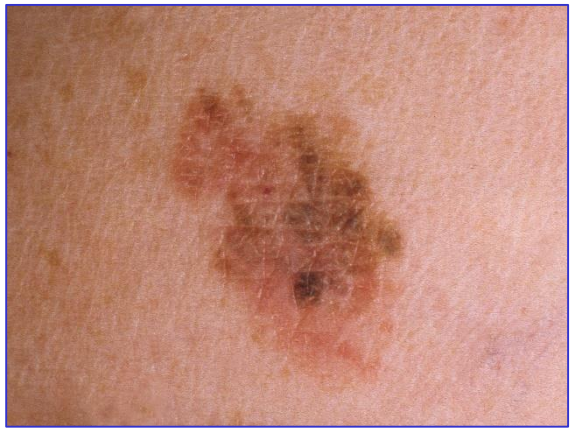


Und selbstverständlich können innerhalb eines Melanoms neue Zellklone entstehen, so dass die bösartigen Zellen geradezu teuflisch werden. In fortgeschrittenen Stadien ist das die Regel.

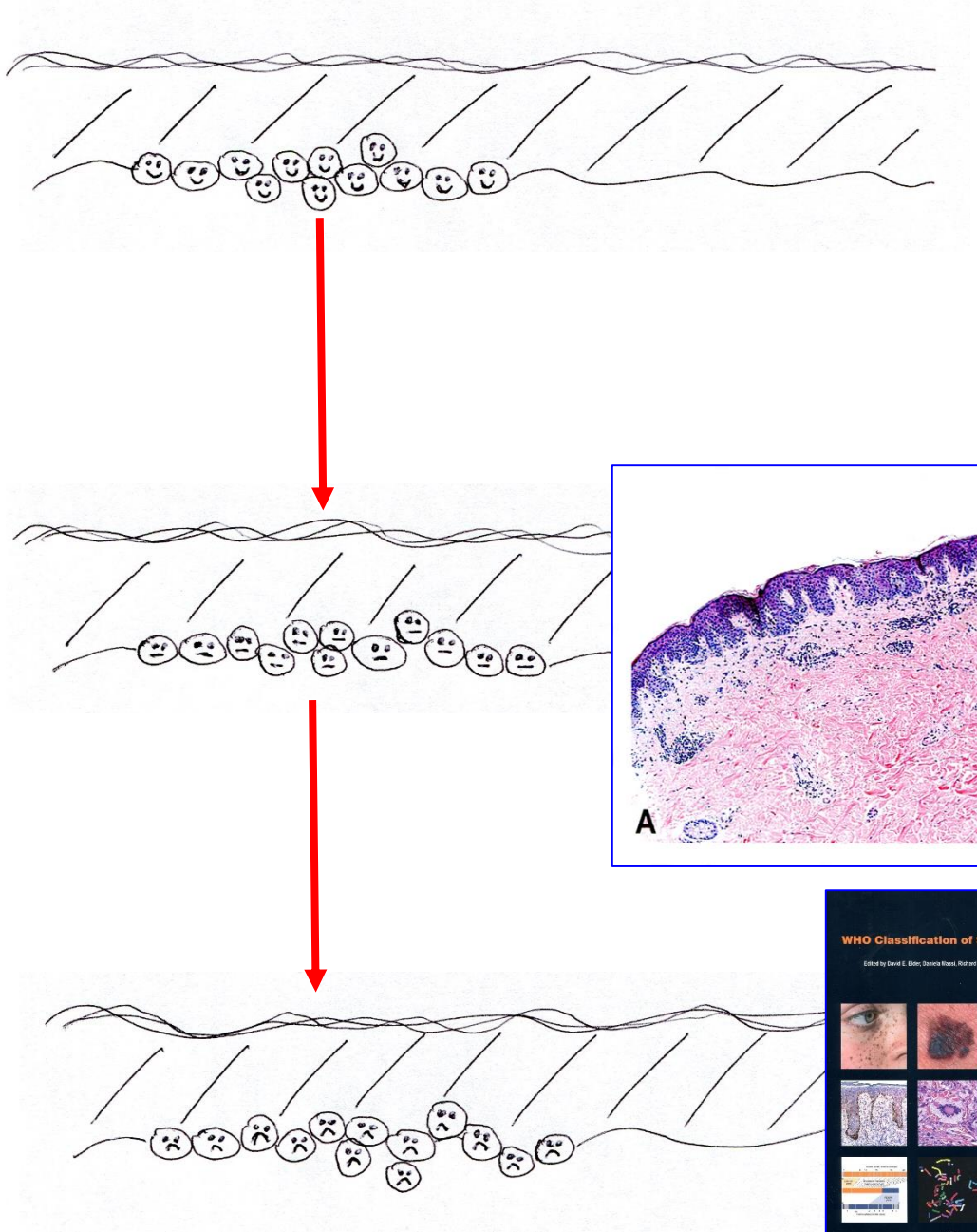


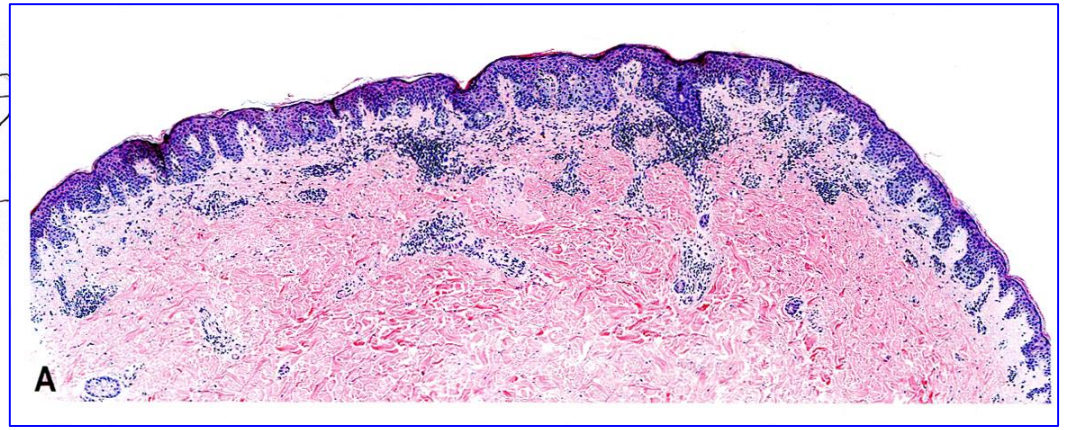






Was es nicht gibt, ist eine allmähliche Umwandlung der gesamten Läsion dergestalt, dass die Zellen erst gut gelaunt, dann leicht verstimmt und schließlich ganz böse sind. Das ist pure Fiktion,



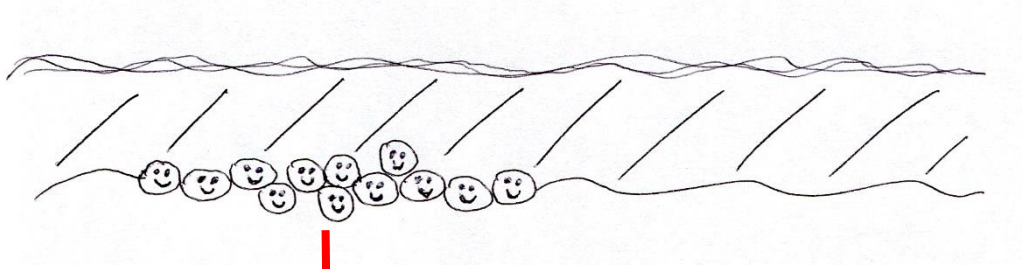


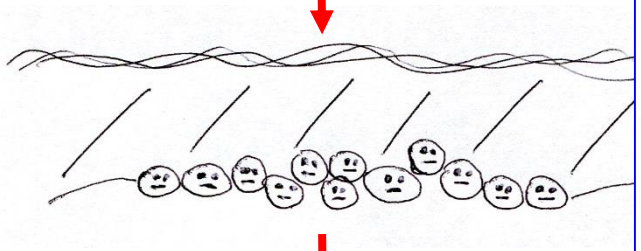
WHO:

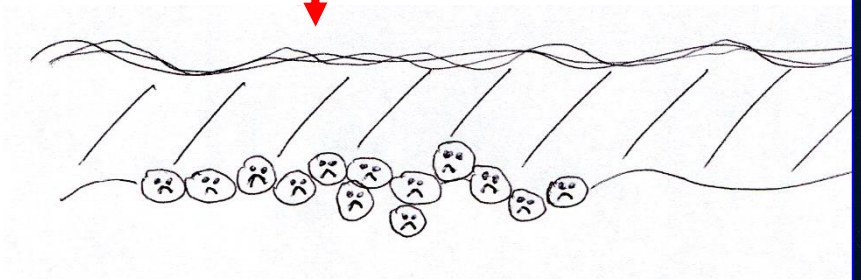
Intermediate lesion

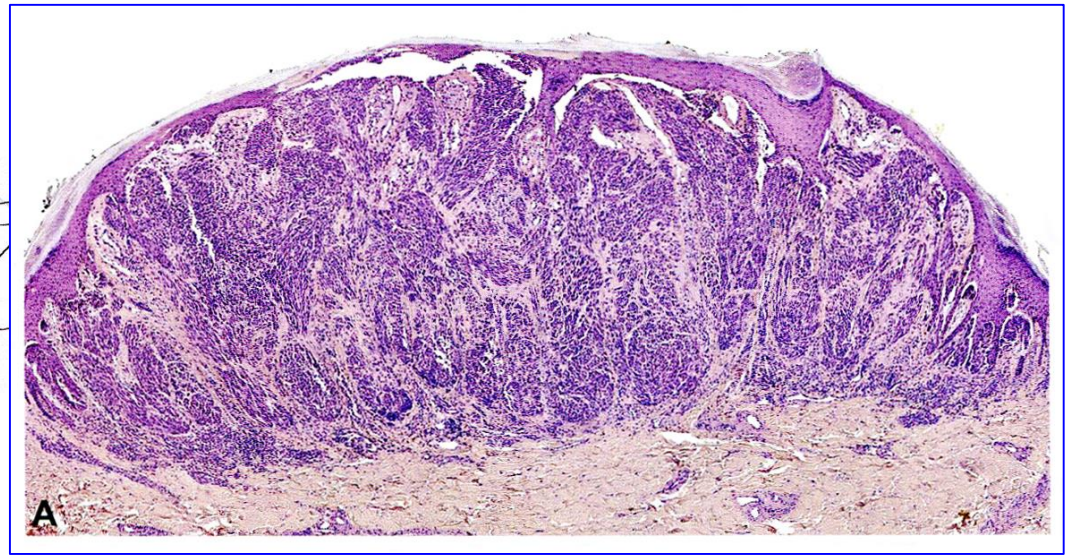
„Compound dysplastic nevus, high grade.“

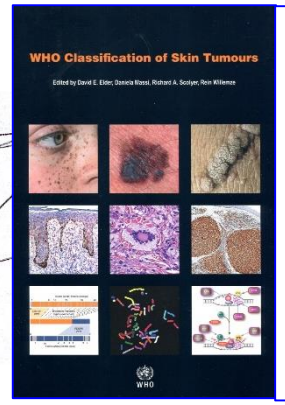
aber genau diese Fiktion wird in der WHO-Klassifikation vermittelt. Dies hier soll ein „Compound dysplastic nevus, high grade“ sein, definitionsgemäß eine „intermediate lesion“. In Wirklichkeit ist es ein völlig harmloser Clark-Naevus, ganz gleichmäßig aufgebaut, mit denselben Zellen und demselben Pattern von rechts bis links, da gibt es keinen Hinweis auf eine neue, aggressivere Zellpopulation.











WHO:

Intermediate lesion

„Atypical Spitz tumour.“

Dasselbe gilt für diese Läsion, einen „atypical Spitz nevus“. Das Wachstumsmuster und die Zellpopulation sind einheitlich. Natürlich sind solche Läsionen oft schwer zu interpretieren, aber eine Läsion, von der man nicht weiß, was sie ist, ist keine „intermediate lesion“, sondern eine Läsion, von der man nicht weiß, was sie ist.

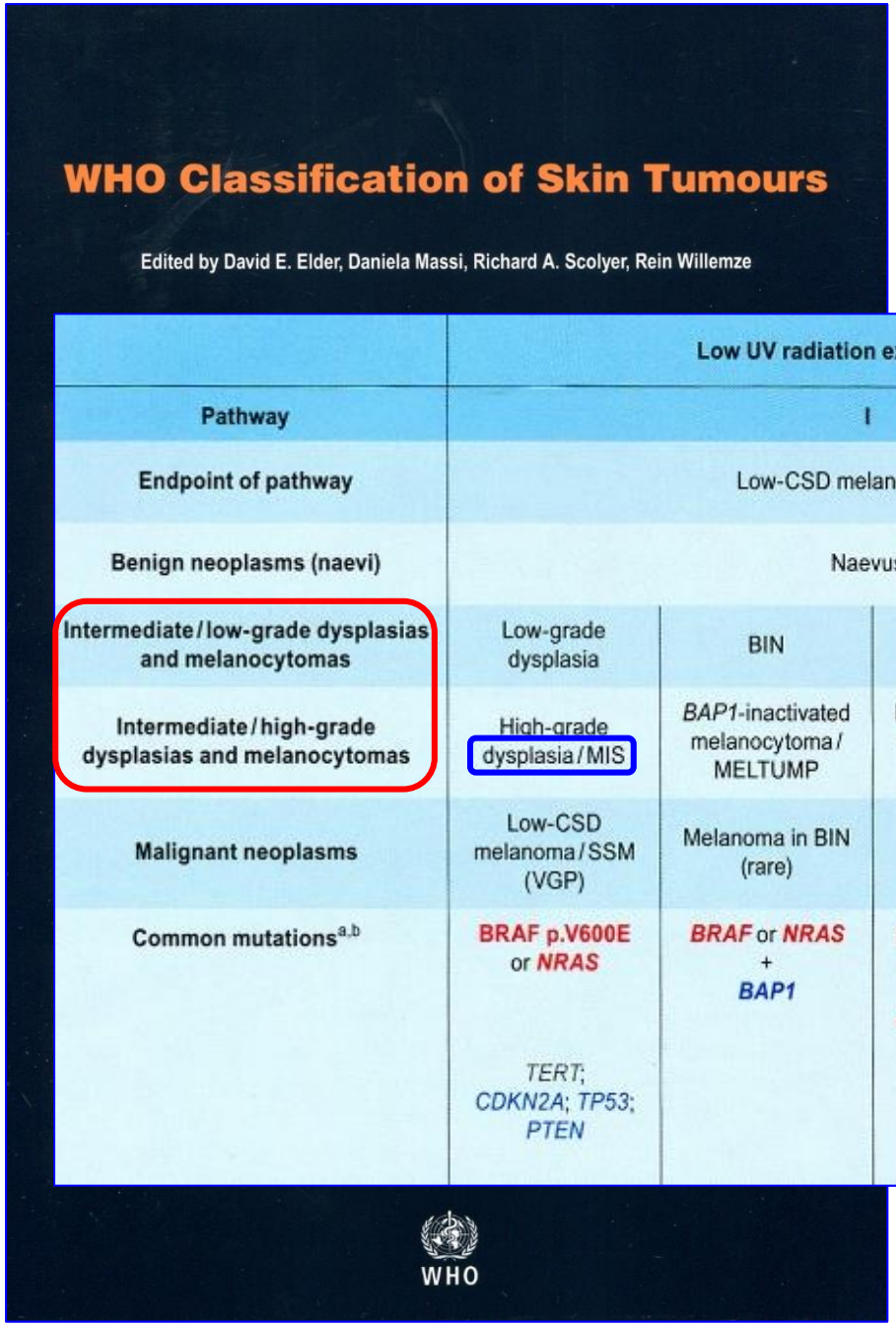
WHO Classification of Skin Tumours

Edited by David E. Elder, Daniela Massi, Richard A. Scolyer, Rein Willemze

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

WHO

Um dies nicht zugeben zu müssen, wurde die diagnostische Unschärfe in eine biologische Unschärfe umgedeutet, als wüssten die Tumore selbst nicht so recht, was sie sind. Das ist natürlich sehr bequem, denn wenn man keine Diagnose stellt, kann man keinen Fehler machen. Deshalb ist das Konzept der „intermediate lesion“ so beliebt. Aber es ist falsch, es ist retrogressiv, und es ist schädlich! Es ist falsch, weil es eine synchrone Umwandlung der Tumorzellen einer Neoplasie nicht gibt. Es ist retrogressiv, weil es dazu beiträgt, Jahrzehnte des Fortschritts in der histopathologischen Beurteilung melanozytärer Neoplasien zunichte zu machen.



	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
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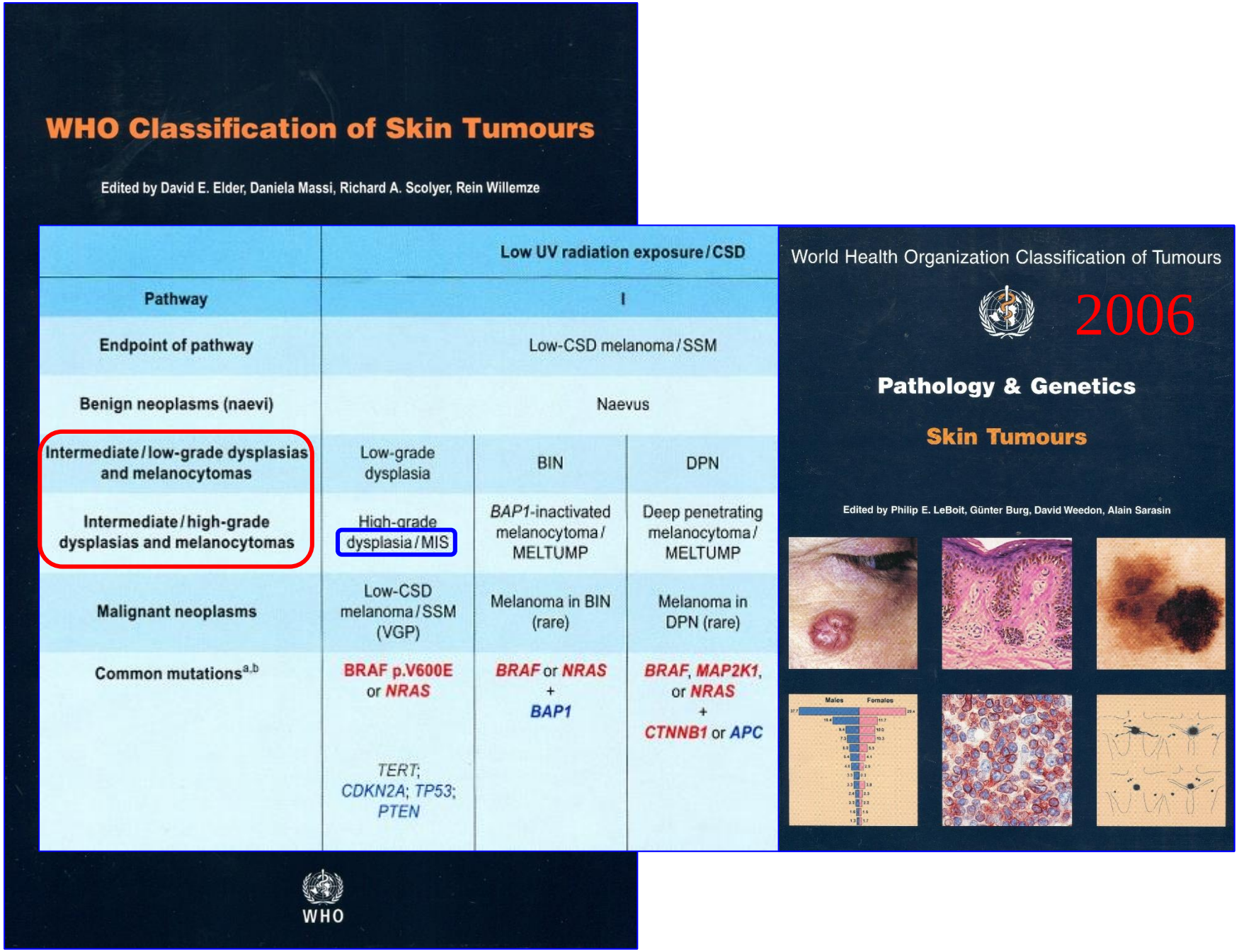
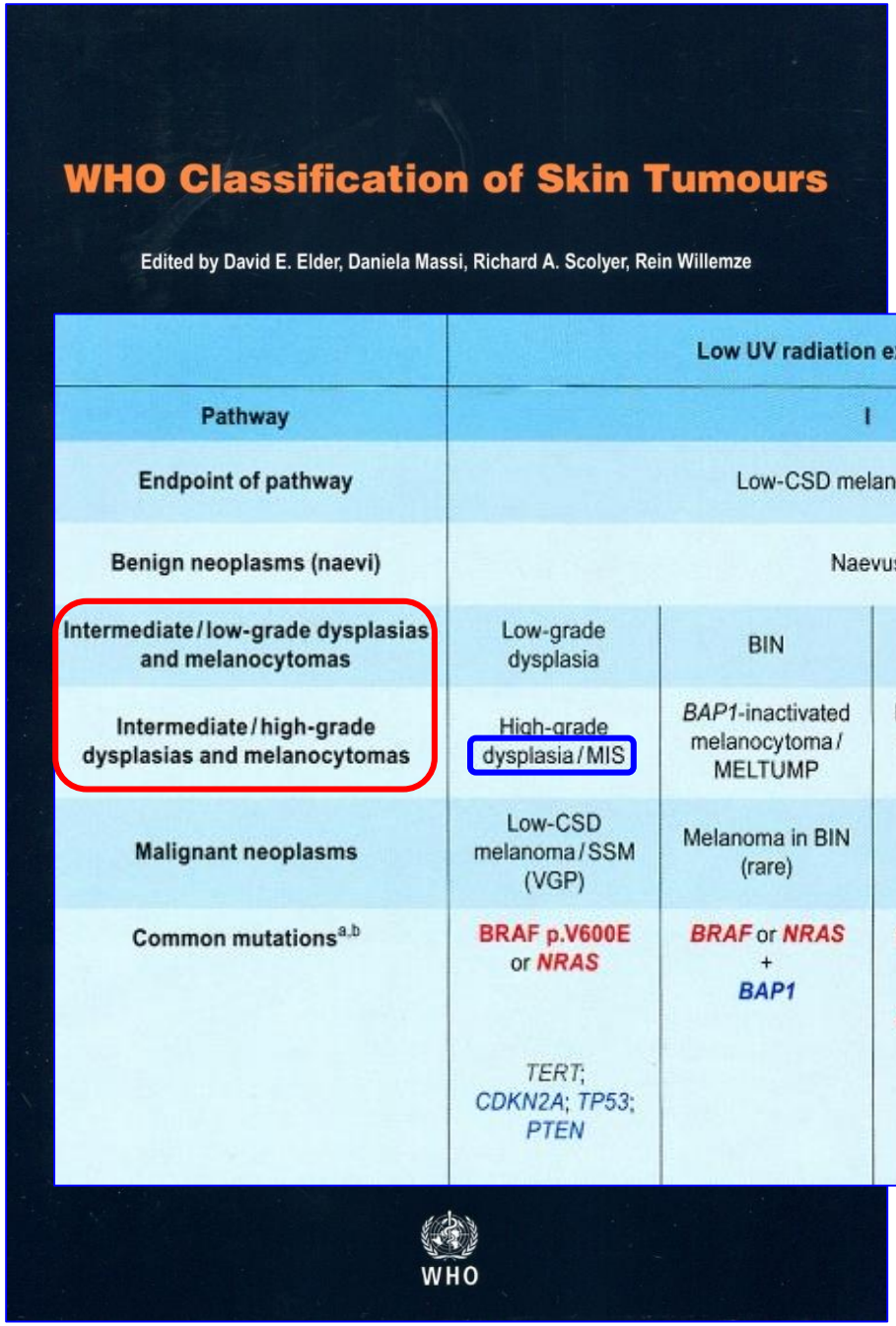
Gutartige und bösartige Tumore werden in einen Topf geworfen, die Begriffe „Dysplasie“ und „Melanoma in situ“ werden synonym verwendet,



und Kriterien zur Unterscheidung zwischen Melanomen und melanozytären Naevi, die in der alten Version der WHO-Klassifikation von 2006 ausführlich diskutiert werden,



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	Low UV radiation exposure/CSD		
Pathway	I		
Endpoint of pathway	Low-CSD melanoma/SSM		
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Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/ MELTUMP	Deep penetrating melanocytoma/ MELTUMP
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WHO

Differential diagnosis

The differential diagnosis of the pagetoid form of low-CSD melanoma/SSM in situ includes Paget disease, carcinoma in situ, spitzoid neoplasms, and other tumours that may display a pagetoid intraepidermal growth pattern. On immunohistochemical evaluation, the tumour cells in melanoma in situ stain positively for the melanocytic markers SOX10 and MITF. Staining for other melanocytic markers also highlights the intraepidermal tumour in melanoma, but may highlight other intraepidermal structures as well, including pigment in keratinocytes (e.g. HMB45 antigen and melan-A) and Langerhans cells (e.g. S100 protein). The dermal component in low-CSD melanoma is composed of cytologically atypical melanocytes that are usually mitotically active and display minimal reduction in nuclear size or amount of cytoplasm, with increased dermal depth; this is distinct from the maturation seen in the dermal component of naevi. Mitoses are rarely observed in benign naevi. The few rare types of benign naevi that display mitoses are not associated with an overlying/adjacent RGP.

finden in der neuen Version von 2018 praktisch keine Erwähnung. Da geht es in der Differenzialdiagnose von „low CSD“-Melanomen um den Morbus Paget und andere Tumore mit pagetoidem intraepidermalen Wachstumsmuster, nicht aber um Naevi, die ja angeblich keine Differenzialdiagnose, sondern Stadien desselben Entwicklungsprozesses sind.

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	Low UV radiation exposure / CSD		
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Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)
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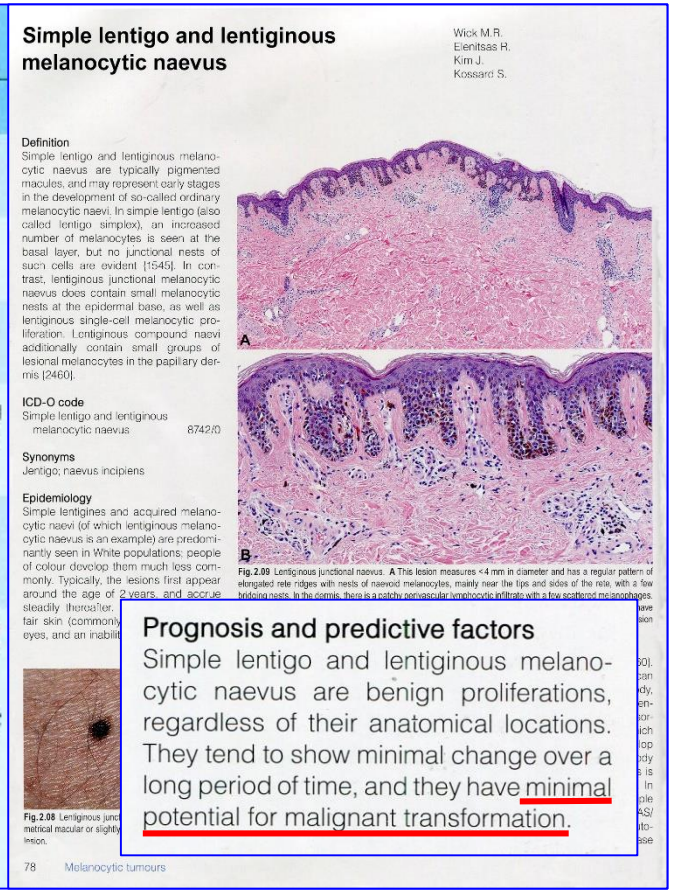
WHO



Simple lentigo and lentiginous melanocytic naevus

Wick M.R.
Elenitsas R.
Kim J.
Kossard S.

Definition
Simple lentigo and lentiginous melanocytic naevus are typically pigmented macules, and may represent early stages in the development of so-called ordinary melanocytic naevi. In simple lentigo (also called lentigo simplex), an increased number of melanocytes is seen at the basal layer, but no junctional nests of such cells are evident [1545]. In contrast, lentiginous junctional melanocytic naevus does contain small melanocytic nests at the epidermal base, as well as lentiginous single-cell melanocytic proliferation. Lentiginous compound naevi additionally contain small groups of lesional melanocytes in the papillary dermis [2460].

ICD-O code
Simple lentigo and lentiginous melanocytic naevus 8742/0

Synonyms
Jentigo; naevus incipiens

Epidemiology
Simple lentigines and acquired melanocytic naevi (of which lentiginous melanocytic naevus is an example) are predominantly seen in White populations; people of colour develop them much less commonly. Typically, the lesions first appear around the age of 2 years, and accrue steadily thereafter.
fair skin (commonly
eyes, and an inability

Fig. 2.09 Lentiginous junctional naevus. **A** This lesion measures <4 mm in diameter and has a regular pattern of elongated rete ridges with nests of naevoid melanocytes, mainly near the tips and sides of the rete, with a few bridging nests. In the cornis, there is a patchy perivascular lymphocytic infiltrate with a few scattered melanophages.

Fig. 2.08 Lentiginous junc
metrical macular or slightly
lesion.

Prognosis and predictive factors
Simple lentigo and lentiginous melanocytic naevus are benign proliferations, regardless of their anatomical locations. They tend to show minimal change over a long period of time, and they have minimal potential for malignant transformation.

78 Melanocytic tumours

Und das ist im höchsten Grade schädlich, denn dadurch wird jede melanozytäre Läsion zur Risikoläsion erklärt. Selbst von der simplen Lentigo heißt es, sie habe ein „minimales Potential zur malignen Transformation“.

WHO Classification of Skin Tumours

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Pathway			
Endpoint of pathway			
Benign neoplasms (naevi)			
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia		
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP
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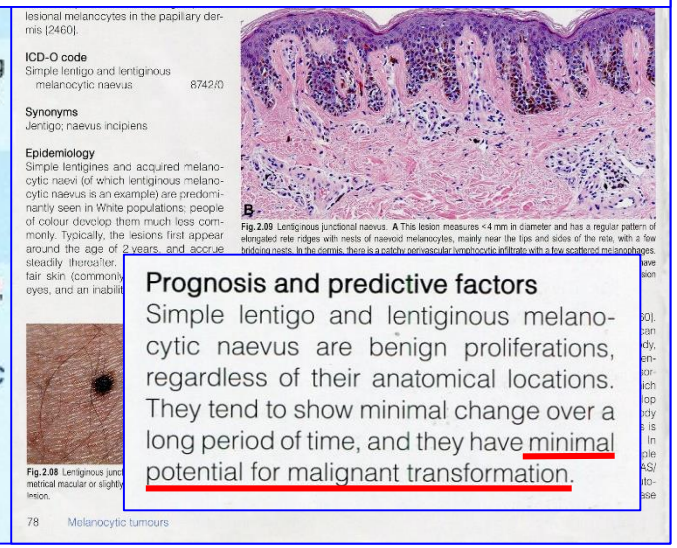
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***

WHO

If DN margins are positive, do you typically re-excise?

	2001 (%)	2015 (%)	
Yes	67	98	Severe
Observe	28	67	Moderate
		12	Mild
		2	Do not re-excise

Winkelmann RR et al., JAAD 2015; 73: 1056



lesional melanocytes in the papillary dermis [2460].

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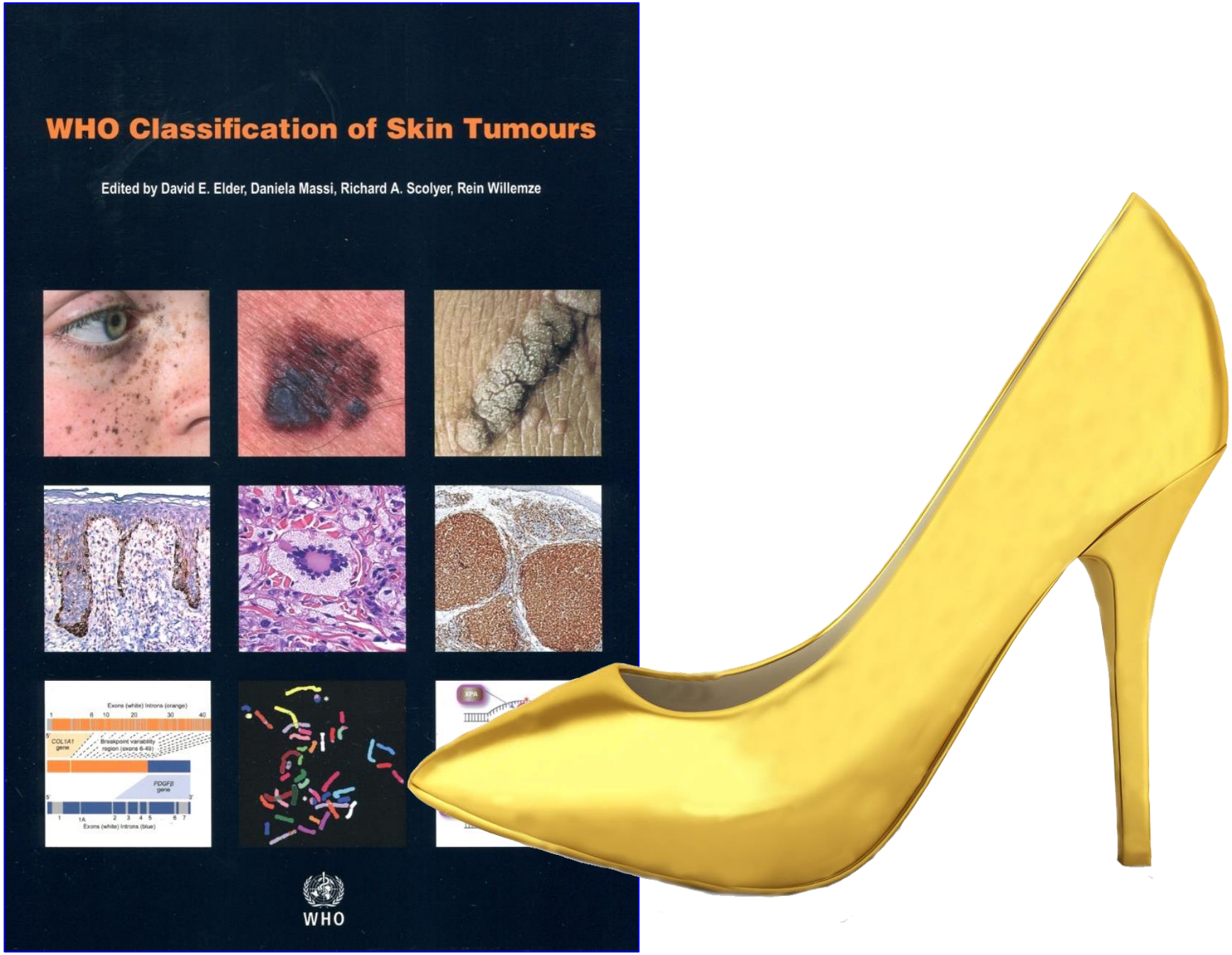
Fig. 2.08 Lentiginous junc... metrical macular or slightly ... lesion.

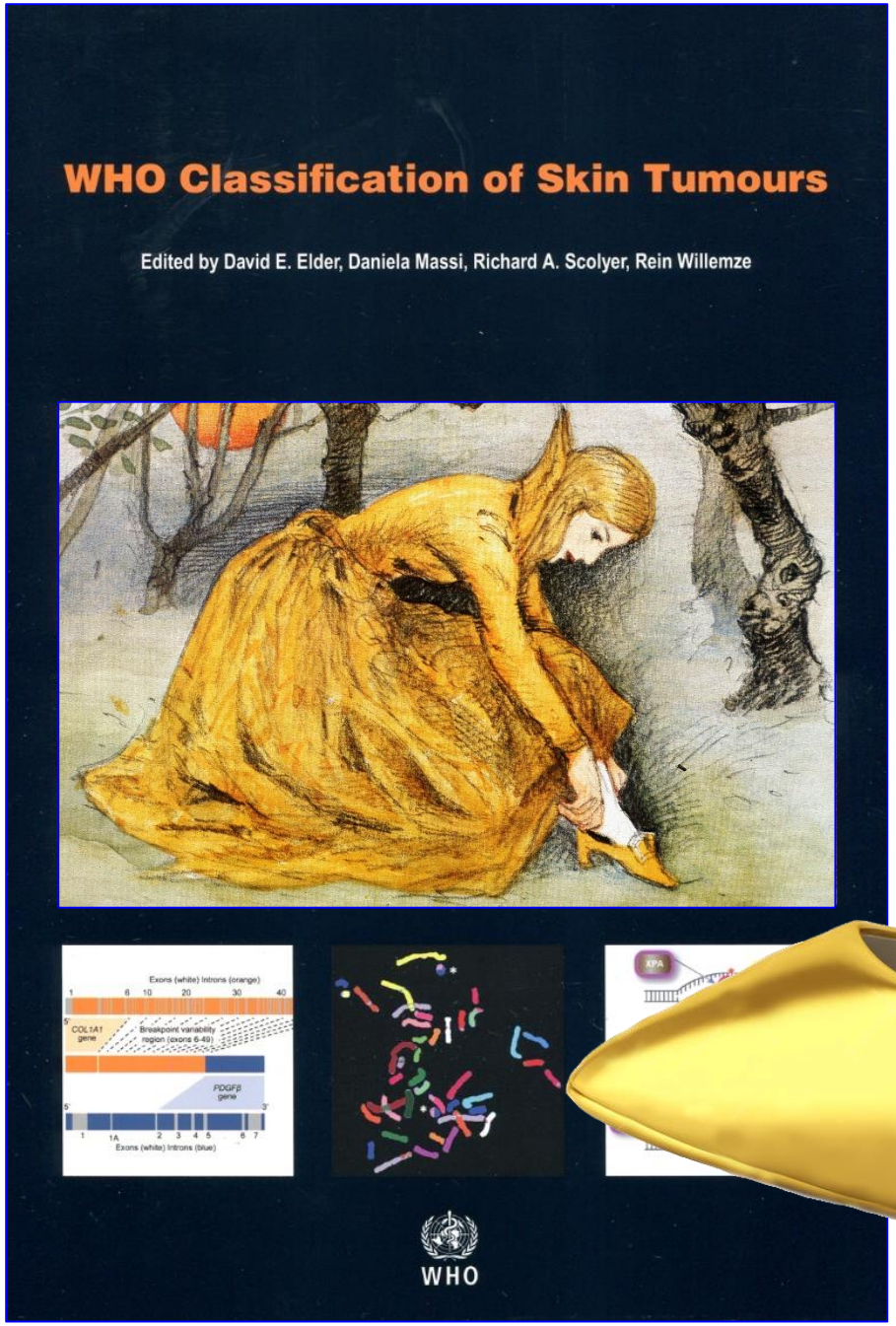
Prognosis and predictive factors
Simple lentigo and lentiginous melanocytic naevus are benign proliferations, regardless of their anatomical locations. They tend to show minimal change over a long period of time, and they have minimal potential for malignant transformation.

78 Melanocytic tumours

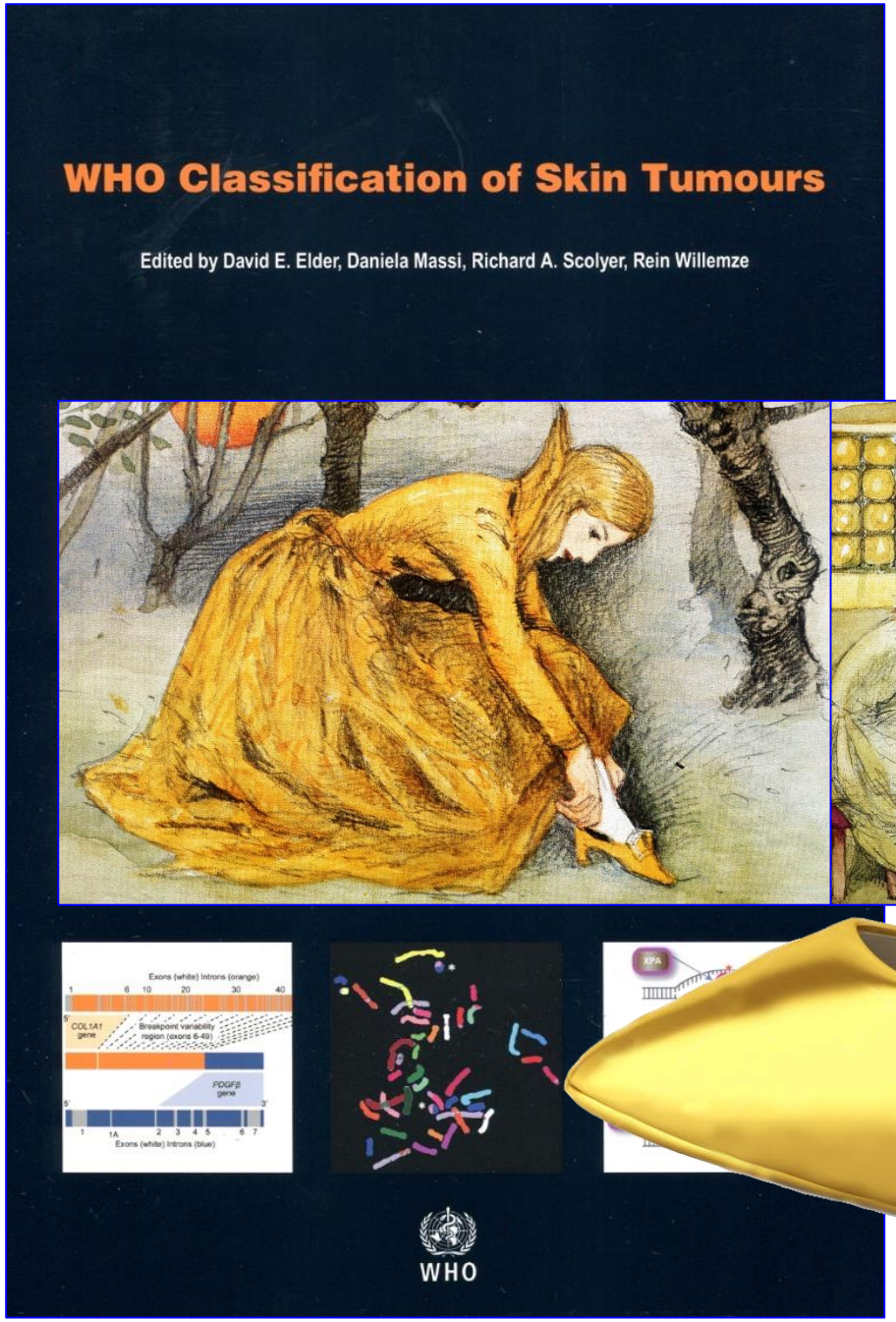
Die praktische Konsequenz dieser konzeptionellen Verirrung ist eine Verunsicherung von Patienten und Ärzten, die sich in unzähligen unnötigen Exzisionen und Nachexzisionen niederschlägt, wie dies aus vergleichenden Untersuchungen hervorgeht: schon 2015 war das Vorgehen bei sogenannten „dysplastischen Naevi“ in den USA viel aggressiver als noch 2001.



Die neue WHO-Klassifikation mit ihren beeindruckenden molekularen Aspekten ist wie ein schicker goldener Schuh.



Der Fuß, der hineinschlüpfen soll, besteht in klinischen und histopathologischen Erfahrungswerten, die etwas größer sind als der Schuh.



In der WHO-Klassifikation werden sie auf Schuhgröße zurechtgestutzt. Das ist im Märchen nicht gut für die Stiefschwestern von Aschenputtel, und in der Mezidin nicht gut für die Patienten.