Staging of Melanoma – the AJCC Classification in Historical Perspective

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Staging of Melanoma – The AJCC Classification in Historical Perspective

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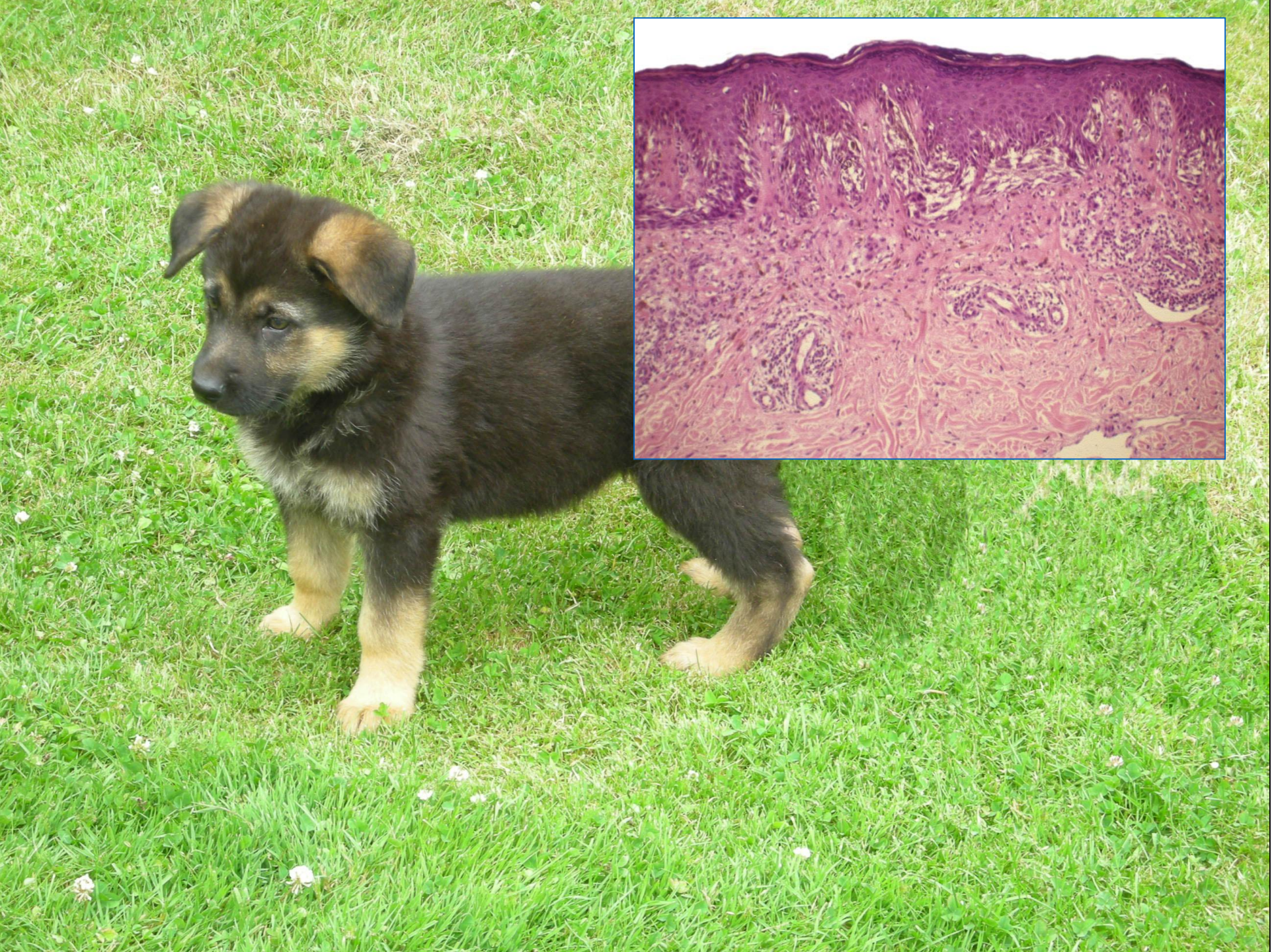
Since many years, melanomas are classified worldwide according to criteria established by the American Joint Committee on Cancer, the AJCC. That classification, however, is not a biologic one. It does not serve to distinguish biologic entities from one another, such as sheep or dogs, nevus or melanoma, but aspires to predict the behavior of individuals of the same entity, its purpose is not diagnosis but prognosis.

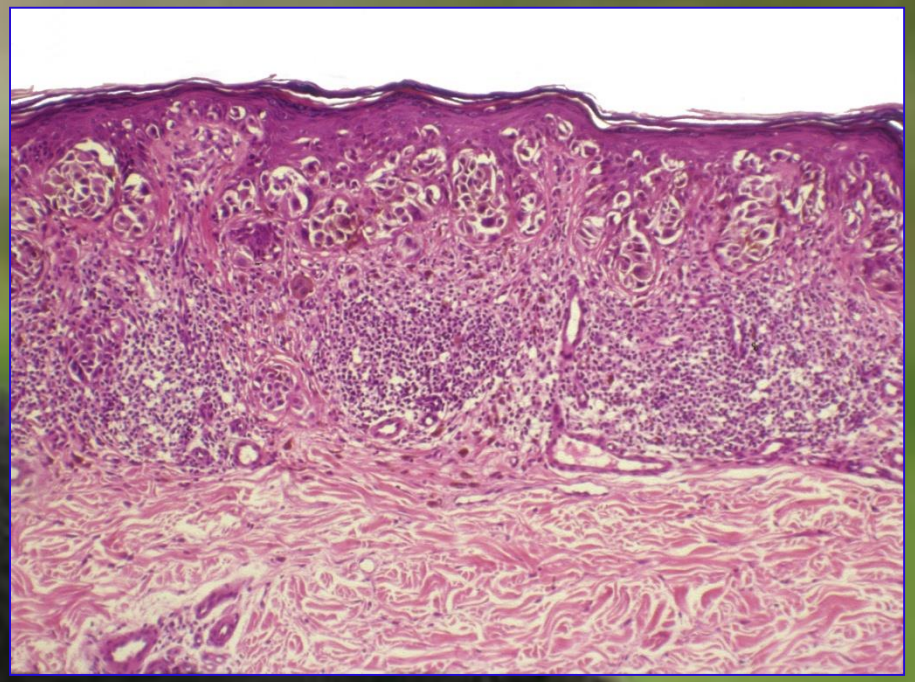
Diagnosis is usually fairly reliable, based as it is on numerous unchangeable criteria, such as shape of the head and the quality of the fur.

Prediction of the behavior of individuals of the same entity is much more difficult because not every friendly looking dog is harmless,

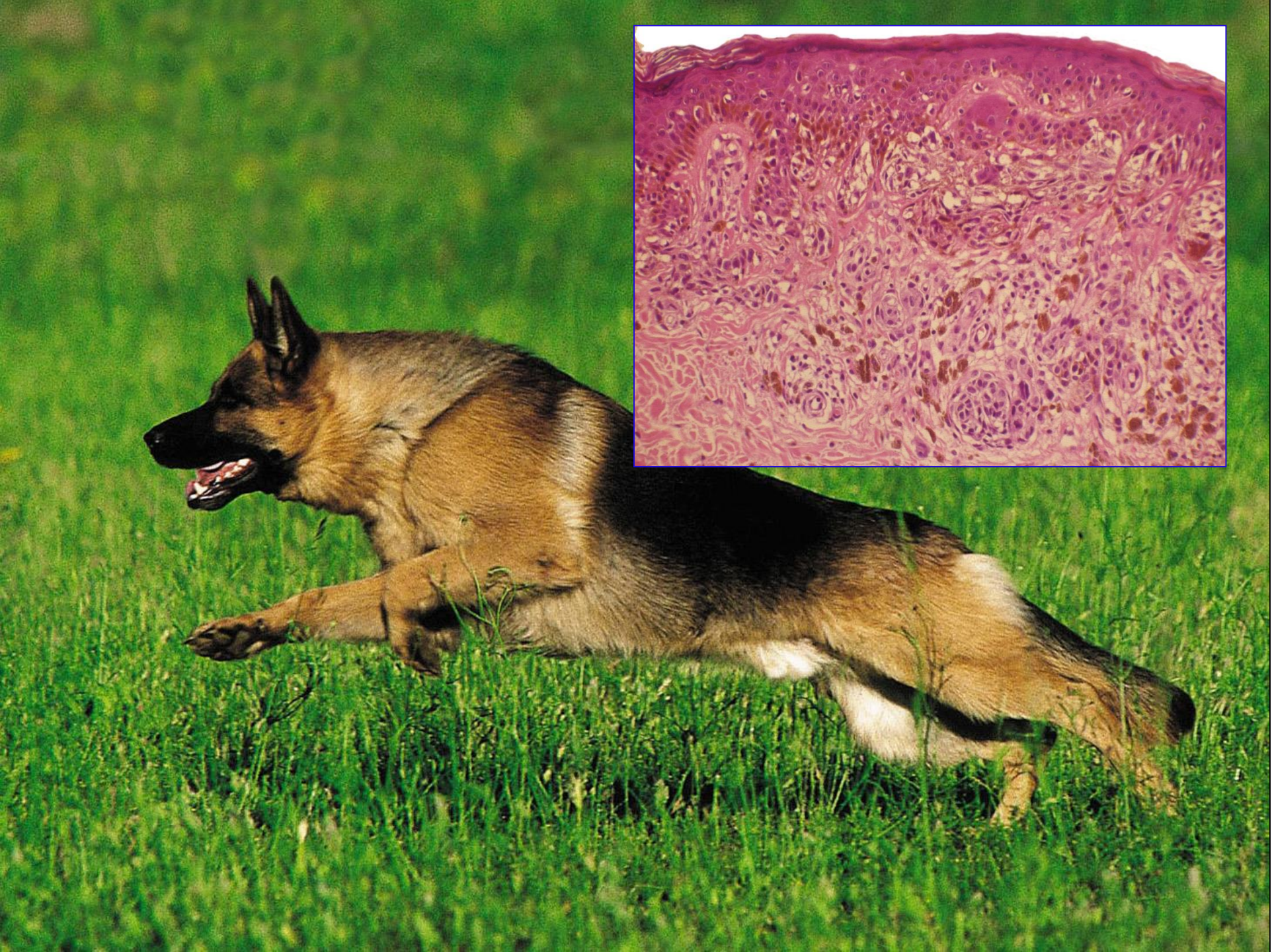
and not every dog with bared teeth is going to bite. For the appraisal of danger, there is only one reliable criterion, namely, the stage of development.



A puppy is never dangerous, and the same applies to melanoma is situ.



When dogs or melanomas have grown a bit, they are still relatively harmless,



but eventually a stage is reached in which one can never be sure and in which danger can, at best, be assessed vaguely on the basis of other, less reliable criteria.

Prognostic factors

- Ambiguity
- Changeability
- Incompleteness

The problem with those prognostic factors is their ambiguity (for example, tail-wagging is not always a sign of friendly intentions), their changeability (tail-wagging and baring of teeth may change from one second to the next), and their incompleteness (we simply do not know enough about training and possible traumatic experiences of a barking dog at the sidewalk to be able to predict behaviour).

Prognostic factors

- Ambiguity
  - Regression
- Changeability
  - Ulceration
- Incompleteness
  - Immunologic State

The same problems pertain to melanoma. For example, regression has been interpreted as a favourable sign because it indicates a strong immune response, and as an unfavourable one because the lesion may have been larger formerly than it appears currently. Any melanoma may ulcerate from one moment to the next, and an ulcer may heal in a matter of days, and many prognostic parameters, such as the immunologic state of the patient, cannot be determined. All those aspects must be considered when dealing with prognosis of a neoplasm, and also in regard to the AJCC classification of melanoma.

Final Version of 2009 AJCC Melanoma Staging and Classification

Charles M. Balch, Jeffrey E. Gershenwald, Seng-jaw Soong, John F. Thompson, Michael B. Atkins, David R. Byrd, Antonio C. Buzaid, Alistair J. Cochran, Daniel G. Coit, Shouluan Ding, Alexander M. Eggermont, Keith T. Flaherty, Phyllis A. Gimotty, John M. Kirkwood, Kelly M. McMasters, Martin C. Mihm Jr, Donald L. Morton, Merrick I. Ross, Arthur J. Sober, and Vernon K. Sondak

ABSTRACT

Purpose
To revise the staging system for cutaneous melanoma on the basis of data from an expanded American Joint Committee on Cancer (AJCC) Melanoma Staging Database.

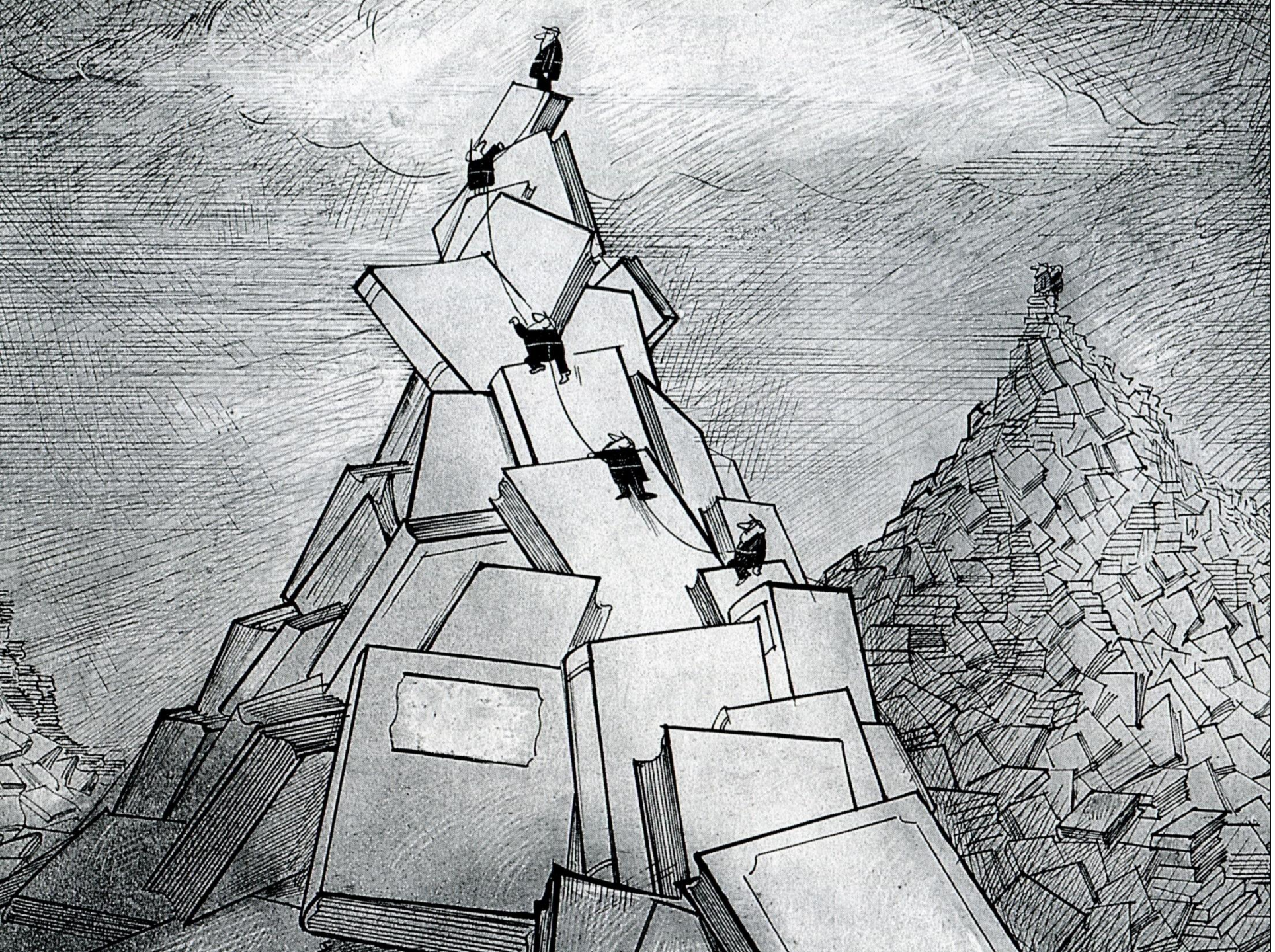
Methods
The melanoma staging recommendations were made on the basis of a multivariate analysis of 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma to revise and clarify TNM classifications and stage grouping criteria.

Results
Findings and new definitions include the following: (1) in patients with localized melanoma, tumor thickness, mitotic rate (histologically defined as mitoses/mm^2), and ulceration were the most dominant prognostic factors. (2) Mitotic rate replaces level of invasion as a primary criterion for defining T1b melanomas. (3) Among the 3,307 patients with regional metastases, components that defined the N category were the number of metastatic nodes, tumor burden, and ulceration of the primary melanoma. (4) For staging purposes, all patients with microscopic nodal metastases, regardless of extent of tumor burden, are classified as stage III. Micrometastases detected by immunohistochemistry are specifically included. (5) On the basis of a multivariate analysis of patients with distant metastases, the two dominant components in defining the M category continue to be the site of distant metastases (nonvisceral *v* lung *v* all other visceral metastatic sites) and an elevated serum lactate dehydrogenase level.

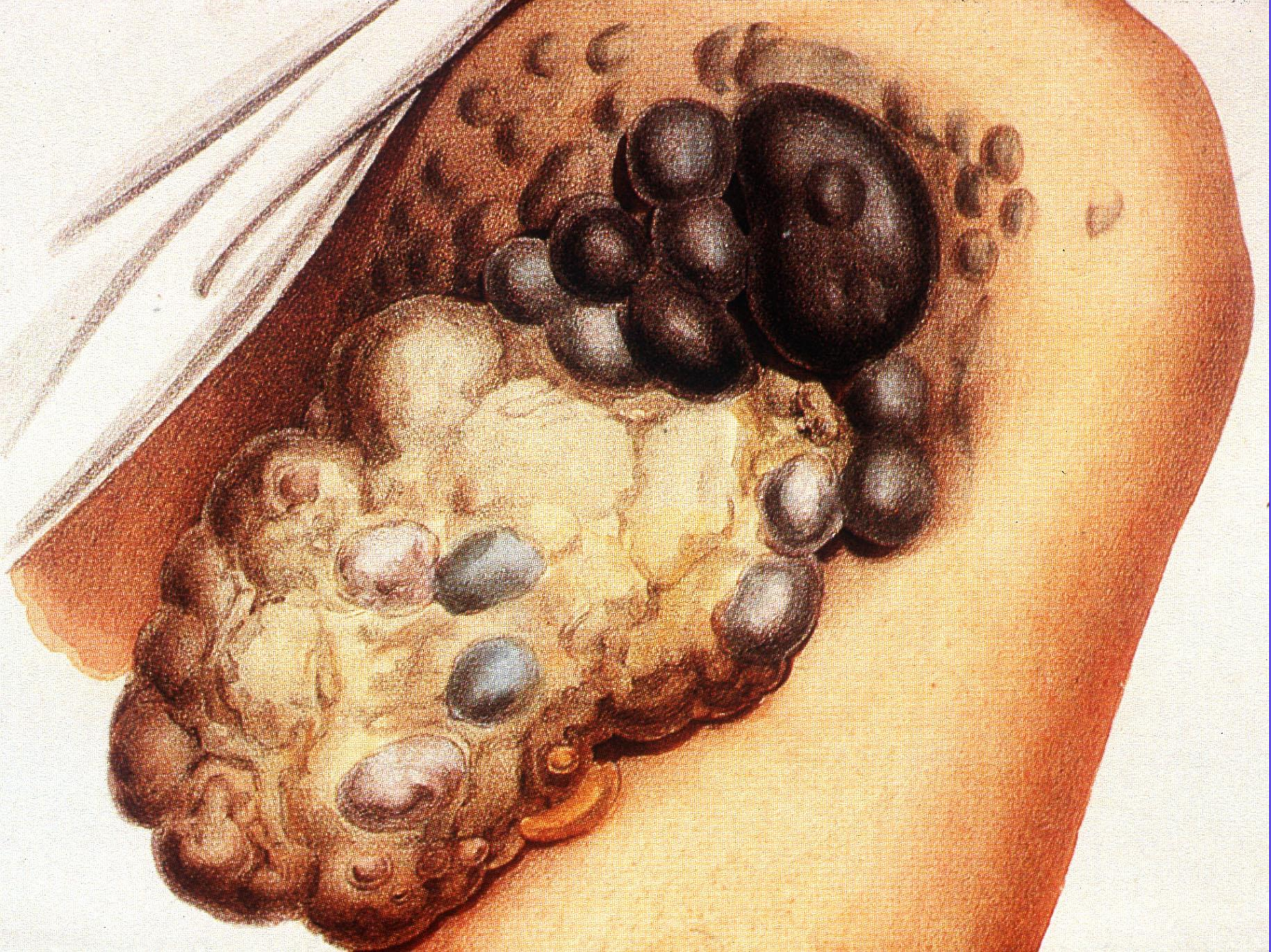
Conclusion
Using an evidence-based approach, revisions to the AJCC melanoma staging system have been made that reflect our improved understanding of this disease. These revisions will be formally incorporated into the seventh edition (2009) of the AJCC Cancer Staging Manual and implemented by early 2010.

J Clin Oncol 27:6199-6206. © 2009 by American Society of Clinical Oncology

The current version of this classification was published in 2009. It was based on the American Joint Committee on Cancer Melanoma Staging Database. Multivariate analysis of data from thousands of patients revealed tumor thickness, mitotic rate, and ulceration as *"the most dominant prognostic factors."* As a consequence, mitotic rate replaced Clark levels in the TNM classification of melanoma, and all this was implemented in early 2010.



In order to get a sense for the relevancy of the current classification, it must be put in historical perspective, and this requires review of mountains of literature. Attempts to stratify melanomas prognostically reach back almost 90 years.



Previously, diagnosis of melanoma was considered to be a death sentence, the reason being that lesions were recognized only in stages far advanced.

Extirpation even of the very first nodules cannot halt the subsequent course. For this reason, the operation is carried out only very rarely, and the first symptom of pigmented cancer is regarded as an ominous sign of a rapidly fatal course.


Moriz Kaposi, 1872

For example, Moriz Kaposi claimed in 1872 that *“extirpation even of the very first nodules cannot halt the subsequent course. For this reason, the operation is carried out only very rarely, and the first symptom of pigmented cancer is regarded as an ominous sign of a rapidly fatal course.“*

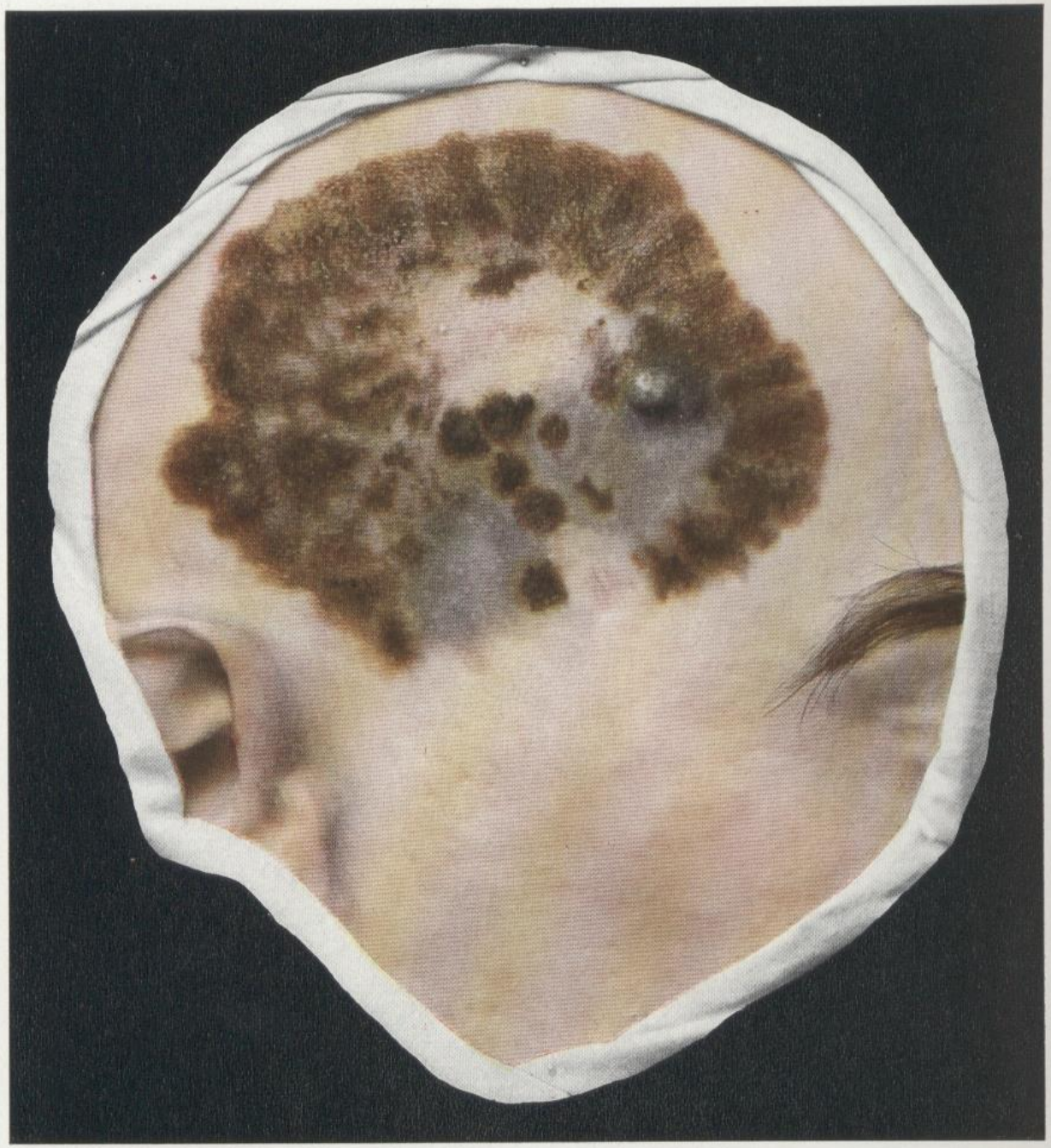
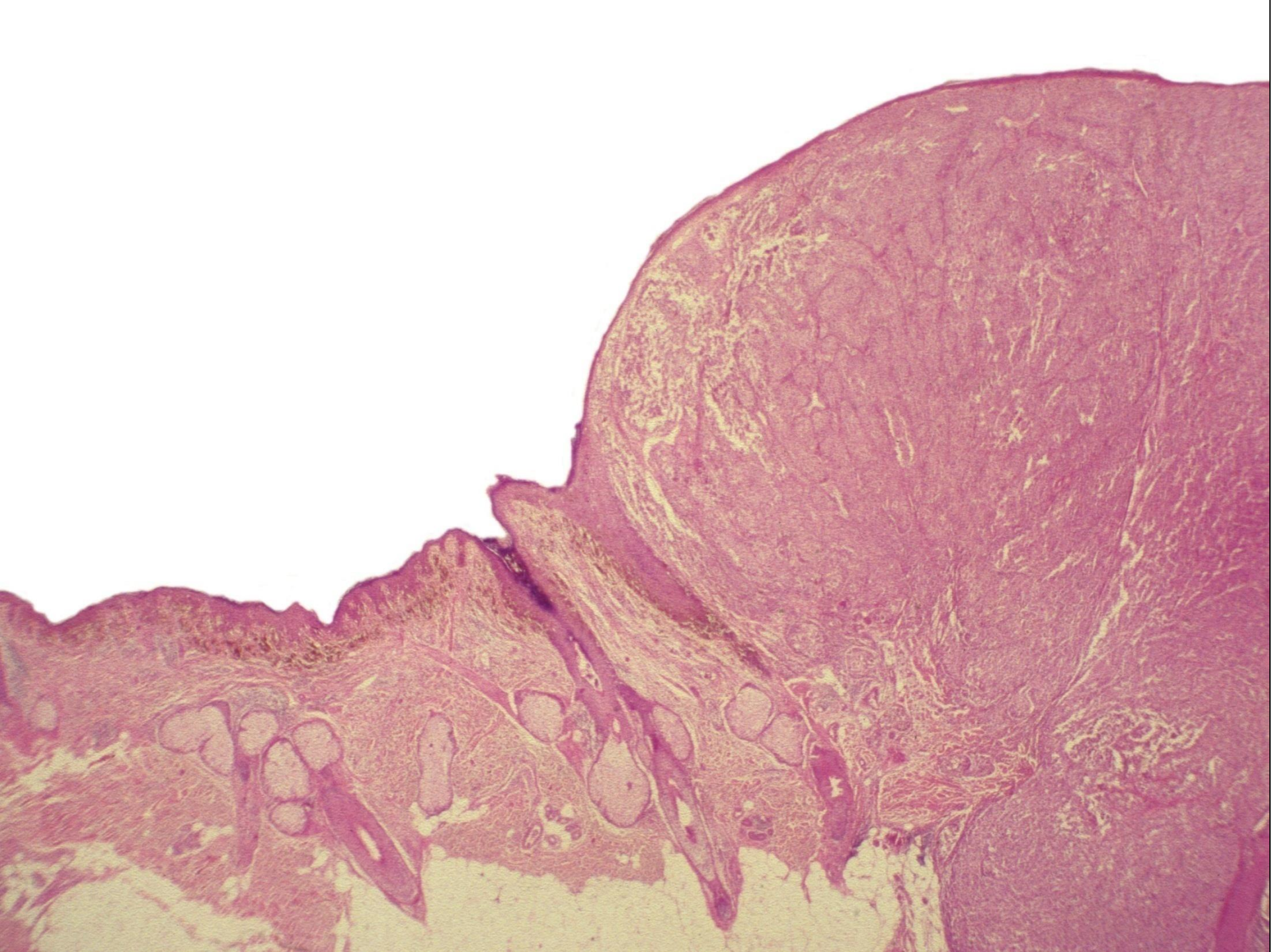
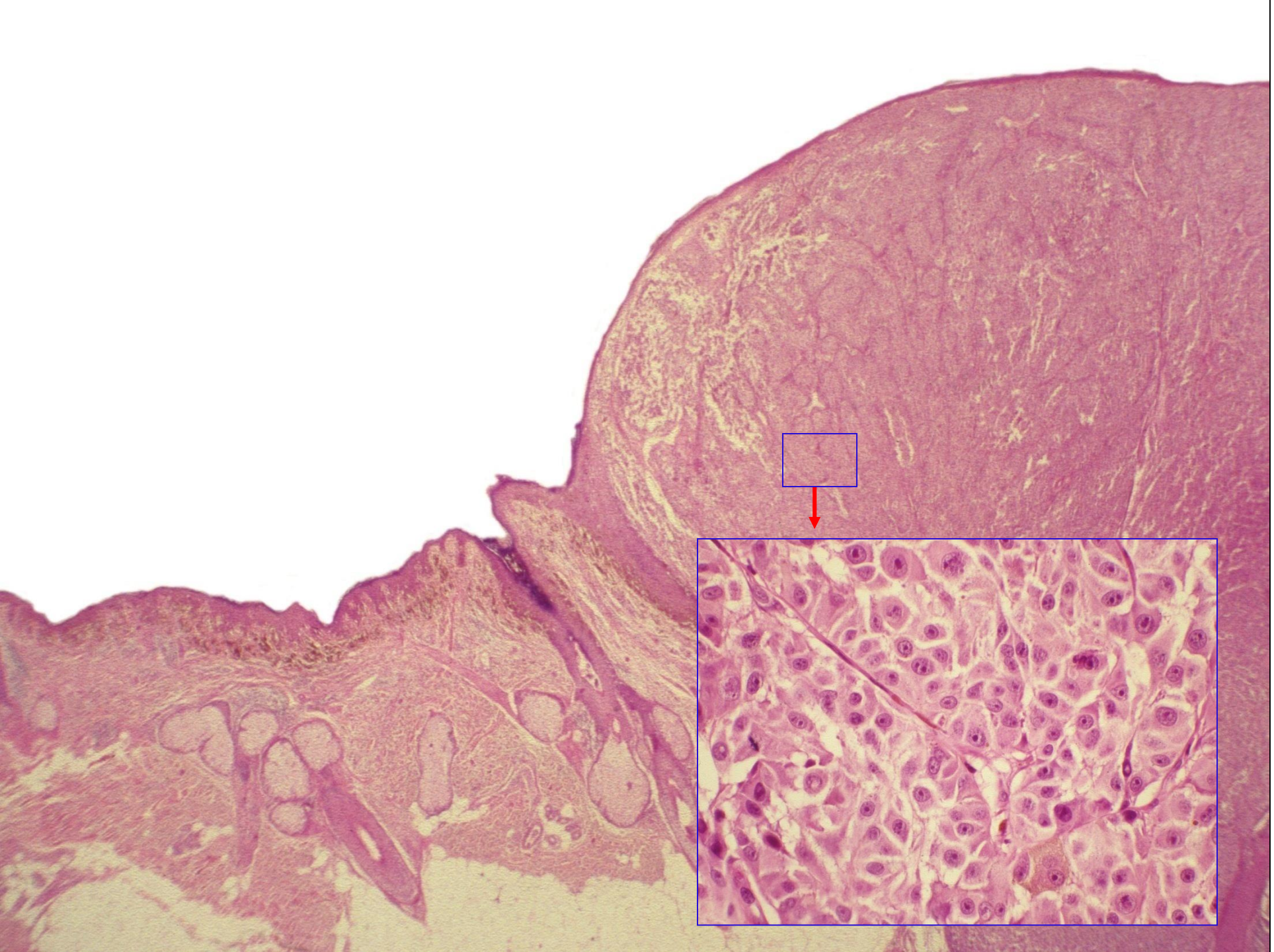


Abb. 47. Ausgedehnte melanotische Präcancerose mit Tumorbildung oder Naevus tardus in maligner Entartung?

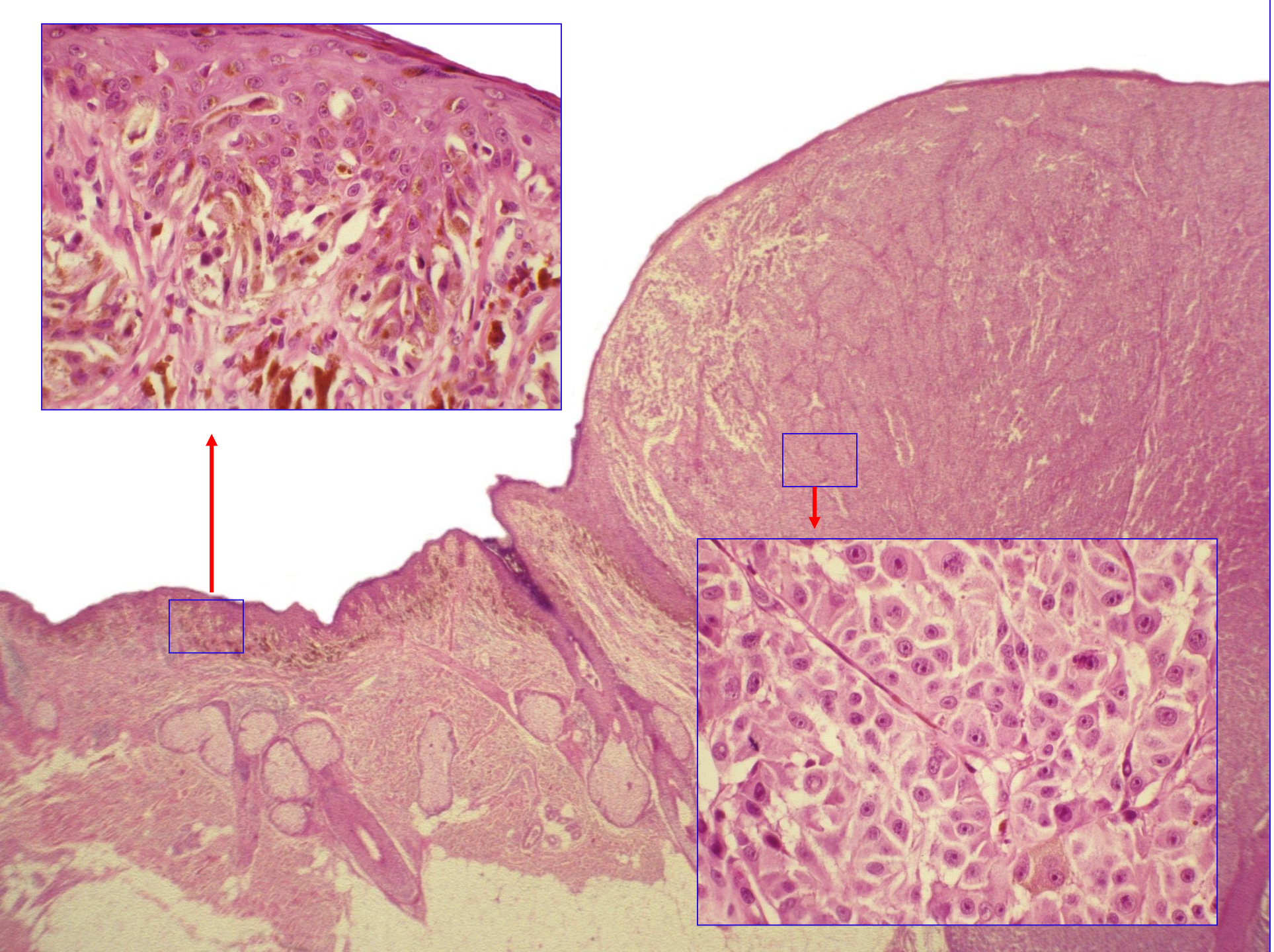
At that time, and for many decades to come, early stages of melanoma were misinterpreted as nevi. For example, in Jadassohn's Handbook of 1929, this lesion was labeled "nevus tardus with malignant transformation." Only the nodule was considered to be melanoma, the flat component was thought to be benign or, at best, "precancerous."



Among reasons for that misconception was slow growth of melanomas, but also genetic instability leading to accumulation of molecular and chromosomal aberrations with development of different populations of cells.



Often cells in exophytic nodules of melanoma are large, poorly pigmented, and highly pleomorphic with many, sometimes atypical mitotic figures,



whereas cells in the flat component are smaller and show few, if any, mitoses. For that reason, they were misinterpreted as cells of a pre-existing nevus.

Nach der Abstammung der Fälle ergibt sich folgendes Bild:

		Total	Geheilt	Ungeheilt
Melanome aus Naevi	a) Gesicht	6	6	—
	b) andere Körperstellen	6	3	3
Melanome aus Präcancerosen	a) Gesicht	8	7	1
	b) andere Körperstellen	—	—	—
Melanome, die spontan entstanden sind	a) Gesicht	4	3	1
	b) andere Körperstellen	3	1	2

Miescher G. Melanom. In: Jadassohn J (ed.) Handbuch der Haut-und Geschlechtskrankheiten, vol. XII/3, 1933, p. 1122.

By that time, however, it had become evident that not all melanomas are deadly. Some could be healed. In Jadassohns Handbook, Guido Miescher in 1933 was the first to propose prognostic criteria, namely, anatomic site – favorable for the face, worse for rest of the body – and association with *"pre-existing lesions"* – favorable for melanomas associated with a so-called "pre-cancerous melanosis," worse for those associated with what was thought to be a pre-existing nevus, worst for lesions appearing spontaneously on normal skin.

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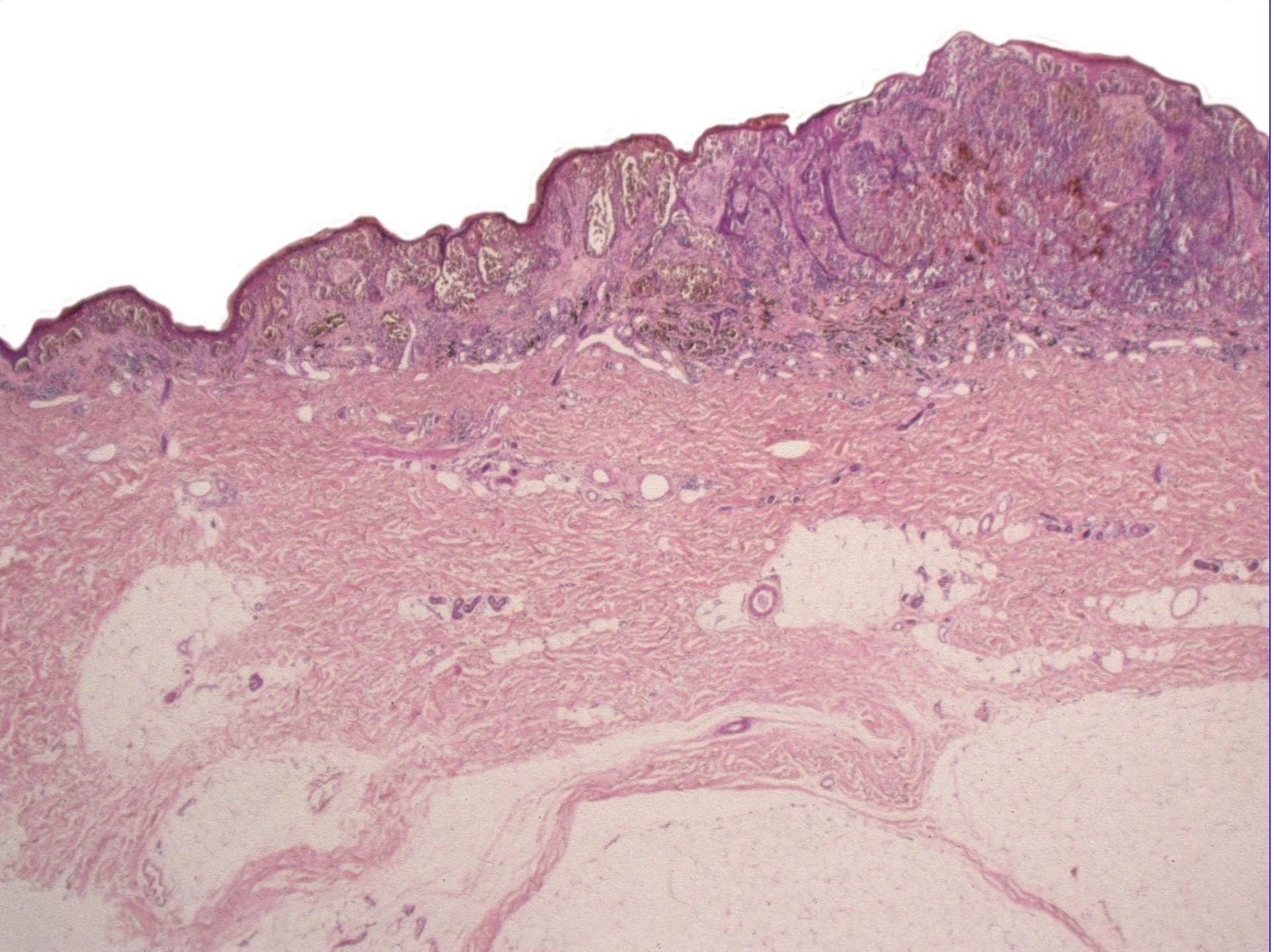
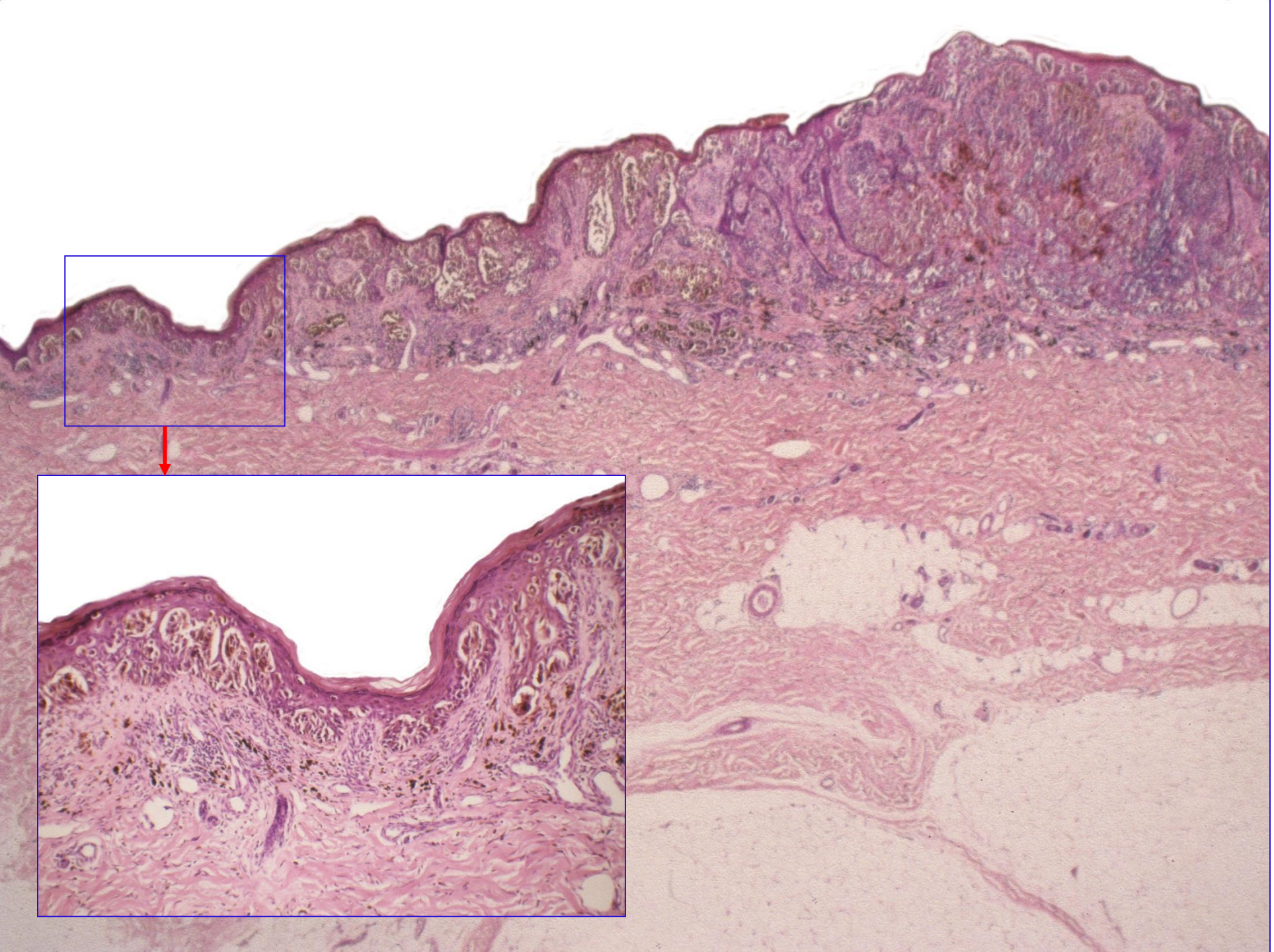
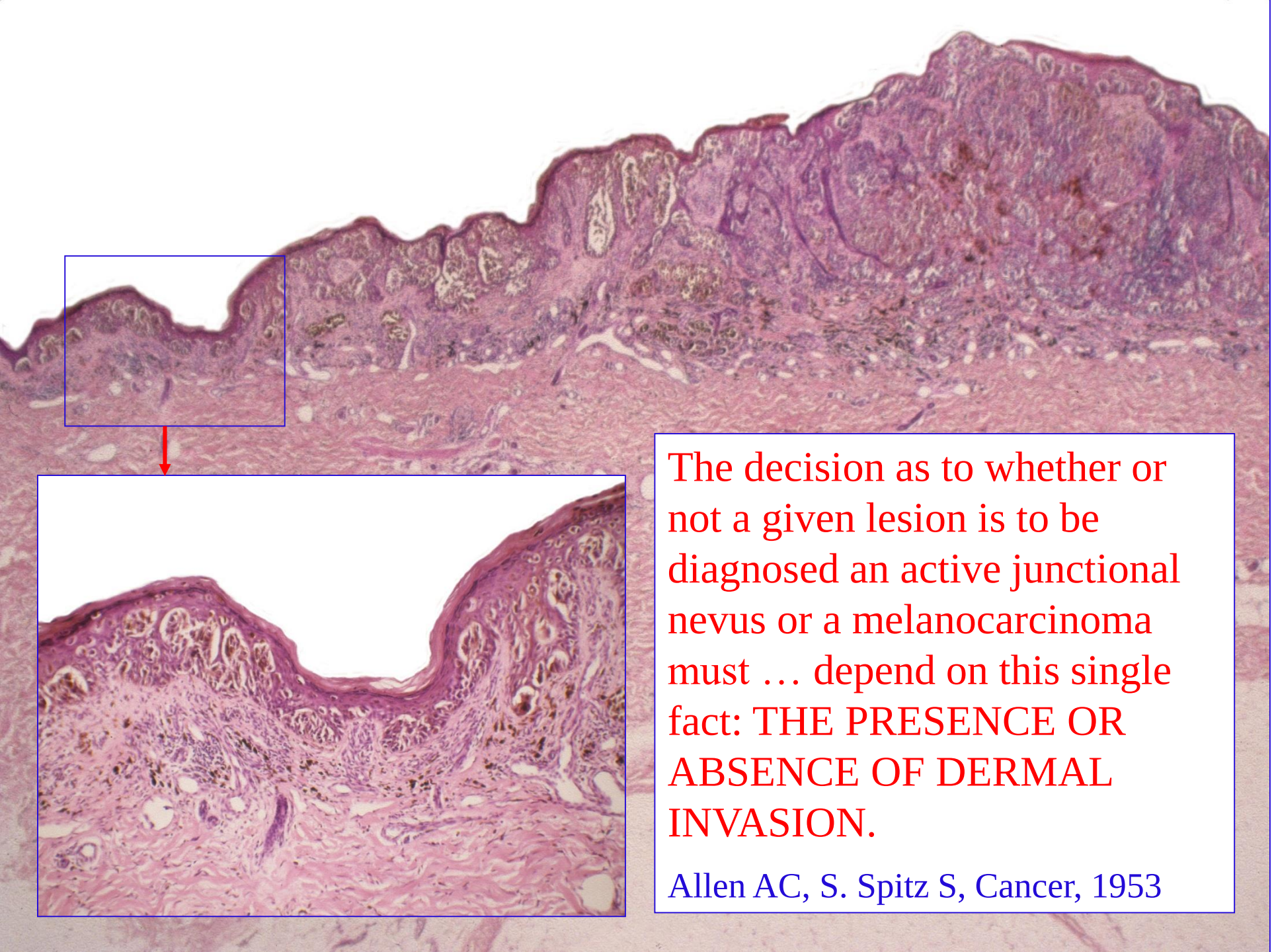
Of course, the “pre-existing lesions” were nothing but flat portions of the melanoma, but Miescher’s three tier classification anticipated by 40 years the later classification of melanoma in superfical, lentigo maligna, and nodular types – including its presumed prognostic implications.



Then came the war, and the progress made in Europe was largely forgotten. Until well into the 1950s, melanoma was thought of as a nodular lesion,



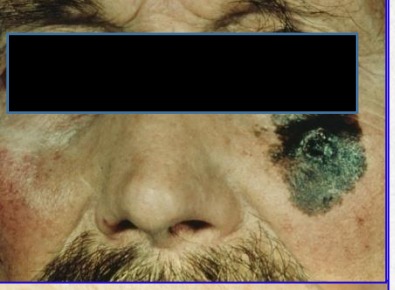
and the macular periphery was misinterpreted as a pre-existing nevus, even if cytological features and architecture were identical, even if nests were confluent, nuclei atypical, and melanocytes present in all reaches of the epidermis.

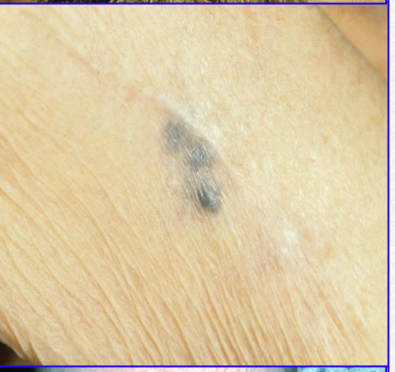


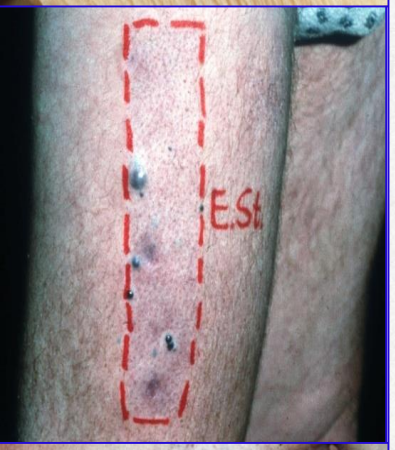
The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must … depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION.

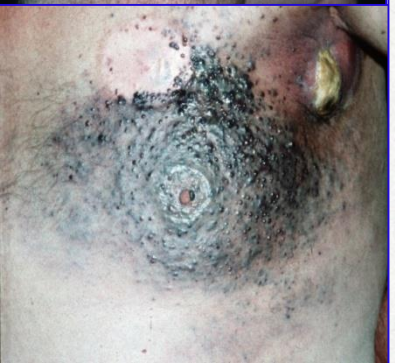
Allen AC, S. Spitz S, Cancer, 1953

In 1953, Arthur Allen and Sophie Spitz claimed that *"the decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must … depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION."*



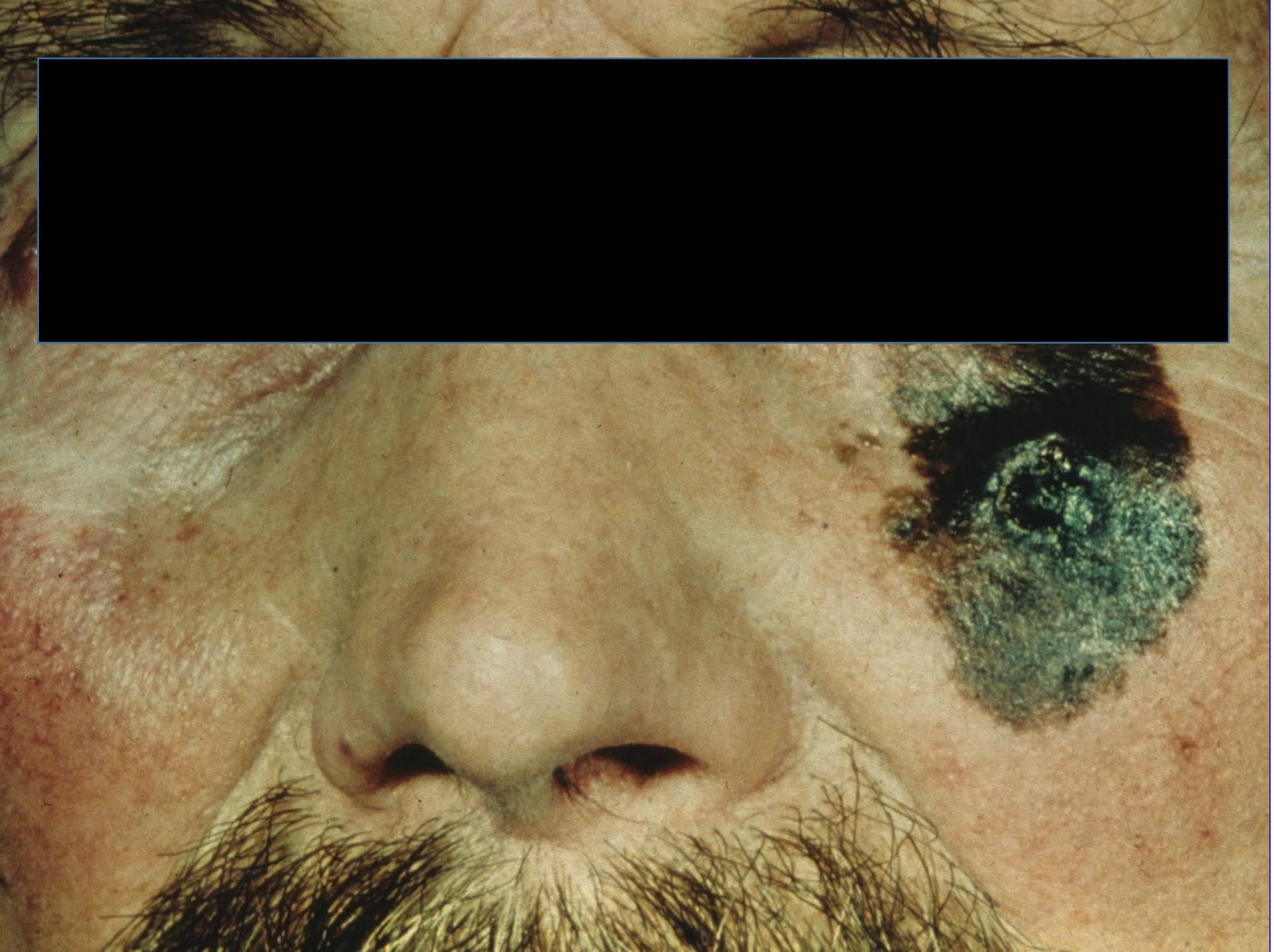






STAGE	ORIGINAL SYSTEM	MODIFIED SYSTEM
I	Localized primary melanoma	Local disease
	Ia Localized recurrence	Ia Primary lesion alone
		Ib Primary and satellites within a 5-cm radius of the primary
		Ic Local recurrence within a 5-cm radius of the resected primary
		Id Metastases more than 5 cm from primary but within the primary lymphatic drainage area
II	Regional nodal or in-transit metastases	Regional nodal disease
III	Disseminated disease	Disseminated disease

That concept delayed diagnosis of melanoma considerably. As a consequence, prognosis remained grim, and the classification was simple. In the 1960s, three stages were distinguished: local disease, including the primary tumor and localized recurrences; regional nodal disease, including regional nodal or in-transit metastases, and disseminated disease.



This changed when it was recognized that the macular component of melanomas is part of the malignant process.

CLINICOPATHOLOGICAL CORRELATIONS IN A SERIES OF 117 MALIGNANT MELANOMAS OF THE SKIN OF ADULTS

NATHAN LANE, M.D., RAFFAELE LATTES, M.D., AND JAMES MALM, M.D.

MALIGNANT melanoma has long been considered one of the most uncontrollable neoplasms encountered. Twenty-six years ago Stout[28] stated "The writer has never come into contact personally with any case of malignant skin melanoma which has remained more than six years without evidence of metastasis or local reappearance." In contrast to this picture, in the last 15 years a number of reports have appeared in the literature indicating that when the condition is adequately treated, the survival rate may be comparable to or better than that obtained in other forms of cancer. Table 1 lists some of the series published since 1940 with the reported survival rates.[4, 6, 9, 17, 23]

TABLE 1
5-YEAR SURVIVAL RATE

Author	Year	No. treated cases	% surv.
de Cholnoky[6]	1941	81	42.3
Sylvén[29]	1949	291	30.8
Raven[23]	1950	72	9.7
Pack et al.[17]	1952	575	21.4
Hall et al.[9]	1952	132	28.0
Stewart et al.[27]	1953	78	24.3
Preston et al.[22]	1954	164	15.4
Catlin[5]	1954	80	36.0
Lund & Ihnen[11]	1955	73	26.0
Brandt[4]	1956	112	20.5
Meyer[14]	1957	107	51.0
Royster & Baker[24]	1957	66	39.0
Col.–Presb. Med. Center	1957	105	34.3

Melanomas were recognized earlier, before nodules developed, the survival rates improved gradually, and it became evident that prognosis depends on the point of time of diagnosis and excision. In 1958, Nathan Lane noticed

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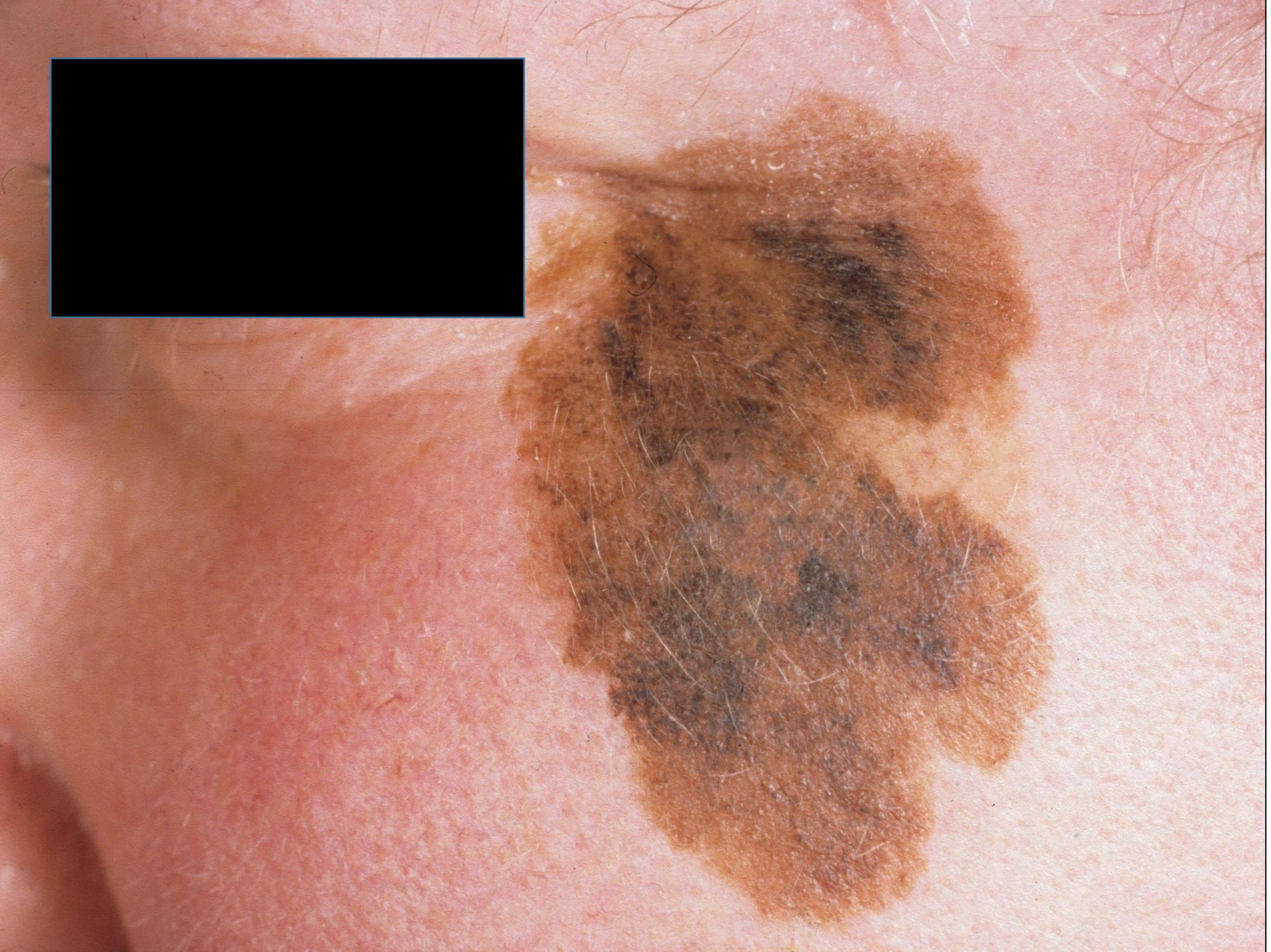
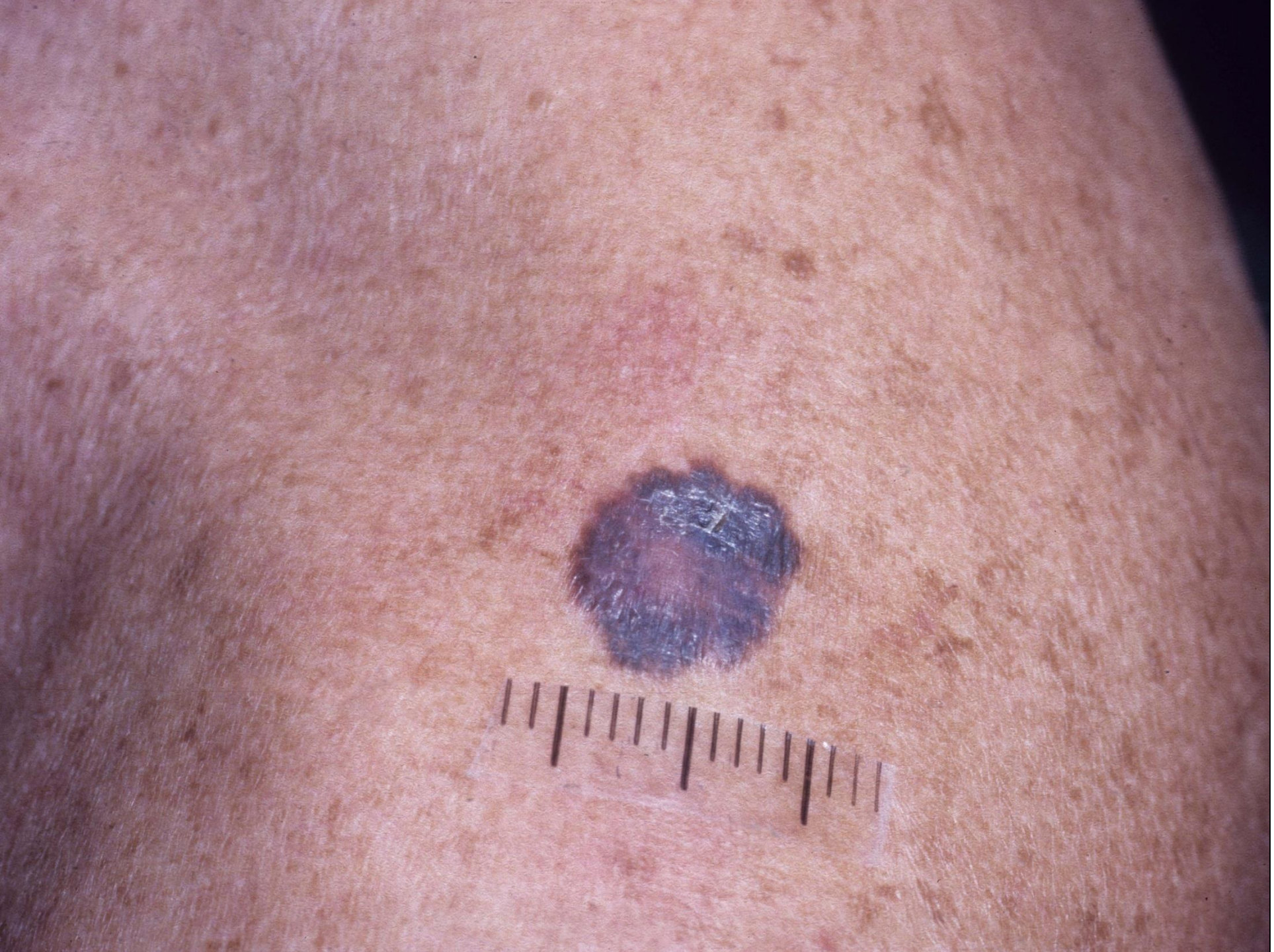
… melanomas 2 cm. and less in size had a 5-year apparent cure rate of 61% as opposed to 16% for melanomas more than 2 cm.

Lane N et al., Cancer 1958

that "m*elanomas 2 cm. and less in size had a 5-year apparent cure rate of 61% as opposed to 16% for melanomas more than 2 cm,"* thus establishing the diameter of melanomas as a prognostic factor.



However, some melanomas grow in situ for many years and acquire a great diameter without risk of metastases,



whereas the diameter of nodular melanomas may be small. The horizontal diameter, therefore, is a poor prognosticator, and the vertical diameter much more important.

Staging of Malignant Melanomas by Depth of Invasion*

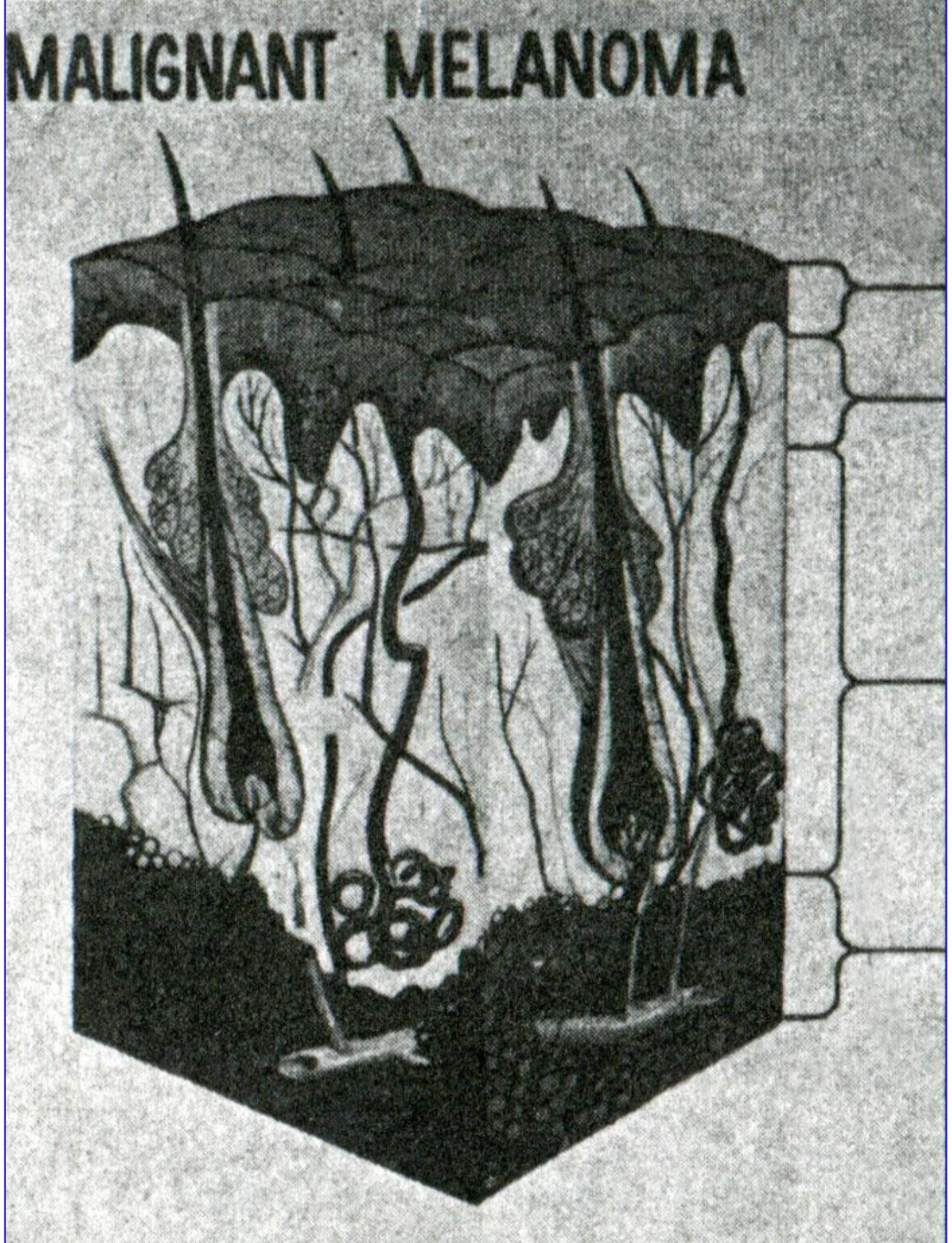
A Proposed Index to Prognosis

JOHN H. MEHNERT, M.D. AND JEROME L. HEARD, M.D., *San Diego, California*

From the Departments of Surgery and Pathology, Mercy Hospital, San Diego, California.

WHEN Bodenham and Lloyd [*1*] stated recently, "One would like to be able to assume that any improvement (in recently reported results) was entirely due to the nature of the treatment, but the evidence seems to be that it is partly due to the composition of the sample," they hit squarely upon one of the most urgent problems blocking better understanding of malignant melanoma. Certain recent reports have shown a remarkable rise in the survival rates [*2–5*]. The resulting dilemma, classify melanomas into groups of varying prognosis. Dobson [*7*], James [*8*], DasGupta [*9*], and others have proposed classifications based upon the clinical extent of the disease. Although we may anticipate some degree of correlation between the extent of spread of any malignancy and its prognosis, such a classification does not take into account variations which may exist in the basic aggressiveness of the tumor. If such variation exists, a classification derived from an examination of the primary lesion would be the more valid one. Petersen, Bodenham, and Lloyd [*2*] proposed a system of staging of this disease, based upon micro-

In 1965, Mehnert and Heard suggested to use the depth of invasion as an index to prognosis and distinguished four prognostic groups,



I epidermis

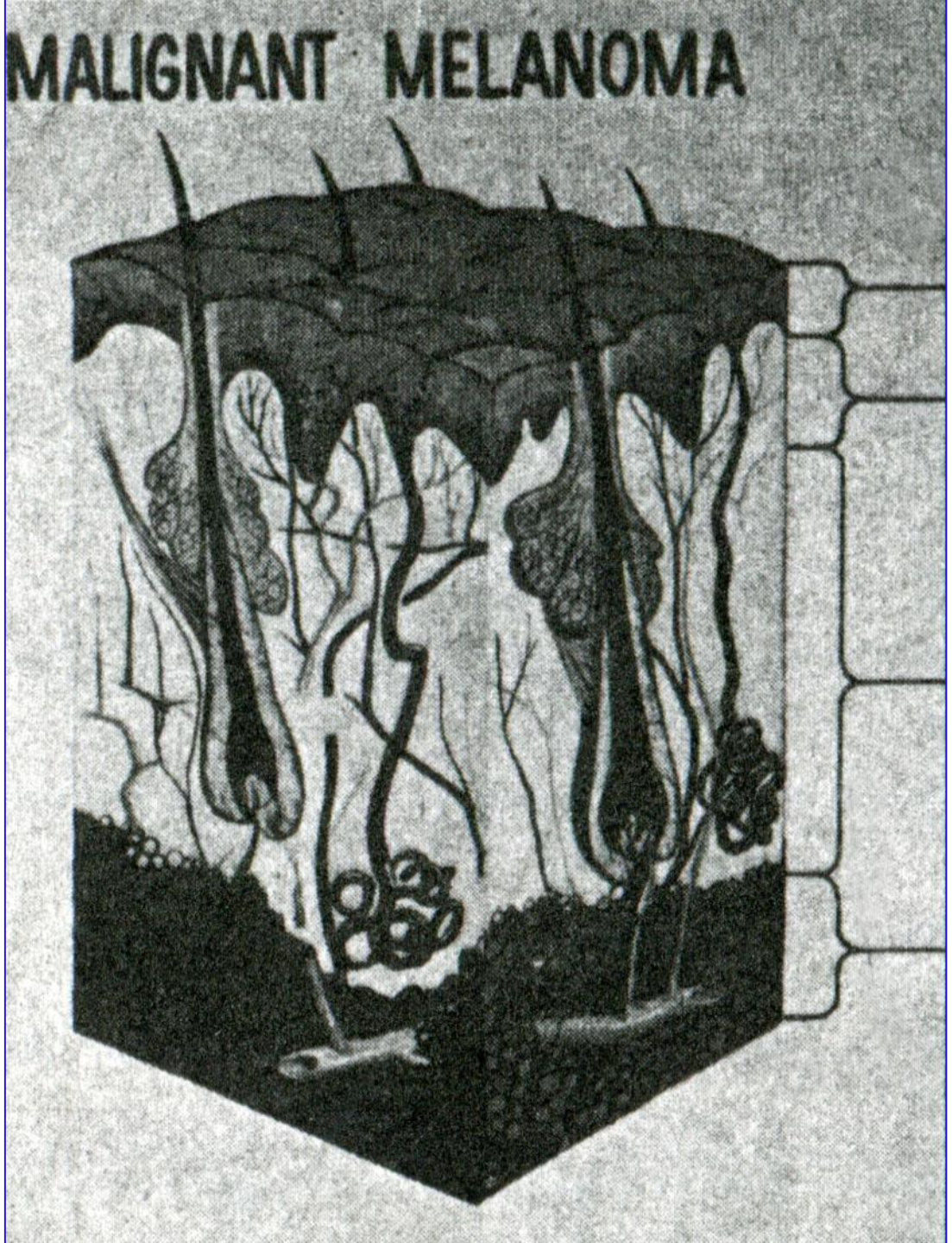
II papillary dermis

III reticular dermis

IV subcutis

Mehnert JH, Heard JL
Am J Surg,1965

namely, wholly intraepidermal lesions and those infiltrating the papillary dermis, the reticular dermis, and the subcutis. This was, in effect, the so-called Clark levels,



I epidermis

papillary dermis

II • infiltrated

III • filled

IV reticular dermis

V subcutis

Clark WH Jr. et al.
Cancer Res, 1969

only that Clark four years later subdivided the second group into lesions infiltrating the papillary dermis superficially and those filling it completely.

Thickness, Cross-Sectional Areas and Depth of Invasion in the Prognosis of Cutaneous Melanoma

ALEXANDER BRESLOW,* M.D.

From The George Washington University School of Medicine, Washington, D. C.

CUTANEOUS melanoma is a most unpredictable lesion. The marked variation in prognosis is probably a function of many variables, one of which is the size of the tumor. Though there is a roughly inverse relationship between the diameter of the lesion and survival,[5] very small lesions have recurred or metastasized. One possible reason for the lack of reliability of tumor size in estimating prognosis may be that studies to date have considered size in only two diamensions and have neglected tumor volume. Two melanomas can have the same diameter but differ greatly in thickness be-

to see if maximal cross-sectional area, thickness, stage of invasion, or a combination of these can be of value in assessing the prognosis of cutaneous melanoma. A total of 98 lesions were so studied.

Materials and Methods

The 98 patients in this study were all free of recurrent or metastatic disease and none had satellite nodules when first seen at the George Washington University Hospital. None of the lesions were related to an antecedent lentigo malignum (melanotic freckle of Hutchinson). Their ages ranged

Only one year later, Alexander Breslow introduced thickness as a prognostic parameter, and within short, Clark levels and tumor thickness became the cornerstones for classification of primary malignant melanoma.

The 1978 UICC Staging System

STAGE	CRITERIA
IA	Tumor invading papillary dermis but not reticular dermis (levels II and III) and ≤1.5 mm thick
IB	Tumor invading reticular dermis or subcutaneous tissues (levels IV and V) and ≥1.51 mm thick
II	Regional lymph node spread
III	Juxtaregional lymph node spread
IV	Distant metastases

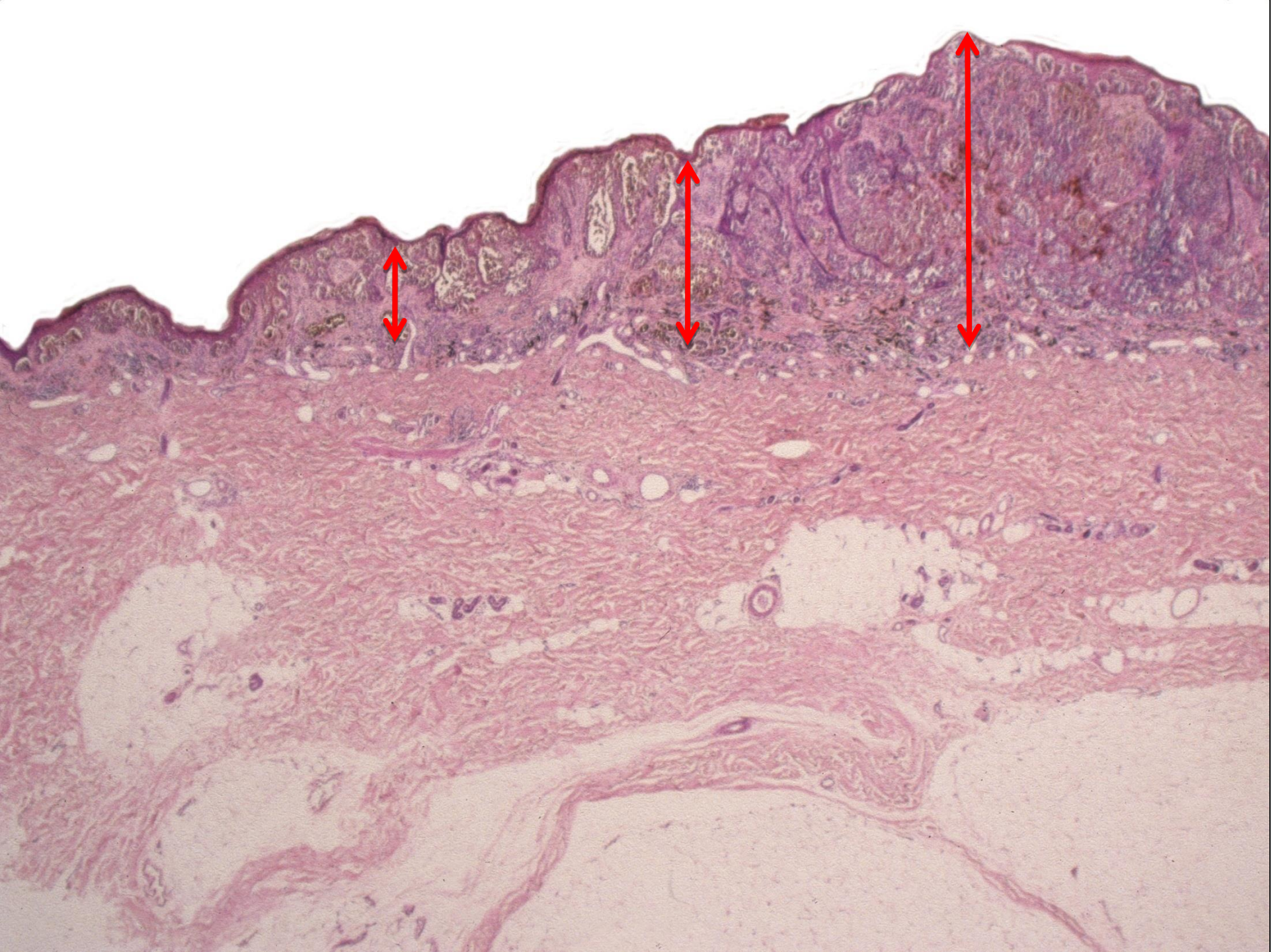
In the UICC staging system of 1978, the border between stage IA and stage IB was set at level III and a thickness of 1.5 mm.

The 1983 AJCC Staging System

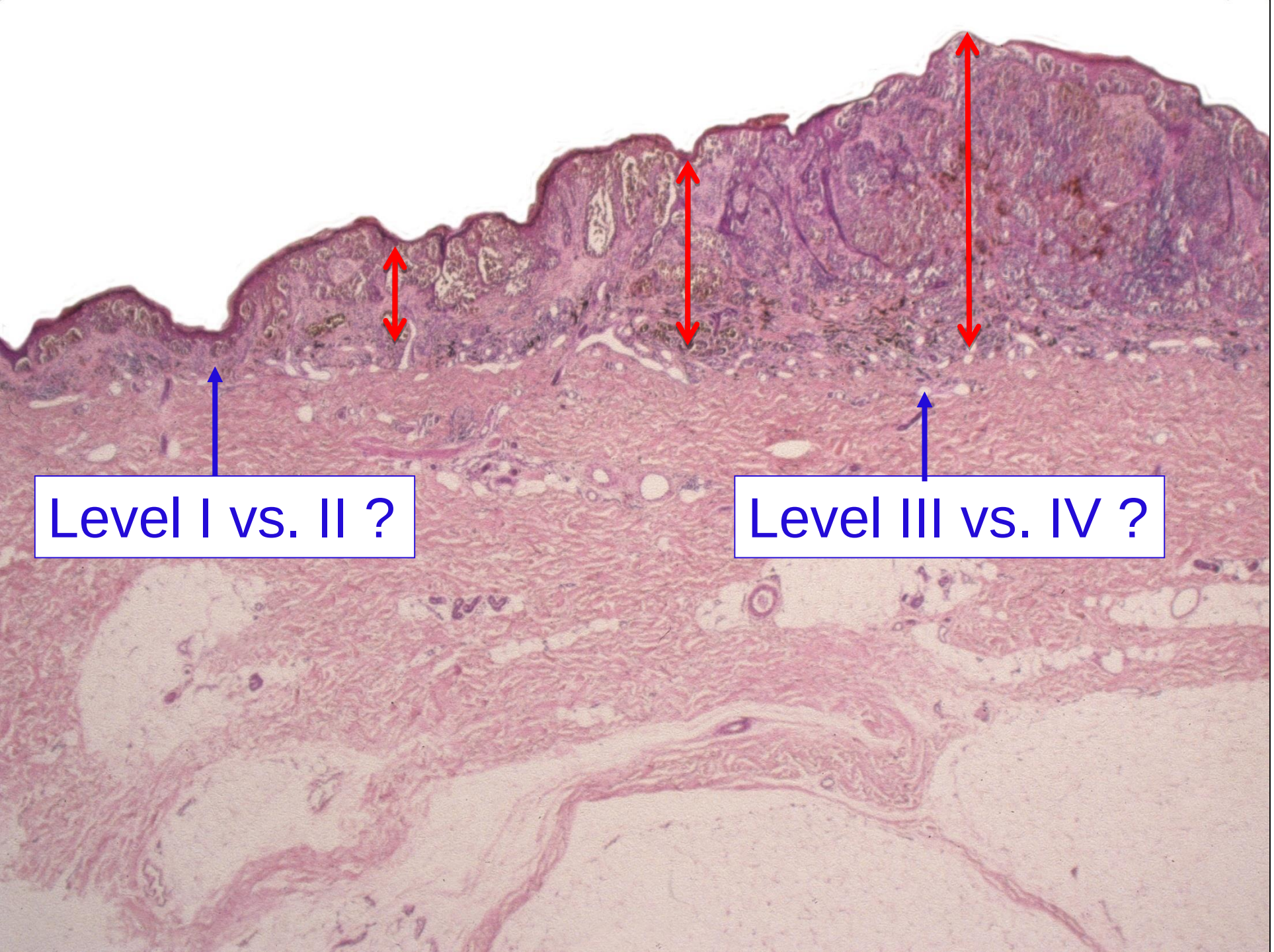
STAGE	CRITERIA
IA	Localized melanoma ≤0.75 mm thick or level II (T1, N0, M0)
IB	Localized melanoma 0.76 to 1.50 mm thick or level III (T2, N0, M0)
IIA	Localized melanoma 1.51 to 4.00 mm thick or level IV (T3, N0, M0)
IIB	Localized melanoma >4.00 mm thick or level V (T4, N0, M0)
III	Limited nodal metastases involving only one regional lymph node basin, or <5 in-transit metastases but without nodal disease (any T, N1, M0)
IV	Advanced regional metastases (any T, N2, M0) or any patient with distant metastases (any T, any N, M1 or M2)

In the first melanoma staging system of the American Joint Committee on Cancer in 1983, stage Ia referred to lesions up to 0.75 mm or level II, stage Ib up to 1.5 mm or level III, stage IIA up to 4 mm or level IV, and stage IIB over 4 mm in thickness or level V.

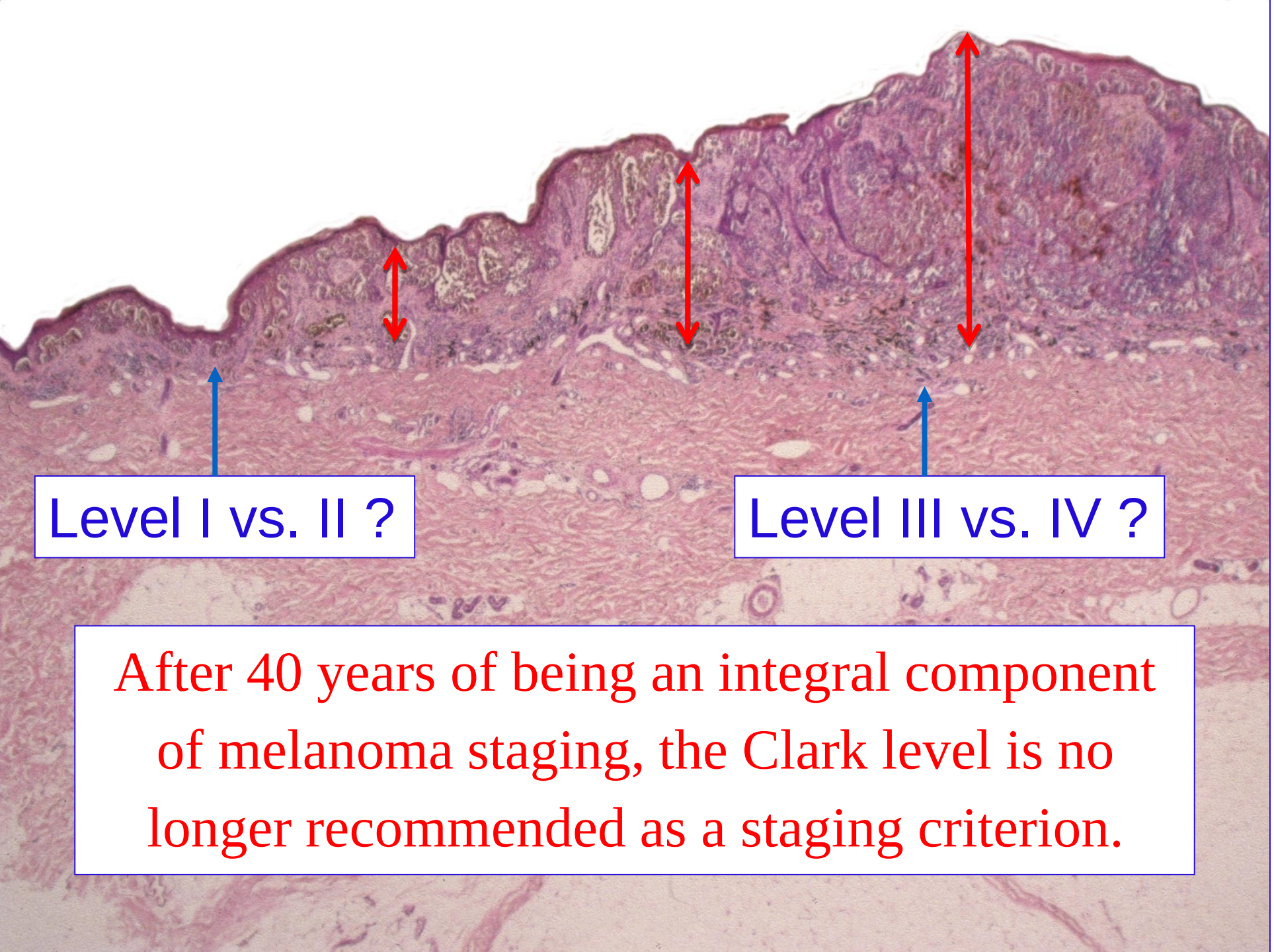
Those two parameters, tumor thickness and Clark levels, reflect the stage of development of melanomas and, therefore, they correlate with prognosis.



Clark levels, however, reflect size only poorly, the reasons being (1) that the anatomy of the skin, such as the thickness of the reticular dermis, is highly variable, so that level IV melanomas on the trunk are usually much bigger than those on the face or forearm, and (2) that the papillary dermis is very expansible. As a consequence, lesions with the same Clark level, in this case level III, may vary greatly in thickness.



Moreover, assessment of levels, such as the border between levels I and II or levels III and IV, may be very subjective.



It is salutary, therefore, that the American Joint Committee on Cancer declared, in its newest classification: *"After 40 years of being an integral component of melanoma staging, the Clark level is no longer recommended as a staging criterion."*

[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

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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.

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LMM

incidence 13.9 %

mortality 10.3 %

SSM

incidence 54.5 %

mortality 31.5 %

NM

incidence 31.6 %

mortality 56.1 %

Let me briefly come back to Clark's seminal article of 1969. In this paper, Clark not only re-defined levels but also types of melanoma. Lentigo maligna melanoma was said to be the least common type with the best prognosis and superficial spreading melanoma the most common type with a worse prognosis. Nodular melanoma was said to account for about one third of melanomas and to carry the highest mortality.

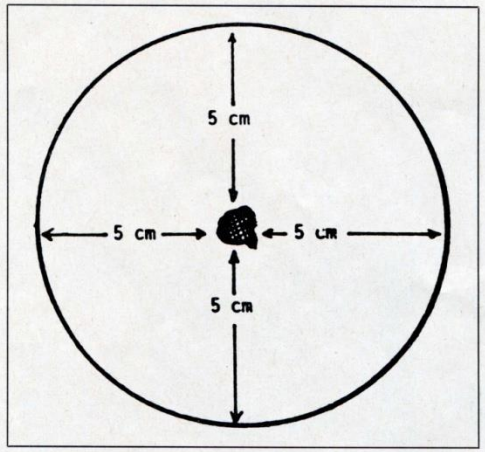

Abb. 6b: Soll der Sicherheitsabstand dagegen über 2 cm »rundum« im Gesunden liegen, und soll eine Unterminierung bzw. Präparation in der Tumorumgebung aus onkologischen Gründen vermieden werden, so ist ein Wundverschluß oft nur mittels Vollhaut- oder Spalthaut-Deckung möglich. Der Schnitt muß also gegen ästhetische Gesichtspunkte kreisrund angelegt werden. Nur dann sind kleinster und größter Sicherheitsabstand wirklich identisch. Wegen des höheren Nekroserisikos einer freien Vollhautübertragung und wegen der besseren Früherkennbarkeit von Rezidiven in loco ist der Spalthautdeckung im Zweifelsfall der Vorzug zu geben (hier 5 cm = WHO-Norm).

New York, Boston, New Orleans und Houston/Texas an.

Die vier prognostischen Risiko-Gruppen als Grundlage der mehrstufigen Melanom-Therapie

Für die niedrigste Prognose-Stufe »no risk« genügt praktisch eine Bestimmung des Mikrostadiums nach Clark und Breslow. Bei der Stufe »low risk« ist es Ermessensfrage, ob man zusätzlich den Tumortyp in Rechnung stellt. Ab Stufe »medium risk« ist es

1. **»No risk«** (10-Jahres-Überleben = 100%)
   In-situ-Melanome (Clark-Level I)
   Clark-Level II
   Breslow-Dicke bis 0,4 mm
2. **»Low risk«** (10-Jahres-Überleben >80%)
   Clark-Level II
   Breslow-Dicke 0,5 bis 0,75 mm
   außer primär nodulärer Typ (NM)
3. **»Medium risk«** (10-Jahres-Überleben = 80 bis 50%)
   Clark-Level III
   Breslow-Dicke über 0,75 mm bis 1,5 mm
   ohne primär nodulären Typ (NM)
   ohne akrale Lokalisation (ALM)
   ohne vorausgegangene Spontanblutung
   ohne vorausgegangene Teilentfernung
4. **»High risk«** (10-Jahres-Überleben <50%)
   Clark-Level IV oder mehr
   Breslow-Dicke >1,5 mm
   alle primär nodulären Melanome (NM)
   alle akrolentiginösen Melanome (ALM)
   alle Melanome mit Spontanblutung/Ulzeration
   alle Melanome nach Teilentfernung ab Breslow-Dicke 0,76 mm
   alle Melanome unbestimmter Invasionstiefe (?)

As a consequence, melanomas for many years were treated differently depending on type, extra centimetres being added to the already generous margins of excision for nodular melanomas,

Successful Treatment of Lentigo Maligna and Lentigo Maligna Melanoma with Mohs' Micrographic Surgery Aided by Rush Permanent Sections

Lisa M. Cohen, M.D., Michael W. McCall, M.D.,* Steven J. Hodge, M.D.,* John D. Freedman, M.D.,† Jeffrey P. Callen, M.D.,* and Robert H. Zax, M.D.**

Background. **Lentigo maligna (LM) is a pigmented neoplasm on sun-exposed skin of elderly patients. LM slowly increases in size and may become lentigo maligna melanoma (LMM), a potentially fatal malignancy. Complete excision is the treatment of choice. Mohs' micrographic surgery (MMS) with frozen and permanent sections may be used for complete eradication of the lesion, while sparing as much normal tissue as possible. The authors studied the efficacy of MMS for the treatment of LM and LMM.**

Methods. **Between 1985 and 1992, 45 patients with LM (26) and LMM (19) were treated with MMS. The authors' technique was to use examination of frozen sections and rush permanent sections (prepared and read within 24 hours). Positive frozen sections warranted further excision. For negative or equivocal frozen sections, surgery was interrupted until the examination of permanent sections was performed.**

Results. **All 45 patients were free of local disease and evidence of metastases at an average of 29.2 months (range, 4–81 months) after therapy.**

Conclusions. **MMS aided by rush permanent sections yielded a prolonged disease free survival for all 45 patients with LM or LMM. Because the MMS technique minimizes the removal of normal tissue, and the local cure rate in this study was superior to that reported for conventional surgery, the authors recommend this technique for the treatment of LM and LMM. *Cancer* 1994; 73:2964–70.**

Key words: lentigo maligna, lentigo maligna melanoma, Mohs' micrographic surgery, therapy.

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Accepted for publication February 14, 1994.

Lentigo maligna (LM) has been called Hutchinson's melanotic freckle,[1] circumscribed precancerous melanosis,[2] primary acquired melanosis (of the conjunctiva),[3] and melanoma in situ.[4] This lesion most commonly affects sun-exposed skin of the head and neck, particularly the face, in an elderly patient, and is characterized by a slowly enlarging, irregularly pigmented macule. LM is a tumor that is histopathologically confined to the epidermis. Invasion of the dermis by similar atypical melanocytes is termed lentigo maligna melanoma (LMM), a potentially fatal tumor. In multivariable analyses, even when controlled for depth of invasion, some authors have found that melanoma arising in LM has a better prognosis than superficial spreading malignant melanoma and nodular melanoma,[5–7] whereas others have found no difference in prognosis.[8,9] LM is believed to be the in situ phase of LMM. Therefore, when feasible, complete excision of LM at its earliest recognition may prevent invasion and will limit cosmetic disfigurement.[10]

The optimal surgical management of malignant melanoma is still being defined. Therapeutic guidelines for early melanoma (defined as melanoma in situ and thin invasive lesions less than 1 mm in depth) were recently proposed at a National Institutes of Health Consensus Conference.[11] Unfortunately, ideal therapeutic strategies of LM and LMM were not defined. Complete surgical excision clearly offers the greatest likelihood of cure, but with lesions of the head and neck, cosmetic and functional impairment can prohibit wide excision.

Histopathologic preparation of surgical specimens using a standard "bread-loafing" technique permits examination of less than 0.1% of the surgical margins,[12] whereas Mohs' micrographic surgery (MMS) allows examination of nearly 100% of the margins. Though MMS has been used experimentally for the treatment of melanoma, the technique has not been studied for LM

and Moh's micrographic surgery with narrow margins being accepted for prognostically favorable lentigo malignant melanomas. But does Clark's classification have legitimacy?

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]

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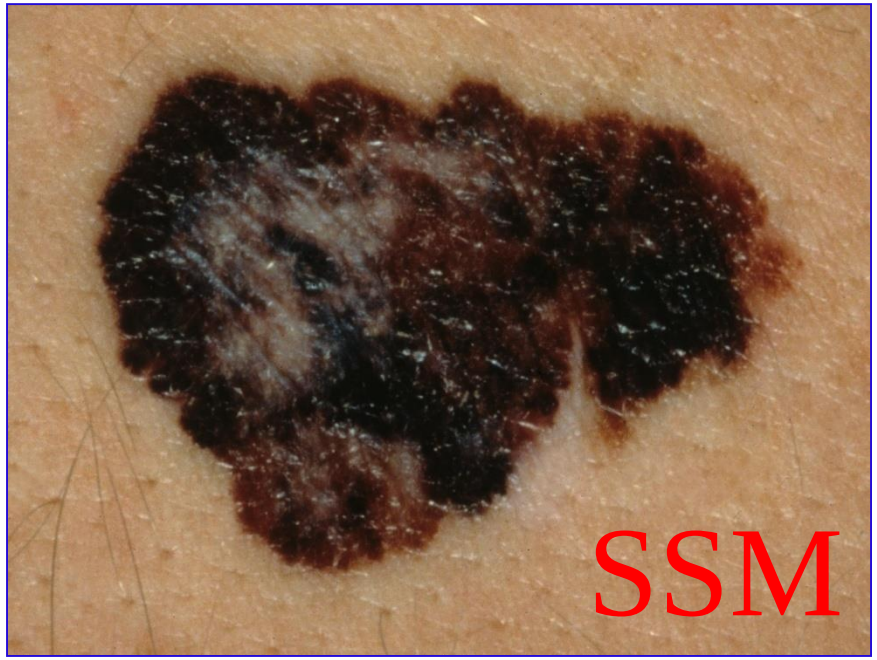
BACKGROUND. Human cutaneous malignant melanoma currently is classified into four principle types: nodular, superficial spreading, lentigo maligna, and acral lentiginous. The criteria for the histopathologic diagnosis of these types are not applied consistently. Nevertheless, the classification has become 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.

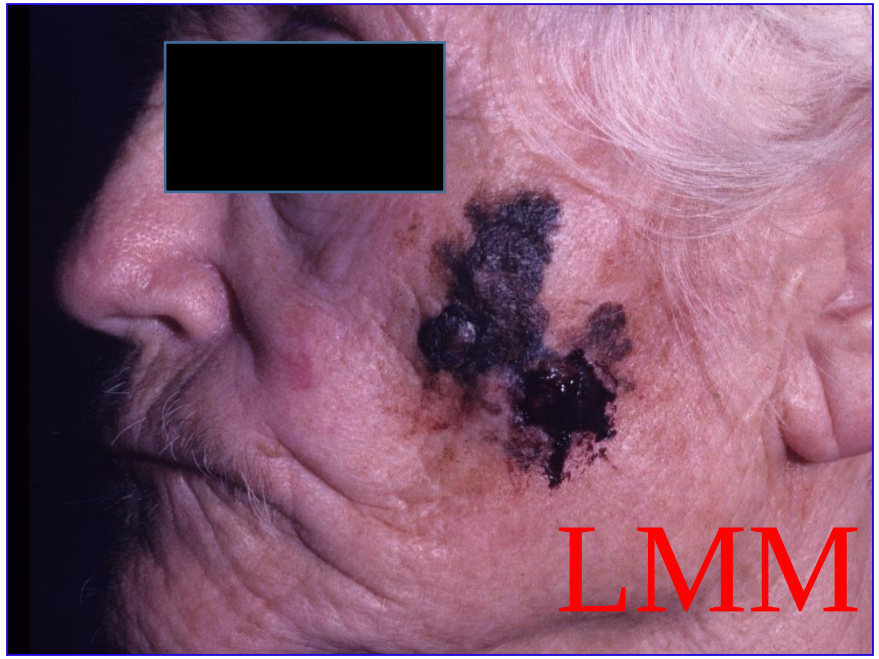
RESULTS. The histopathologic criteria advocated for the distinction of different types of melanoma were found not to correlate with one another. A logistic regression analysis did not detect any other repeatable constellation of morphologic findings that may reflect a distinct biologic subgroup.

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.**

A few years ago, we re-assessed histopathologic criteria for distinction of different types in a study of more than 900 melanomas.

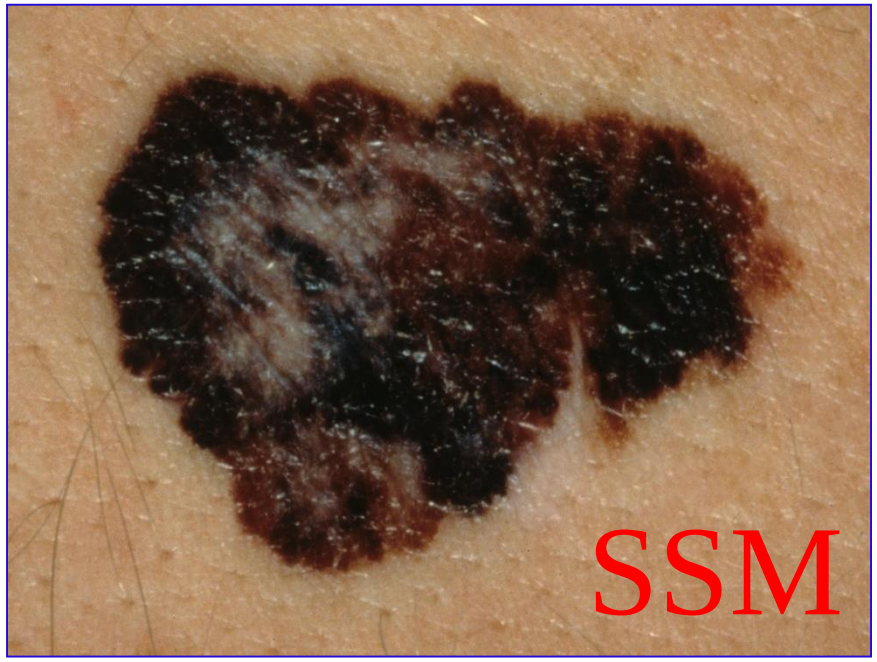


- chiefly epithelioid melanocytes
- prominent pagetoid spread
- mild pleomorphism



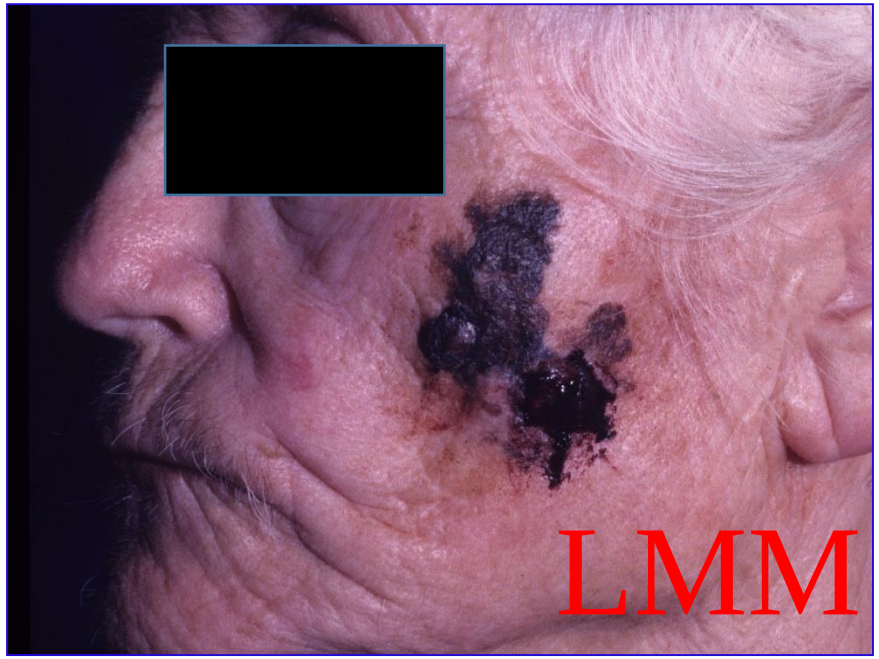
- chiefly spindled melanocytes
- minimal pagetoid spread
- marked pleomorphism

For distinction between SSM and LMM, Clark originally advanced three criteria, namely, chiefly epithelioid melanocytes, prominent pagetoid spread, and slight pleomorphism in superfical spreading melanoma versus chiefly spindled melanocytes, minimal pagetoid spread, and marked pleomorphism in lentigo maligna melanoma.

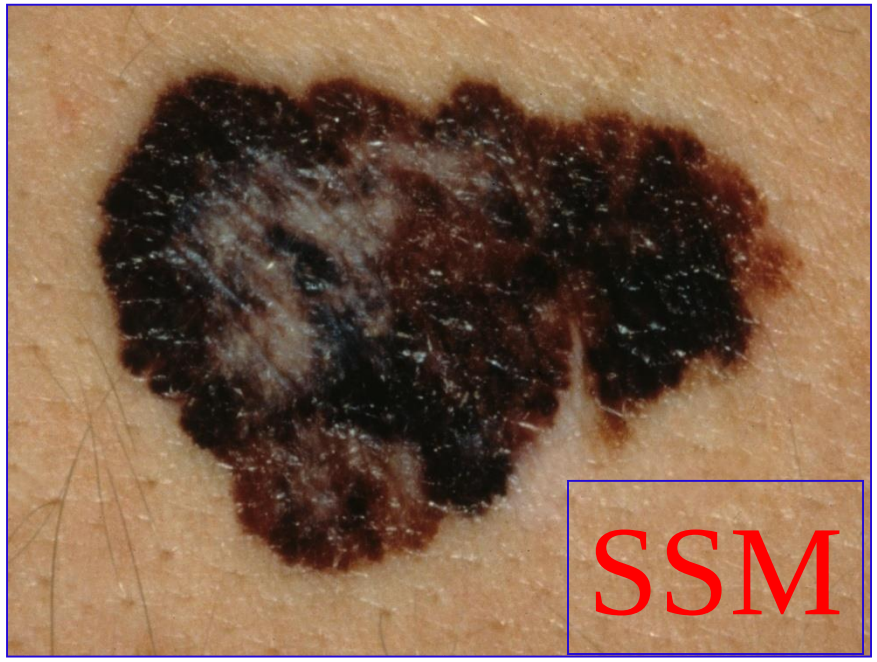


- chiefly epithelioid melanocytes
- prominent pagetoid spread

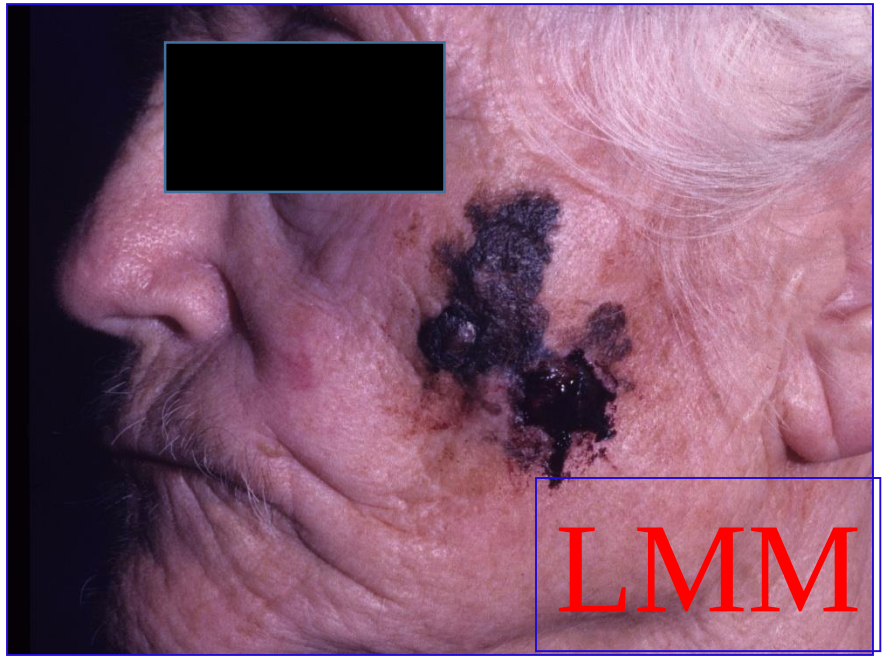
In subsequent studies, pleomorphism was no longer mentioned, but two other criteria were added,



- chiefly spindled melanocytes
- minimal pagetoid spread

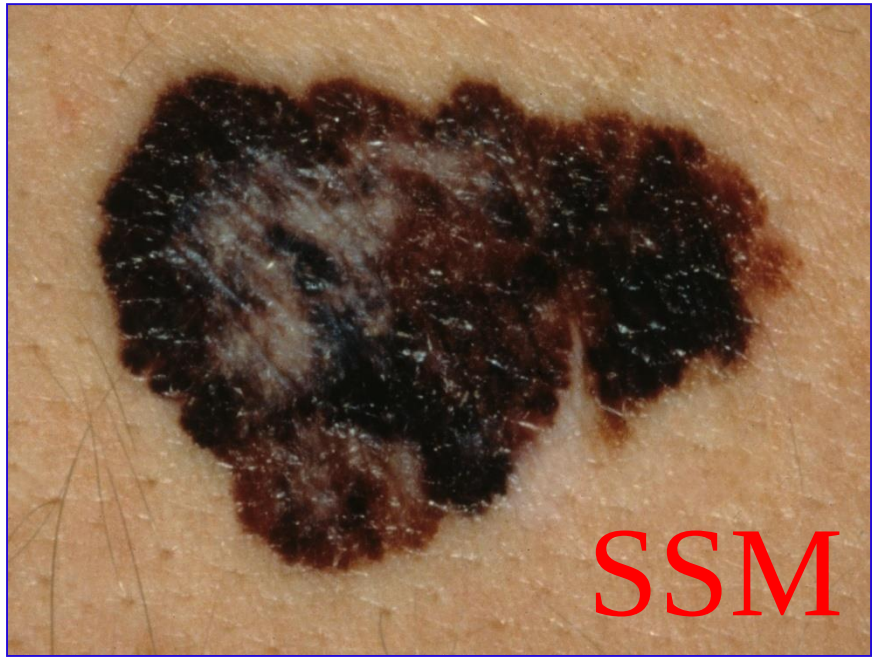


- chiefly epithelioid melanocytes
- prominent pagetoid spread
- no epidermal atrophy
- no solar elastosis



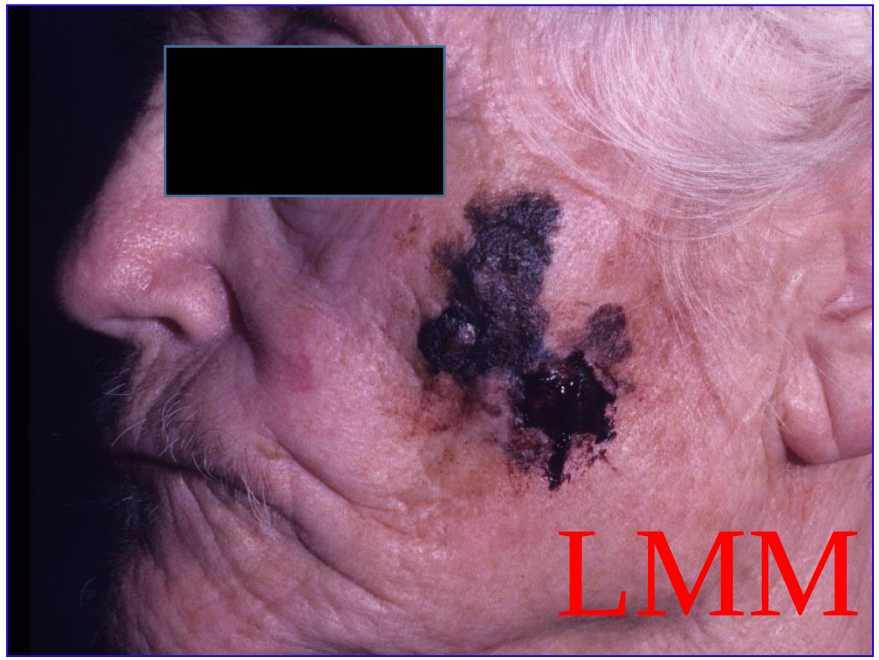
- chiefly spindled melanocytes
- minimal pagetoid spread
- epidermal atrophy
- solar elastosis

namely, absence of epidermal atrophy and solar elastosis in SSM, and presence of those features in LMM. The problem is that those criteria are correlated only poorly.



- chiefly epithelioid melanocytes
- prominent pagetoid spread
- no epidermal atrophy
- no solar elastosis

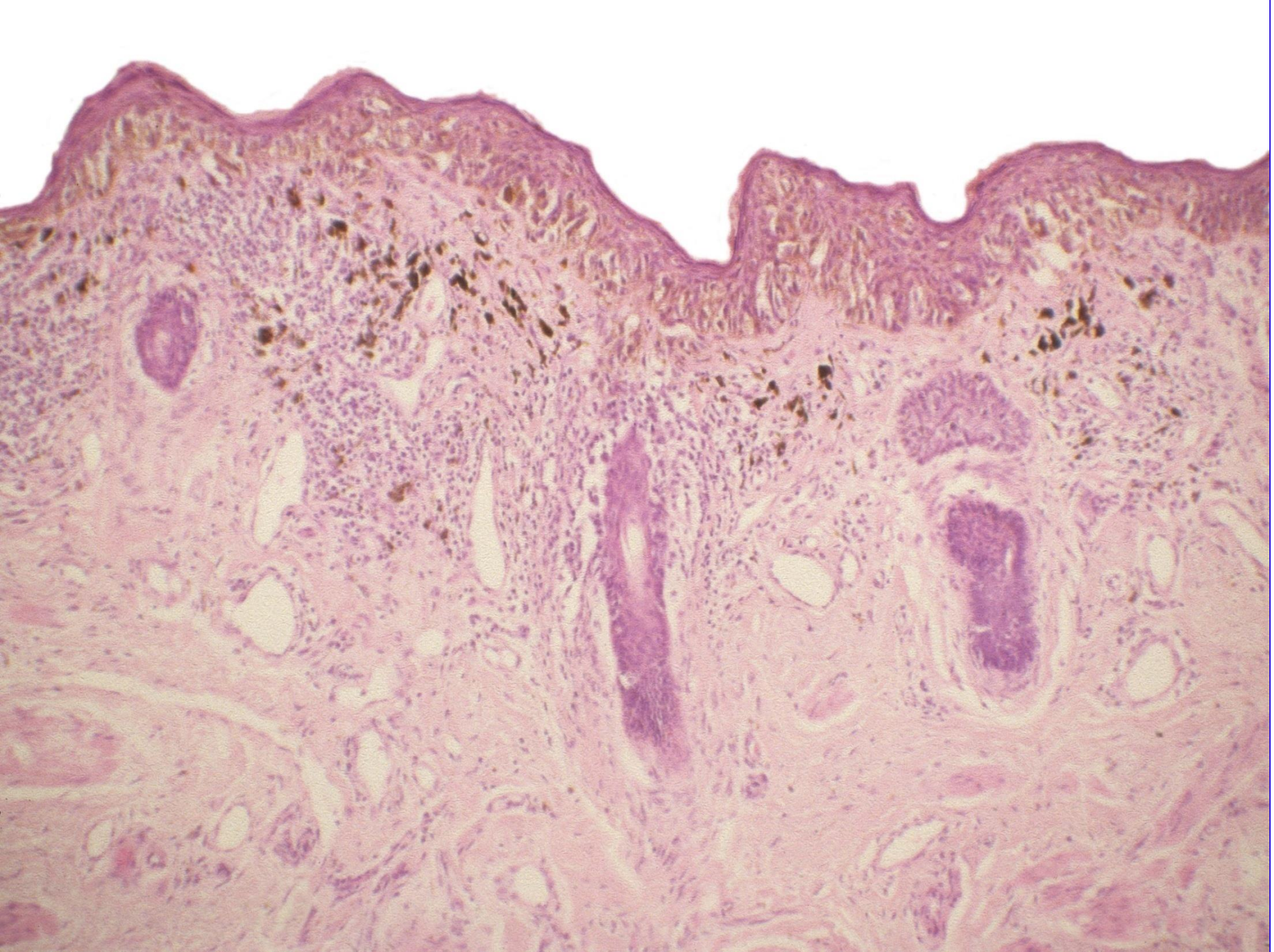
26/830 (3.1%)



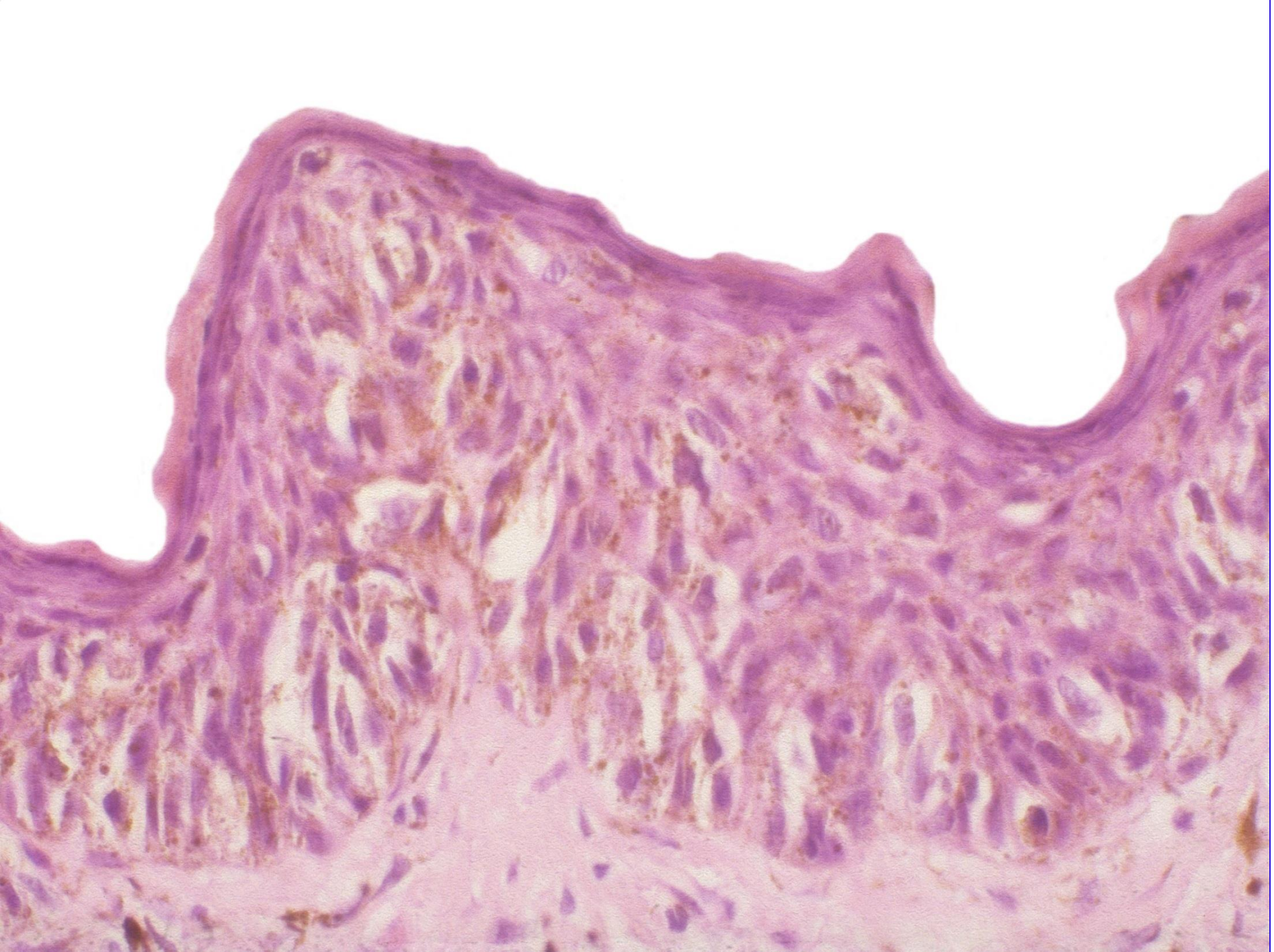
- chiefly spindled melanocytes
- minimal pagetoid spread
- epidermal atrophy
- solar elastosis

7/830 (0.7%)

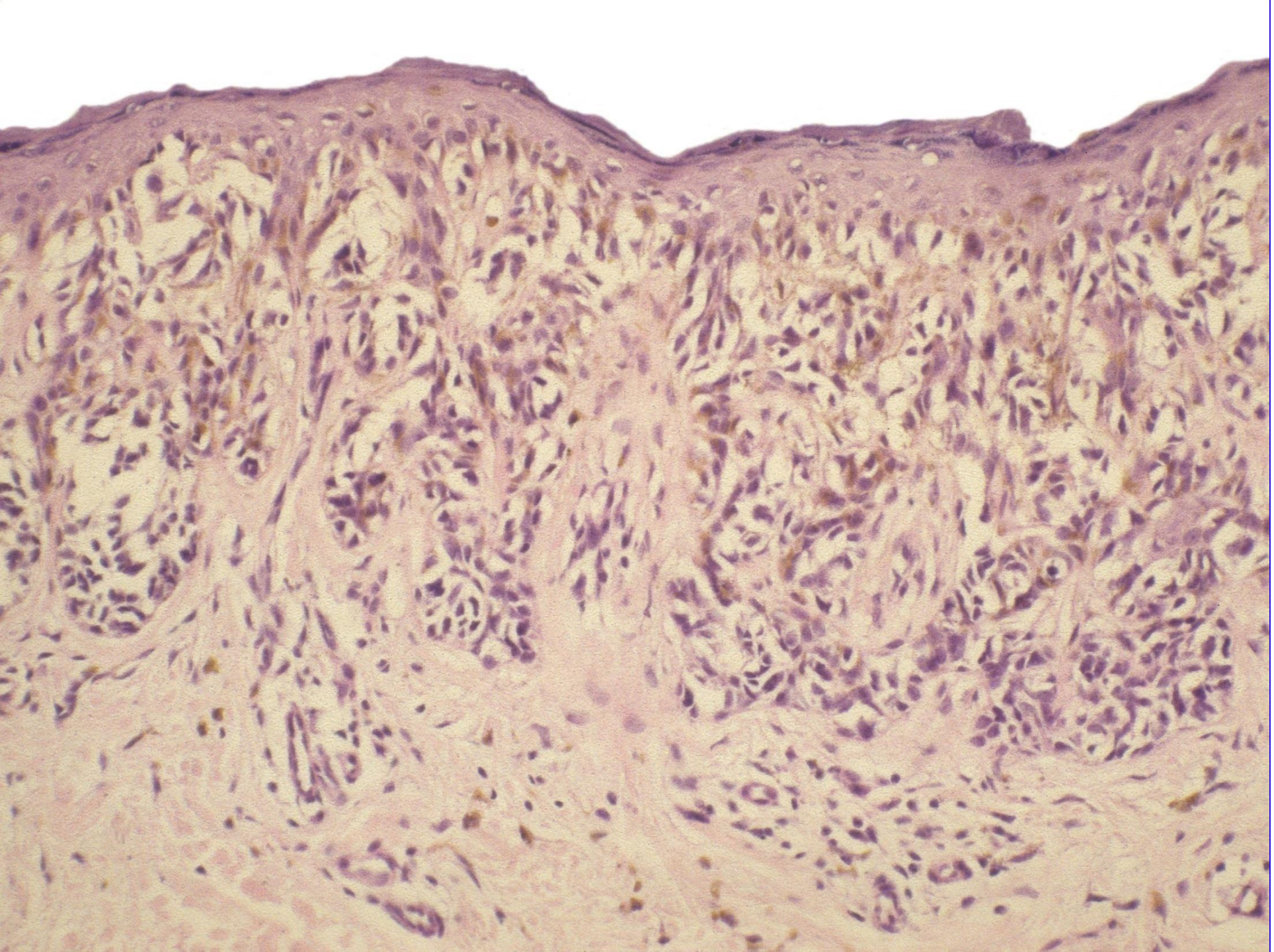
In our study, all four criteria for SSM were fulfilled in only 26 cases or 3.1%, and all criteria for LMM in only 7 cases or 0.7%.



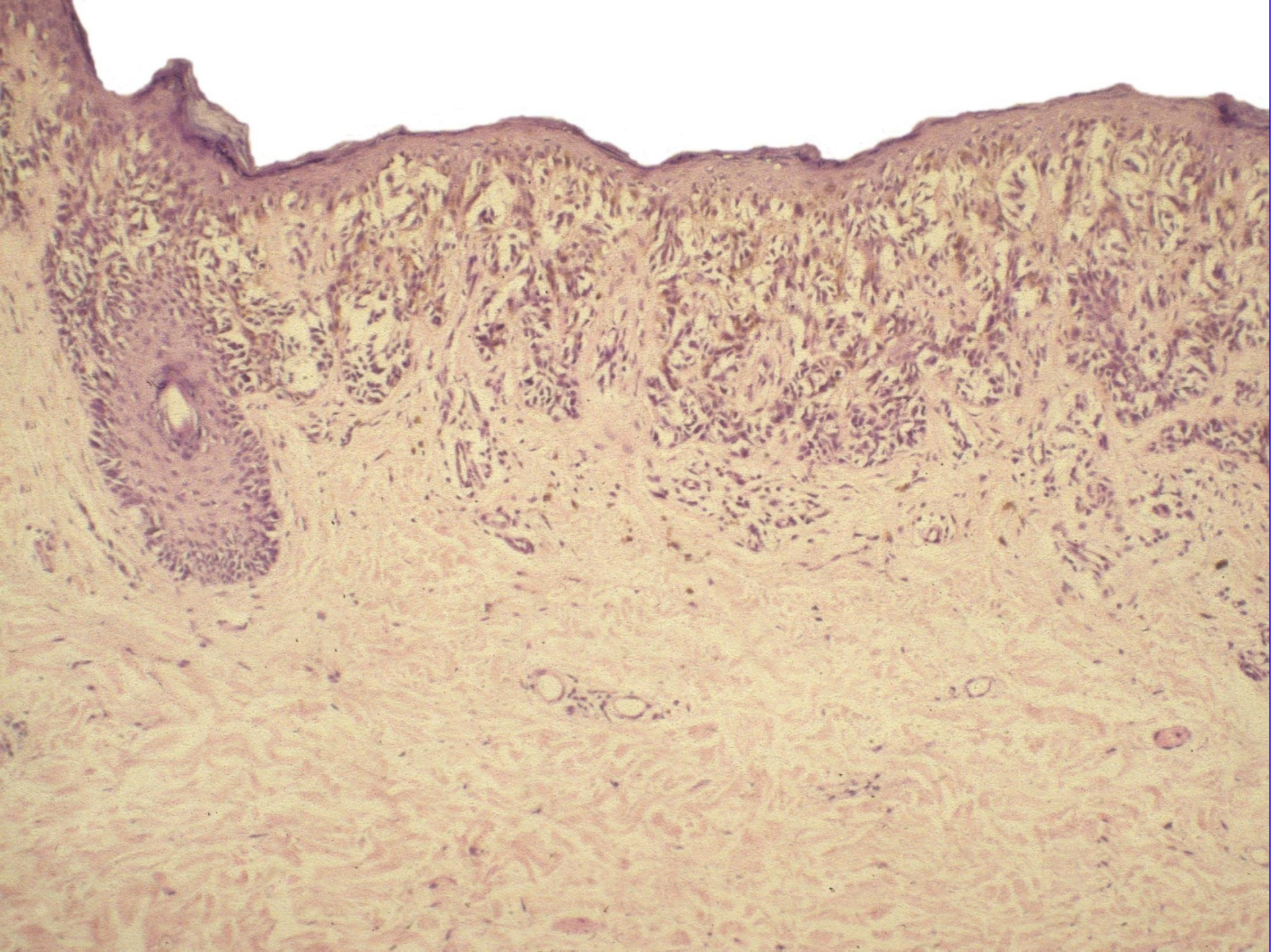
Two examples: a melanoma in sun-damaged skin with predominance of spindle cells, as demanded for LMM,



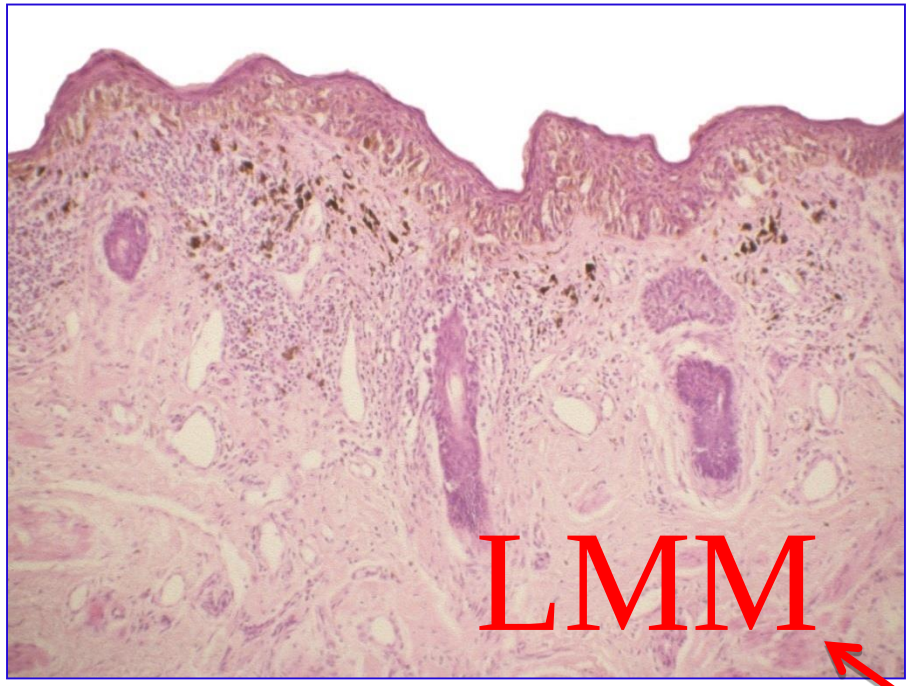
but with prominent pagetoid spread typical of SSM;

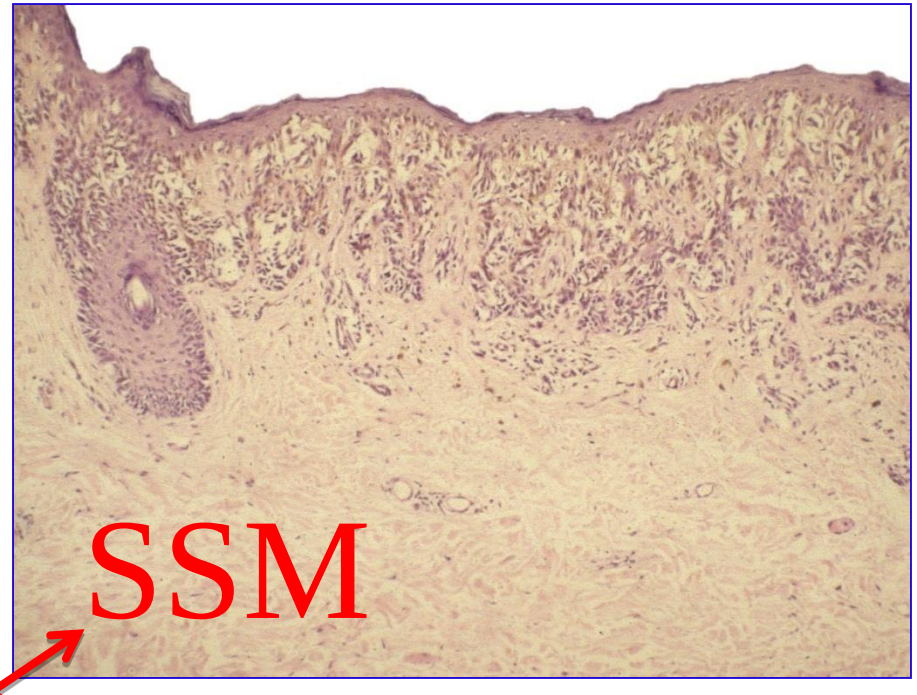


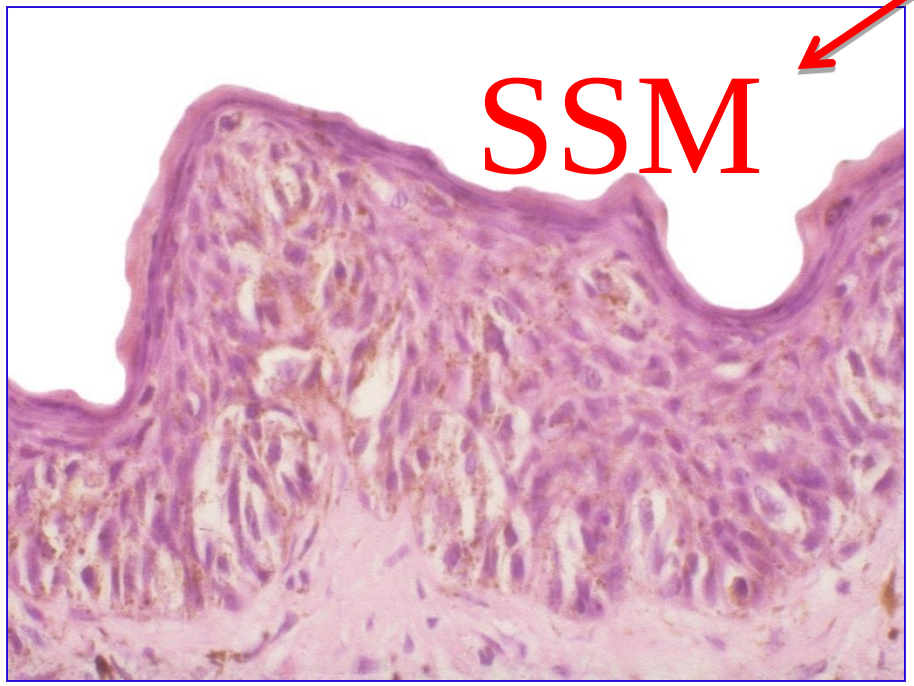
then a melanoma with predominance of spindle cells and no pagetoid spread, seemingly LMM,

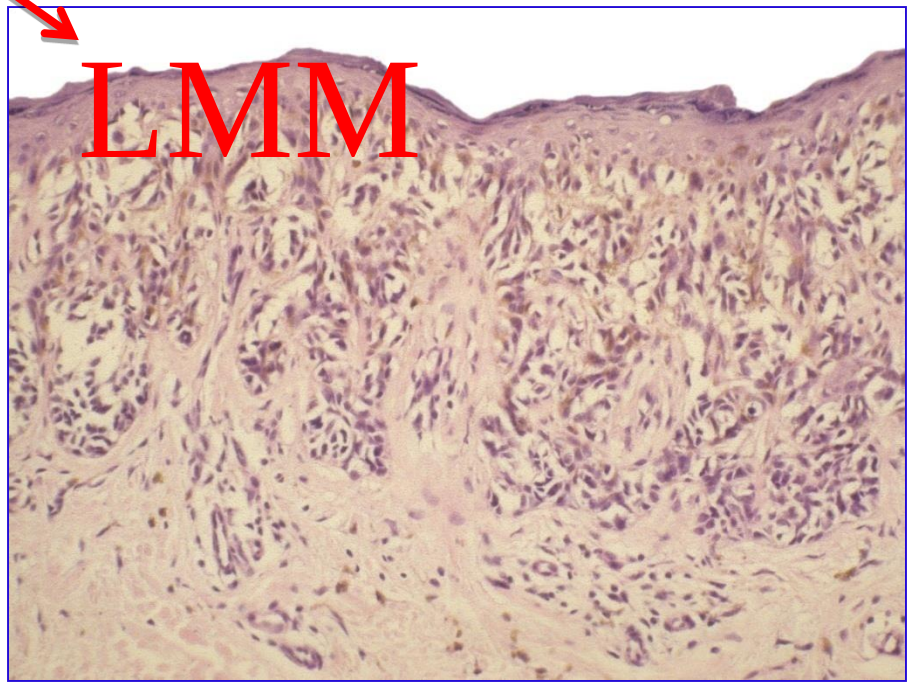


but where is the solar elastosis?









Those examples are the rule, rather than the exception, and, therefore, it usually depends on the taste of the pathologists whether he labels a melanoma SSM or LMM. This being the case, how dependable can prognostic implications be?

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

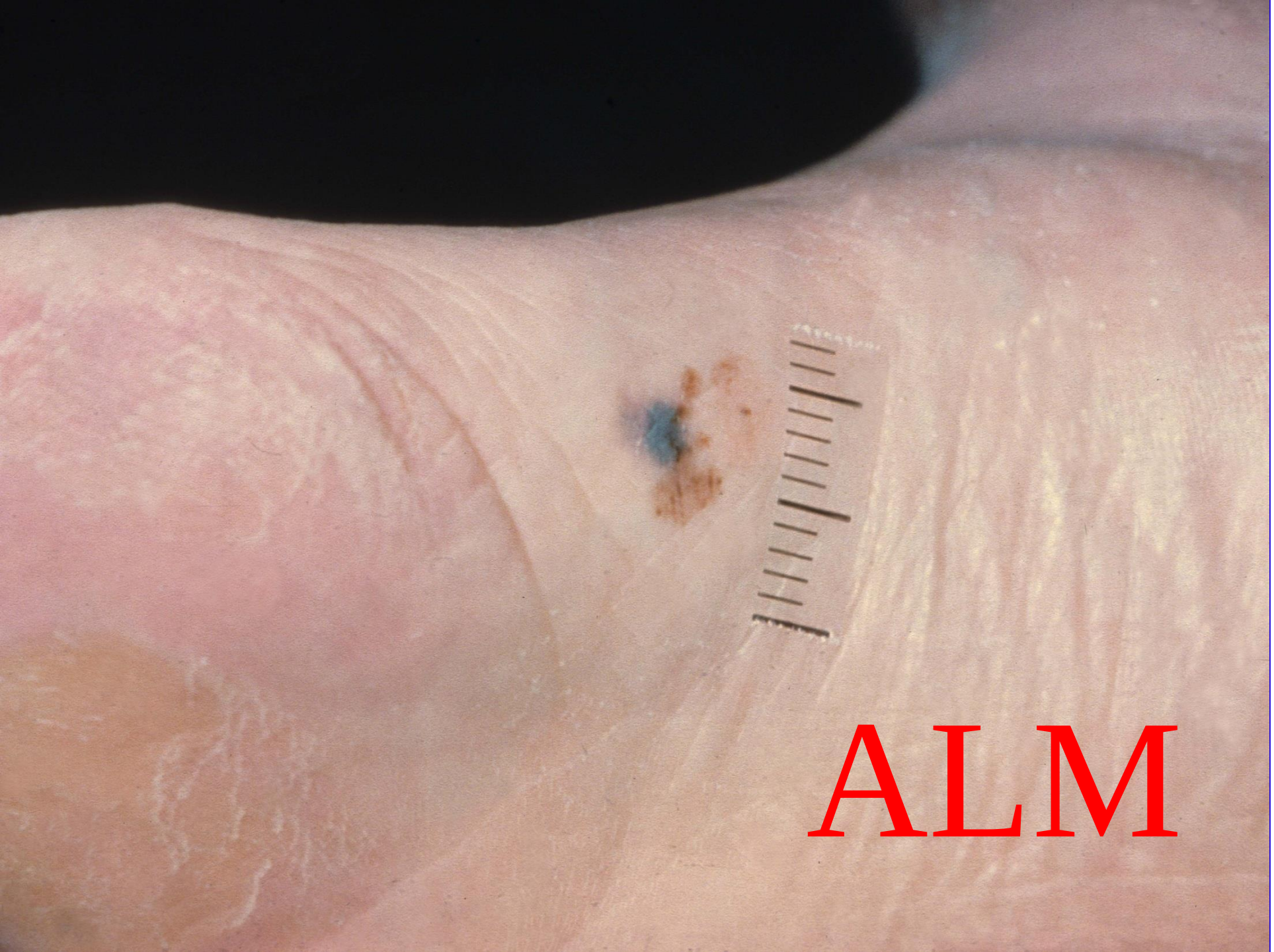
By Howard K. Koh, Edna Michalik, Arthur J. Sober, Robert A. Lew, Calvin L. Day, Wallace Clark, Martin C. Mihm, Alfred W. Kopf, M. Scott Blois, and Thomas B. Fitzpatrick

We studied 48 patients with lentigo maligna melanoma (LMM) and compared the clinical stage I patients with non-LMM melanoma patients (matched by site and thickness) to see if prognosis differed. There was no significant difference in mortality from melanoma between the two groups ($P = .68$) after a mean follow-up time of five years (67.5 months for LMM, 60.5 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 (LMM *v* non-LMM) did not make a significant contribution ($P = .61$). Our data suggest that after accounting for primary tumor thickness and site, LMM and non-LMM have the same prognosis and biologic behavior, in contrast to the widely held belief that LMM has a better prognosis than other forms of melanoma.

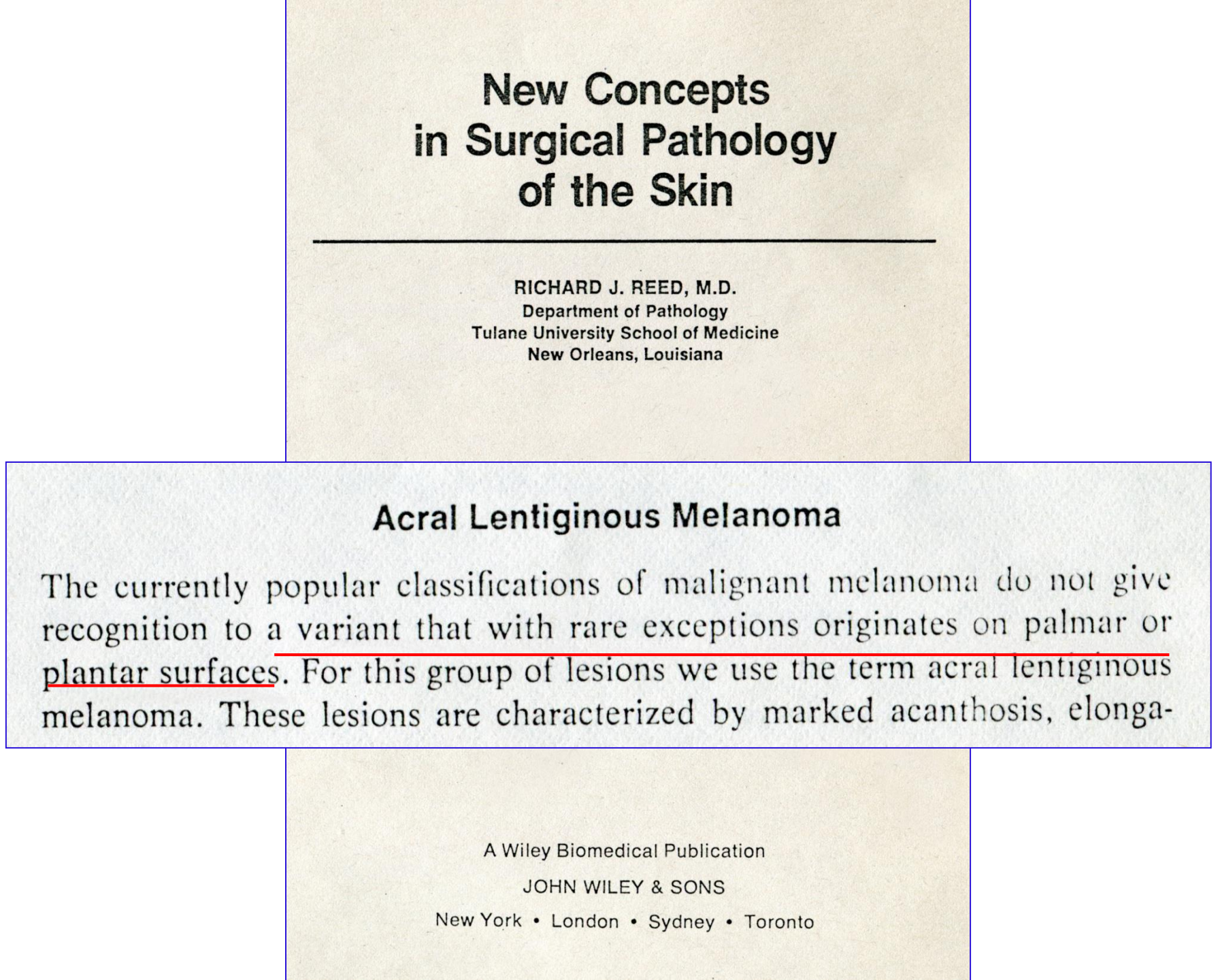
ALTHOUGH it was the first tumor type to be distinguished from other forms of melanoma,[1–4] lentigo maligna melanoma (LMM) is the least common of the principal forms of cutaneous malignant melanoma. Until recently, few investigators have questioned the clinical impression

the members of the Melanoma Clinical Cooperative Group (Massachusetts General Hospital, New York University, Temple University, and the University of California at San Francisco). Each lesion was excised and step sections were performed from the edges inward. Of these 1,130 patients, 48 were classified as having LMM by two pathologists (M.C.M. and W.C.). In these 48 patients the following tumor characteristics were

In fact, the very same authors who advanced the concept of prognostically different types of melanoma, including Clark and Mihm, acknowledged later that *"lentigo malignant melanoma has no better prognosis than other types of melanoma."*



Like SSM and LMM, acro-lentiginous melanoma is defined poorly. Usually, that term is applied to melanomas on palms and soles,



New Concepts in Surgical Pathology of the Skin

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Department of Pathology
Tulane University School of Medicine
New Orleans, Louisiana

Acral Lentiginous Melanoma

The currently popular classifications of malignant melanoma do not give recognition to a variant that with rare exceptions originates on palmar or plantar surfaces. For this group of lesions we use the term acral lentiginous melanoma. These lesions are characterized by marked acanthosis, elonga-

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but when Richard Reed described acro-lentiginous melanoma in 1976, he referred to it as a *“variant that with rare exceptions originates on palmar and plantar surfaces.“*

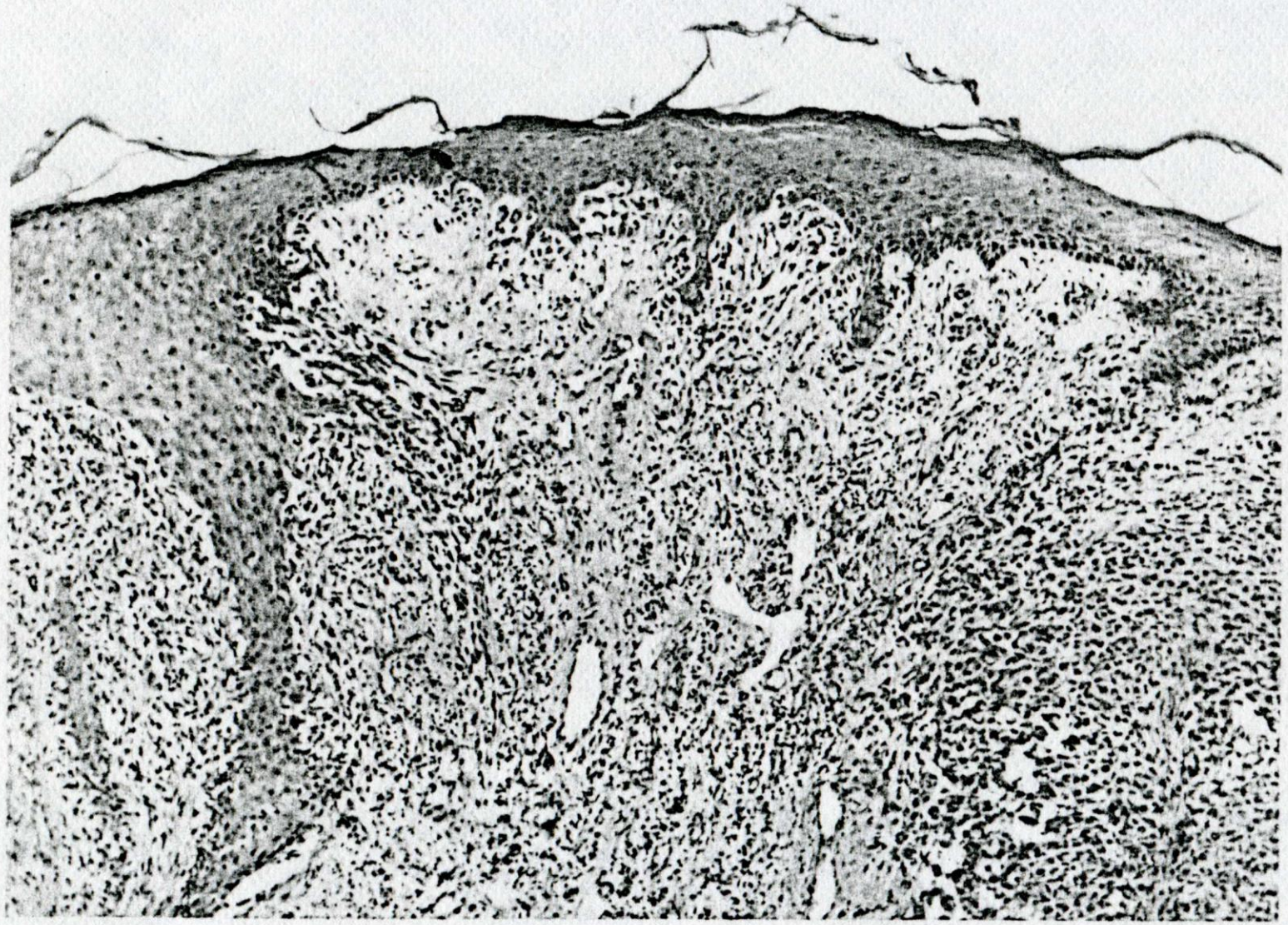
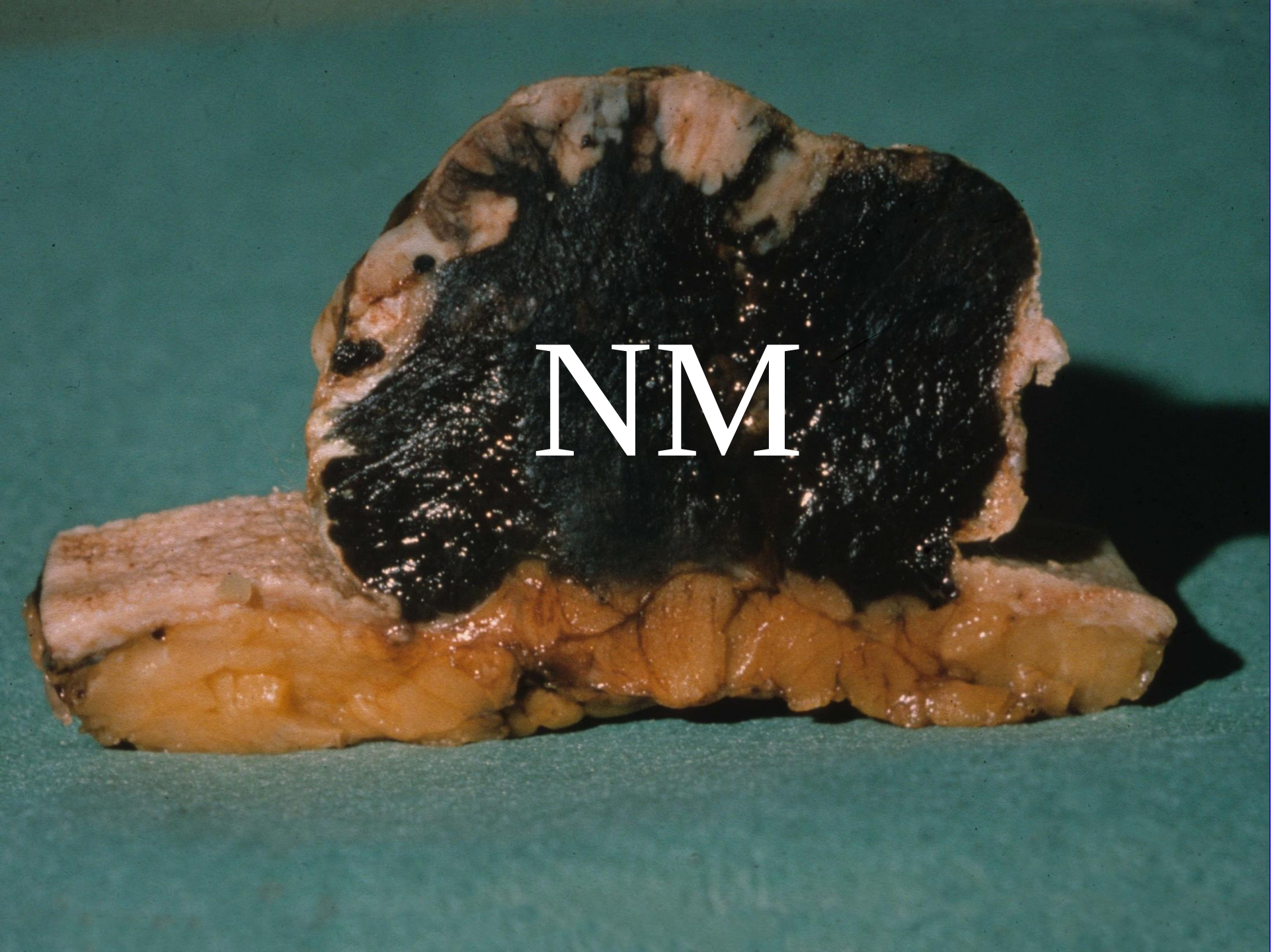


Fig. 6-31. Acral lentiginous melanoma (plantar surface) showing lentiginous pattern of atypical melanocytes at dermoepidermal interface. Fascicles of spindle-shaped tumor cells extend into a dense fibrous matrix. This type of stromal response is common in acral melanomas and may be related in part to the repeated trauma in a weight-bearing area.

Reed emphasized criteria other than anatomic site, such as a *"lentiginous pattern of atypical melanocytes at dermoepidermal interface."* As a consequence, acro-lentiginous melanomas were described not only on palms and soles, and not all melanomas on palms and soles were diagnosed as acro-lentiginous melanoma. Reed's description of ALM was so vague that one never knows what it meant by that term.



The only type of melanoma that was defined clearly was nodular melanoma.

[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

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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-

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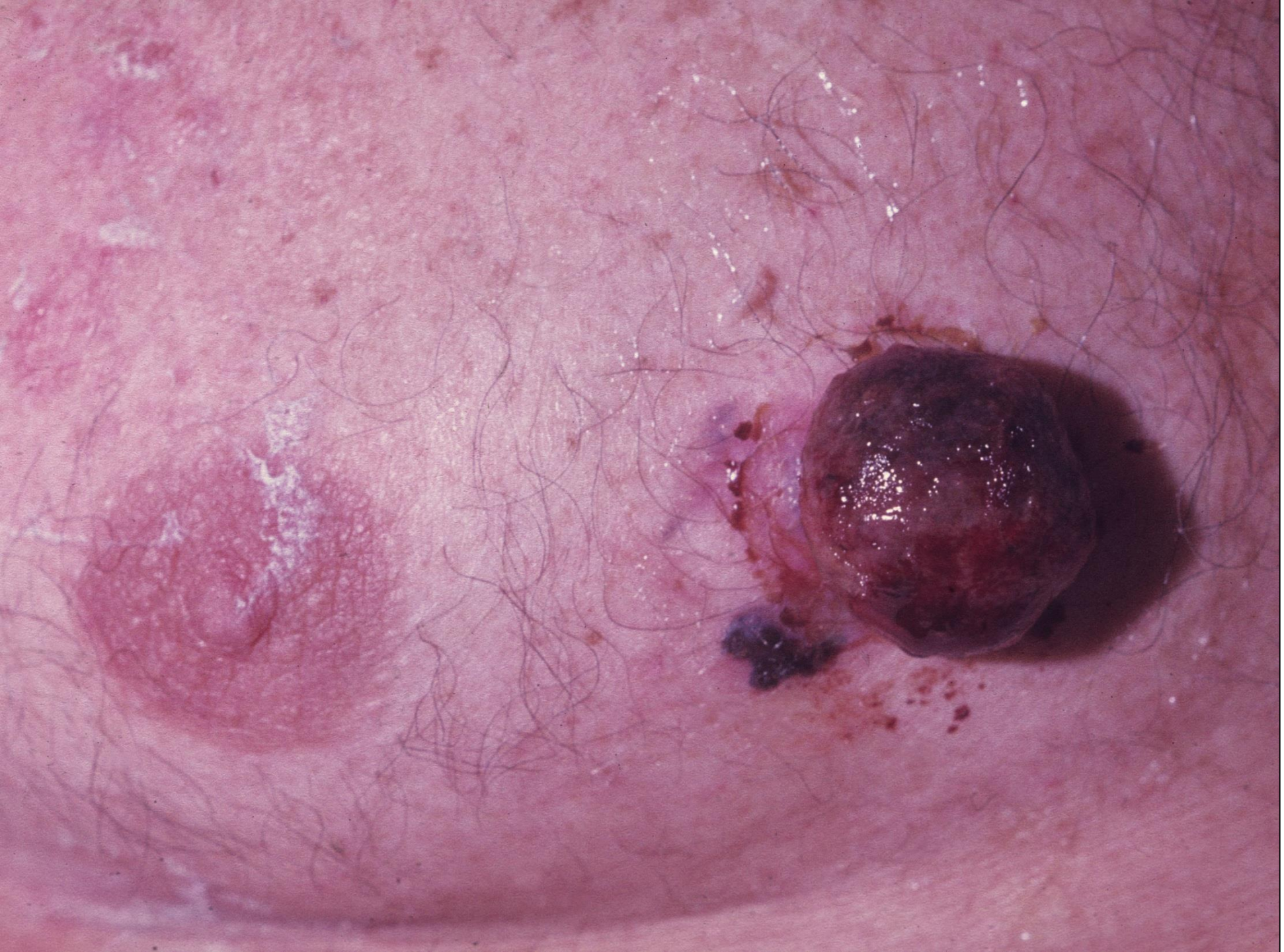
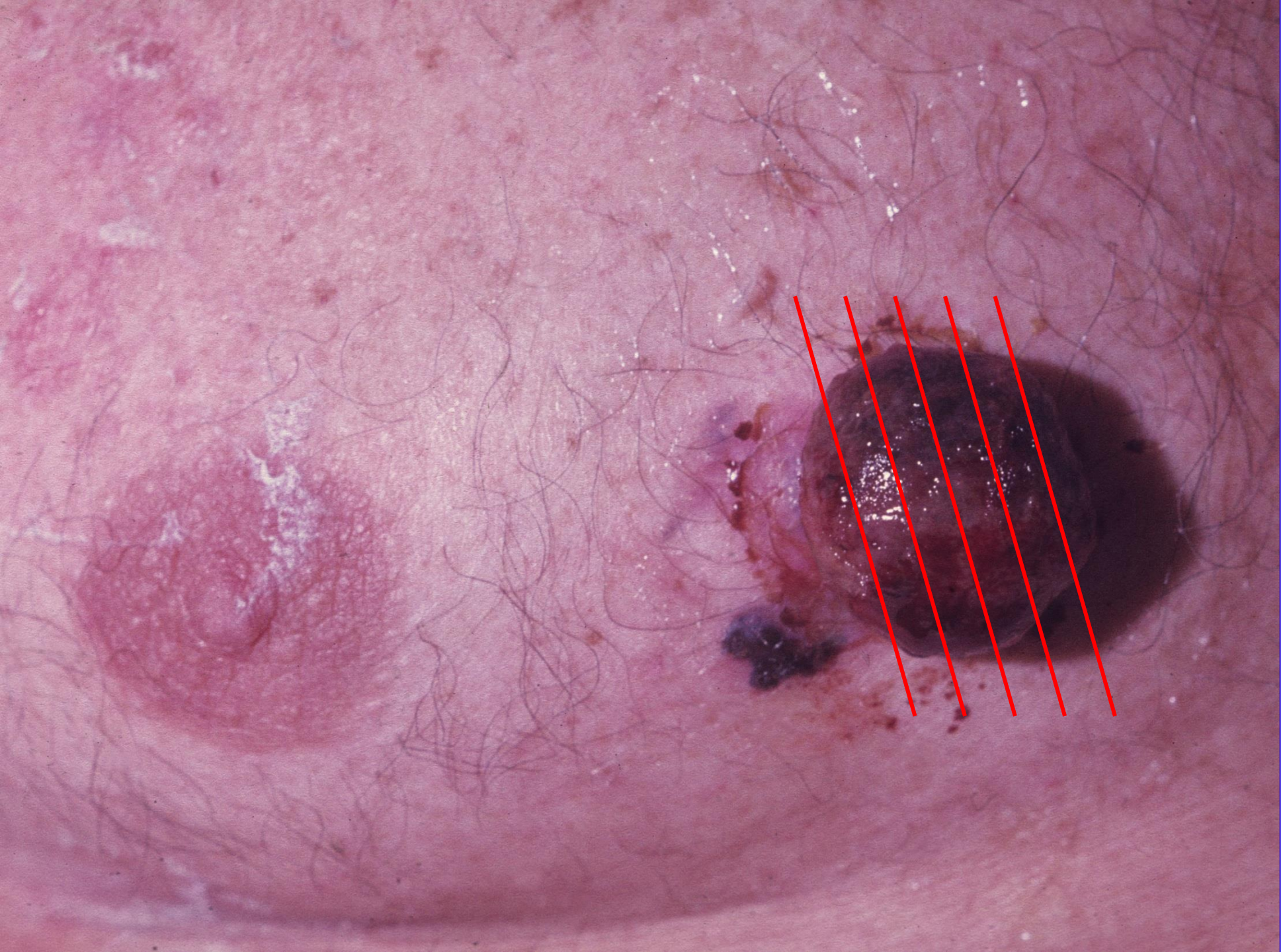
The demonstration of dermal invasion throughout the lesion, whereever there is intraepidermal growth, is nodular melanoma by definition. If this growth extends beyond the width of 3 rete ridges in any section, the tumor is classified as a superficial spreading melanoma.

Clark WH Jr. et al.
Cancer Res, 1969

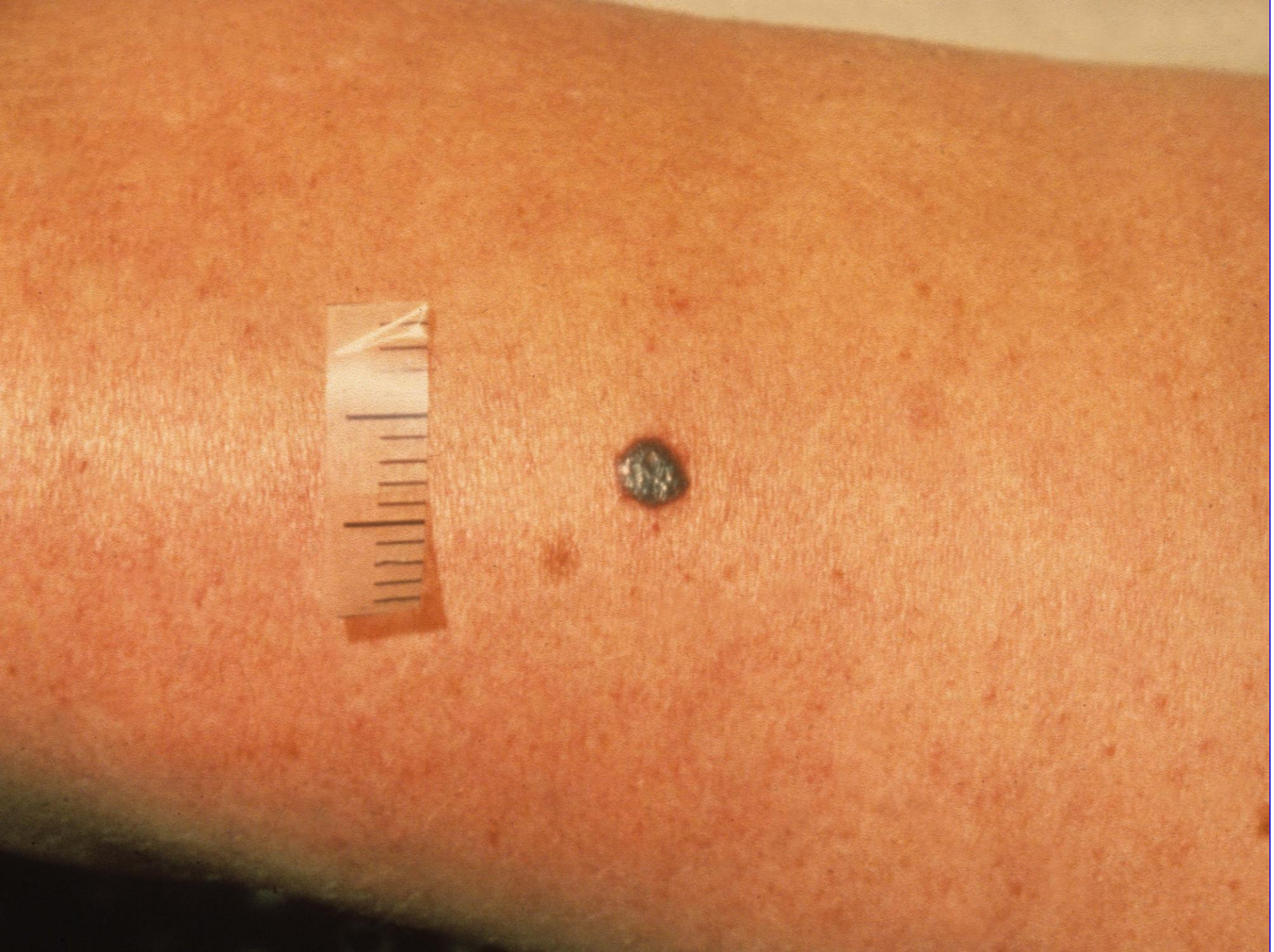
According to Clark, *"the demonstration of dermal invasion throughout the lesion, whereever there is intraepidermal growth, is nodular melanoma by definition. If this growth extends beyond the width of 3 rete ridges in any section, the tumor is classified as a superficial spreading melanoma."* In this case, we at least know what is meant if the definition is observed, but this is not always done.



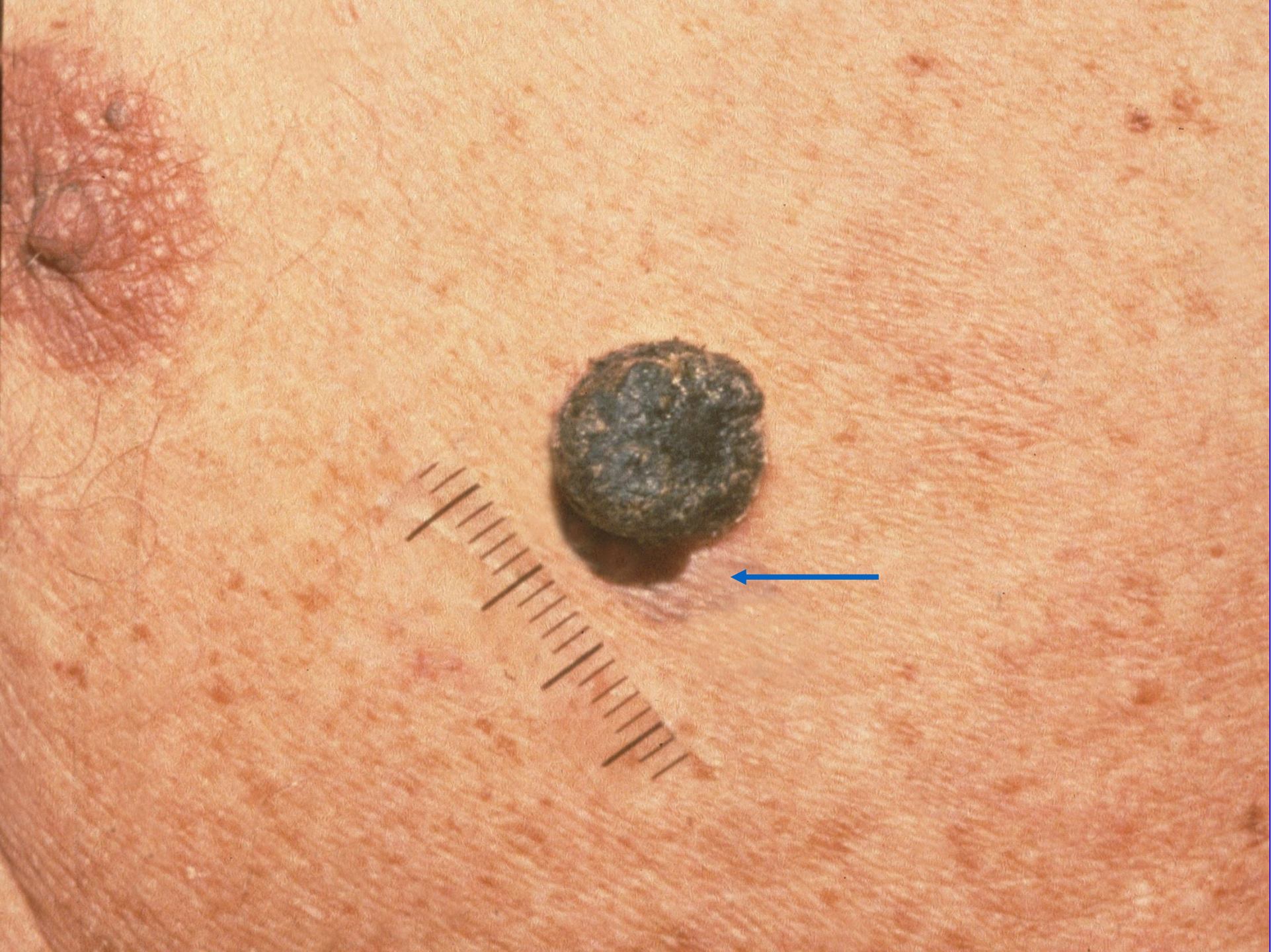
Often melanomas are referred to as “nodular” despite presence of a flat peripheral rim



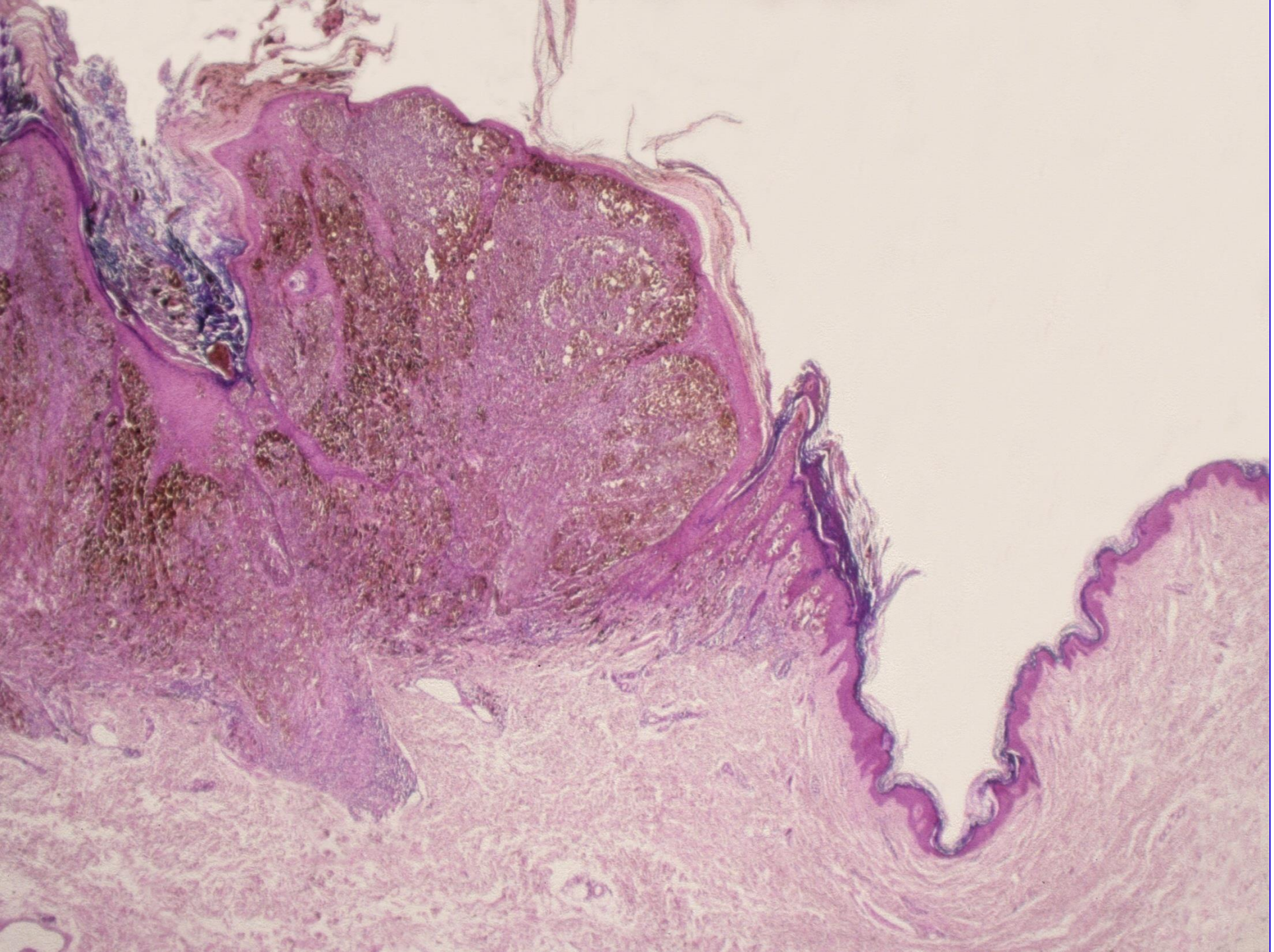
and, depending on the angle of the section, that rim may not be visible.



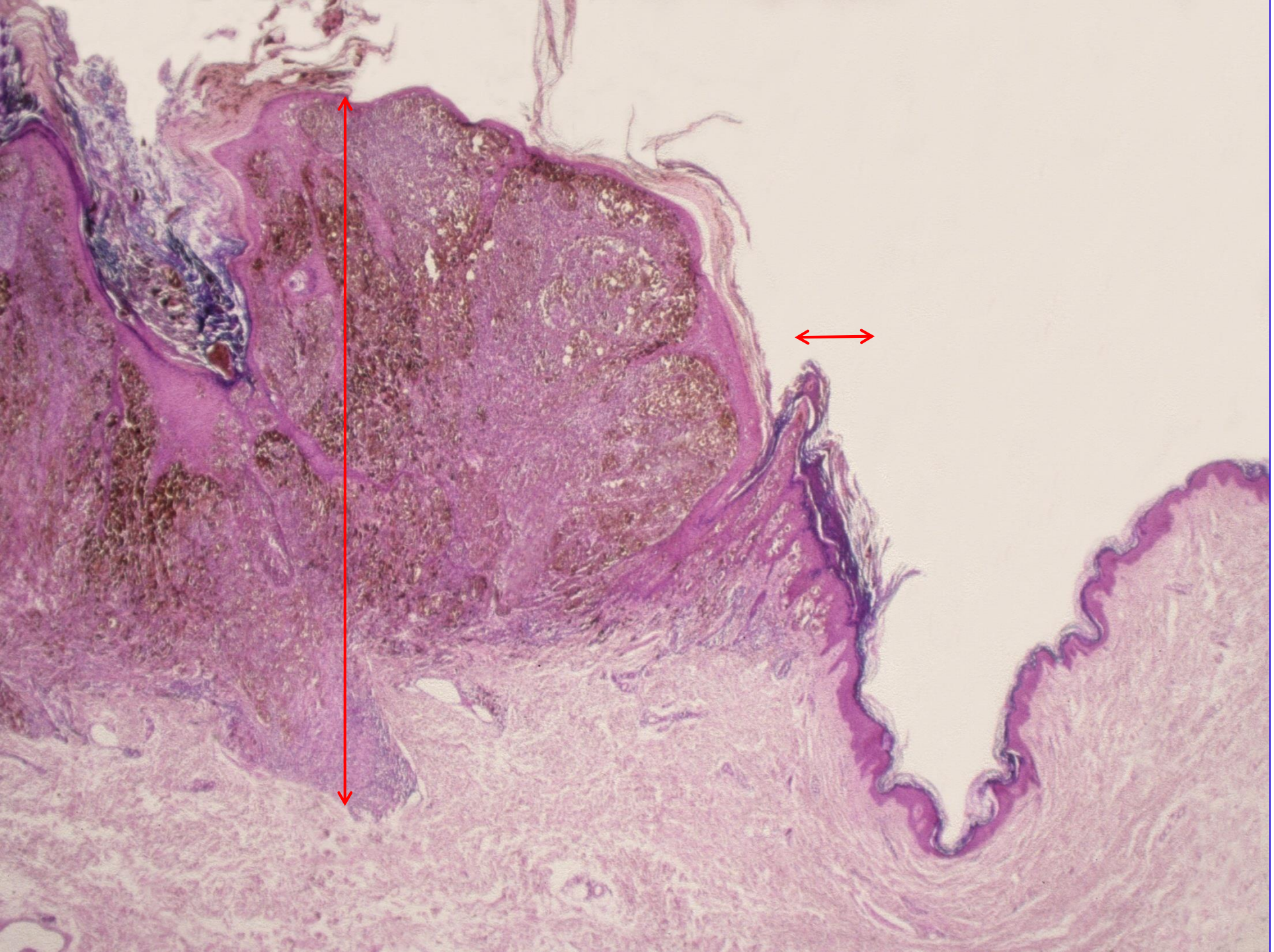
Moreover, Clark's definition is fulfilled by two types of lesions, those infiltrating the dermis early-on, corresponding to Clark's original concept,



and, much more commonly, those with disappearance of the peripheral rim secondary to regression.



Whether or not nests can be detected in the periphery may change from one section to the next.



And in regard to the asserted prognostic implications, it is advisable to use one's brain. It should be clear that, in an advanced melanoma, prognosis depends on the thick nodule and not on the question whether it extends as melanoma in situ for three or four rete ridges beyond that nodule.

Prognostic factors associated with sentinel lymph node positivity and effect of sentinel status on survival: an analysis of 1049 patients with cutaneous melanoma

Christian Kunte[a], Till Geimer[a], Jens Baumert[a,b], Birger Konz[a], Matthias Volkenandt[a], Michael Flaig[a], Thomas Ruzicka[a], Carola Berking[a] and Monika-H. Schmid-Wendtner[a,c]

Sentinel lymph node biopsy (SLNB) is a widely accepted staging procedure in patients with melanoma. However, it is unclear which factors predict the occurrence of micrometastasis and overall prognosis and whether SLNB should also be performed in patients with thin primary tumors. At our Department of Dermatology, University of Munich (Germany), 1049 consecutive melanoma patients were identified for SLNB between 1996 and 2007, and were followed-up to assess disease-free and overall survival. Of those, a total of 854 patients were analyzed prospectively. Patients with positive SLN were subjected to selective lymphadenectomy. The association of patient characteristics with SLN was assessed by multivariate logistic regression. Survival curves were performed using the Kaplan–Meier method. Cox proportional hazard regression with different adjustments was used to estimate the effect of SLN on survival. The detection rate of SLN was 97.24%, of which 24.9% were metastatic. Significant parameters upon SLN positivity were tumor thickness and nodular type of melanoma. The 5-year overall survival was 90.1 and 58.1% in SLN-negative and SLN-positive patients, respectively. Upon multivariate analysis tumor thickness and SLN status were significant factors influencing both disease-free survival and overall survival. In conclusion, our data confirm that SLNB is relevant as a diagnostic and staging procedure and that tumor thickness is of predictive importance. SLN status should be taken into account when designing clinical trials and informing patients about the probable course of their disease. Our data suggest that in case of a nodular melanoma subtype SLNB should also be considered at a tumor thickness below 1 mm. ***Melanoma Res*** **20:330–337 © 2010 Wolters Kluwer**

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Fortunately, the type of melanoma is not included in the AJCC classification, but assessment of it continues to be recommended by the AJCC, and management of patients continues to be influenced by it. For example, in this article of 2010, the authors suggest that *"in case of a nodular melanoma subtype, sentinel lymph node biopsies should also be considered at a tumor thickness below 1 mm."*

Prognostic factors associated with sentinel lymph node positivity and effect of sentinel status on survival: an analysis of 1049 patients with cutaneous melanoma

Christian Kunte[a], Till Geimer[a], Jens Baumert[a,b], Birger Konz[a], Matthias Volkenandt[a], Michael Flaig[a], Thomas Ruzicka[a], Carola Berking[a] and Monika-H. Schmid-Wendtner[a,c]

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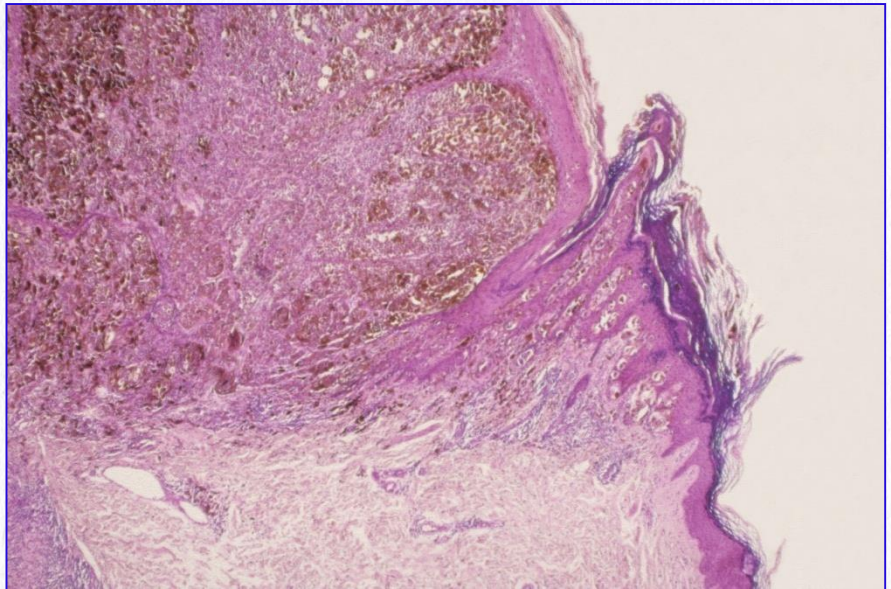

In other words, the authors advise that management of patients be based on presence of a few cells in the periphery accounting for maybe one ten thousandth of the entire tumor volume and located wholly within the epidermis. This does not make sense.

In a conflict of statistics with basic rules of logic, one should not follow curves and numbers but one’s own brain; logic should triumph.

The reason is that the human body is far too complex to be calculable even for the most aspiring mathematicians,

Statistics

and that all data entering the meat chopper of statistics are based on subjective assessment of morphologic findings. Those truths seem to be self-evident, but they were neglected

Statistics

Cox Proportional Hazard Model

as methods of statistics became more and more advanced. In 1972, the Cox proportional hazard model was introduced that allows estimation of the influence of several independent variables on a dependent variable,

Statistics

Cox Proportional Hazard Model

such as the influence of production and sales on the storage period of industrial goods.

independent

production

sales

↓

dependent

storage period

Statistics

Cox Proportional Hazard Model

In oncology, the method was used to assess the influence of factors such as ulceration and mitoses on the survival rate of patients

independent

ulceration

mitoses

↓

dependent

survival rate

Statistics

Cox Proportional Hazard Model

and was praised, in 2009, as *"the most important methodological development in the area of survival data analysis in over three decades."*

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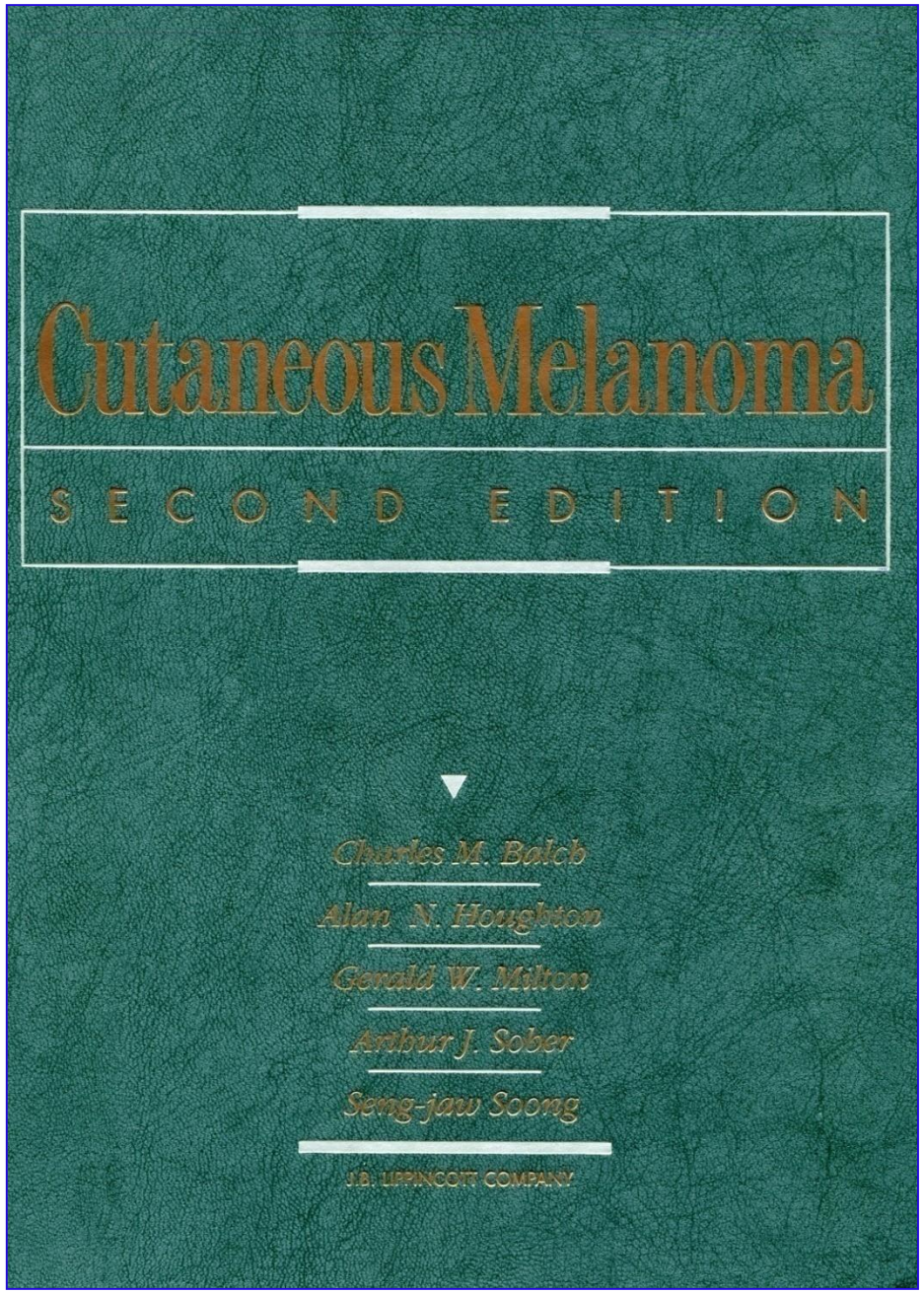
Ding et al.
J Biopharm Med, 2009



The Hazard Function

The hazard function at time t, denoted by $\lambda(t)$, is defined as the instantaneous risk of death or failure at time t, provided that death or failure has not already occurred. It can roughly be interpreted as the rate of death or failure per unit time. In the multifactorial analysis of survival data, the hazard is often expressed as a function of the concomitant information related to patients' survival times. Cox's model describes this relationship in terms of the following mathematical form:

$$\lambda(t) = \lambda_0(t)\exp[\beta_1(X_1 - \bar{X}_1) + \beta_2(X_2 - \bar{X}_2) + \ldots + \beta\rho(X\rho - \bar{X}\rho)]$$

where X_1, X_2, . . ., $X\rho$ are the values of ρ measured patient characteristics (or prognostic factors), $\bar{X}_1$, $\bar{X}_2$, . . ., $\bar{X}\rho$ are the mean values of those variables, β_1, β_2, . . ., $\beta\rho$ are regression coefficients to be estimated from the data, and $\lambda_0(t)$ is an arbitrary baseline hazard function where all prognostic variables are at their average values.

Cox's model can also be written in terms of the relative risk; this is defined by $\lambda(t)/\lambda_0(t)$, which is equal to

$$\exp[\beta_1(X_1 - \bar{X}_1) + \beta_2(X_2 - \bar{X}_2) + \ldots + \beta\rho(X\rho - \bar{X}\rho)].$$

In the textbook on melanoma by Balch and co-workers, the mathematical formula is shown, and the different variables are explained, including *"measured patient characteristics (or prognostic factors), …the mean values of those variables, … regression coefficients to be estimated from the data, and $\lambda_0(t)$ …, an arbitrary baseline hazard function where all prognostic variables are at their average values."*

TUMOR THICKNESS SUBGROUP	PROGNOSTIC MODEL	DEFINITION AND CODING OF THE COVARIATE (X_i) WITHIN THE TUMOR THICKNESS SUBGROUP
<0.76 mm	$\hat{S}_1(t) = [\hat{S}_{10}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -1.11316(X_1 - 0.55769) + 0.73644(X_2 - 0.40247)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (level of invasion) = 0, if level II; = 1, if other levels.
0.76–1.49 mm	$\hat{S}_2(t) = [\hat{S}_{20}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -1.02481(X_1 - 0.90731) - 0.78450(X_2 - 0.55459) + 1.21636(X_3 - 0.89395)$	X_1 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_2 (lesion location) = 0, if axial; = 1, if extremity. X_3 (level of invasion) = 0, if level II; = 1, if other levels.
1.50–2.49 mm	$\hat{S}_3(t) = [\hat{S}_{30}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.61149(X_1 - 0.52813) - 0.58611(X_2 - 0.66705) - 0.79938(X_3 - 0.49024)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_3 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.
2.50–3.99 mm	$\hat{S}_4(t) = [\hat{S}_{40}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.35556(X_1 - 0.50000) - 0.33959(X_2 - 0.56157) - 0.38754(X_3 - 0.41791) - 0.46234\ (X_4 - 0.54851)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_3 (sex) = 0, if male; = 1, if female. X_4 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.
4.00–7.99 mm	$\hat{S}_5(t) = [\hat{S}_{50}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.56653(X_1 - 0.41690) + 0.54407(X_2 - 0.81690) - 0.76193(X_3 - 0.45352)$	X_1 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_2 (level of invasion) = 0, if levels II, III; = 1, if levels IV, V. X_3 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.

All those variables entered into complex computations, and in the apparel of numbers, up to the fifth place after the decimal point, oncology almost looked like exact science.

However, the quality of results of statistics depends on the quality of data entering into them.

The latter is influenced by their validity, which can be enhanced by precise definitions, their reliability, which can be enhanced by focusing on findings easy to assess, and the size of the database. The American Joint Committee on Cancer neglected validity and reliability

Prognostic Factors Analysis of 17,600 Melanoma Patients: Validation of the American Joint Committee on Cancer Melanoma Staging System

By Charles M. Balch, Seng-Jaw Soong, Jeffrey E. Gershenwald, John F. Thompson, Douglas S. Reintgen, Natale Cascinelli, Marshall Urist, Kelly M. McMasters, Merrick I. Ross, John M. Kirkwood, Michael B. Atkins, John A. Thompson, Daniel G. Coit, David Byrd, Renee Desmond, Yuting Zhang, Ping-Yu Liu, Gary H. Lyman, and Aberto Morabito

Purpose: **The American Joint Committee on Cancer (AJCC) recently proposed major revisions of the tumor-node-metastases (TNM) categories and stage groupings for cutaneous melanoma. Thirteen cancer centers and cancer cooperative groups contributed staging and survival data from a total of 30,450 melanoma patients from their databases in order to validate this staging proposal.**

Patients and Methods: **There were 17,600 melanoma patients with complete clinical, pathologic, and follow-up information. Factors predicting melanoma-specific survival rates were analyzed using the Cox proportional hazards regression model. Follow-up survival data for 5 years or longer were available for 73% of the patients.**

Results: **This analysis demonstrated that (1) in the T category, tumor thickness and ulceration were the most powerful predictors of survival, and the level of invasion had a significant impact only within the subgroup of thin (≤ 1 mm) melanomas; (2) in the N category, the following three independent factors were identified: the number of metastatic nodes, whether nodal metastases were clinically occult or clinically apparent, and the presence or absence of primary tumor ulceration; and (3) in the M category, nonvisceral metastases was associated with a better survival compared with visceral metastases. A marked diversity in the natural history of pathologic stage III melanoma was demonstrated by five-fold differences in 5-year survival rates for defined subgroups. This analysis also demonstrated that large and complex data sets could be used effectively to examine prognosis and survival outcome in melanoma patients.**

Conclusion: **The results of this evidence-based methodology were incorporated into the AJCC melanoma staging as described in the companion publication.**

J Clin Oncol 19:3622-3634.

and tried to improve the quality of statistics exclusively by enhancing the number of cases. In 2001, “prognostic factors analysis of 17,600 melanoma patients”

resulted in a classification of primary melanoma based on thickness, ulceration, and Clark levels, ulceration being newly introduced as a prognostic factor.

Melanoma TNM Classification

T classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III
		b: with ulceration or level IV/V
T2	1.01-2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01-4.0 mm	a: without ulceration
		b: with ulceration
T4	> 4.0 mm	a: without ulceration
		b: with ulceration

AJCC, 2001

Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis $< 1/mm^2$
		b: With ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2.00	a: Without ulceration
		b: With ulceration
T3	2.01-4.00	a: Without ulceration
		b: With ulceration
T4	> 4.00	a: Without ulceration
		b: With ulceration

AJCC, 2009

By 2009, the database had been expanded more than twofold, and another new factor was introduced, namely, mitoses.

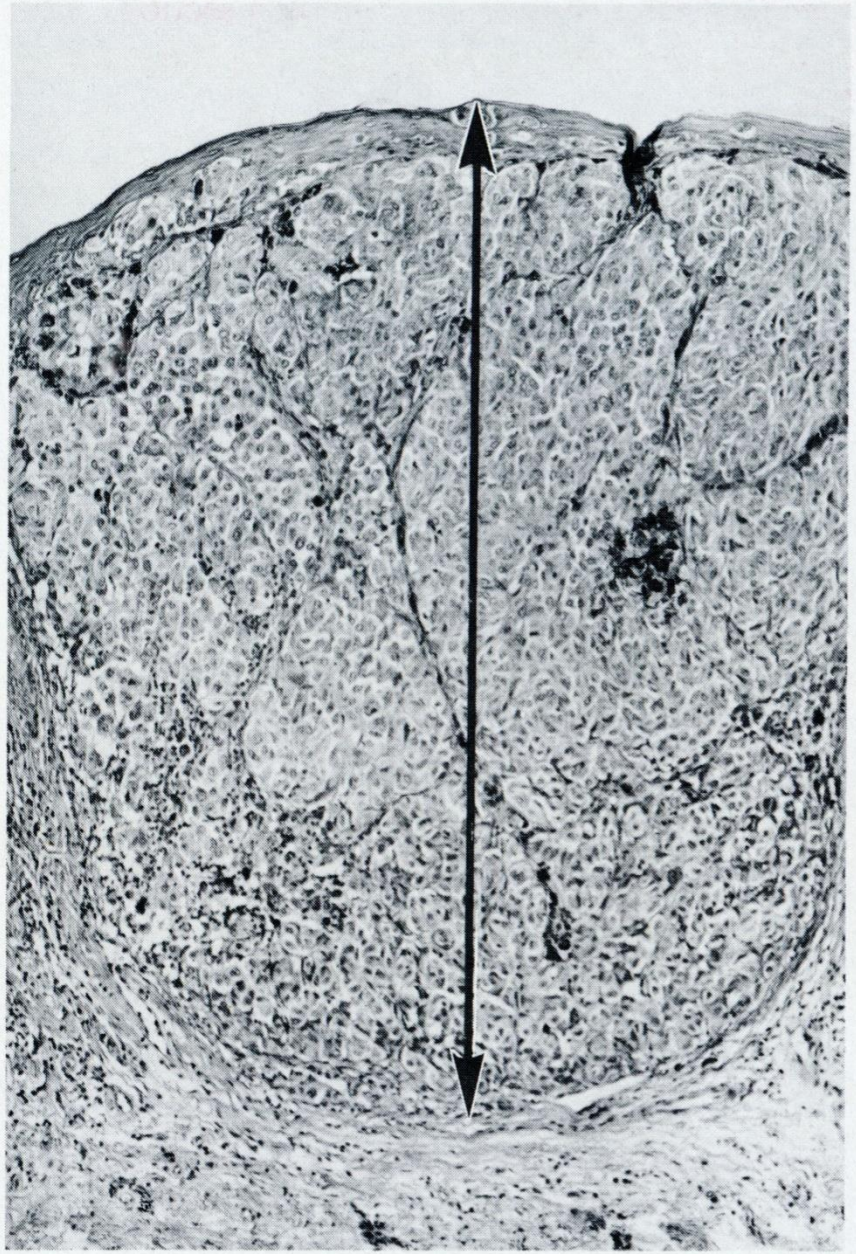
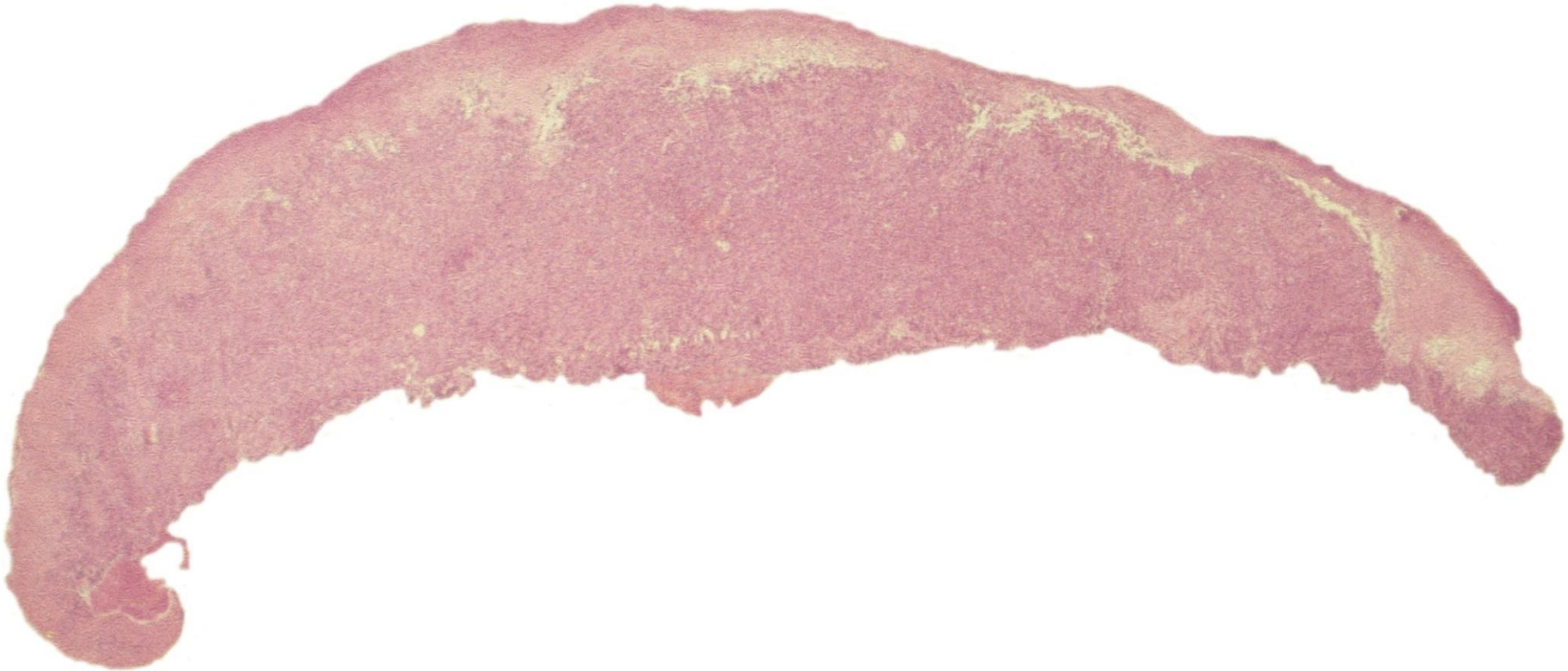
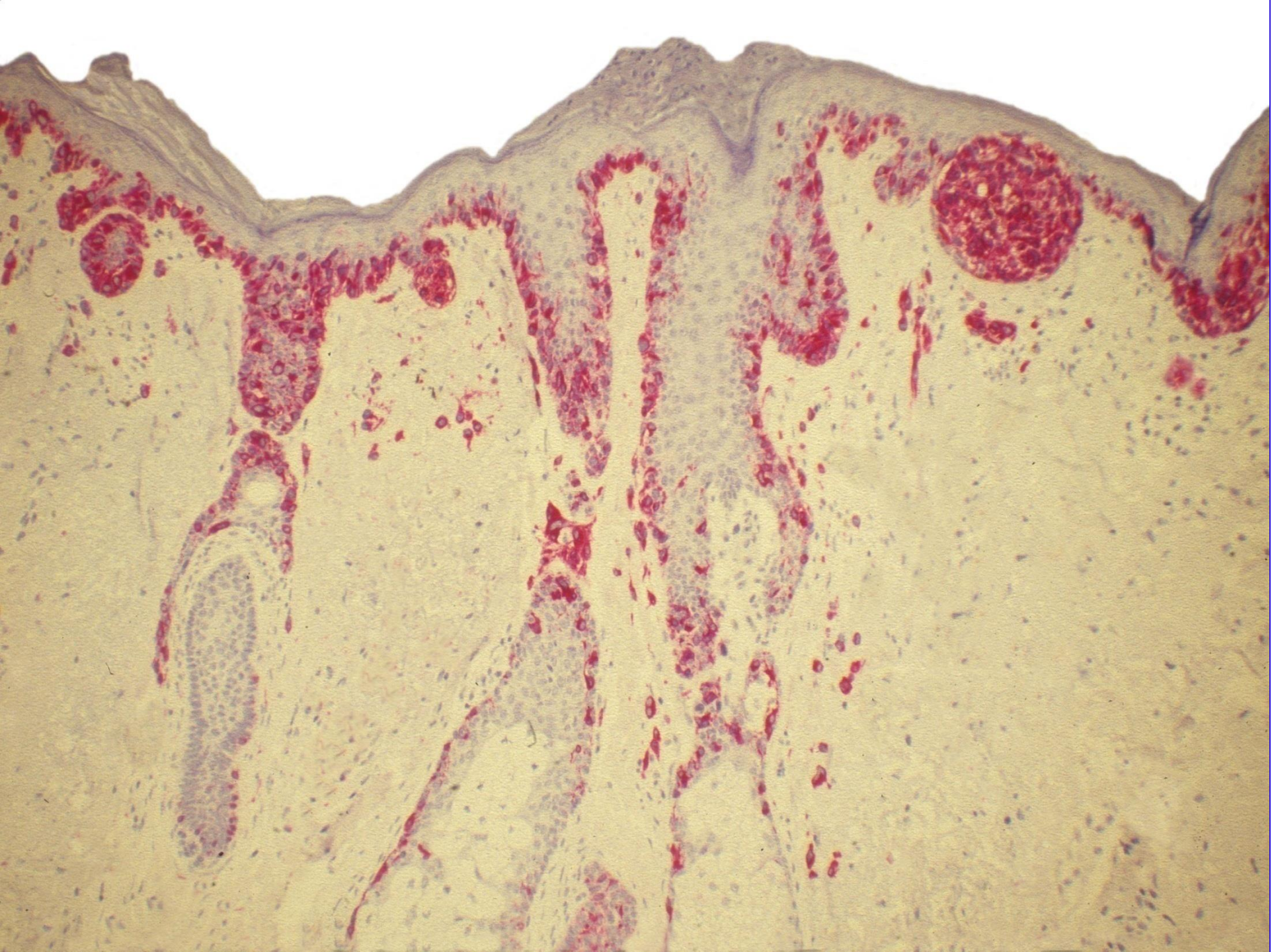


Fig. 1. Tumor thickness. The distance between the stratum granulosum (or, when absent, between the uppermost tumor cells) and the lowermost tumor cells is measured in millimeters microscopically at the thickest portion of the tumor.

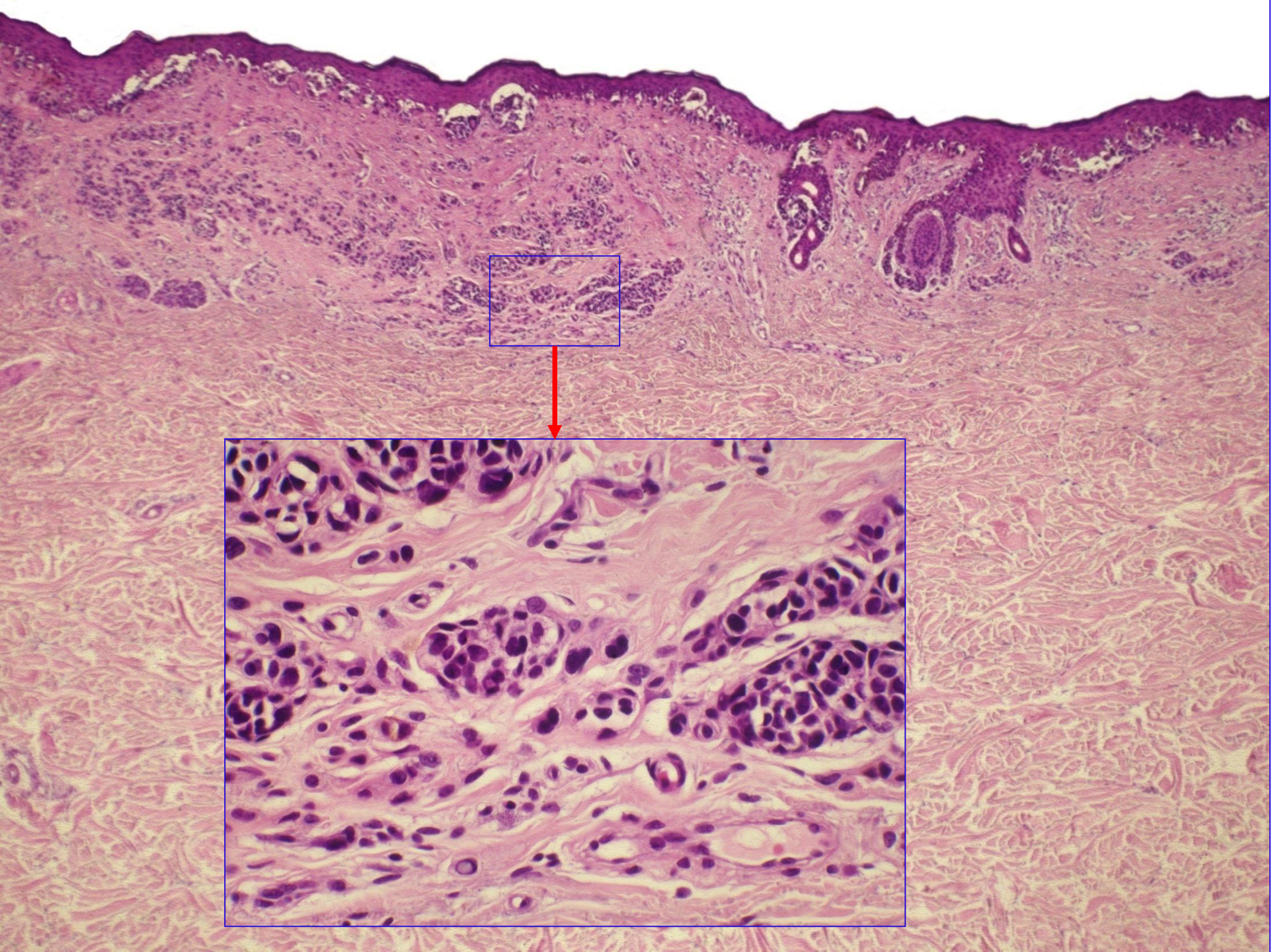
Let us take a look at validity and reliability of those variables. The most important one is thickness that is clearly defined as the greatest vertical distance between granular zone and the deepest melanoma cell in the dermis. Assessment of thickness is usually easy and, therefore, reliable. However, a number of problems may arise.



1) Melanomas are increasingly often excised incompletely so that their true thickness cannot be determined.



2) Many melanomas show extensions of neoplastic cells along adnexal structures, and it is unclear if, and how, those extensions into the depth should be included in the measurement.



3) There are often nevus-like cells in the dermis, and it is difficult to decide whether those cells belong to the melanoma or to an associated nevus. That subjective decision may influence measurement of thickness significantly.

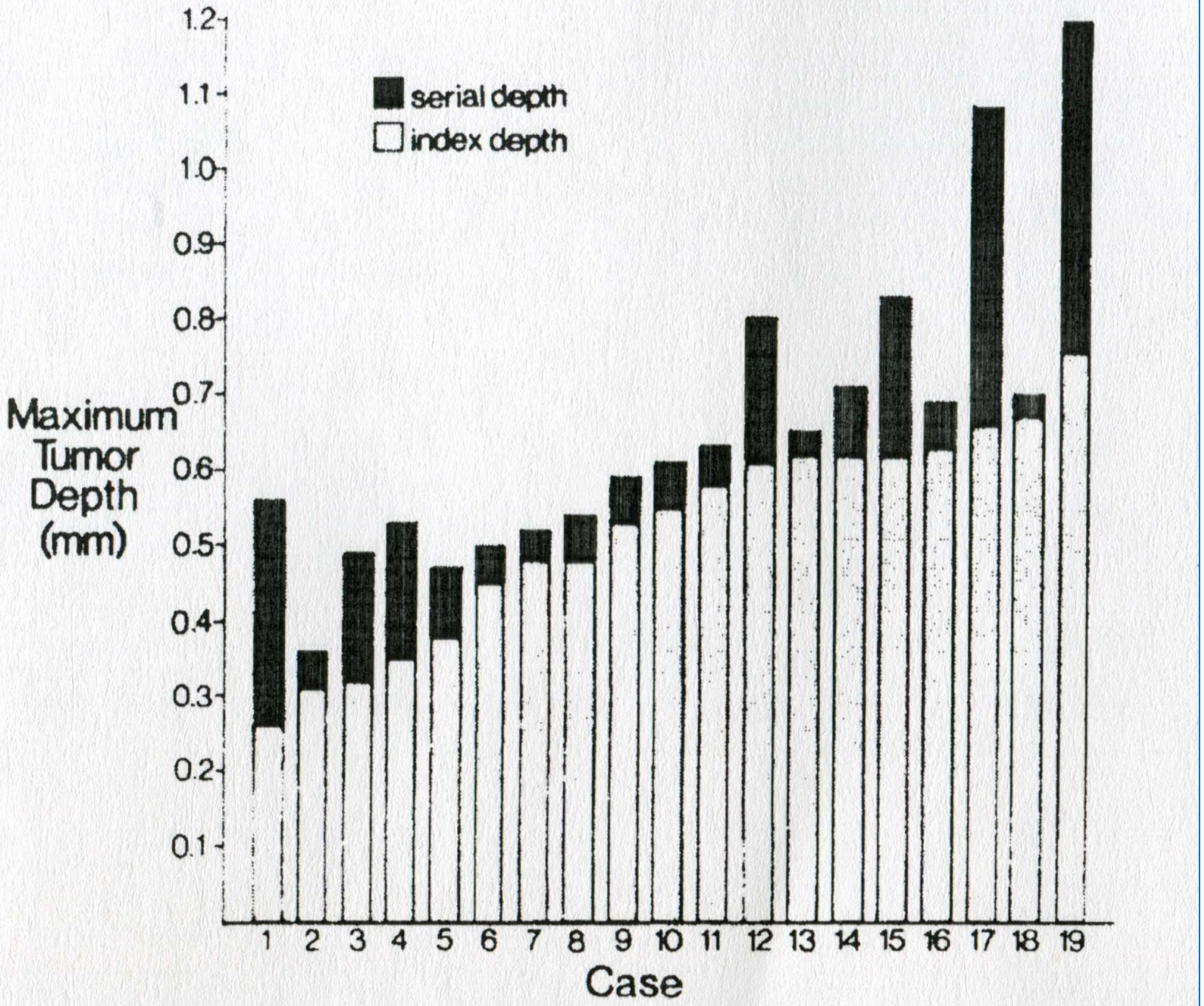
An Evaluation of Vertical Growth in Thin Superficial Spreading Melanomas by Sequential Serial Microscopic Sections

ALVIN R. SOLOMON,*† MD, CHARLES N. ELLIS,†‡ MD, AND JOHN T. HEADINGTON,*† MD

In the decade since Breslow first described the technique of measuring tumor thickness in cutaneous melanoma and its prognostic significance, this measurement has become an integral part of the histologic evaluation of these tumors. In an attempt to define the effect of specimen sampling on this measurement, the authors compared their routine sampling method in which microscopic sections were examined at consecutive 3 mm intervals with one utilizing sequential microscopic serial sections of approximately 5 μm each in 19 cases of thin (<0.76 mm in depth) superficial spreading melanomas. All cases showed an increase in the measured maximum tumor thickness when serially sectioned, but neither deep dermal extension of melanoma nor angiolymphatic invasion by tumor were observed. Measured thickness in thin cutaneous melanoma is a function of the number of sections examined. The method of specimen sampling needs to be carefully defined and standardized in studies that attempt to define prognosis on the basis of tumor thickness. It is proposed that the routine sampling technique of the authors meets these criteria and that it be adopted as a standardized method of examining pigmented cutaneous specimens.

Cancer **52:2338–2341, 1983.**

4) Measurement of thickness depends on the technique of procession of the specimen. Nearly thirty years ago, Salomon and co-workers compared routine sampling with sequential serial microscopic sections and found that *"measured thickness in thin cutaneous melanoma is a function of the number of sections examined."*



Thickness was significantly higher when serial sections were assessed. 5) One always has to be aware of the limitations of the method.

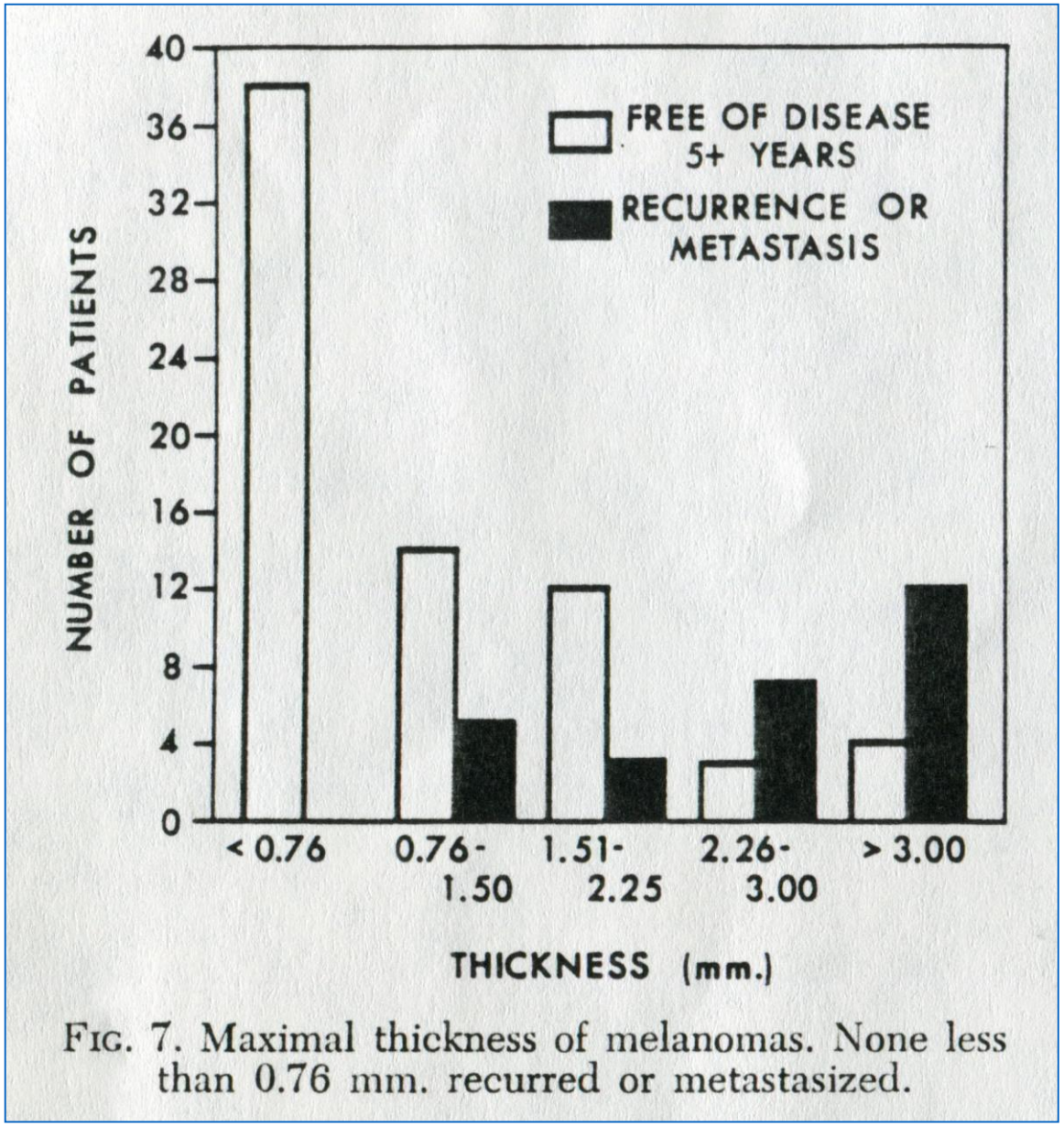
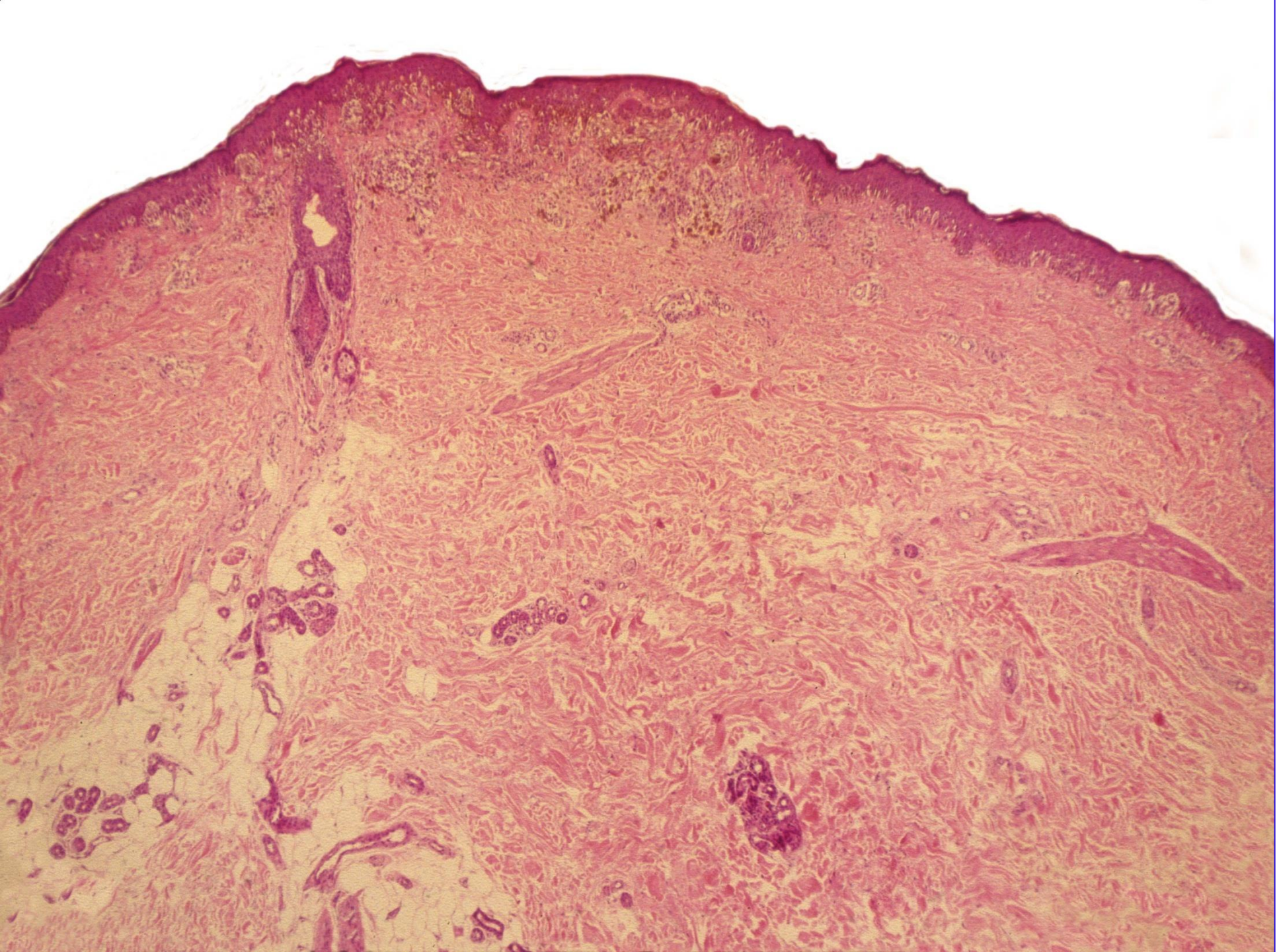


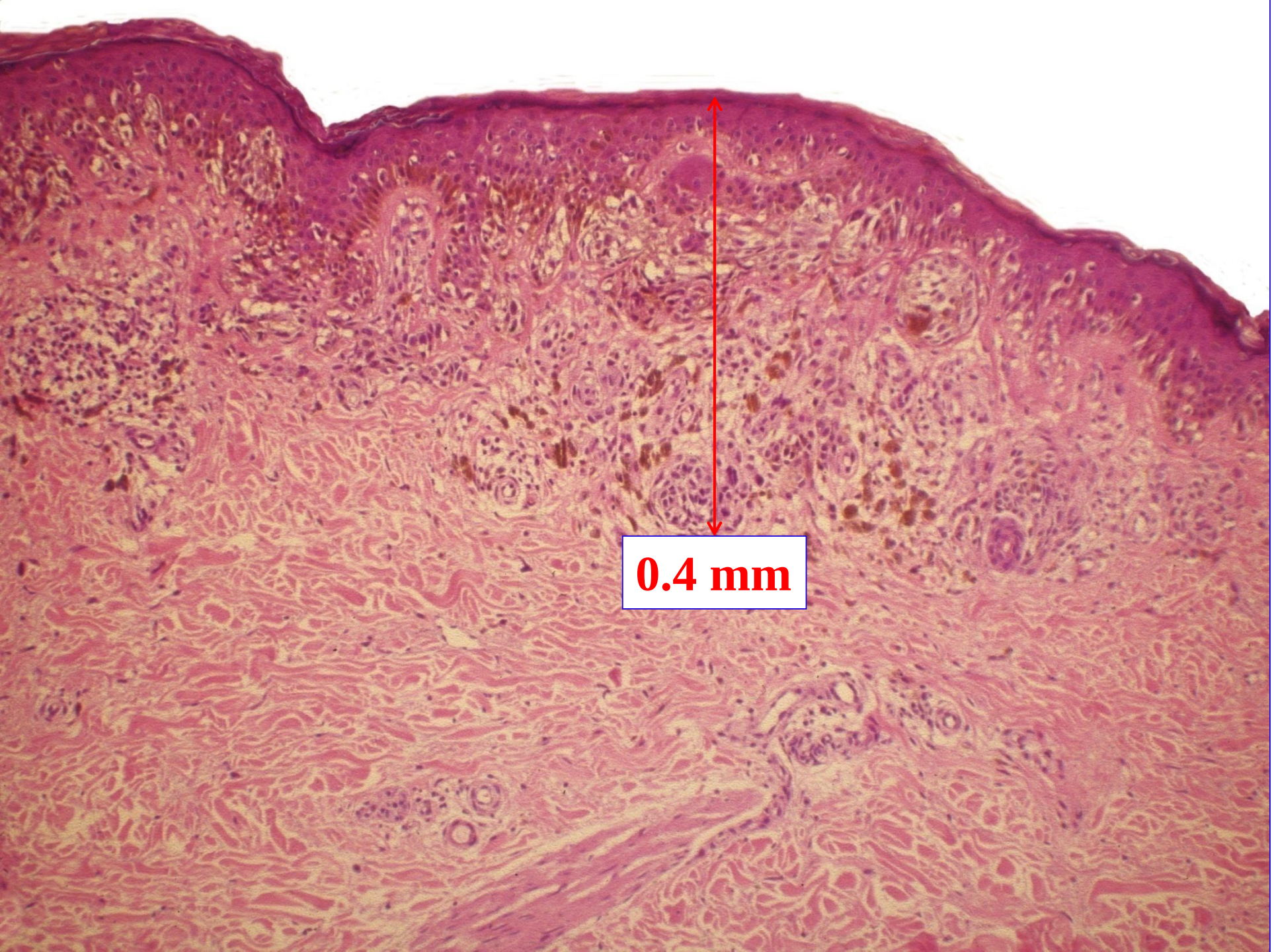
FIG. 7. Maximal thickness of melanomas. None less than 0.76 mm. recurred or metastasized.

Breslow A. Ann Surg 1970; 172: 902

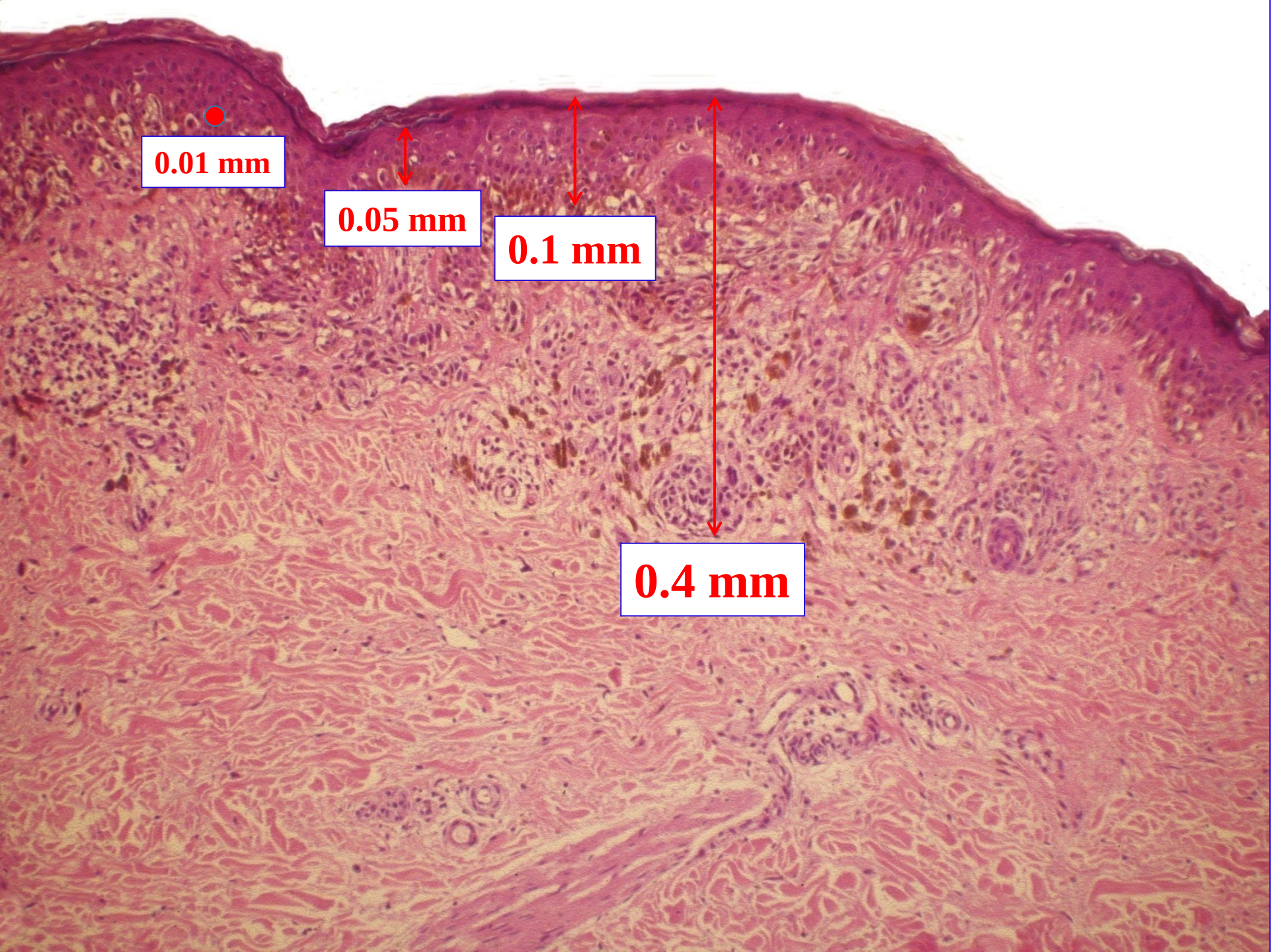
This principle was already violated by Alexander Breslow who, in his original article about melanoma thickness in 1970, defined prognostic categories on the basis of values such as 0.76 and 1.51 mm. Those numbers in the range of one hundredth of a millimetre make no sense because they exceed by far the limitations of the method.



Take this melanoma: It is confined to the epidermis and papillary dermis.



Thickness must be measured here, and it is 0.4 mm. If these are 0.4 mm,



this is 0.1 mm, and this 0.05 mm. 0.01 can only be represented as a spot, and a slightly oblique section suffices to enhance thickness by several of those spots.

Relation between size of skin excision, wound, and specimen

M. J. Hudson-Peacock, BSc(Hons), MRCP,[a] J. N. S. Matthews, PhD,[b] and C. M. Lawrence, MD, FRCP[a] *Newcastle-upon-Tyne, United Kingdom*

Background: Skin wounds differ in shape and size compared with the planned excision, and skin shrinks after excision and fixation.
Objective: This study was designed to quantify and to analyze the differences between the size and shape of the planned excision, wound, and specimen.
Methods: Eighty-six patients with 93 benign or malignant skin tumors were prospectively studied. Length and width measurements were made of the lesion, planned surgical excision, postexcision wound, and prefixation and postfixation specimens. The results were analyzed to identify the effects of patient age and sex, and lesion type and site.
Results: Wound size was larger than planned excision size in 90% of wounds, and this effect was greatest in young patients and at trunk and limb sites. Excision and fixation caused the specimens to shrink so that the postfixation area was on average 48% of the planned excision area; benign tumors shrank more than malignant tumors.
Conclusion: Significant differences among planned excision, wound, and specimen sizes are influenced by patient age and by lesion site and type. These results demonstrate that wound size is not equivalent to tumor size, a conclusion often made in Mohs surgery. Furthermore, assessment of tumor clearance margins from fixed tissue does not reflect in vivo clearance margins.
(J Am Acad Dermatol 1995;32:1010-5.)

An even greater influence is exerted by shrinkage of the specimen following excision. In this study, excision and fixation caused the specimens to shrink by an average of 48%, and shrinkage was influenced by factors such as age and anatomic site.

	n	Age (yr)	Lesion (mm^2)	Planned excision (mm^2)	Postexcision (mm^2)	Excised tissue* (mm^2)	Fixed tissue* (mm^2)
All wounds	93	63	113	237	285	184	163
Patient gender							
F	48	64	105	220	267	171	147
M	45	61	122	257	306	199	182
Age (yr)							
≤50	22	36	69	174	236	128	125
51-70	32	61	94	198	226	152	136
≥71	39	79	175	326	384	262	224
Site							
Eyes/lip	4	56	69	165	162	123	118
Ears	16	72	171	319	358	258	243
Nose	10	65	61	123	127	104	93
Other facial	31	63	105	200	245	163	144
Neck/scalp	6	68	240	429	548	331	329
Trunk	12	44	73	226	325	161	147
Limbs	14	65	414	654	749	504	481
Benign	30	50	101	215	282	151	136
Malignant	63	69	120	248	286	201	176

Fixation in formalin is also important because the specimen continues to shrink, and this depends on the amount of formalin and the duration of fixation.

Poor fixation caused, for example, by a small container with insufficient formalin, will result in lower measurements of thickness.

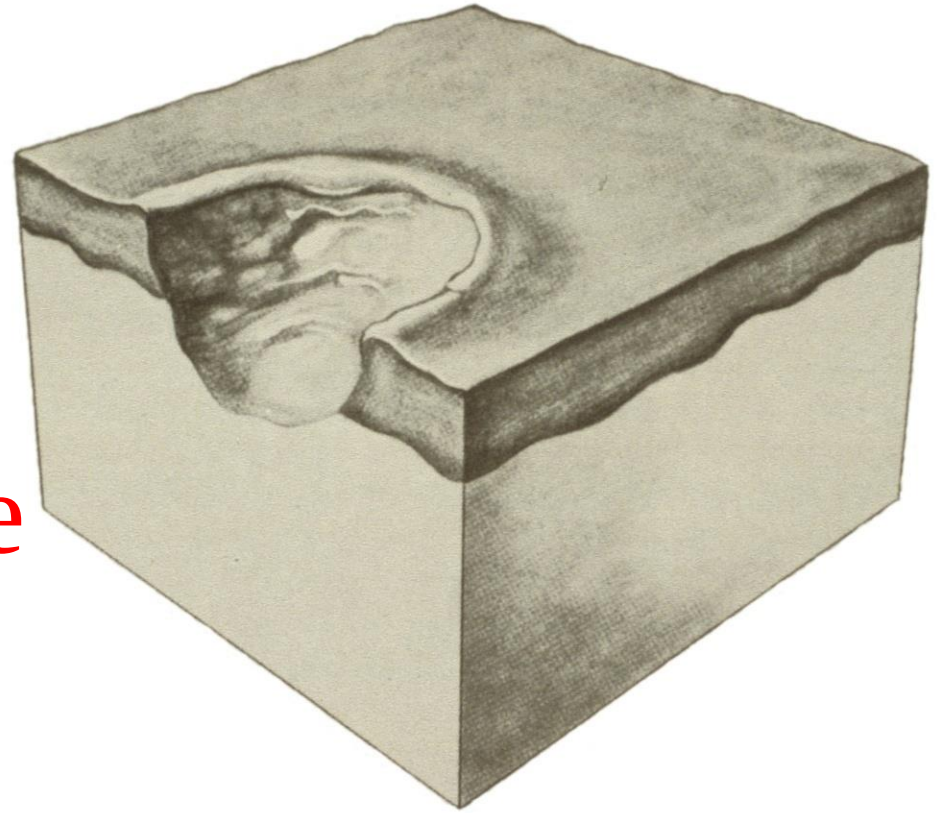
Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis $< 1/mm^2$
		b: With ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2.00	a: Without ulceration
		b: With ulceration
T3	2.01-4.00	a: Without ulceration
		b: With ulceration
T4	> 4.00	a: Without ulceration
		b: With ulceration

It is welcome, therefore, that since 2001 even numbers – 1, 2, and 4 mm – are used for melanoma staging, although the second place after the decimal point continues to appear in the current classification. The fact that the issue of measuring accuracy has never been addressed by the American Joint Committee on Cancer indicates great laxness in dealing with the subject.

Ulcer

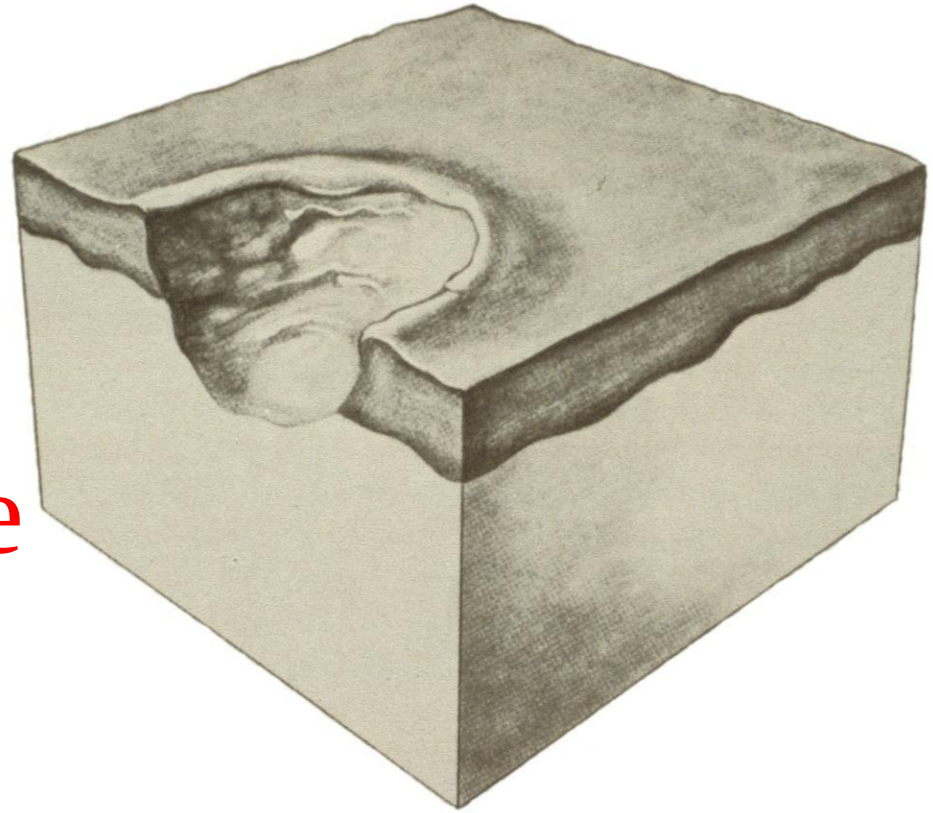
... Loss of portions of skin reaching into the dermis.



If further evidence of laxness is needed, it is provided by the other criteria for melanoma staging, namely, ulceration and mitoses. In the language of dermatology, an ulcer is defined as *“loss of portions of skin reaching into the dermis,”* but not by the AJCC

Ulcer

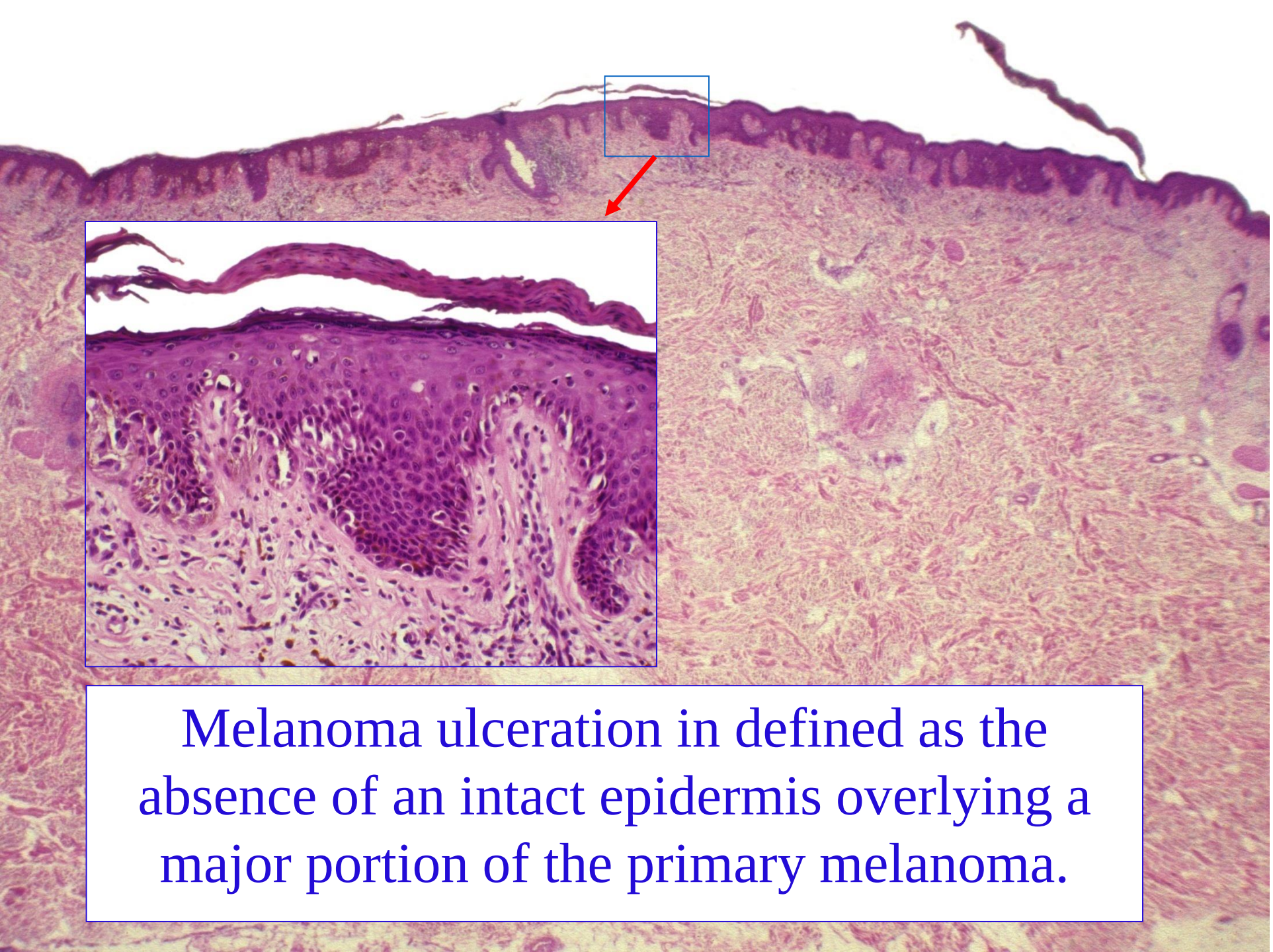
... Loss of portions of skin reaching into the dermis.



AJCC:

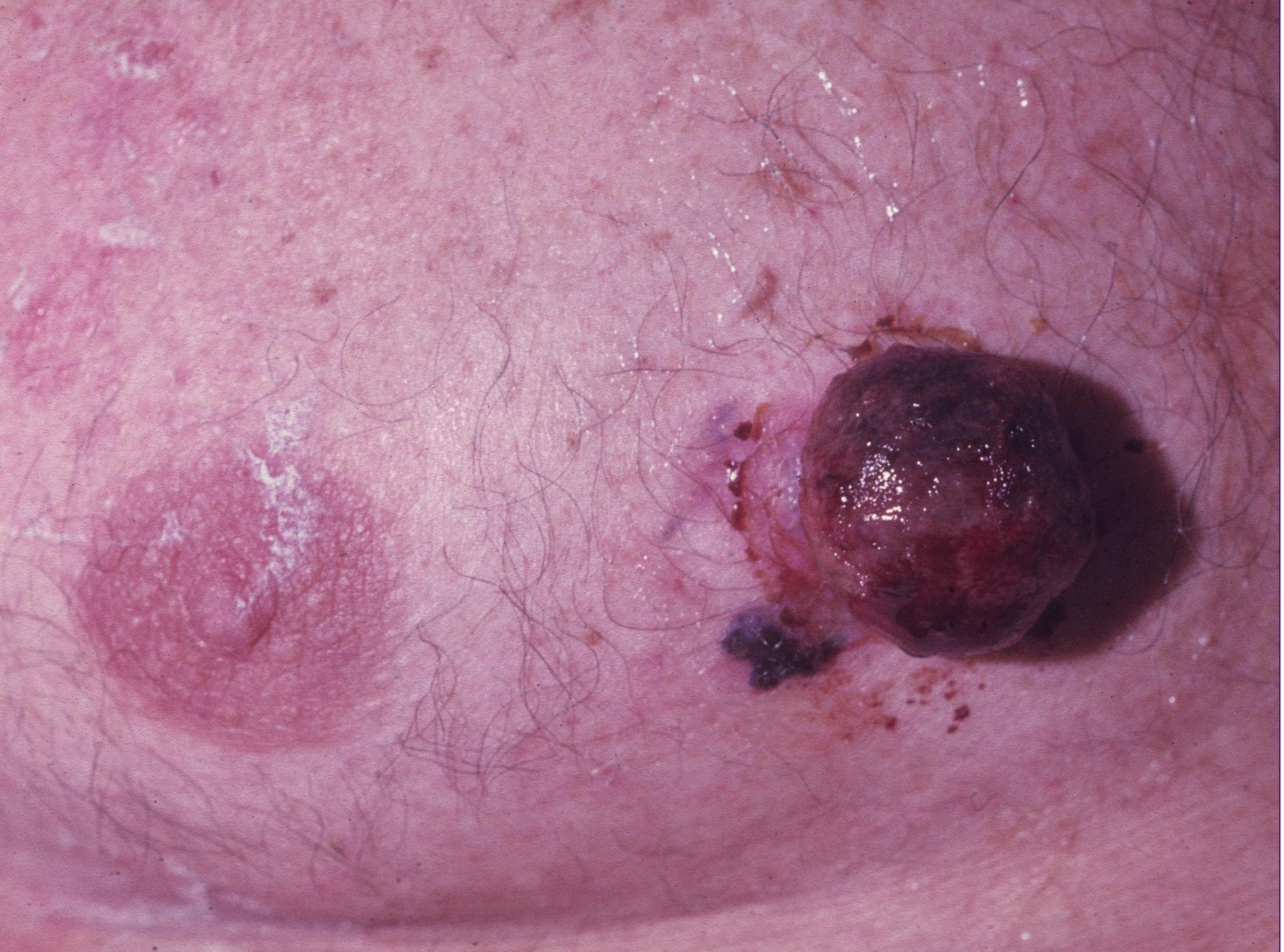
Melanoma ulceration is defined as the absence of an intact epidermis overlying a major portion of the primary melanoma.

that defines “melanoma ulceration” as *“absence of an intact epidermis overlying a major portion of the primary melanoma.”* According to that definition, a melanoma is ulcerated if its epidermis is not intact.

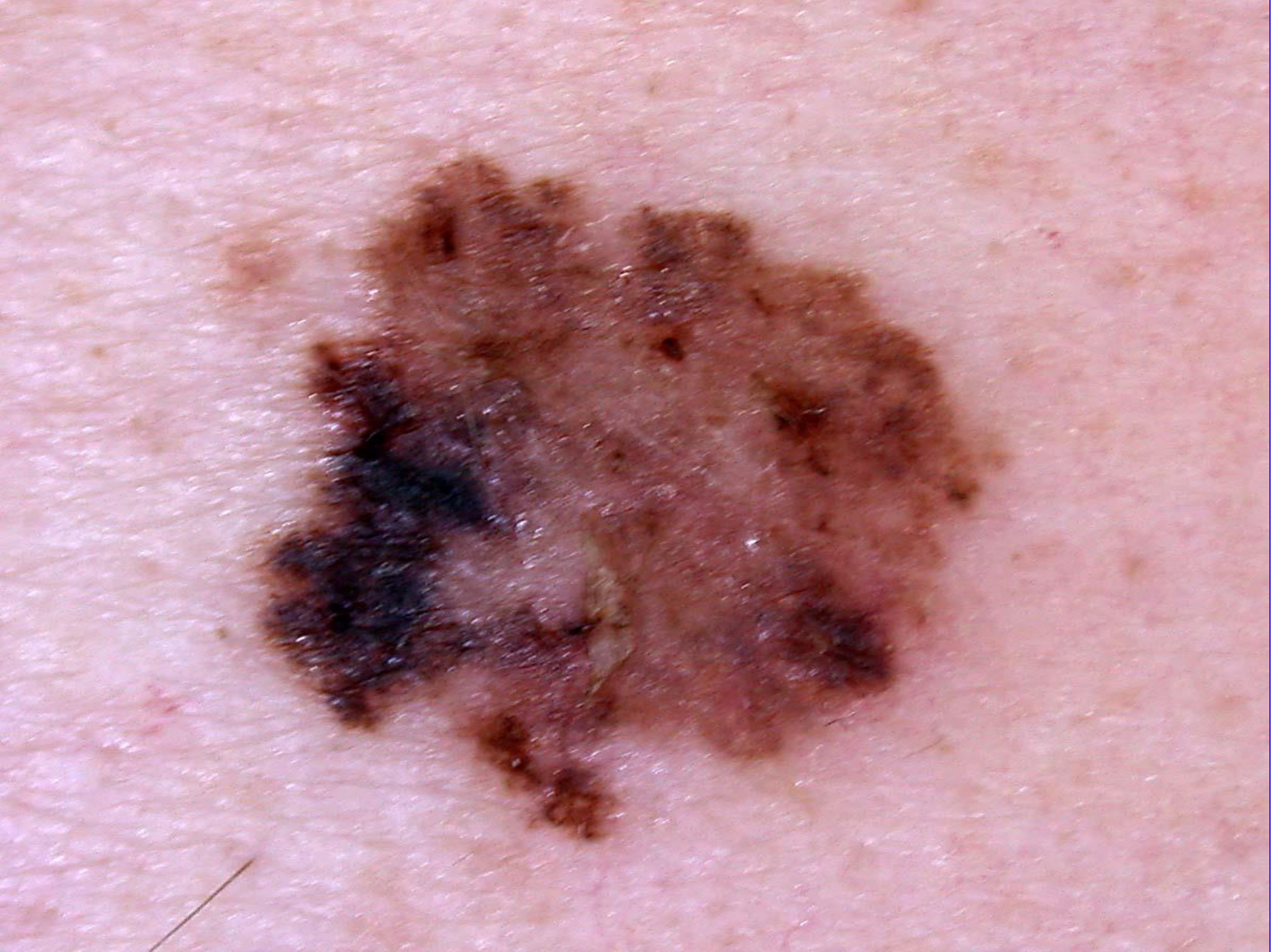


Melanoma ulceration in defined as the absence of an intact epidermis overlying a major portion of the primary melanoma.

This melanoma, for example, should be ulcerated because the epidermis is not intact but shows parakeratosis. Of course, this is not meant, but it illustrates the flippancy with which work was done.



And what is *“a major portion of the primary melanoma”*? This melanoma is clearly ulcerated,

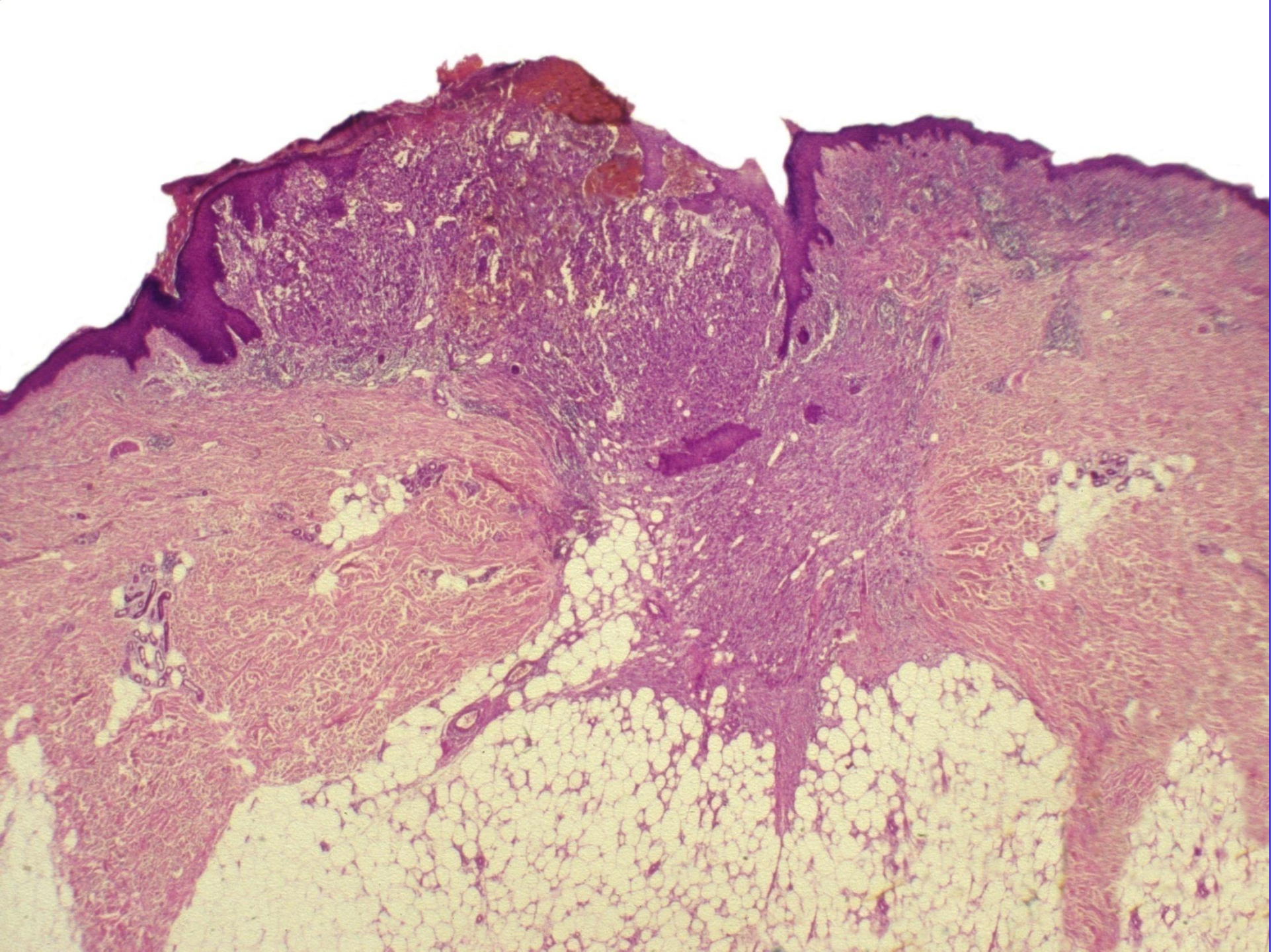


but how about this one? Does this already qualify as *“a major portion”*? And if it does, maybe the ulcer did not exist yesterday and will be healed next week.

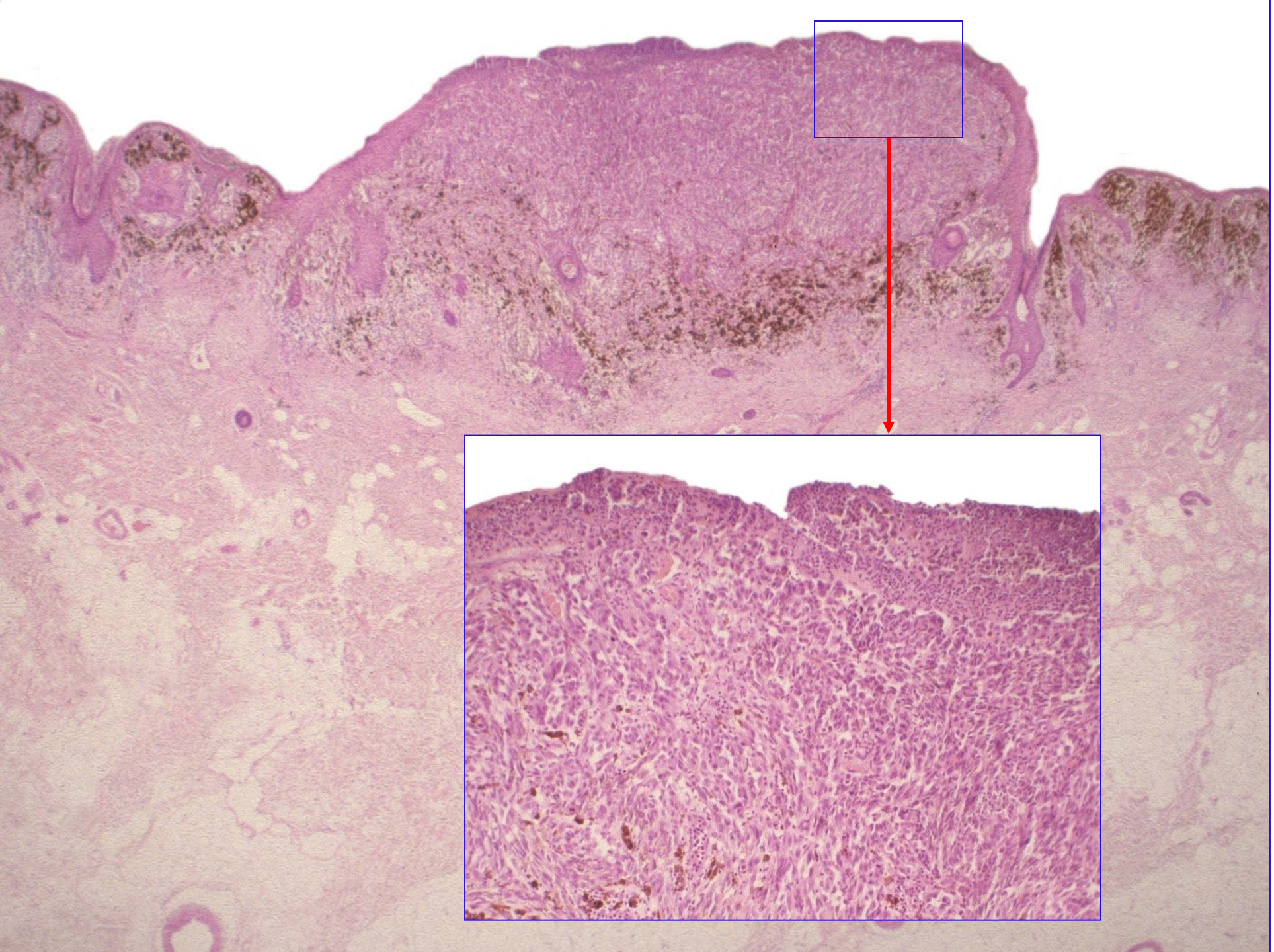
Melanoma Ulceration

Melanoma ulceration is defined as the absence of an intact epidermis overlying a major portion of the primary melanoma based on microscopic examination of the histologic sections.[6,7,13,14] It can easily be distinguished from artifactual or traumatic disruption of the epidermis. Traumatically induced defects are associated with hemorrhage, brightly eosinophilic fibrin exudation at the site, and an architectural defect that usually defines the agent leading to the trauma, such as an insect bite or an excoriation. In fact, the interpretation of melanoma ulceration among patholo-

The AJCC distinguishes "melanoma ulceration" from any *"artifactual or traumatic disruption of the epidermis,"* the latter do not qualify as ulceration, and then the committee declares, *"traumatically induced defects are associated with hemorrhage, brightly eosinophilic fibrin exudation at the site, and an architectural defect that usually defines the agent leading to the trauma, such as an insect bite or an excoriation."*



This is pure confabulation. In general, histopathologic attributes of an ulcer do not reveal its cause, and traumatic influences are usually at least partially involved in it. For example, is the ulcer in this melanoma caused by a previous biopsy or, not being situated immediately above the scar, evidence of “melanoma ulceration”?



And who can exclude that the ulcer in this melanoma is not caused by minor trauma, such as rubbing clothes?

version, the T-category thresholds of melanoma thickness are defined in even integers (ie, 1.0, 2.0, and 4.0 mm) because they represent both a statistical best fit and are the most compatible with current thresholds in clinical decision making and to classify prognostic groups of node-negative (N0) patients.[6-12]

Because the majority of patients with clinically localized melanoma present with T1 melanomas, a separate statistical analysis was performed to examine different thresholds at 0.1-mm increments of measured thickness between 0.90 mm and 1.1 mm. Because no significant survival differences were observed, a more clinically convenient and widely used threshold of ≤ 1.0 mm could appropriately be used for the threshold of T1 melanomas, while T2 melanomas were defined as those measuring 1.01 mm to 2.0 mm in thickness. T3 melanomas are defined as those with a thickness of 2.01 to 4.0 mm and T4 melanomas as those with a thickness of more than 4.0 mm.

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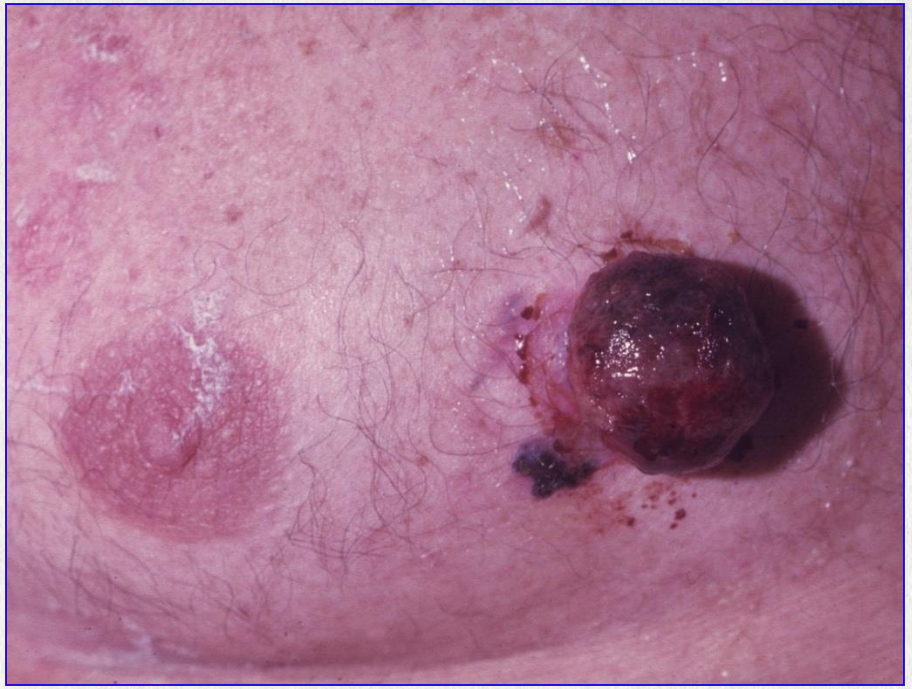
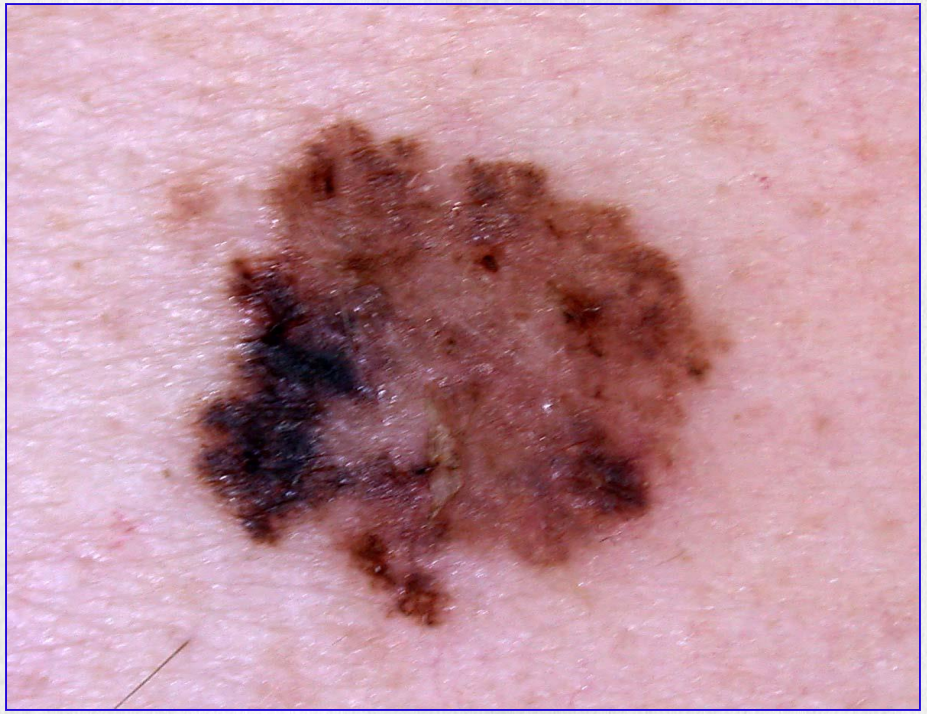
Melanoma ulceration heralds such a high risk for metastases that its presence upstages the prognosis of all such patients, compared with patients who have melanomas of equivalent thickness without ulceration. Thus, survival rates for patients with an ulcerated melanoma are proportionately lower than those of patients with a nonulcerated melanoma of equivalent T category but are remarkably similar to those of patients with a nonulcerated melanoma of the next highest T category (Fig 2, Table 3).



When ulceration was introduced as a staging criterion, the AJCC claimed that *"the interpretation of melanoma ulceration among pathologists is one of the most reproducible of all the major histopathologic features."* This, however, depends on the melanomas examined.

version, the T-category thresholds of melanoma thickness are defined in even integers (ie, 1.0, 2.0, and 4.0 mm) because they represent both a statistical best fit and are the



Melanoma Ulceration

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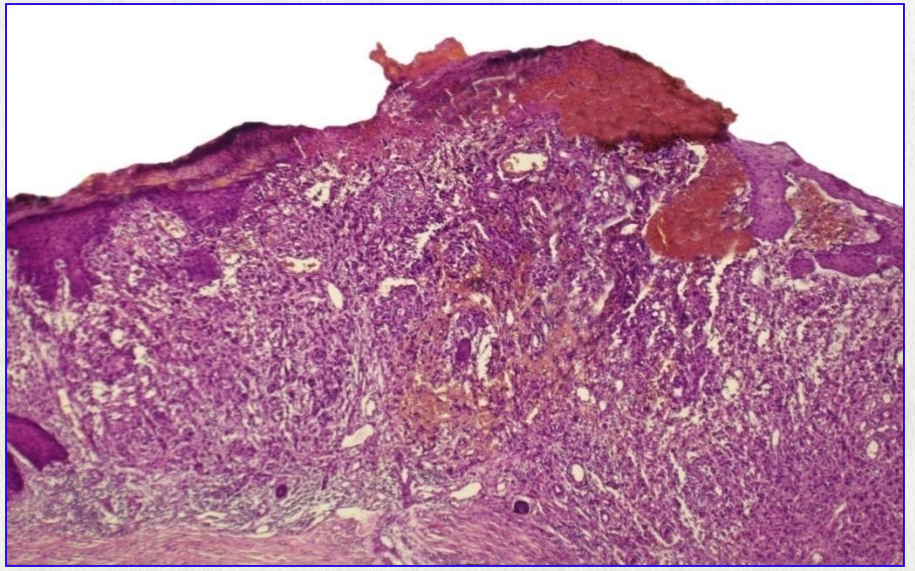

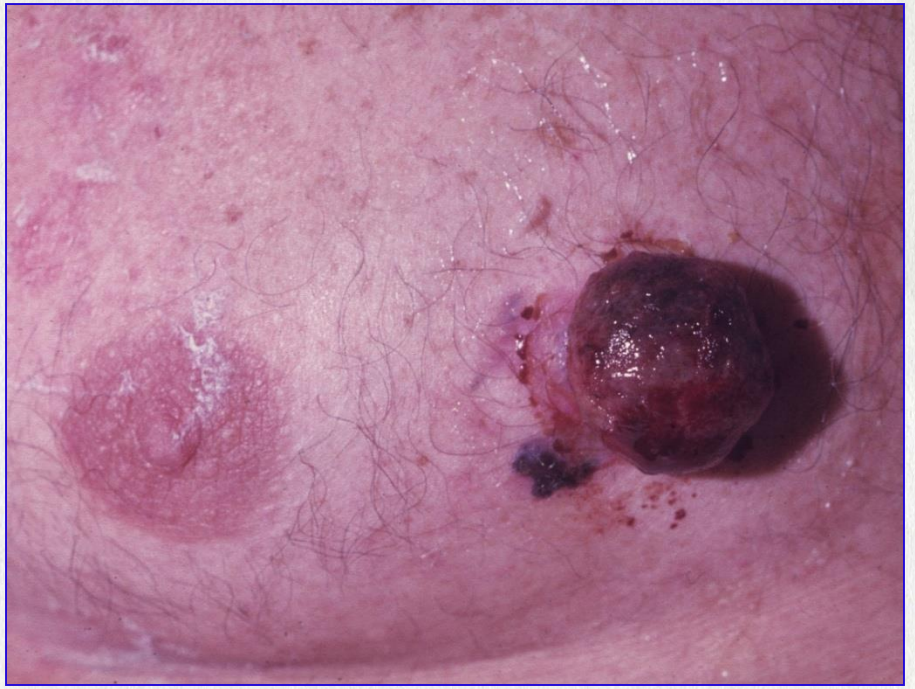

As soon as it becomes difficult, the definition of "melanoma ulceration" is worthless, and it is irresponsible to adjust treatment of patients to the notion of ulceration in a pathology report.

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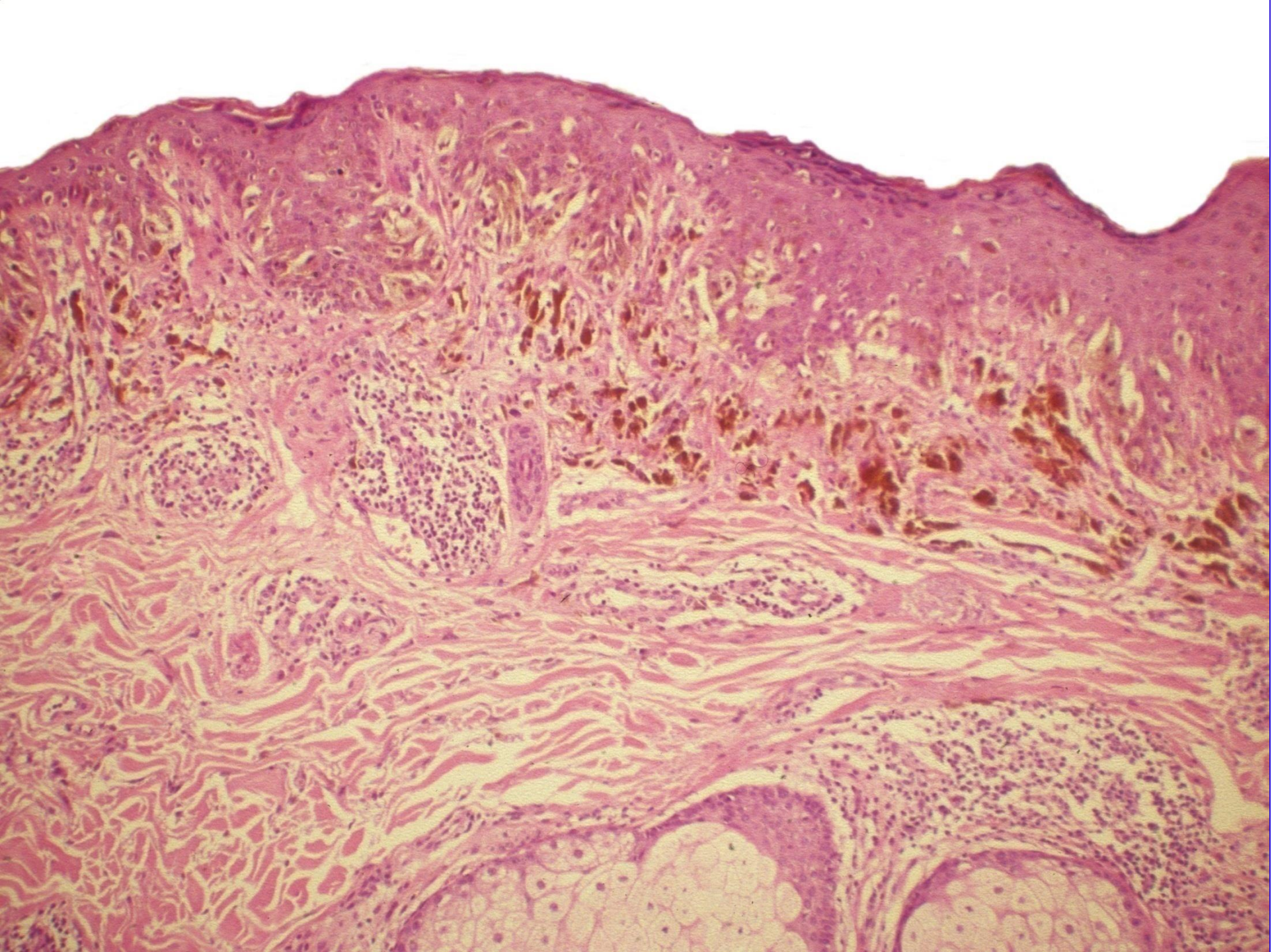
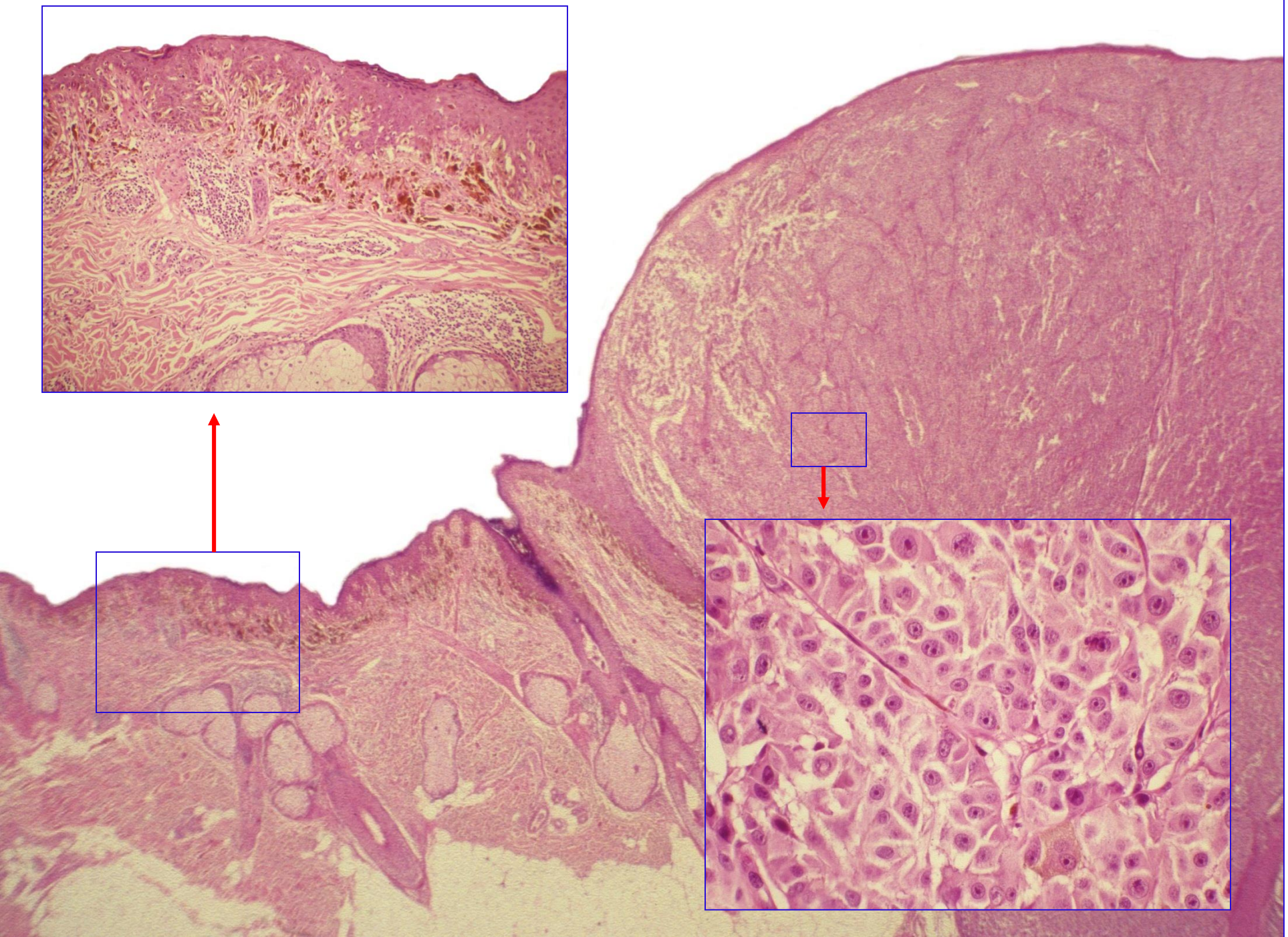
AJCC, 2009

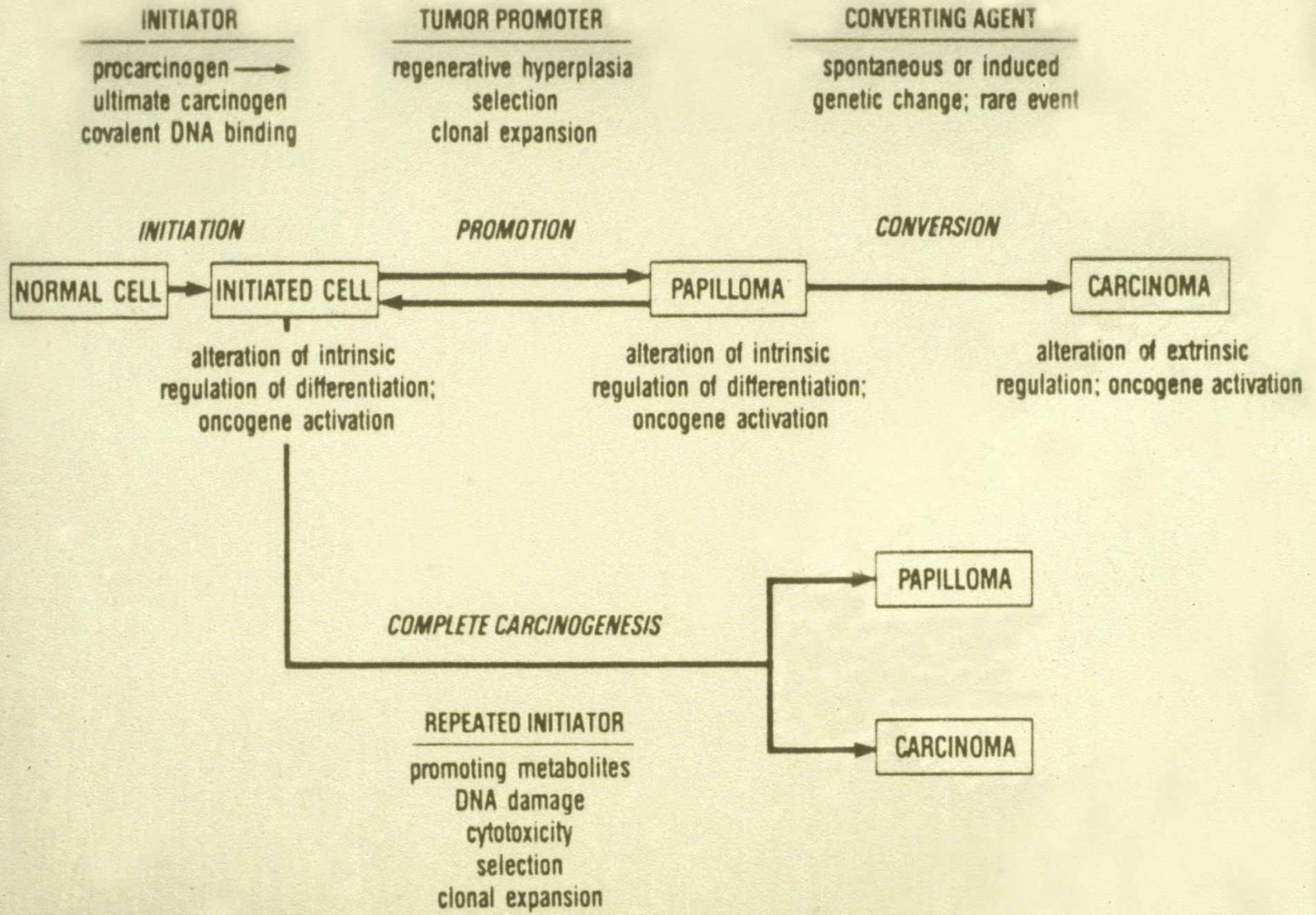
Even more problematic than ulceration is the newest staging criterion, namely, mitotic rate. The introduction of mitotic rate as a staging criterion has a long history that is closely connected to the concept of so-called “growth phases of melanoma.”



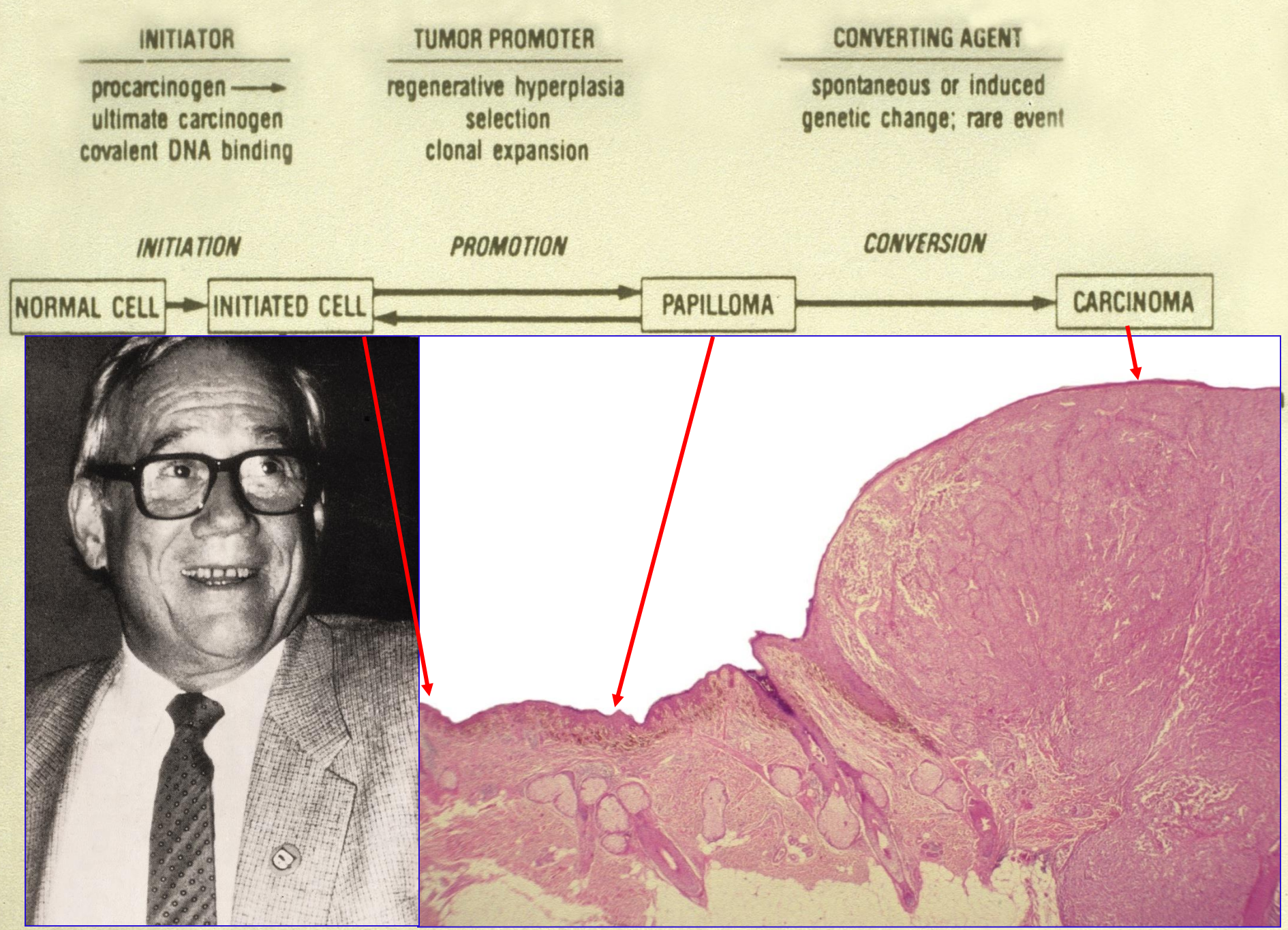
In most superficial melanomas, mitoses are rare, and they often can only be found



when new populations of cells arise. For Clark, the striking differences between those portions of melanoma were intriguing because they seemed to be evidence of the, at that time, relatively new hypothesis of multistep carcinogenesis.



According to that hypothesis, normal cells become initiated and start to multiply by clonal expansion, forming a benign neoplasm that, through additional genetic changes, converts into a malignant neoplasm.



Melanoma was conceived of by Clark as a model tumor for multistep carcinogenesis, and this conviction was the foundation on which all his later concepts were built, ranging from dysplastic nevi to the radial and vertical growth phase.

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.

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.

to the directional growth of the radial growth phase. As a rule, the cells of the vertical growth phase grow in an expansile fashion, expansile as a balloon expands: a growth form char-

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

In a “study of tumor progression” 1984, Clark claimed that melanomas result from *“six evident lesional steps of tumor progression,”* namely, *“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 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.”*

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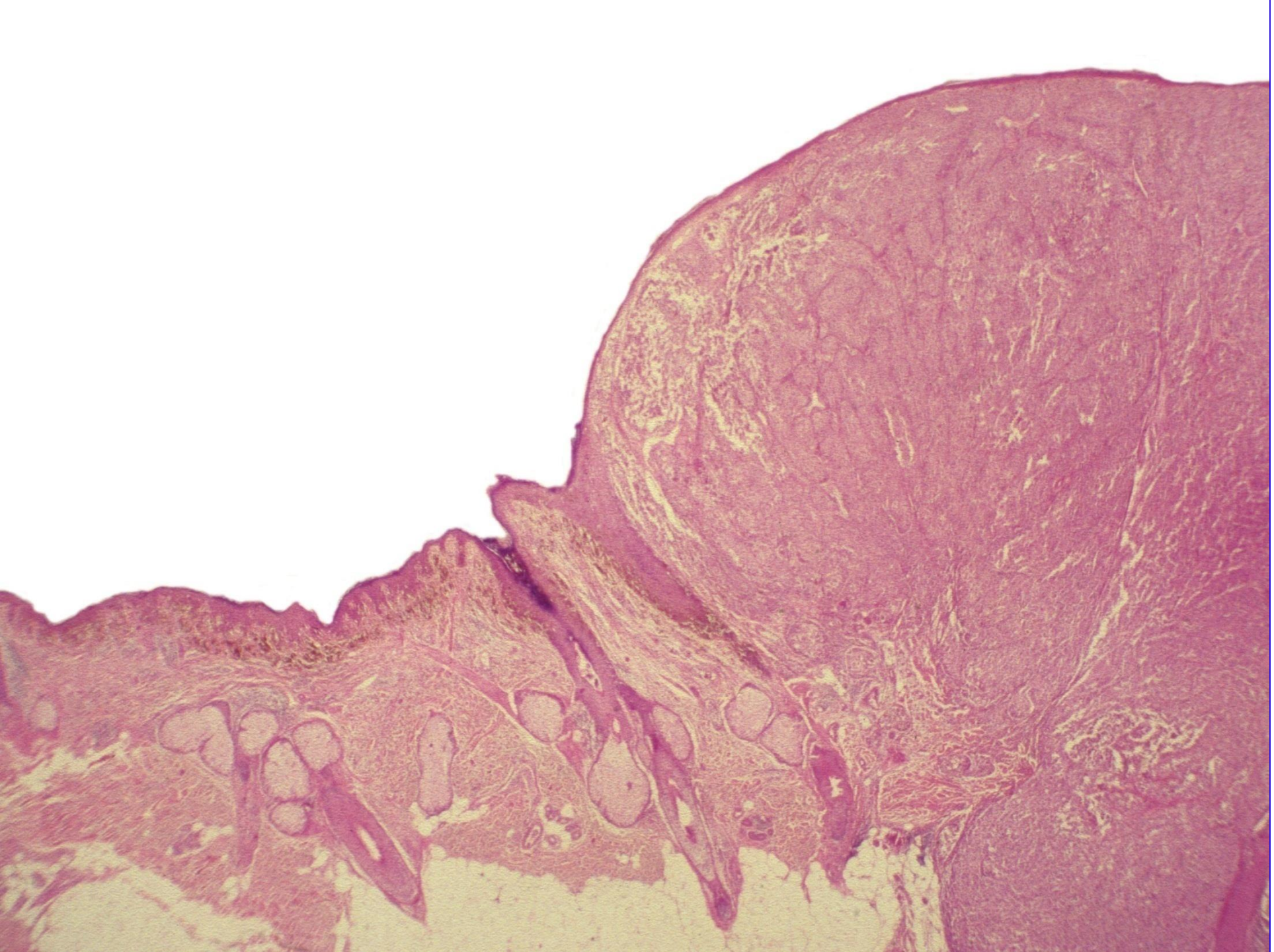
... the radial growth phase is ... not associated with metastasis, and it is hypothesized that such tumors do not have competence for metastasis. For a melanoma to acquire competence for metastasis it must progress to the next step of tumor progression – the vertical growth phase. This lesional step is characterized by the appearance of a new population of cells within the melanoma, not an expansion of the cells forming the pre-existing radial growth phase.

and time. Rather, primary melanomas, with the exception of nodular melanoma, also evolve in a stepwise fashion. The first step, termed the radial growth phase, is characterized by the net enlargement of the tumor at its periphery, along the radii of an imperfect circle. Tumors in this stage of development show a characteristic pattern of growth within the epidermis and a distinctive form of invasion of the papillary dermis. Such melanomas are not associated with metastasis, and it is hypothesized that such tumors do not have competence for metastasis. For a melanoma to acquire competence for metastasis it must progress to the next step of tumor progression—the vertical growth phase. This lesional step is characterized by the appearance of a new population of cells within the melanoma, not an expansion of the cells forming the pre-existing radial growth phase. The net growth of the cells of the vertical growth phase is perpendicular to the directional growth of the radial growth phase. As a rule, the cells of the vertical growth phase grow in an expansile fashion, expansile as a balloon expands: a growth form char-

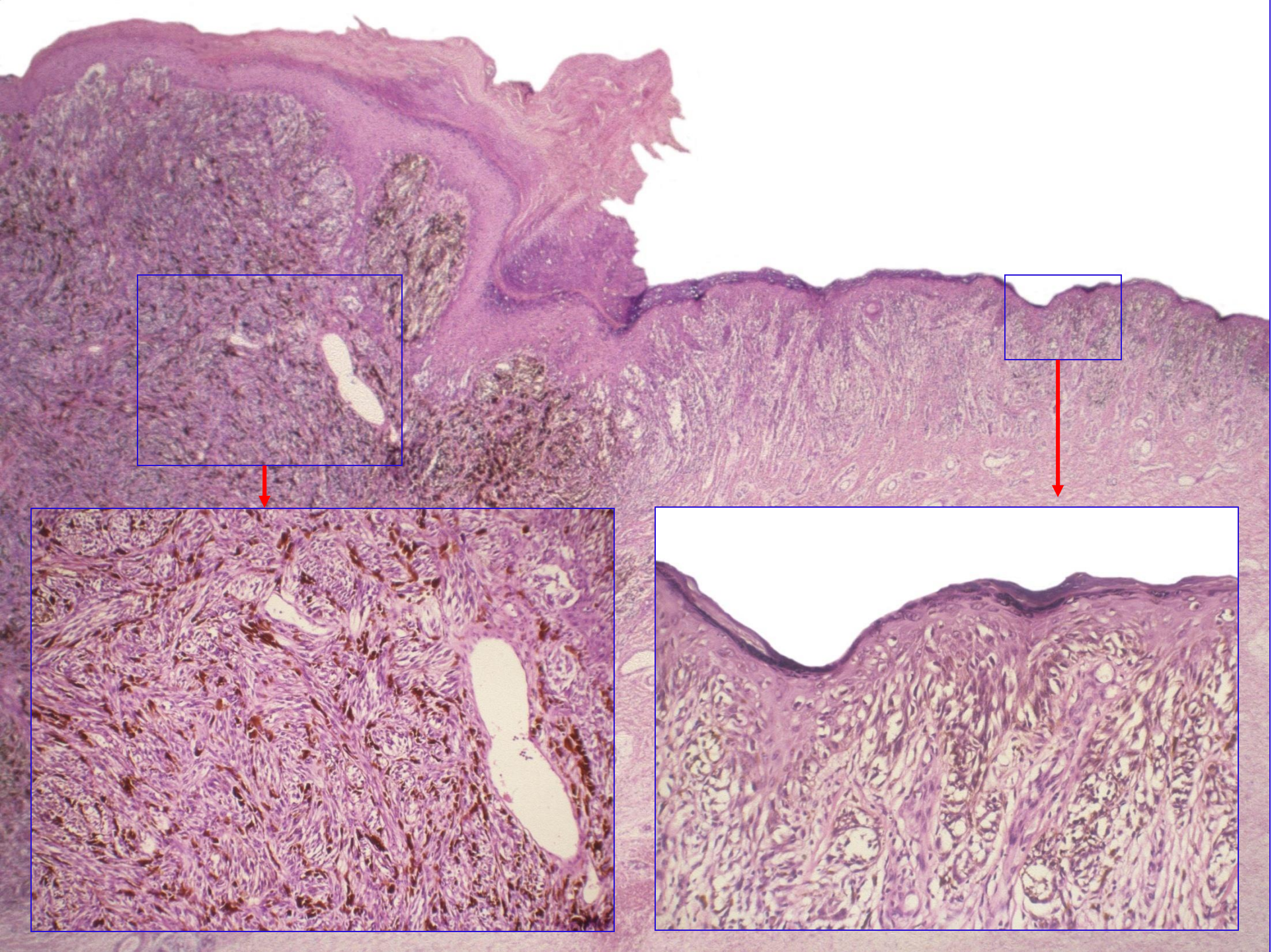
for all neoplastic systems. Thus, the lessons learned from observation of the focal proliferative lesions of melanocytic tumor progression, which appear seriatim, should be generally applicable to studies of the development and evolution of cancer. This statement is based on the following considerations. Melanocytes are unique in that they are capable of pigment synthesis. Their proliferative lesions, therefore, are readily apparent. Pigment synthesis and the epidermal location of much of the melanocytic system have permitted observers to record detailed and comprehensive features of the evident steps of tumor progression as it affects melanocytes.

The remarkable visibility of melanocytic neoplasia is exemplified by the first evident lesion of the system: a focal proliferation in the basilar epidermal

In regard to melanoma, he contended that *"the radial growth phase is ... not associated with metastasis, and it is hypothesized that such tumors do not have competence for metastasis. For a melanoma to acquire competence for metastasis it must progress to the next step of tumor progression – the vertical growth phase. This lesional step is characterized by the appearance of a new population of cells within the melanoma, not an expansion of the cells forming the pre-existing radial growth phase."*



In these words, Clark described accurately the qualitative change that can be noted in the growth of many advanced melanomas.



However, circumscribed nodules arising in the midst of a larger melanoma are not always formed by a different population of cells. In many melanomas, cells of the exophytic nodule and of the adjacent flat component look just the same. Because those melanomas are also thick and associated commonly with metastases,

The Developmental Biology of Primary Human Malignant Melanomas

Wallace H. Clark, Jr., Ann M. Ainsworth, Evelina A. Bernardino,
Chang-Hsu Yang, Martin C. Mihm, Jr., and Richard J. Reed

THIS PAPER WILL DESCRIBE the various forms of primary cutaneous and mucous membrane melanomas. The central theme of the paper will be the exposition of the developmental biology of the primary lesions of the commonest forms of cutaneous malignant melanoma. Developmental biology, in the context of this presentation, encompasses the entire series of cellular events occurring within a primary melanoma from its earliest recognizable stage to those stages which are associated with the development of metastases. Malignant melanomas of the superficial spreading and nodular types will serve as the prime models for the discussion of lesional developmental biology. We will document, using malignant melanoma of the superficial-spreading type as the model, that the initial developmental stages of a primary neoplasm are characterized by a long period of invasive growth associated with a well-developed host-cellular response. The initial period of growth is rarely associated with metastases and is termed the radial-growth phase. The radial-growth phase precedes and leads to, probably in a causal way, a *qualitatively* different growth pattern, the vertical-growth phase. The vertical-growth phase may, in turn, give rise to cell populations commonly associated with metastatic disease, a phenomenon referred to as intralesional transformation. In our view, an appreciation of the developmental pathways of the common forms of melanoma is vitally important for understanding the biology of primary neoplasms and the cellular events occurring within them which are apparently associated with metastases. Furthermore, knowledge of the clinical aspects of the radial-growth phase of malignant melanoma of the superficial-spreading type and of the lentigo-maligna type should lead to clinical control, and probably cure, of over 80% of cutaneous melanomas.

It is to be emphasized that the series of cellular events occurring during the development of a primary neoplasm includes both the neoplastic cells

Clark had to change his definitions in order to adhere to the concept of growth phases as distinct biologic steps of tumor progression; the definition of the vertical growth phase had to be expanded and that of the radial growth phase constricted. Clark still emphasized that *"the vertical-growth phase may … give rise to cell populations commonly associated with metastatic disease, a phenomenon referred to as intralesional transformation,"* but evidence of "intralesional transformation" was no longer required for the vertical growth phase.

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

vasive growth associated with a well-developed host-cellular response. The initial period of growth is rarely associated with metastases and is termed

the radial-growth phase. The radial-growth phase precedes and leads to, probably in a causal way, a *qualitatively* different growth pattern, the vertical-growth phase. The vertical-growth phase may, in turn, give rise to cell populations commonly associated with metastatic disease, a phenomenon referred to as intralesional transformation. In our view, an appreciation of the developmental pathways of the common forms of melanoma is vitally important for understanding the biology of primary neoplasms and the cellular events occurring within them which are apparently associated with

It is to be emphasized that the series of cellular events occurring during the development of a primary neoplasm includes both the neoplastic cells

Instead, Clark made the pronouncement: *"Invasion to levels III, IV, and V is, by definition, the vertical-growth phase."* In other words, nature was no longer observed but defined,

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M. Van Horn
W.H. Clark, Jr.

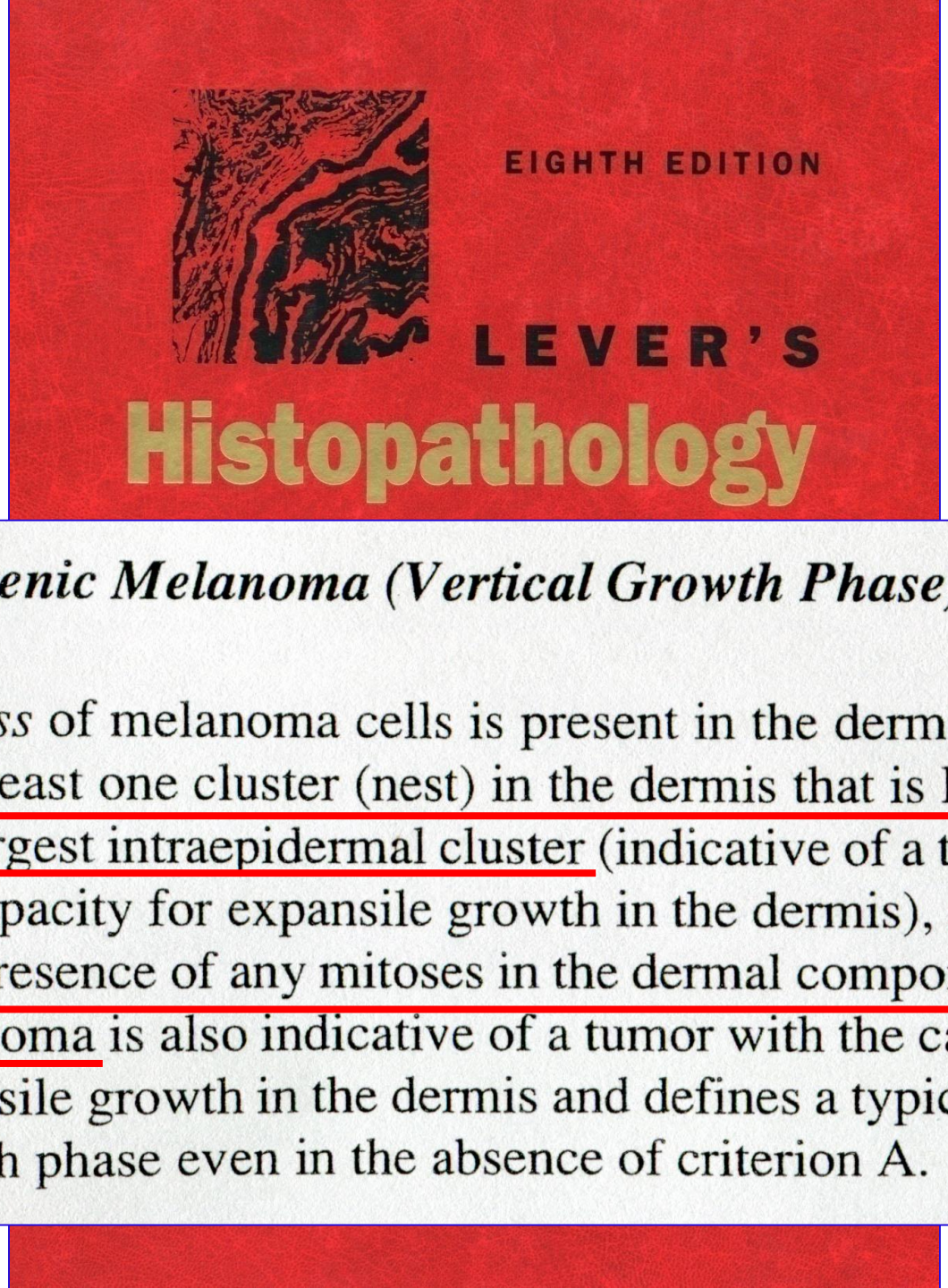
Invasive malignant melanomas lacking competence for metastasis

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 traditional means (level of invasion and thickness) identifies groups of patients at low and high risk of metastasis. Our data suggest that the absence of vertical progression of growth identifies a group of patients whose risk of metastasis is close to zero.

Am J Dermatopathol 6 (Suppl 1): 55–61, 1984.

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. Histologicaliy, 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"). Malignant melanomas *in situ* lack competence for metastasis (disease-free survival is 100%).[2] Survival from invasive melanoma may be predicted for groups of patients by various microstaging criteria.[3] The most important of these for prediction of low risk of metastasis are level (I or II) of invasion[4]

but that change in attitude allowed Clark and co-workers to adhere to the concept of radial growth phase as a stage of *"invasive malignant melanomas lacking competence for metastasis."* Unfortunately, it turned out that level II melanomas may also metastasize, and so definitions had to be changed again.

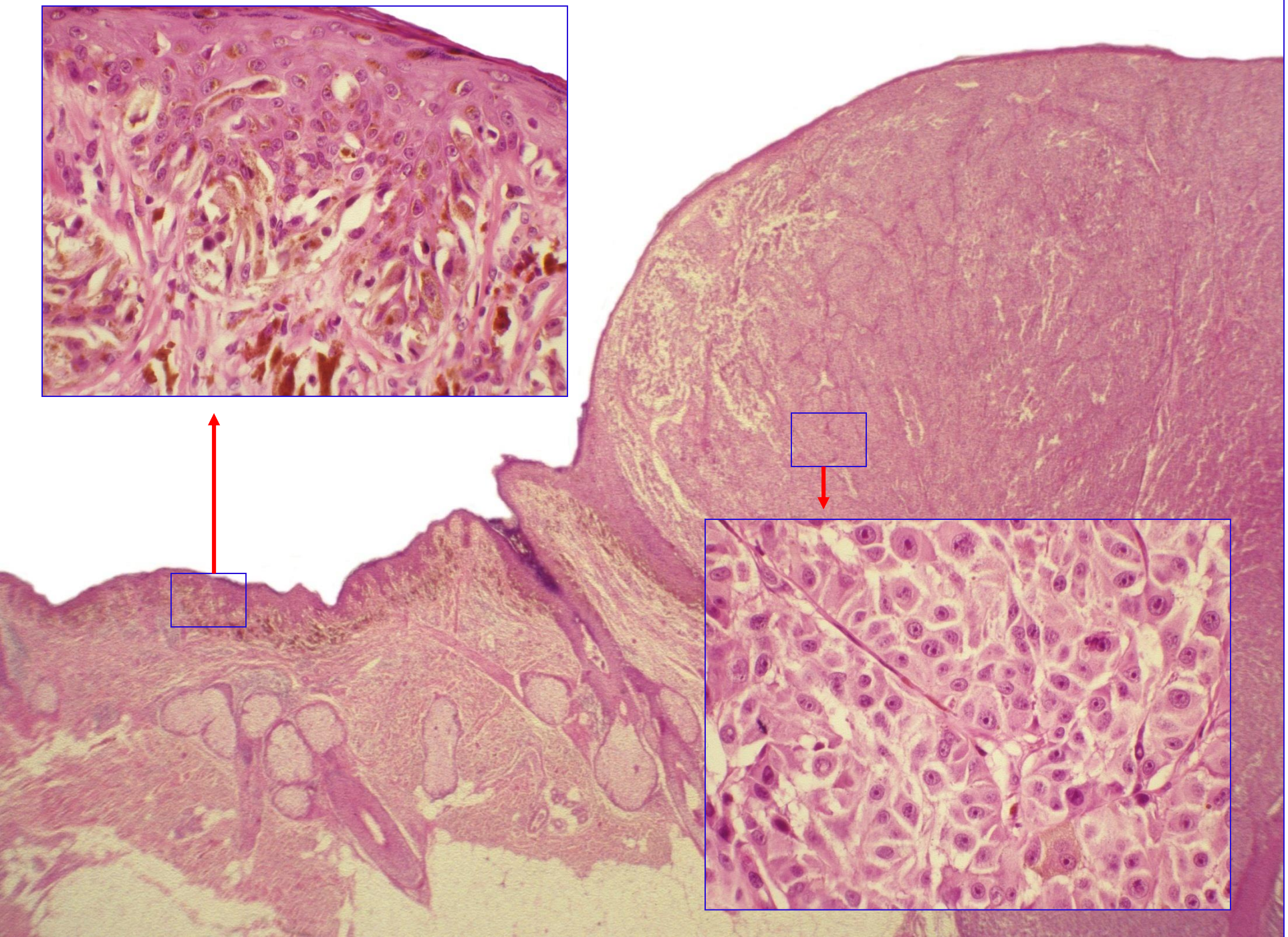


Tumorigenic Melanoma (Vertical Growth Phase)

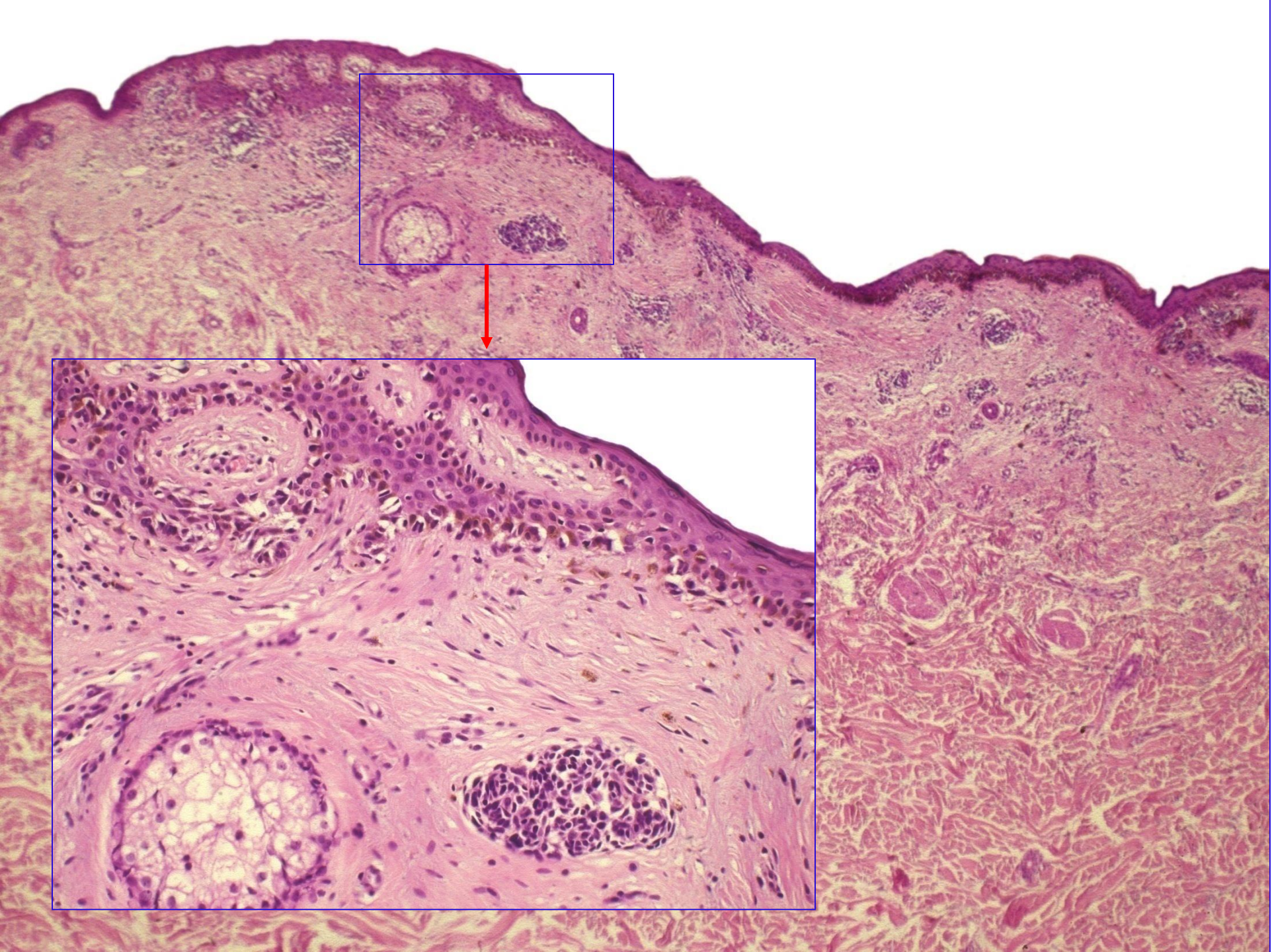
A. A *mass* of melanoma cells is present in the dermis, defined as at least one cluster (nest) in the dermis that is larger than the largest intraepidermal cluster (indicative of a tumor with the capacity for expansile growth in the dermis), *or*

B. The presence of any mitoses in the dermal component of the melanoma is also indicative of a tumor with the capacity for expansile growth in the dermis and defines a typical vertical growth phase even in the absence of criterion A.

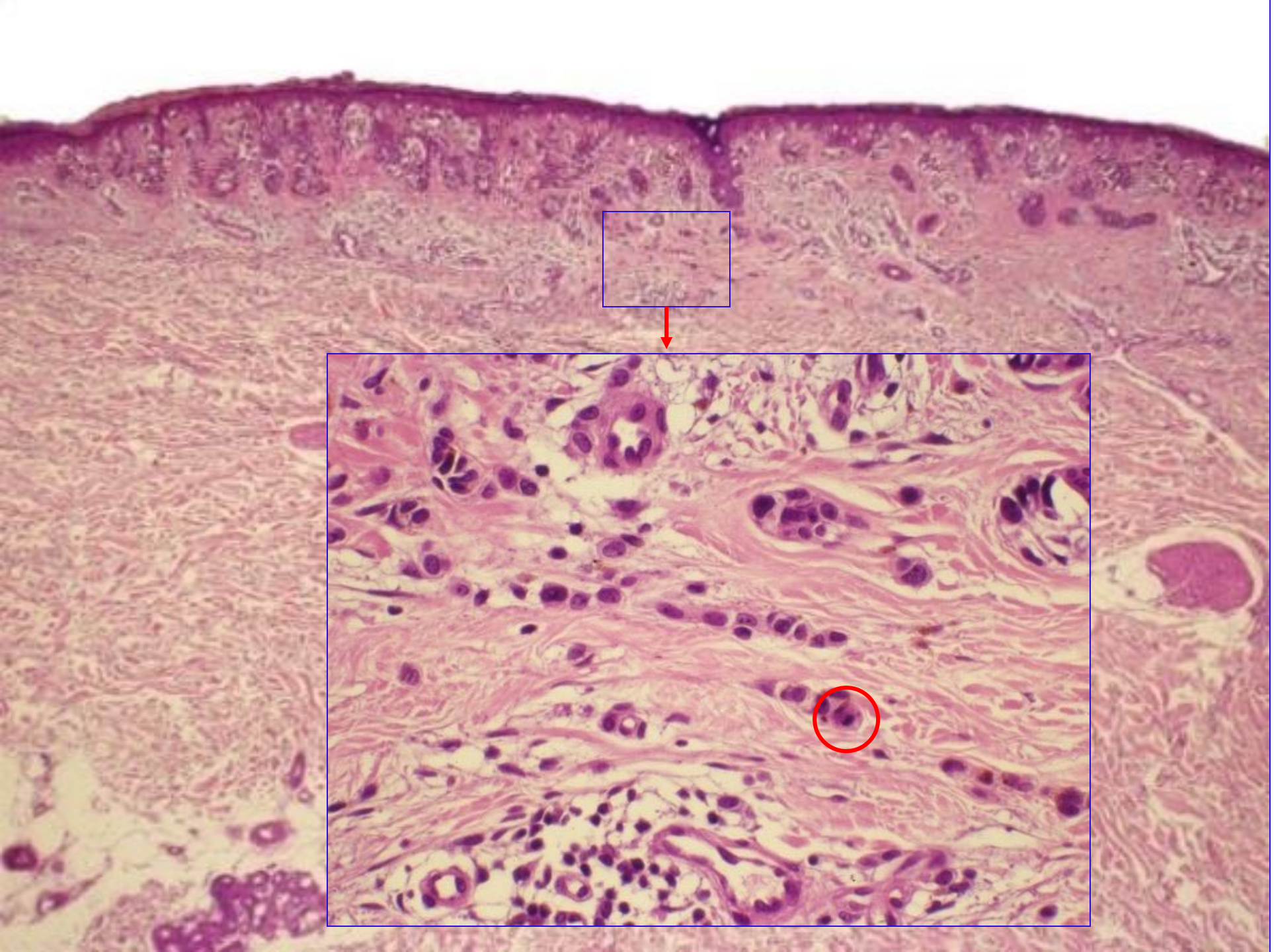
One of Clark's closest co-workers, David Elder, defined the vertical growth phase of melanoma by either *"at least one cluster (nest) in the dermis that is larger than the largest intraepidermal cluster"* or *"the presence of any mitoses in the dermal component of the melanoma."*



It was a long way from the point of origin of the concept of growth phases, namely, the authentic observation of a qualitative change in the growth of melanoma caused by development of a new population of cells,



to the single larger nest in the dermis



or the single mitotic figure, but the new definition of growth phases caused the spotlight of attention to focus on mitoses.

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0277-5379/83/020227-09$03.00/0

Low- and High-risk Malignant Melanoma—I. Evaluation of Clinical and Histological Prognosticators in 585 Cases

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Abstract—*In 585 cases with primary cutaneous stage I malignant melanoma (294 disease-free for at least 5 yr, 291 with later metastases) prognostic parameters were examined. The most effective proved to be tumor thickness and mitotic activity, particularly when combined as a prognostic index. Furthermore, vascular invasion, ulceration in thick tumors (thickness ⩾ 3.0 mm), severe cellular atypia, the small, lymphocytic-like cell type and the absence of an inflammatory reaction were closely associated with a high rate of metastatic cases. Less relevant prognostic factors were the level of invasion, sex, site, tumor breadth, clinical diameters and infiltrative growth. Tumor type, age, duration and an adjacent nevocellular nevus were not significantly associated with the occurrence of later metastases. Furthermore, the growth-type (exo- or endophytic) did not have a bearing on the prognosis.*

The value of mitoses as a gauge for prognosis of melanoma had been assessed before. For example, Schmoeckel reported in 1983 that, in an *"evaluation of clinical and histological prognosticators"* of melanoma, *"the most effective proved to be tumor thickness and mitotic activity."*

Histopathology 1979, 3, 385–393

Prognostic significance of the histological features of malignant melanoma

V. J. McGOVERN, H. M. SHAW,* G. W. MILTON & G. A. FARAGO

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Accepted for publication 16 March 1979

McGovern V.J., Shaw H.M., Milton G.W. & Farago G.A. (1979 *Histopathology* **3**, 385–393

Prognostic significance of the histological features of malignant melanoma

A review of 694 patients with localized cutaneous malignant melanoma (clinical stage I) revealed that three histological features of the primary lesion had no effect of their own on survival rate but derived their prognostic significance only because of their close correlation with tumour thickness. Primary lesions of superficial spreading histogenetic type, or of low mitotic activity or showing evidence of partial regression appeared to have a more favourable prognosis than lesions of nodular histogenetic type or of high mitotic activity or showing no regression. However, the former three histological features were predominant in thin lesions which had a better prognosis than thicker lesions. It was concluded that these features exerted only an indirect effect upon survival, tumour thickness being the most important prognostic determinant.

By contrast, McGovern claimed that *"high mitotic activity … exerted only an indirect effect upon survival, tumour thickness being the most important prognostic determinant."*

In the 2001 version of the American Joint Committe on Cancer Staging System for Cutaneous Melanoma, mitotic figures were not mentioned at all.

Melanoma TNM Classification

T classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III
		b: with ulceration or level IV/V
T2	1.01-2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01-4.0 mm	a: without ulceration
		b: with ulceration
T4	> 4.0 mm	a: without ulceration
		b: with ulceration

AJCC, 2001

Then they were taken out of the can.

Tumor Mitotic Rate Is a More Powerful Prognostic Indicator than Ulceration in Patients with Primary Cutaneous Melanoma

An Analysis of 3661 Patients from a Single Center

Manuela F. Azzola, M.D.[1]
Helen M. Shaw, Ph.D.[1,2]
John F. Thompson, M.D.[1,2]
Seng-jaw Soong, Ph.D.[3]
Richard A. Scolyer, M.B.B.S.[4]
Geoffrey F. Watson, M.B.B.S.[4]
Marjorie H. Colman, B.Sc.[1]
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BACKGROUND. The current study was performed to determine whether tumor mitotic rate (TMR) is a useful, independent prognostic factor in patients with localized cutaneous melanoma.

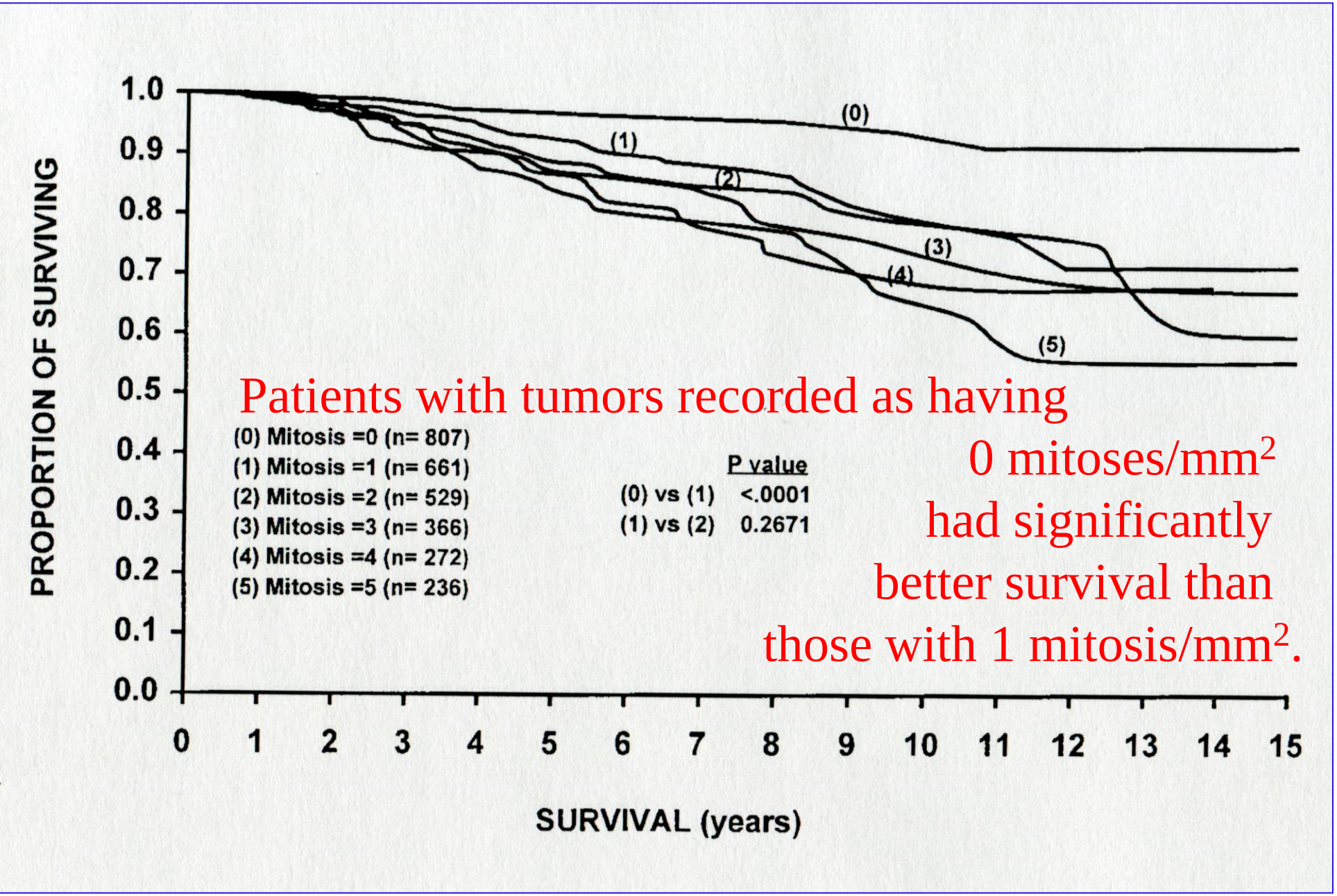
METHODS. From the Sydney Melanoma Unit database, 3661 patients with complete clinical information and details of primary tumor thickness, ulcerative state, and TMR were studied. TMR was expressed as mitoses per mm^2 in the dermal part of the tumor in which most mitoses were seen, as recommended in the 1982 revision of the 1972 Sydney classification of malignant melanoma. To determine which was the more prognostically useful method of grouping TMR, two separate methods (A and B) were used. Factors predicting melanoma-specific survival were analyzed using the Cox proportional hazards regression model.

RESULTS. Patients with a TMR of 0 mitoses/mm^2 had a significantly better survival than those with 1 mitosis/mm^2 ($P < 0.0001$) but no significant survival differences were recorded for the stepwise increases from 1–2, 2–3, 3–4, and 4–5/mm^2. Tumor thickness, ulceration, and TMR were closely correlated, whether TMR was grouped using Method A (0, 1–4, 5–10, and $\geq$ 11 mitoses/mm^2) or Method B (0–1, 2–4, and $\geq$ 5 mitoses/mm^2). However, Cox regression analysis indicated that the TMR was a highly significant independent prognostic factor, particularly when grouped according to Method A, in which it was second only to tumor thickness as the most powerful predictor of survival ($P < 0.0001$).

CONCLUSIONS. TMR is an important independent predictor of survival for melanoma patients. If confirmed by studies from other centers, it has the potential to further improve the accuracy of melanoma staging, as well as to define more rigidly the risk categories for patients entering clinical trials. ***Cancer* 2003;97:1488–98.**

DOI 10.1002/cncr.11196

In 2003, a group from the University of Sydney reported results of an *"analysis of 3661 patients from a single center,"* according to which *"tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma."*



Survival rates were influenced by the number of mitotic figures, and the greatest difference was noted between none and one. The authors concluded *"that patients with tumors recorded as having 0 mitoses/mm^2 had significantly better survival than those with 1 mitosis/mm^2."*

These findings, of course, were like wind for the mills of proponents of the new definition of growth phases. Stimulated by the new data, they did not hesitate to reassess their own material in regard to mitoses

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Identification of High-Risk Patients Among Those Diagnosed With Thin Cutaneous Melanomas

Phyllis A. Gimotty, David E. Elder, Douglas L. Fraker, Jeffrey Botbyl, Kimberly Sellers, Rosalie Elenitsas, Michael E. Ming, Lynn Schuchter, Francis R. Spitz, Brian J. Czerniecki, and DuPont Guerry

From The Melanoma Program of the Abramson Cancer Center, Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Department of Pathology and Laboratory Medicine, Department of

A B S T R A C T

Purpose

Most patients with melanoma have microscopically thin (≤ 1 mm) primary lesions and are cured with excision. However, some develop metastatic disease that is often fatal. We evaluated

A new prognostic factor, VGP mitogenicity, was identified.

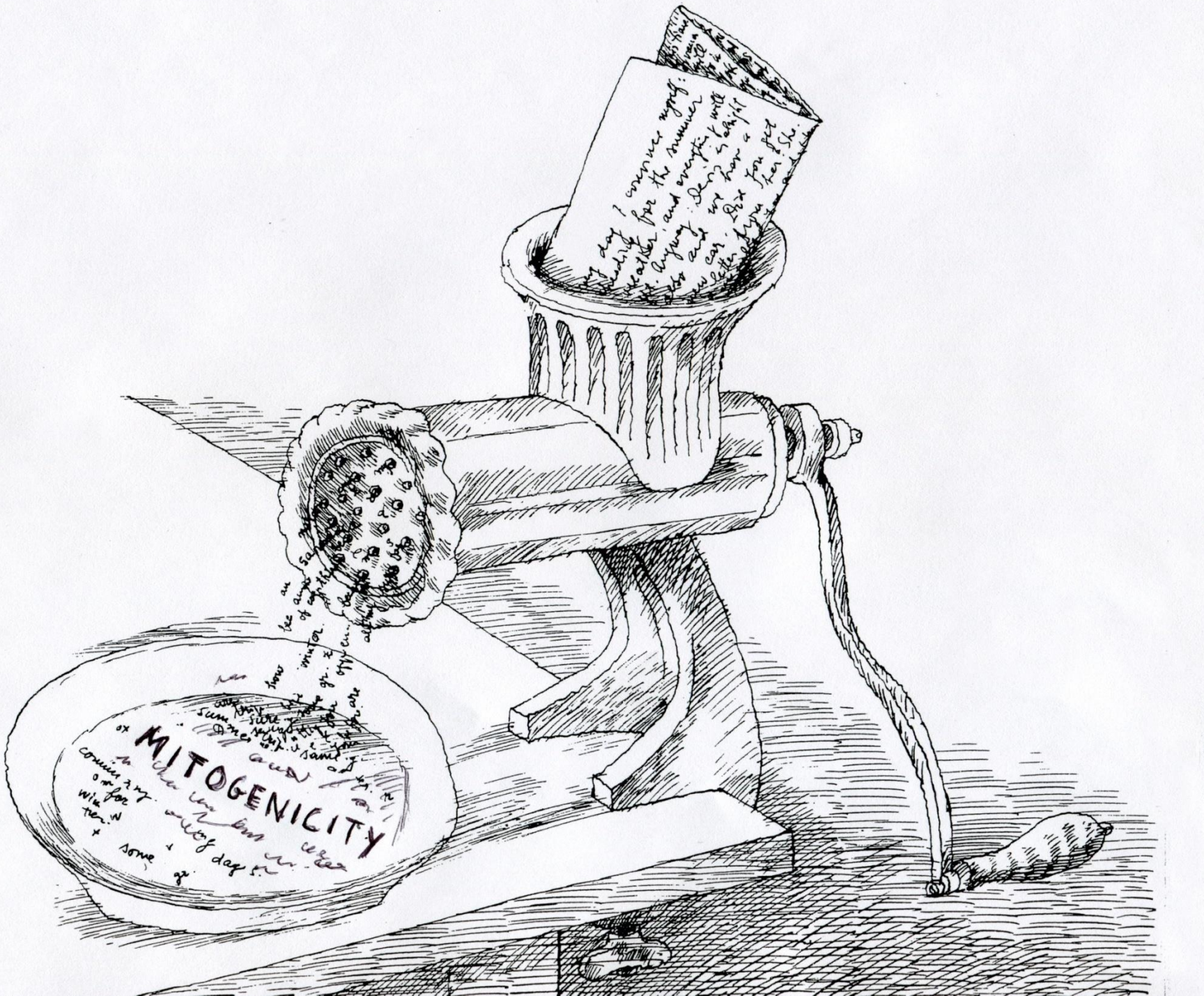
Conclusion

Prognostication and related clinical decision making in the majority of patients with melanoma can be improved now using the validated, SEER-based classification. Tumor cell mitotic rate should be incorporated into the next iteration of AJCC staging.

tions are found at the end of this article.

Address reprint requests to Phyllis A.

and soon announced that *"a new prognostic factor, VGP mitogenicity, was identified."* The new term, "mitogenicity," referred to melanomas *"with a mitotic rate greater than zero."*



Of course, that term made no sense. One may refer to mitoses as being “tumorigenic,” because mitoses may be regarded as formative elements of the tumor, but to refer to a tumor as being “mitogenic,” implying that the tumor is the formative element of mitoses, is obviously absurd. Yet, introduction of the new term may be regarded as a stroke of genius because “mitogenicity” sounds much more scientific than the paltry word, “mitosis.”

Mitogenicity, a feature of the VGP,[8,9,12] is important beyond those factors that are used at present to stage thin melanomas. It also reflects the biology of tumor progression. Based on lesion histology, rates of tumor cell mitoses, and the expression of Ki67 (an immunohistochemical marker of cell division), we have shown that tumor progression in primary melanomas may be characterized by three stages: a phase of rapid tumor cell proliferation in the epidermis (the in situ RGP), followed first by a phase of invasion into the dermis and decreased proliferation (the invasive RGP), and then by a phase in which higher proliferative rates resume in the dermis as the VGP ensues.[9,17] Mitogenicity, scored in the dermis as either present or absent, or as a mitotic rate, has been validated widely and is readily ascertainable, transportable, and generalizable.[18] It has been demonstrated in other studies to be an independent prognostic factor for disease-free survival and metastasis,[19-21] including metastasis to sentinel lymph nodes (SLNs)[22-25] for patients with thin melanomas. Our data support the incorporation of mitogenicity into the next version of AJCC staging for melanoma, as suggested in a recent international consensus statement.[26]

The authors concluded that *"mitogenicity, a feature of the VGP, is important beyond those factors that are used at present to stage thin melanomas. … Our data support the incorporation of mitogenicity into the next version of AJCC staging for melanoma."*

Table 1. TNM Staging Categories for Cutaneous Melanoma

AJCC, 2009

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis $< 1/mm^2$
		b: With ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2.00	a: Without ulceration
		b: With ulceration
T3	2.01-4.00	a: Without ulceration
		b: With ulceration
T4	> 4.00	a: Without ulceration
		b: With ulceration

That recommendation was heeded, one explanation probably being that applicants and decision-makers were more or less identical, and so mitogenicity entered the TNM classification of melanoma. Since 2009, T1b melanomas are defined as melanomas measuring up to 1 mm in thickness that are either ulcerated or have a mitotic rate of $\geq 1/mm^2$.

Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis $< 1/mm^2$ b: With ulceration or mitoses $\geq 1/mm^2$

AJCC, 2009

The melanoma staging committee recommended that mitotic rate be determined by the "hot spot" approach and expressed as the number of mitoses per square millimeter of primary tumor.

Moreover, *"the melanoma staging committee recommended that mitotic rate be determined by the 'hot spot' approach and expressed as the number of mitoses per square millimeter of primary tumor."* How is this done?

Protocol for the Examination of Specimens From Patients With Melanoma of the Skin

David P. Frishberg, MD; Charles Balch, MD; Bonnie L. Balzer, MD, PhD; A. Neil Crowson, MD; Mikund Didolkar, MD; Jennifer M. McNiff, MD; Roger R. Perry, MD; Victor G. Prieto, MD, PhD; Priya Rao, MD; M. Timothy Smith, MD; Bruce Robert Smoller, MD; Mark R. Wick, MD; for the Members of the Cancer Committee, College of American Pathologists

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations. The College regards the reporting
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tive January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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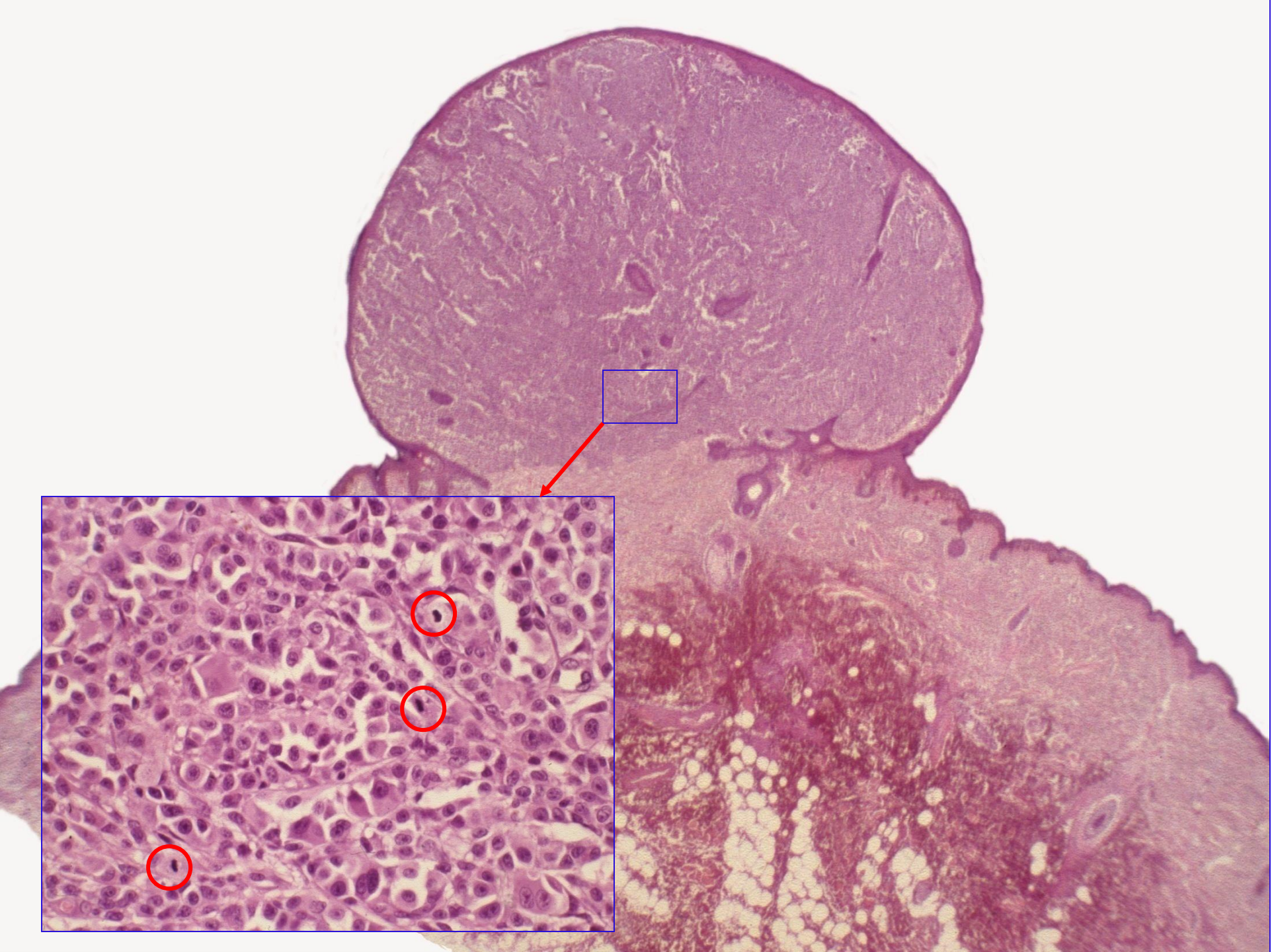
First, find the area in the vertical growth phase containing most mitotic figures, the so-called hot spot. After counting the mitoses in the hot spot, the count is extended to adjacent fields until an area corresponding to 1 mm^2 is assessed.

Select a Single Response Unless Otherwise Indicated

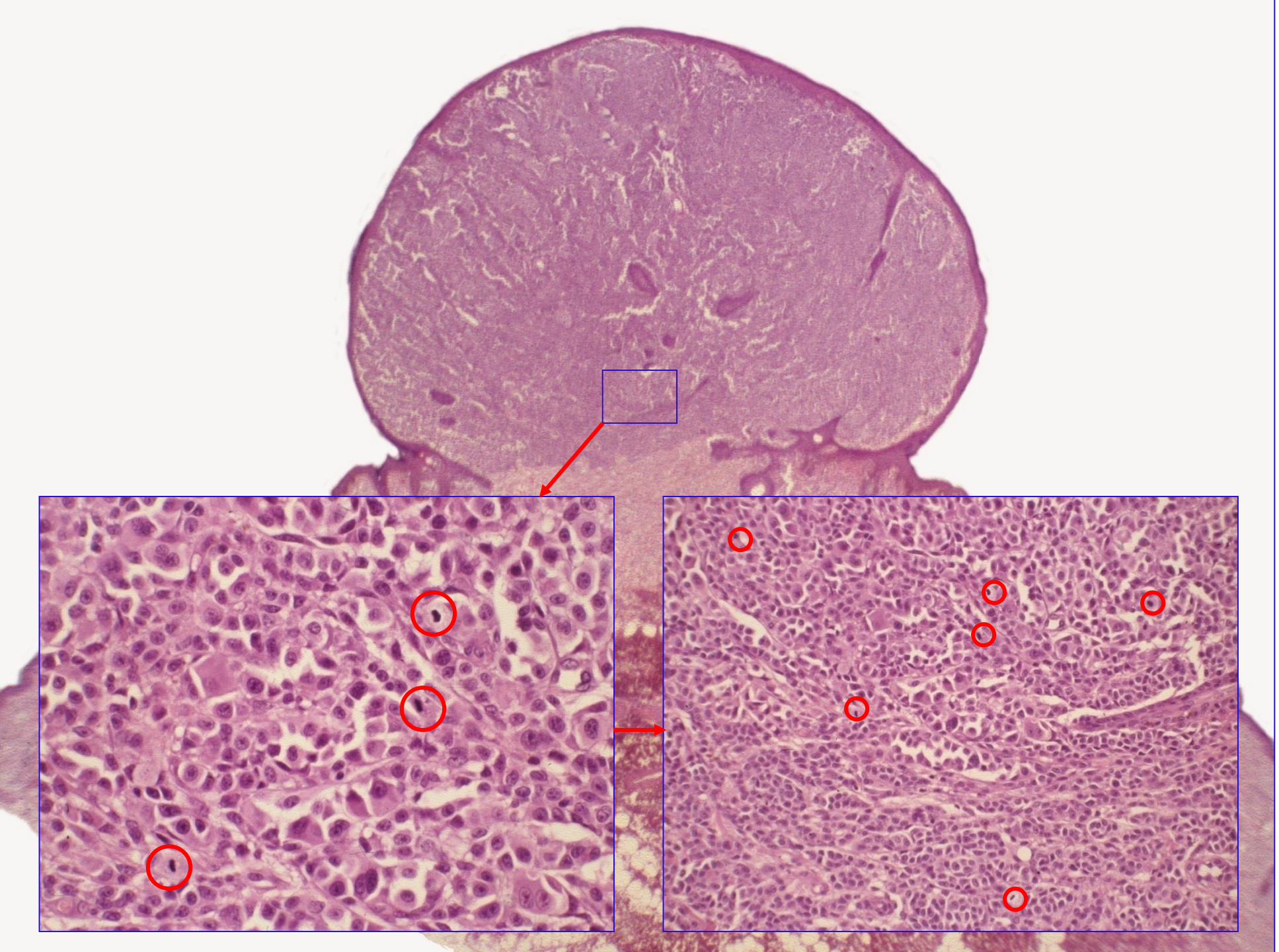
* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Procedure (select all that apply)

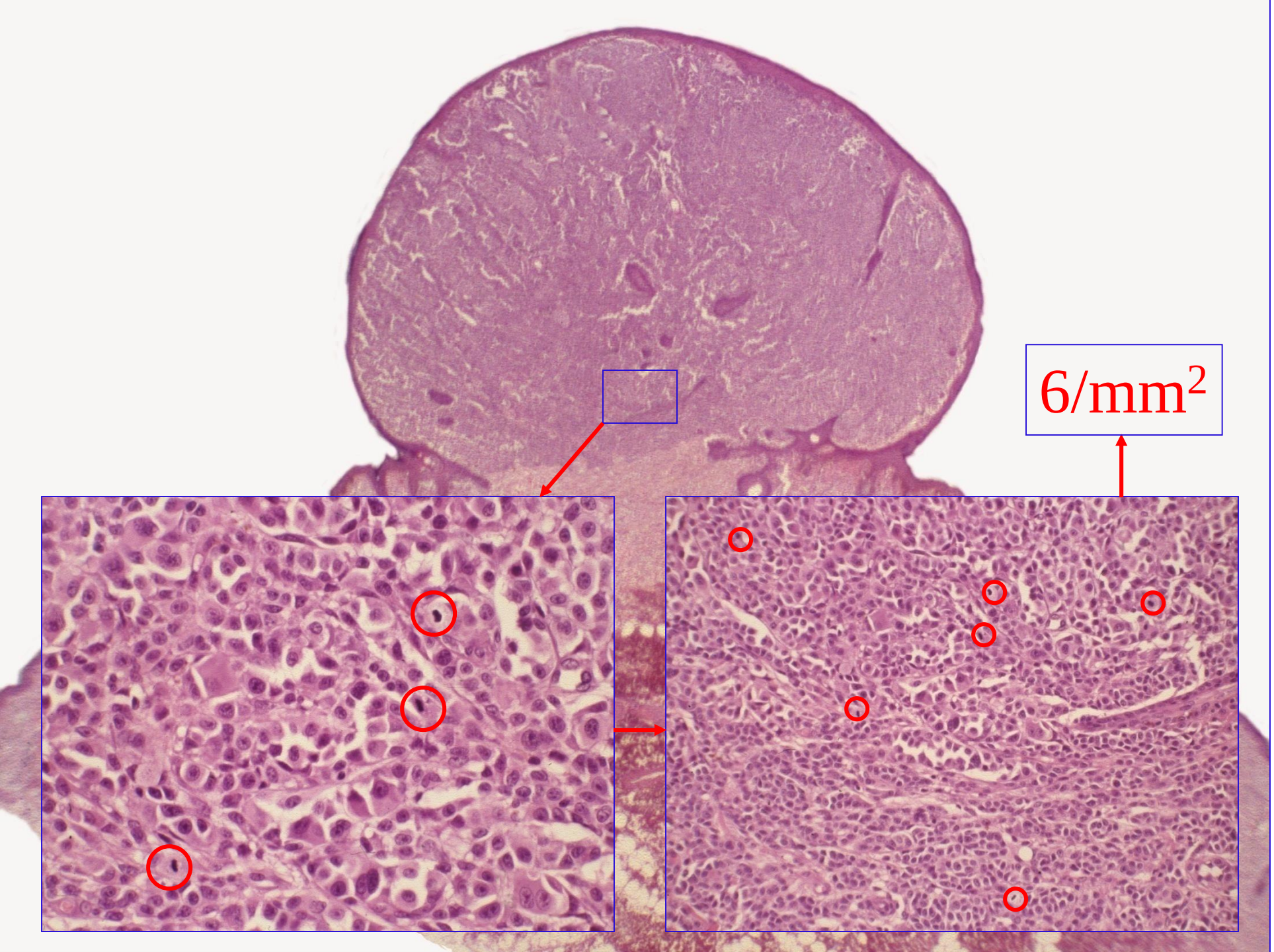
Details are specified in a "Protocol for the Examination of Specimens From Patients With Melanoma of the Skin," in which the committee demands to, "*first, find the area in the vertical growth phase containing most mitotic figures, the so-called hot spot. After counting the mitoses in the hot spot, the count is extended to adjacent fields until an area corresponding to 1 mm^2 is assessed.*"



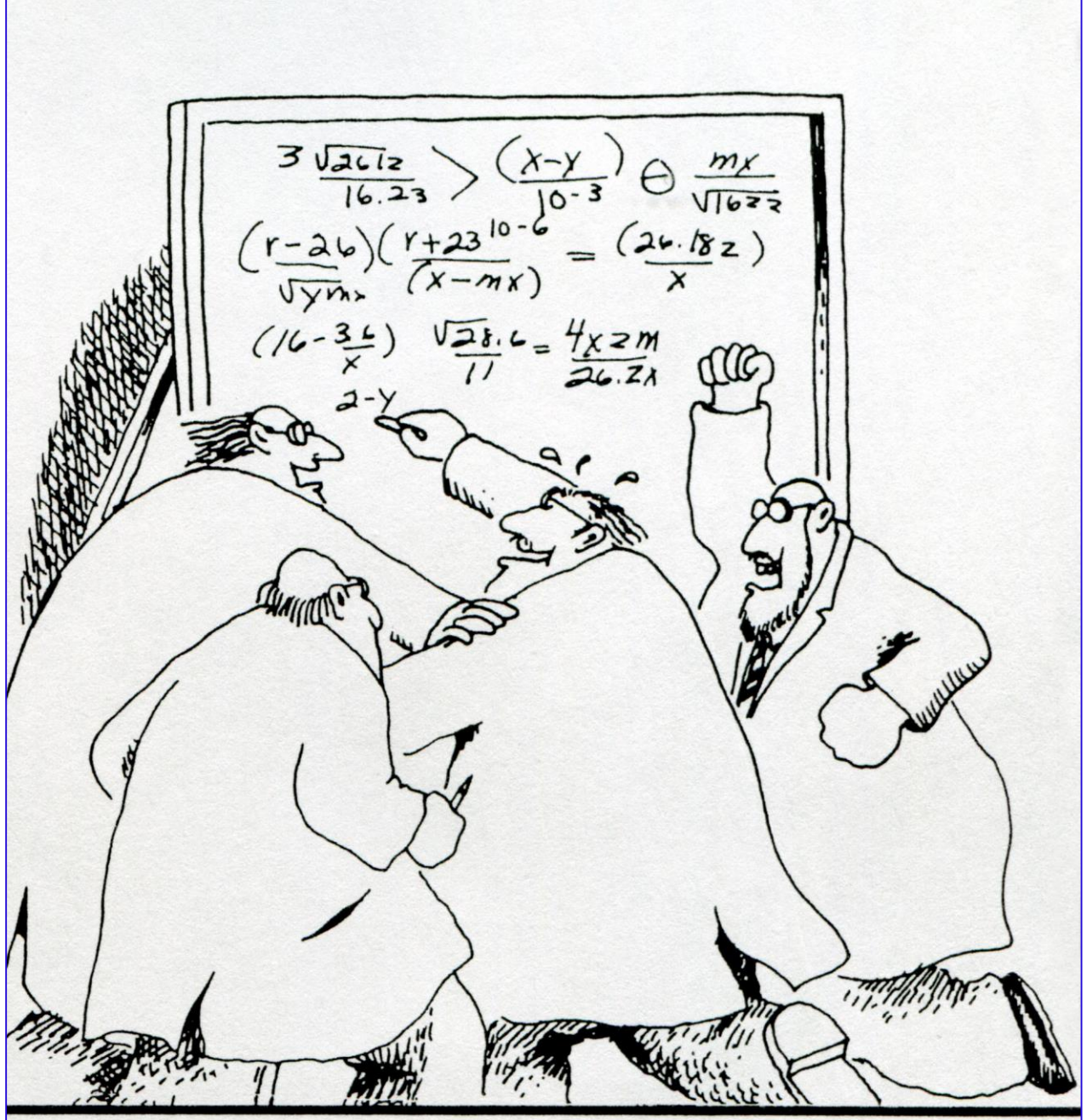
Now we know how to proceed. We have a melanoma, we look, at highest magnification, for the field containing most mitotic figures, count them,



and then extend our count to adjacent fields until 1 mm^2 is assessed.

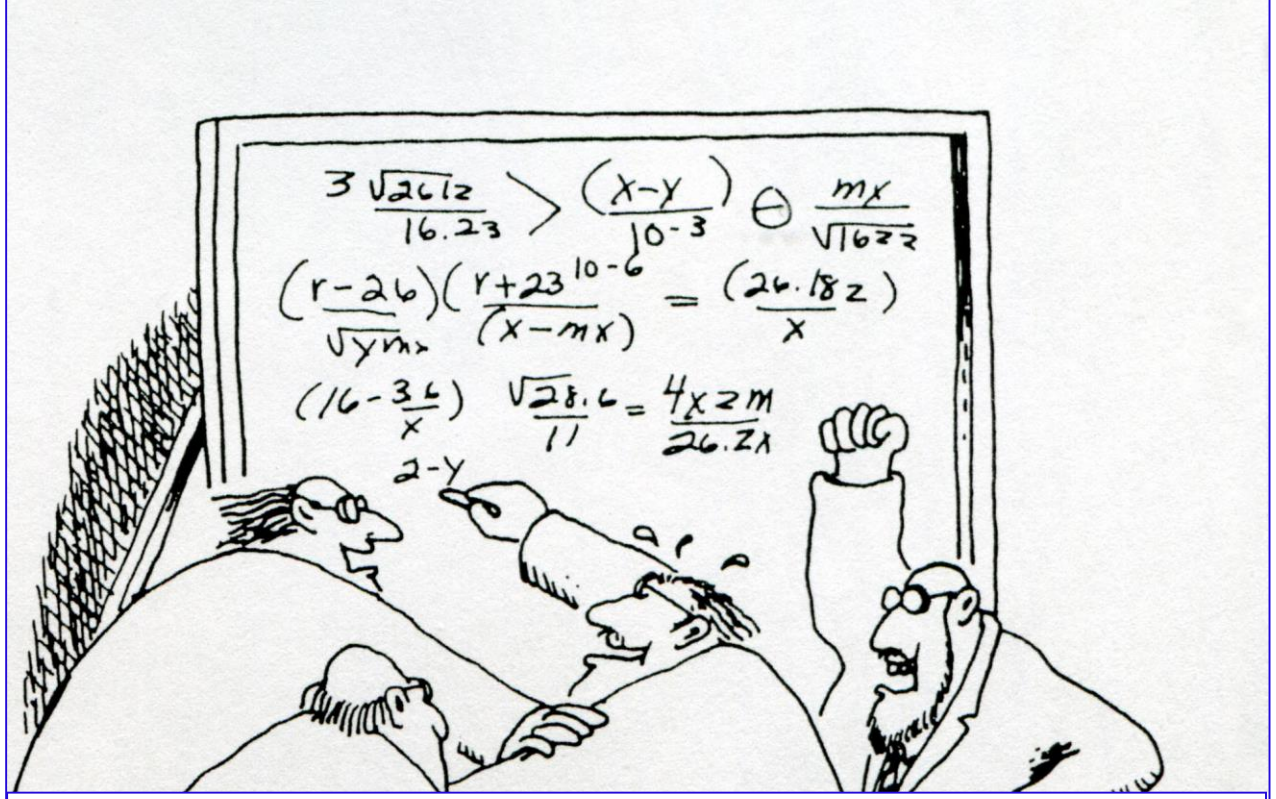


Then we have our result, in this case 6 per mm^2. Clinical experience teaches that a mitotic rate that high is associated with an adverse prognosis,



"Go for it, Sidney! You've got it! You've got it! Good hands! Don't choke!"

but when the statisticians of the AJCC analyzed their data, they found that already 1 mitotic figure makes the difference.



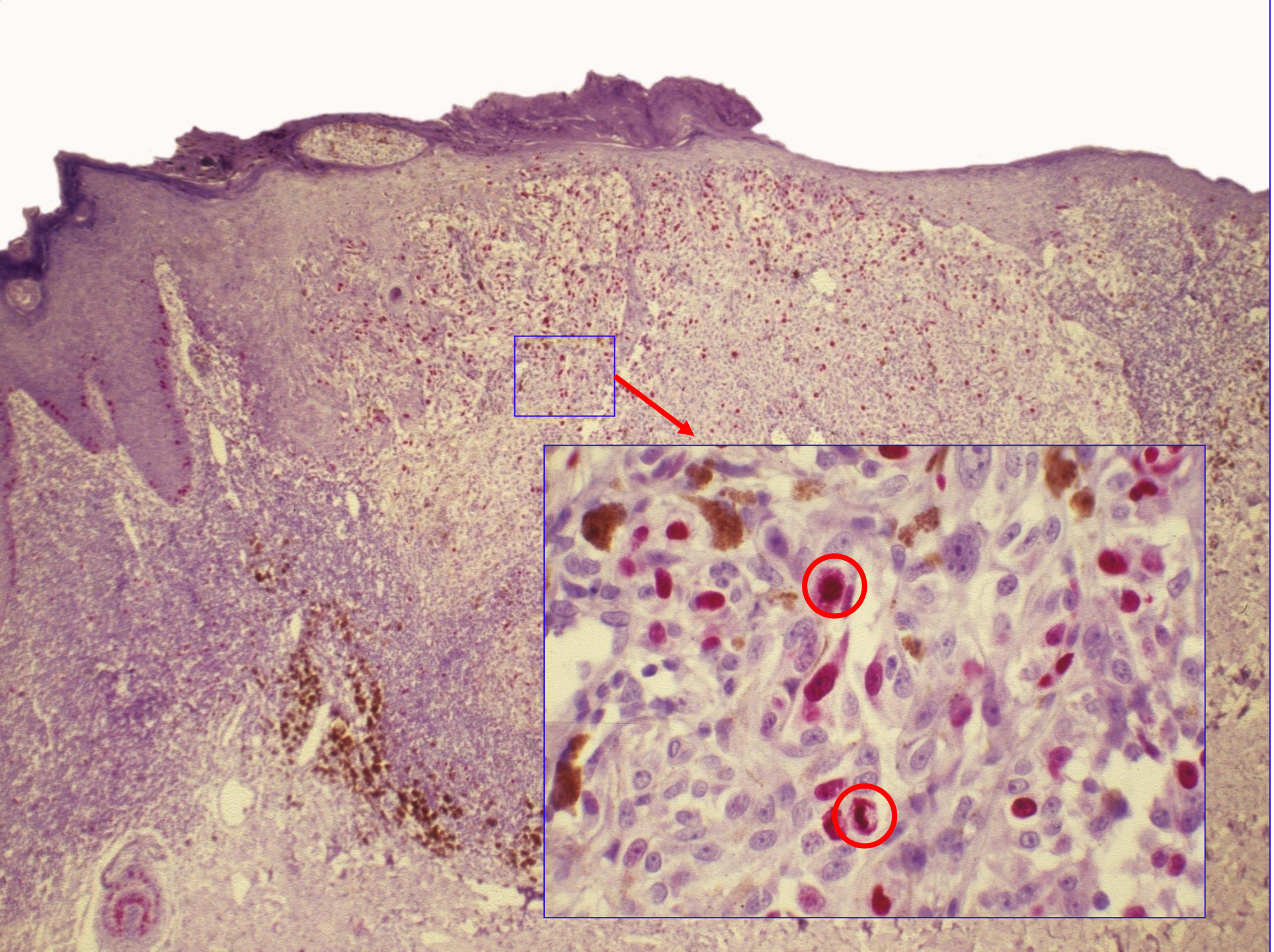
Multiple thresholds of mitotic rate were examined statistically, and the most significant correlation with survival was identified at a threshold of at least 1/mm^2.

"Go for it, Sidney! You've got it! You've got it! Good hands! Don't choke!"

They explained that *"multiple thresholds of mitotic rate were examined statistically, and the most significant correlation with survival was identified at a threshold of at least 1/mm^2."* But in their great joy about those beautiful results, the reliability of data entering into them was sacrificed completely.

- Mitoses also in epidermis ?
- How many sections?
- Which detection method?

The committee did not even bother to specify whether the count of mitoses should include only those in the dermis or also those in the epidermis. It did not specify how many sections must be examined – obviously, it makes a big difference whether mitoses are searched for in one, five, or ten sections. It not specify the detection method.



Most data concerning mitotic rate are based on sections stained with hematoxylin and eosin, but immunohistochemical markers for mitoses are far more sensitive. Here is an example. In this area, many nuclei are stained, but, morphologically, mitoses are detectable in only two of them.

Use of Anti-phosphohistone H3 Immunohistochemistry to Determine Mitotic Rate in Thin Melanoma

David J. Casper, MD, Kate I. Ross, BS,† Jane L. Messina, MD,*‡ Vernon K. Sondak, MD,§ Cheryl N. Bodden, BS, ASCP, HTL,* Tim W. McCardle, MD,§ and L. Frank Glass, MD*§*

Abstract: The seventh edition of the American Joint Committee on Cancer (AJCC) melanoma staging system, slated for release in 2010, will introduce mitotic rate (MR) as one of the primary criteria for staging thin melanoma (≤1.0 mm). Accurate counts are essential because the finding of a single mitotic figure (MF) will alter the staging and management of these patients. The traditional manner of counting of mitotic figures (MFs) using a ×40 objective is time consuming and prone to inter- and intraobserver variability. We employed an antibody to phosphohistone H3 (pHH3, ser10) that labels MFs in all stages of mitosis, to evaluate mitotic counts at ×20 in tissue sections from 30 melanoma patients with thin lesions 0.45 to 1.2 mm in depth, and compared results with routine hematoxylin and eosin (H&E) in a double-blind fashion. The mean MR was 1.63 by anti-pHH3, and 0.67 for H&E, representing a mean increase of 243%. The Spearman correlation coefficient for MR in H&E and anti-pHH3 sections was 0.88 ($P < 0.0001$). When melanomas were designated as "mitotically active," if the MR by anti-pHH3 was ≥2 and ≥1 by H&E, the correlation coefficient increased to 1.0. No thin melanomas were

The mean MR was 1.63 by anti-pHH3, and 0.67 for H&E, representing a mean increase of 243%.

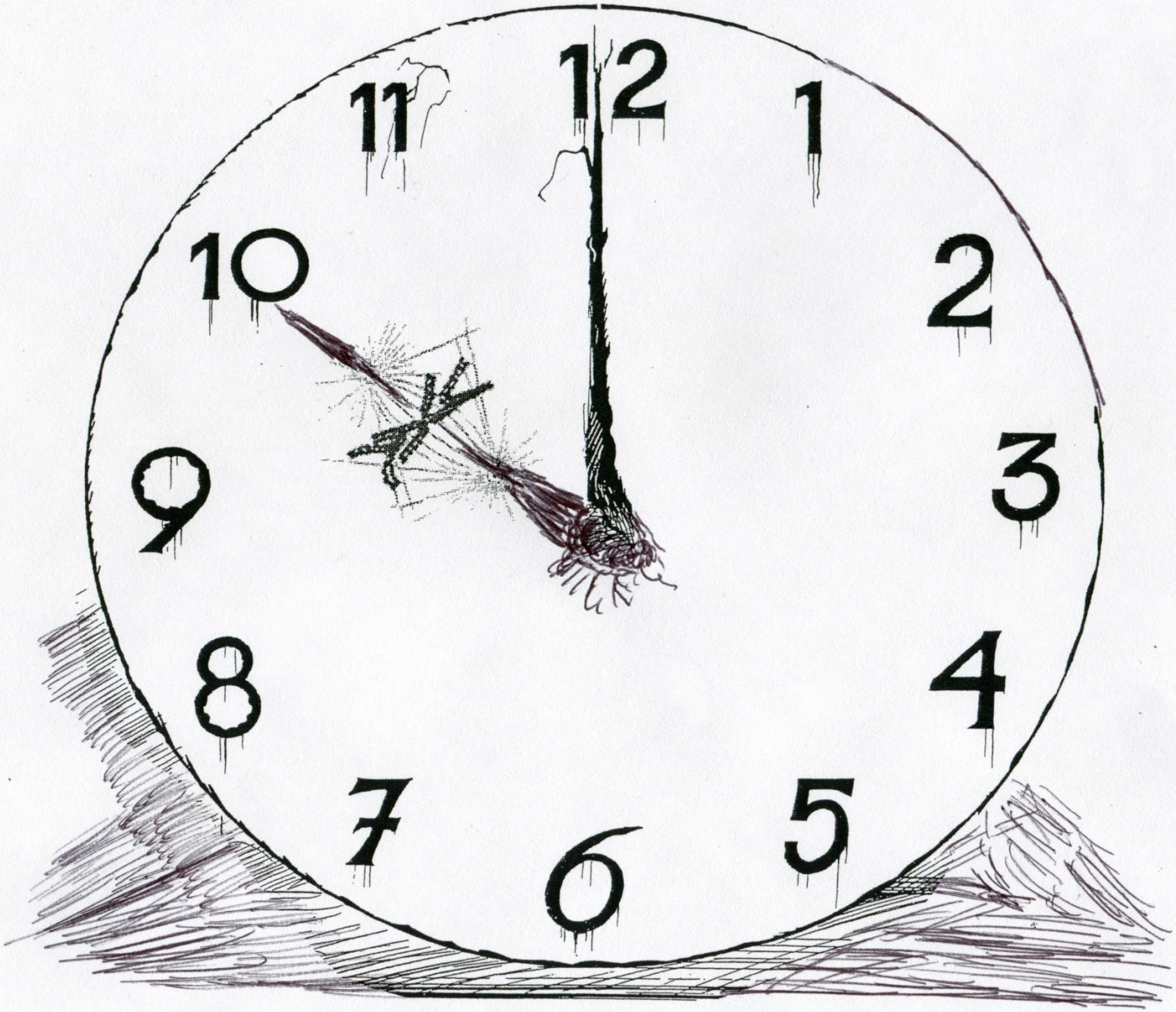
Key Words: mitotic rate, phosphohistone H3, melanoma, immunohistochemistry, melanoma staging

(*Am J Dermatopathol* 2010;32:650–654)

(≤1.0 mm). This revision in the staging system is based on multivariate analyses of over 30,000 patients in the AJCC Melanoma staging database, and the conclusions are supported by previous studies that highlight the importance of MR as a prognostic indicator for thin melanomas, ranking second only to the Breslow thickness.[1–3] MR has not been uniformly accepted as an independent prognosticator for melanoma.[4] Some of this stems from the difficulty in separating its prognostic importance from ulceration and tumor thickness. There is also difficulty comparing large series because of the lack of uniform reporting of mitotic activity.

Currently, MR in melanoma is calculated by counting mitotic figures (MFs) with light microscopy in tissue sections stained with hematoxylin and eosin (H&E) using a ×40 objective and expressed as number per mm^2. Counts begin in the field with the greatest number of mitoses ("hot spot") and are determined by counting in 4 successive high-power fields (HPFs).[5,6] However, this method is prone to both practical and theoretical difficult and time consuming. Despite a relatively high level of concordance among pathologists in the assessment of certain key factors for melanoma, reliable staging is not possible in all cases because of pitfalls that lead to errors in microstaging, thus negatively impacting treatment and

In a recent study about "mitotic rate in thin melanoma," *"the mean mitotic rate was 1.63"* by immunohistochemistry *"and 0.67 for H&E, representing a mean increase of 243%."*



Mitotic rate is influenced by many other factors. One of them is time. In general, the duration of mitoses is between 30 and 120 minutes, and the metaphase is much shorter. Hence, in a tumor with only scant proliferation,

mitotic rate may depend on whether or not the surgeon takes a coffee break before the next biopsy.

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Printed in Great Britain © The Company of Biologists Limited 1993

Proliferative behaviour of high-ploidy cells in two murine tumour lines

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SUMMARY

The presence of high-ploidy cells in malignant tumours has long been documented. However, the biological significance of these cells is not known and there is a great deal of controversy over their proliferative potential. We have analysed the behaviour of these cells in two murine tumour lines, B16F10 melanoma and 3T3A31M angiosarcoma, determining their DNA content by microspectrophotometry and using time-lapse film studies. We have found a discrepancy between the presence of high-ploidy cells in metaphase and the absence of hyperploid telophases. High-ploidy metaphases may be aborted (mitotic polyploidization), prolonged in time or evolve in the form of multipolar, generally tripolar, mitoses. Our results suggest that high-ploidy cells are capable of proliferating, despite certain peculiarities in their cell cycle, and constitute a tumour subpopulation whose role in neoplasia merits further study.

Key words: tumour proliferation, high-ploidy cells, malignancy

In high-ploidy cells, metaphases have been found to be prolonged in time. Hence, the increased number of mitoses commonly found in nodules of melanoma composed of markedly atypical cells may be caused not only by enhanced proliferation but also by prolongation of the metaphase.

Changes in Mitotic Rate and Cell Cycle Fractions Caused by Delayed Fixation

K. DONHUIJSEN, MD, U. SCHMIDT, MD, H. HIRCHE, D. VAN BEUNINGEN, MD, AND V. BUDACH, MD

The mitosis frequency and flow cytometric data of malignant neoplasms are important, both for diagnosis and for prognosis. It is unclear to what extent these factors are affected by a delay in the fixation of tumor biopsies. We have thus studied the mitotic activity and DNA content in human soft-tissue sarcoma xenotransplants, fixed for periods of 5 minutes and 3, 6, 9 and 12 hours after biopsy. On average, the mitoses counted by two observers were 13% and 10% below initial values after 3 hours, and decreased by 46% and 39% after 12 hours. The mitosis decrease was related to the degree of mitotic activity of individual tumors, and was minimal in the sarcomas with the lowest mitotic rate. These results were reproducible. However, numerous pyknotic mitotic figures were observed, so the decrease in counts is largely due to their reduced identifiability, and only partly attributable to a completion of the cell cycle. Well-preserved mitotic figures demonstrable after 12 hours appear to indicate that the proliferation activity only gradually decreases in unfixed biopsies. The flow cytometric data did not change substantially; only a slight increase in the G2+M-phase fraction was observed. General conclusions from the results are limited by the fact that the investigated sarcomas had a higher mitotic activity than most carcinomas. Nevertheless, early fixation of biopsies is desirable to accurately measure mitosis counts for the grading of malignancy.
HUM PATHOL 21:709–714.

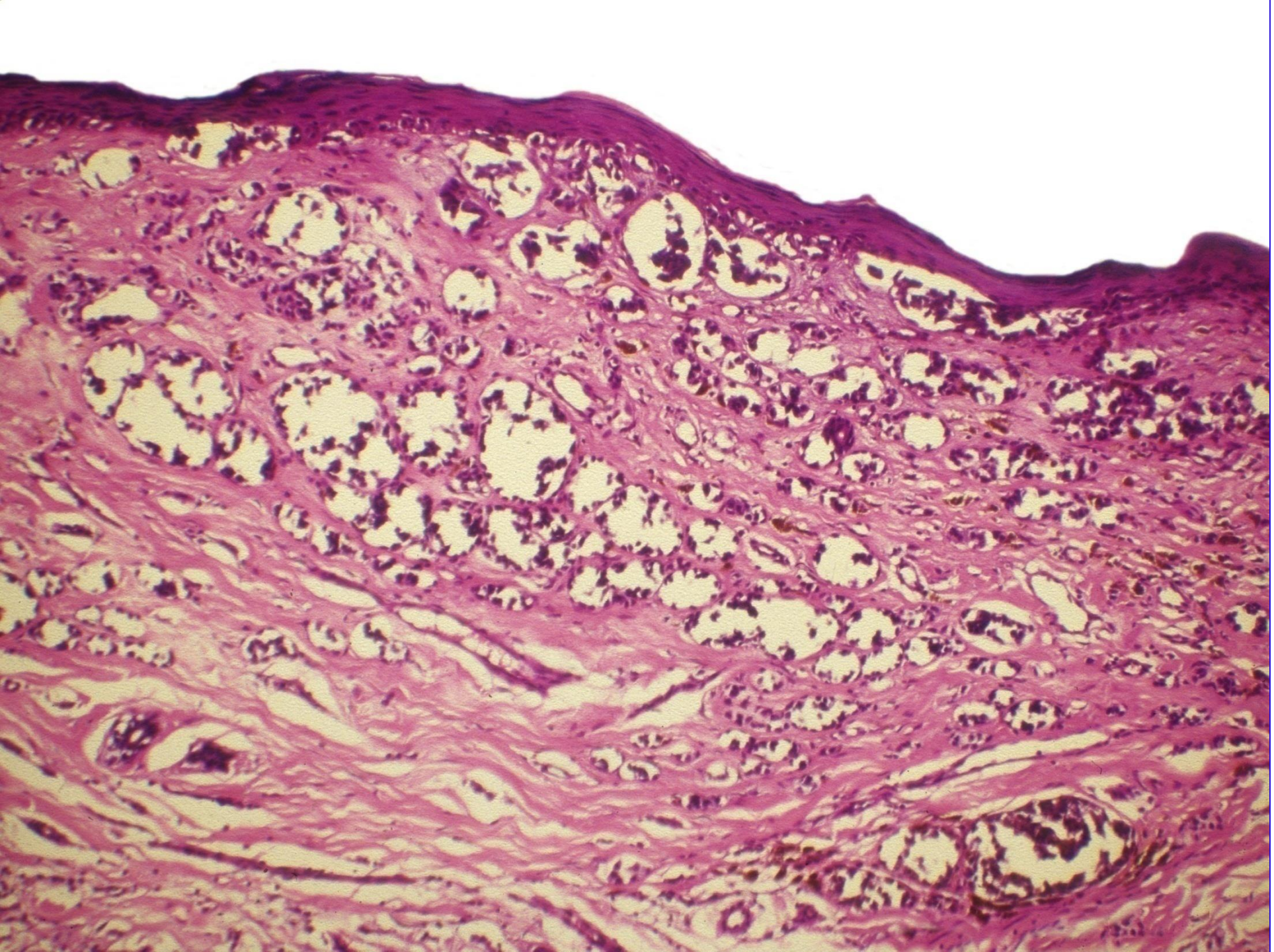
1. Does a delay in fixation lead to a decrease in mitosis counts?
2. Is this decrease explained by a completion or condensation/pyknosis of the mitotic figures?
3. Is there a close and constant correlation between the decrease in mitosis frequency and time?
4. Can inter- and intra-individual differences be identified?
5. Are the mitosis counts reproducible?

Accordingly, the question arises whether a delay in fixation can affect the prognostic significance of flow cytometric DNA measurements of malignant tumors,[13-16] in particular, whether there is a shift in the percentage distribution of cell cycle phases.[17] A reduction in both the S- and G2+M-phase fractions would be expected on completion of the cell cycle.

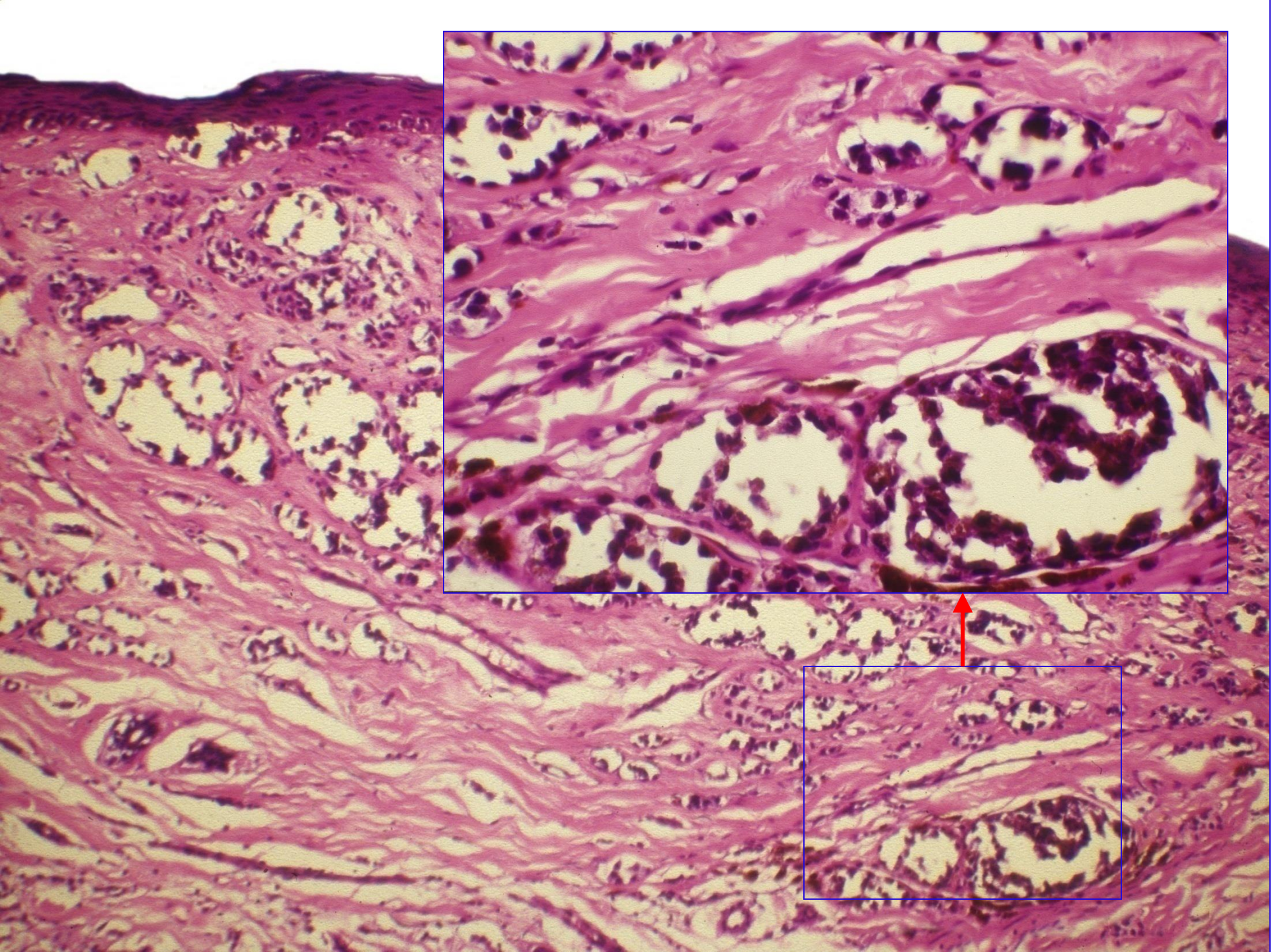
MATERIAL AND METHODS

Case Selection

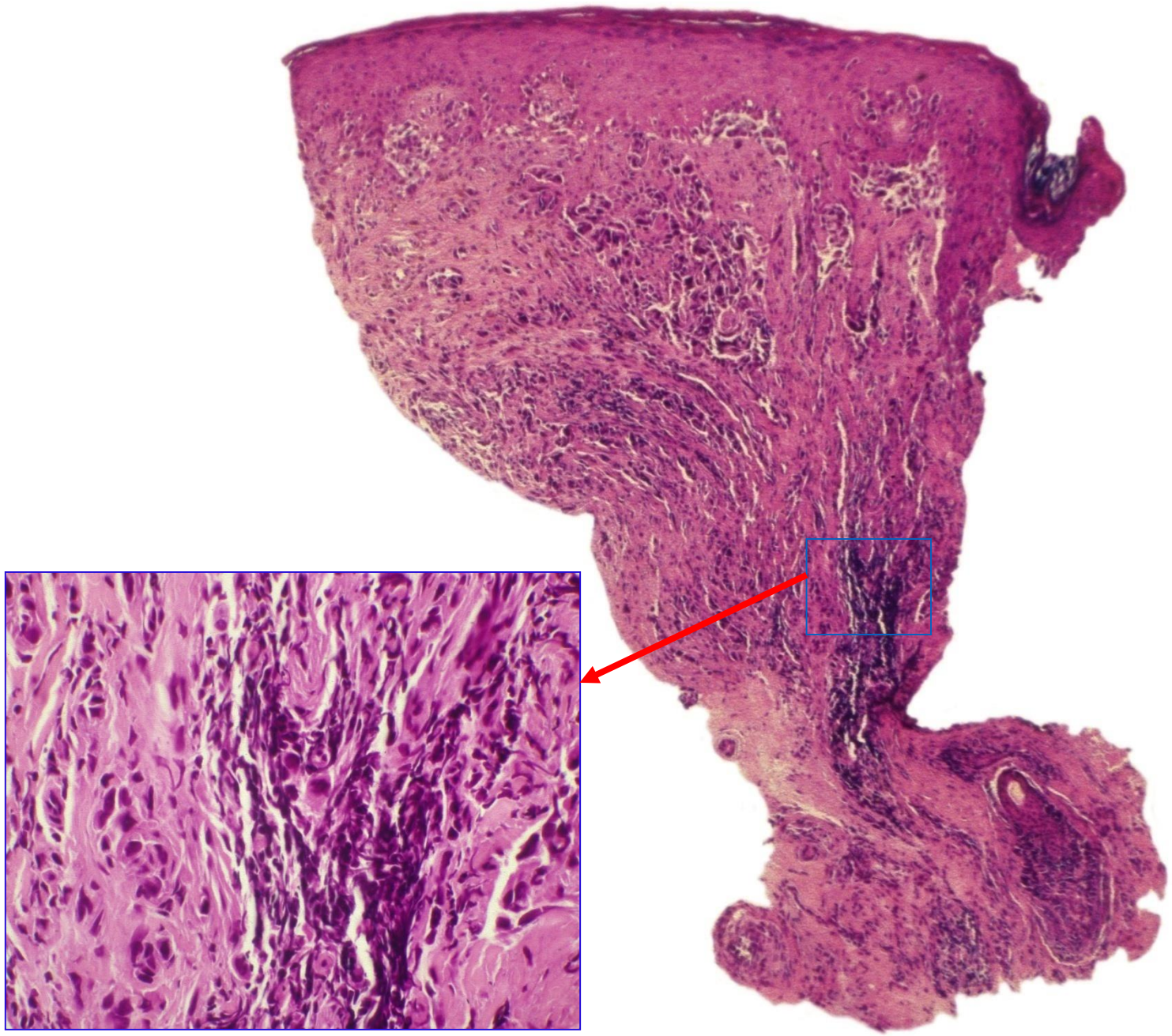
Once a melanoma has been excised, mitotic rate is influenced by fixation. Poor or delayed fixation results in a reduced mitotic rate, a finding attributed, in part, to completion of the cell cycle and, in part, to reduced identifiability of mitoses.



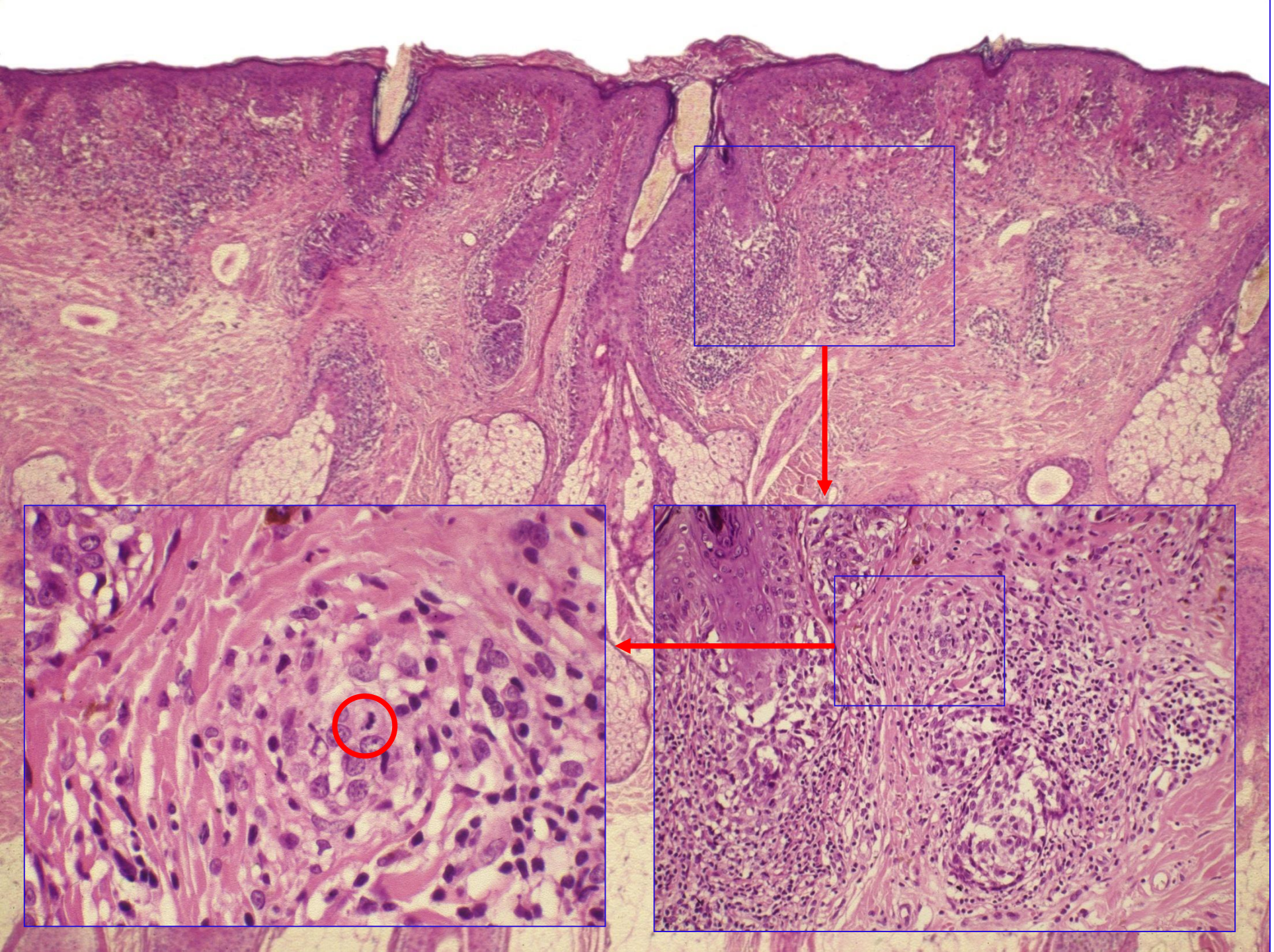
The latter is a major problem, especially in the case of thick sections and poor fixation.



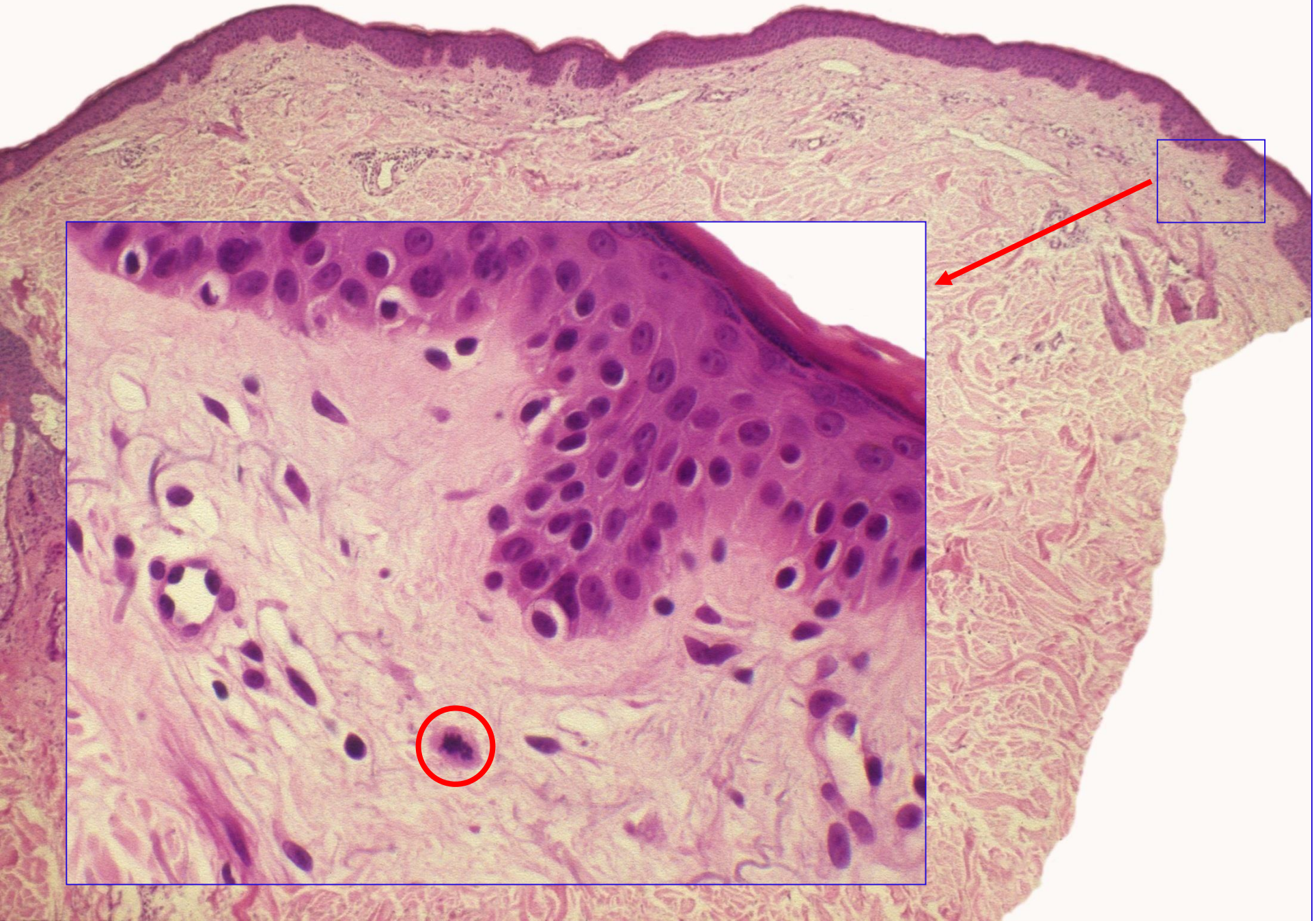
How could anybody exclude mitotic figures in those nests?



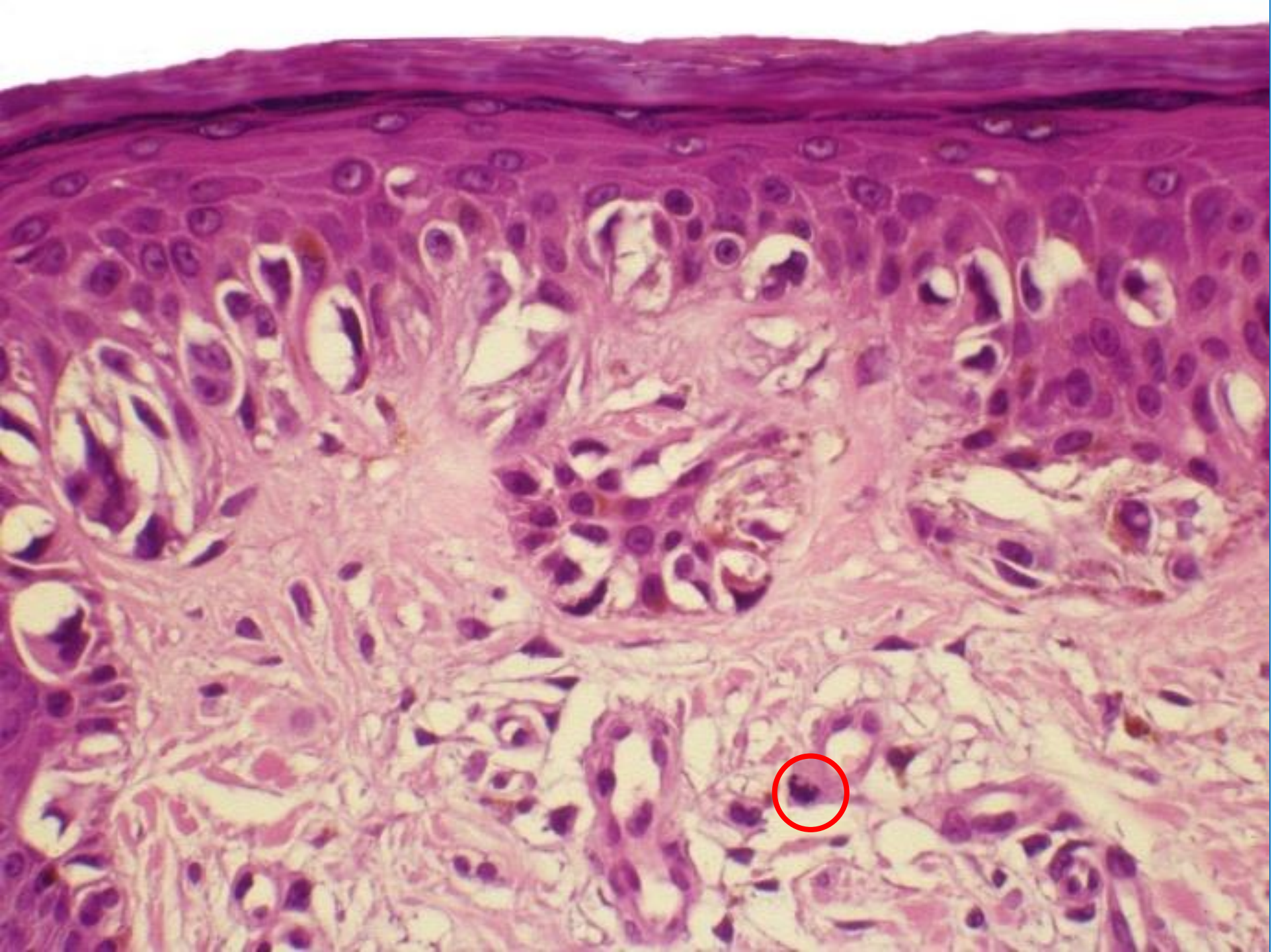
Identification of mitoses becomes absolutely impossible if there are crush artefacts.



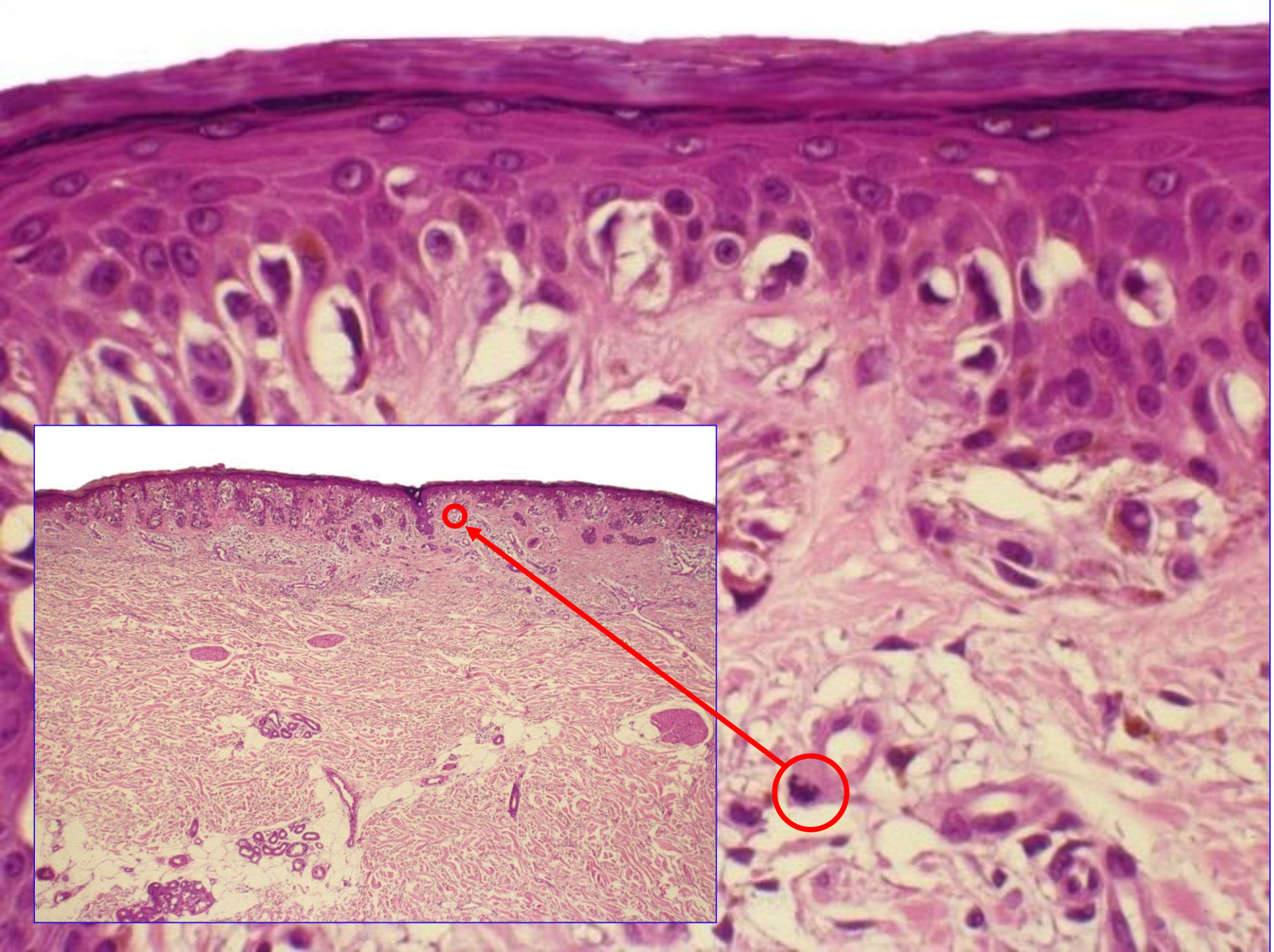
And if a mitotic figure is found, it may be difficult to decide whether it is situated in extensions of epidermal or adnexal epithelium or in the uppermost portion of papillary dermis.



Moreover, mitotic figures do not necessarily belong to neoplastic cells. Here we have a biopsy of a drug reaction. In the papillary dermis, there is an isolated mitotic figure, possibly a fibrocyte.



But what happens if the very same cell is seen in a melanoma? This is an example: a melanoma with a single mitotic figure in the dermis, but is this a tumor cell or, possibly, an endothelial cell?



In lesions with high mitotic rate, one can neglect those doubtful findings, but what if this mitotic figure suffices for a different staging and management?

ORIGINAL ARTICLE

Interobserver Reproducibility of Histopathologic Prognostic Variables in Primary Cutaneous Melanomas

Richard A. Scolyer, MB BS,† Helen M. Shaw, PhD,†‡ John F. Thompson, MD,†‡ Ling-Xi L. Li, PhD,†*
Marjorie H. Colman, BSc,† Sing Kai Lo, PhD,§ Stanley W. McCarthy, MB BS,†*
A. Allan Palmer, MB BS, Katherine D. Nicoll, MB BS,*¶ Bish Dutta, MB BS,‖ Eric Slobedman, MB BS,#*
Geoff F. Watson, MB BS, and Jonathan R. Stretch, D Phil†‡*

Background: The prognosis for patients with localized primary cutaneous melanoma is known to depend principally on tumor thickness, and to a lesser extent on ulcerative state and Clark level. We have recently found in an analysis of 3661 patients that tumor mitotic rate (TMR) is also an important prognostic parameter, ranking second only to tumor thickness. However, few studies have assessed the accuracy and reproducibility with which these features of a melanoma are recorded by histopathologists. curately and reproducibly. Given our recent finding of the significance of TMR in determining prognosis, it is important that this feature be assessed by a standardized method and documented for all primary cutaneous melanomas.

Key Words: melanoma, pathology, mitotic rate, prognosis, reproducibility, precision, observer variation, quality control, kappa statistics

(*Am J Surg Pathol* 2003;27:1571–1576)

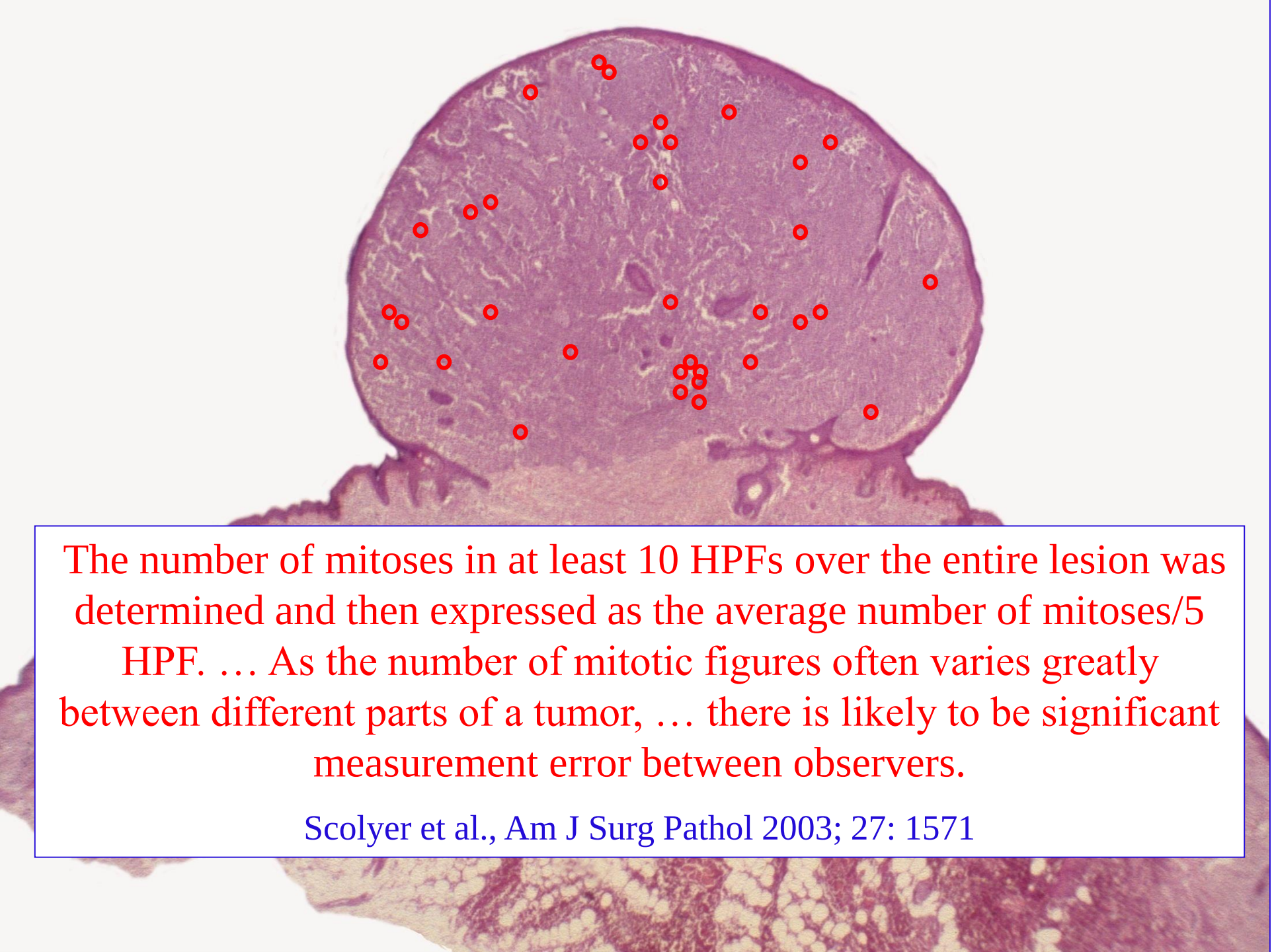
In recent years, the reproducibility of histopathologic prognostic variables in melanomas has been assessed in numerous studies.

TABLE 2. Interobserver Reproducibility of Important Pathologic Prognostic Parameters in 64 Primary Cutaneous Melanomas

Pathologic Feature	Whole Group	SMU Pathologists	Non-SMU Pathologists
Breslow thickness (ICC)	0.96	0.95	0.94
Tumor mitotic rate (ICC)	0.76	0.72	0.80
Clark level (kappa score)			
Overall	0.60	0.56	0.59
Clark level II	0.59	0.58	0.62
Clark level III	0.53	0.39	0.62
Clark level IV	0.55	0.51	0.50
Clark level V	0.76	0.84	0.66
Ulceration (kappa score)	0.83	0.91	0.73

SMU, Sydney Melanoma Unit; ICC, intraclass correlation coefficient.

Mitotic rate always did worse than other parameters, including thickness and ulceration. The best values for mitotic rate were found in this study by the Sydney Melanoma Unit, a finding attributed by the authors to the advantages of the "hot spot approach" vis-á-vis former methods of assessment.

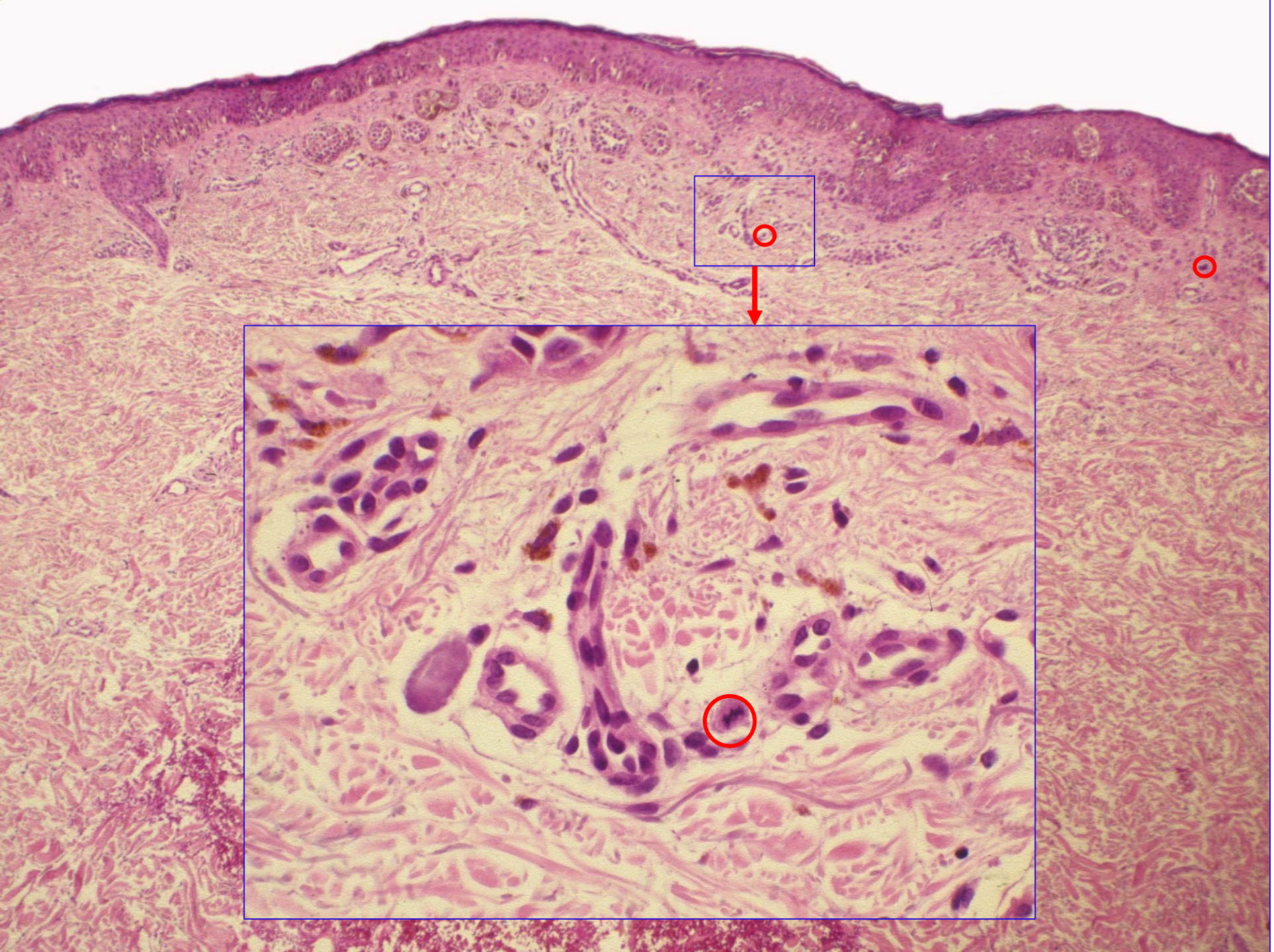


The number of mitoses in at least 10 HPFs over the entire lesion was determined and then expressed as the average number of mitoses/5 HPF. … As the number of mitotic figures often varies greatly between different parts of a tumor, … there is likely to be significant measurement error between observers.

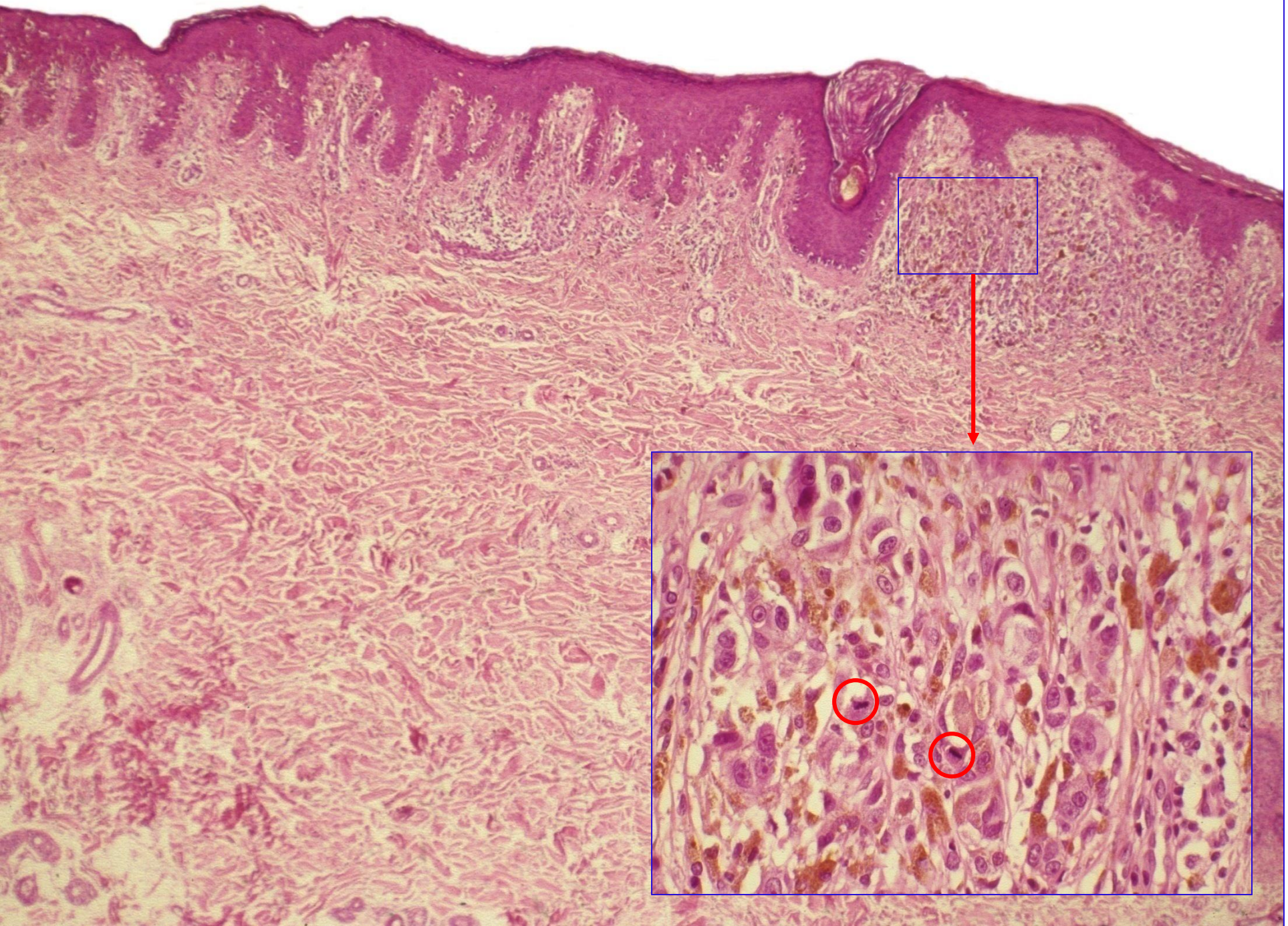
Scolyer et al., Am J Surg Pathol 2003; 27: 1571

The authors explained that, formerly, *"the number of mitoses in at least 10 HPFs over the entire lesion was determined and then expressed as the average number of mitoses/5 HPF. … As the number of mitotic figures often varies greatly between different parts of a tumor, … there is likely to be significant measurement error between observers."* And they were right: the number of mitoses may vary greatly in a given neoplasm, and by focusing on the "hot spot", reproducibility of mitotic rate can be enhanced significantly.

However, they overlooked a pitfall that they dug themselves and into which the entire melanoma group of the American Joint Committee on Cancer fell in a slapstick comedy manner, namely, the consequences of combining the “hot spot approach” with a threshold of 1 mitotic figure.



With the original approach, counting mitoses in a broad area and then giving an average number per 5 high power fields, a threshold of 1 mitotic figure might have made sense because the average mitotic rate is usually lower in thin melanomas.



With the “hot spot approach,” a threshold of 2 or more mitotic figures also might have made sense because more than one mitotic figure in a circumscribed area implies enhanced proliferation. Detection of a single mitosis, however, implies nothing.

Frequent Mitotic Activity in Banal Melanocytic Nevi Uncovered by Immunohistochemical Analysis

Katharina Glatz, MD, Christoph Hartmann, MD,* Milos Antic, MD,* and Heinz Kutzner, MD†*

Abstract: The presence and distribution of mitotic figures is an important discriminatory parameter in the assessment of melanocytic lesions. We evaluated the number and distribution of mitotic figures in 353 randomly collected melanocytic nevi of various subtypes by hematoxylin and eosin (H&E) staining and immunohistochemically with the 2 mitotic markers Phospho-Histone H3 Ser28 (PHH3) and MPM2. At least 1 mitotic figure was present in 19.5%, 31.3%, and 42.8% of H&E-, PHH3-, and MPM2-stained lesions, respectively. In common compound nevi, the mean number of dermal mitoses amounted to 0.024/mm^2 dermal surface area in the H&E staining (PHH3: 0.061; MPM2: 0.087) and to 0.175/mm^2 in Spitz nevi (PHH3: 0.325; MPM2: 0.45). Nevi exhibiting mitotic figures were significantly more frequent in the youngest age group (0–20 years) than in patients older than 50 years ($P < 0.0001$). In the upper half of the dermis, mitotic activity was roughly 3 times as frequent as compared with the lower half. Clusters of mitotic figures within the dermis were not observed. Mitotic activity in obviously benign melanocytic nevi is not rare even in the deep dermal part. More than 2 mitotic figures per lesion can usually be explained either by the nevus subtype, young patient age, traumatization, or inflammation. PHH3 and MPM2 are a valuable diagnostic adjunct in the evaluation of melanocytic tumors allowing more sensitive and faster recognition of mitotic figures and their distribution.

Key Words: mitotic activity, nevus, immunohistochemistry

(*Am J Dermatopathol* 2010;32:643–649)

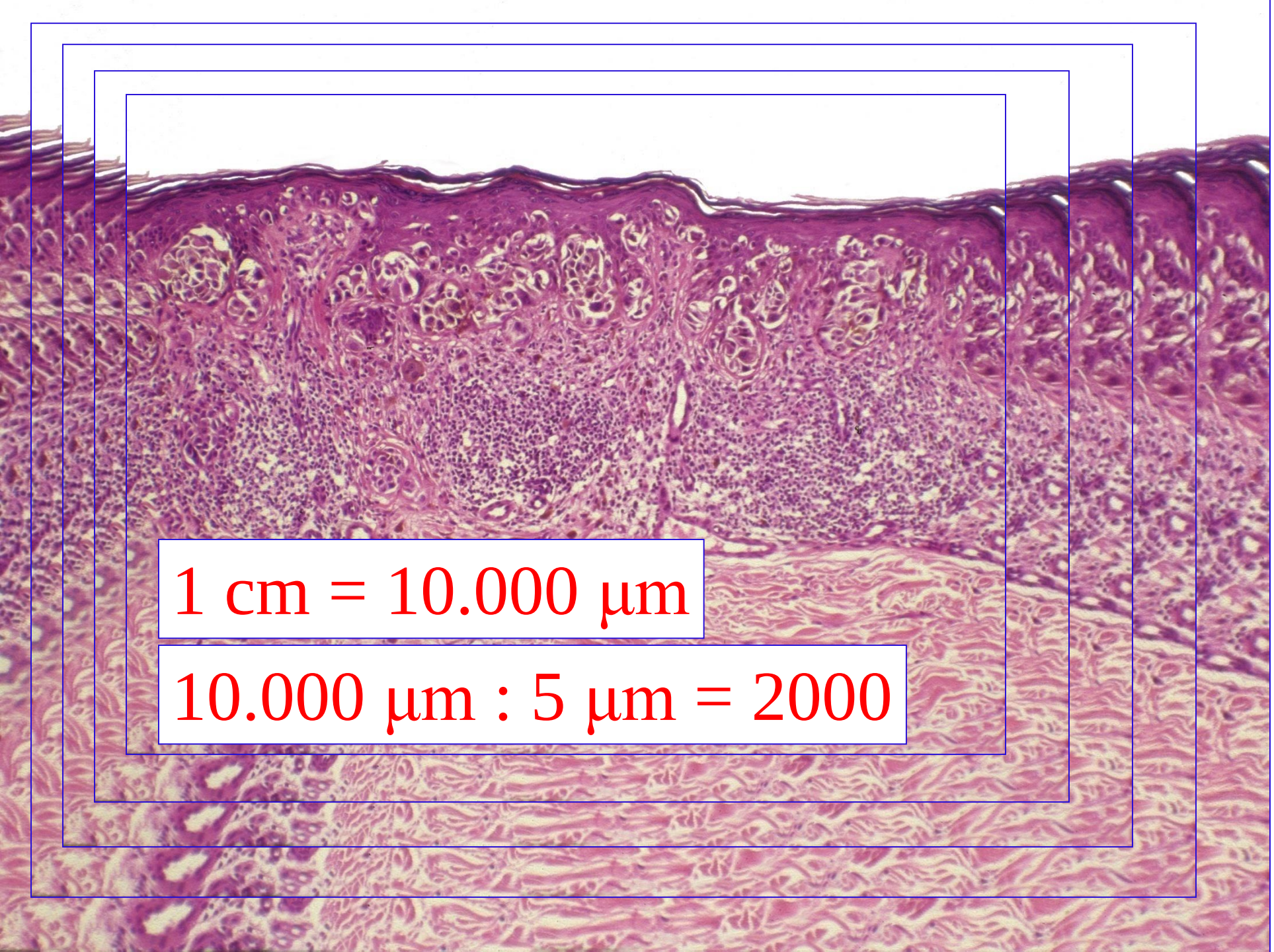
levels are examined they will almost always be identified."[1] There are only 2 recent publications on mitoses in benign melanocytic nevi with only 157 and 48 samples, respectively.[2,3] In past publications on the subject, proliferative activity in melanocytic nevi has mostly been determined by immunohistochemical evaluation of proliferation markers, for example, Ki-67.[4–7] We have recently shown that the application of the commercially available mitotic markers Phospho-Histone H3 Ser28 (PHH3) and MPM2 improves the efficiency and reproducibility of mitotic counting in various tumor types.[8] Both markers can be assessed immunohistochemically on routinely processed formalin-fixed, paraffin-embedded tissue specimens. For this study, PHH3 and MPM2 were used in addition to traditional hematoxylin and eosin (H&E) staining to evaluate the occurrence and distribution of mitotic figures in a random sample of 353 benign melanocytic nevi.

MATERIALS AND METHODS

Patients

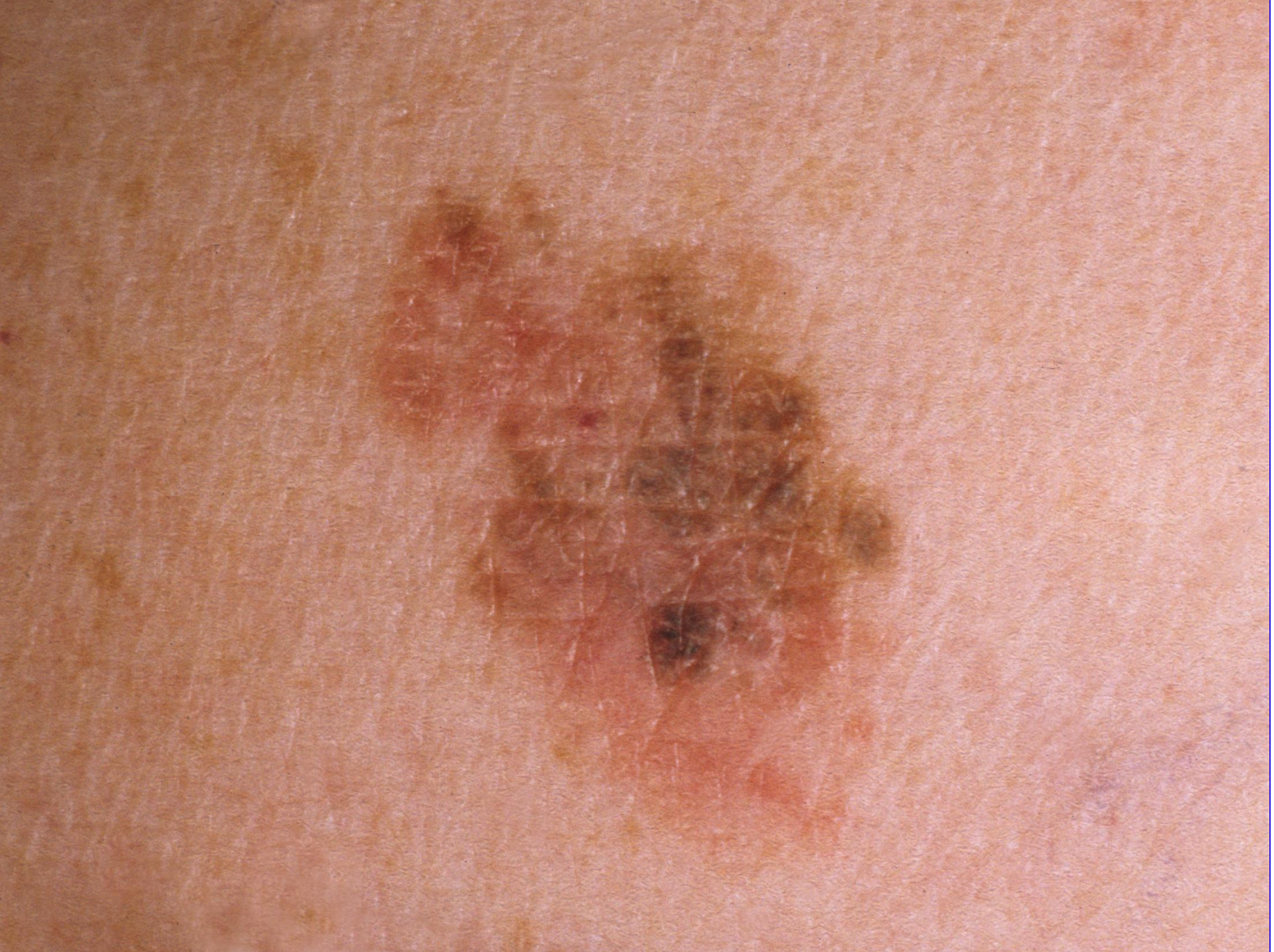
Paraffin-embedded blocks of 353 consecutively excised benign melanocytic nevi of 206 female and 147 male patients were retrieved from the routine files at Dermatopathologie, Friedrichshafen. The mean age of the patients was 34.3 years (range 2–78 years). In 8 cases, the referring clinician suspected a melanoma. Histologically, these clinically suspicious lesions

One mitotic figure can be found in any melanoma and almost any nevus. In a recent study of banal melanocytic nevi, at least one mitotic figure was present in 19.5 to 42.8%, depending on the method of detection. Those numbers could have been raised to nearly 100% if lesions had been examined entirely. The high priests of melanoma prognostication love complex computations, but one easy computation has never been made by them:



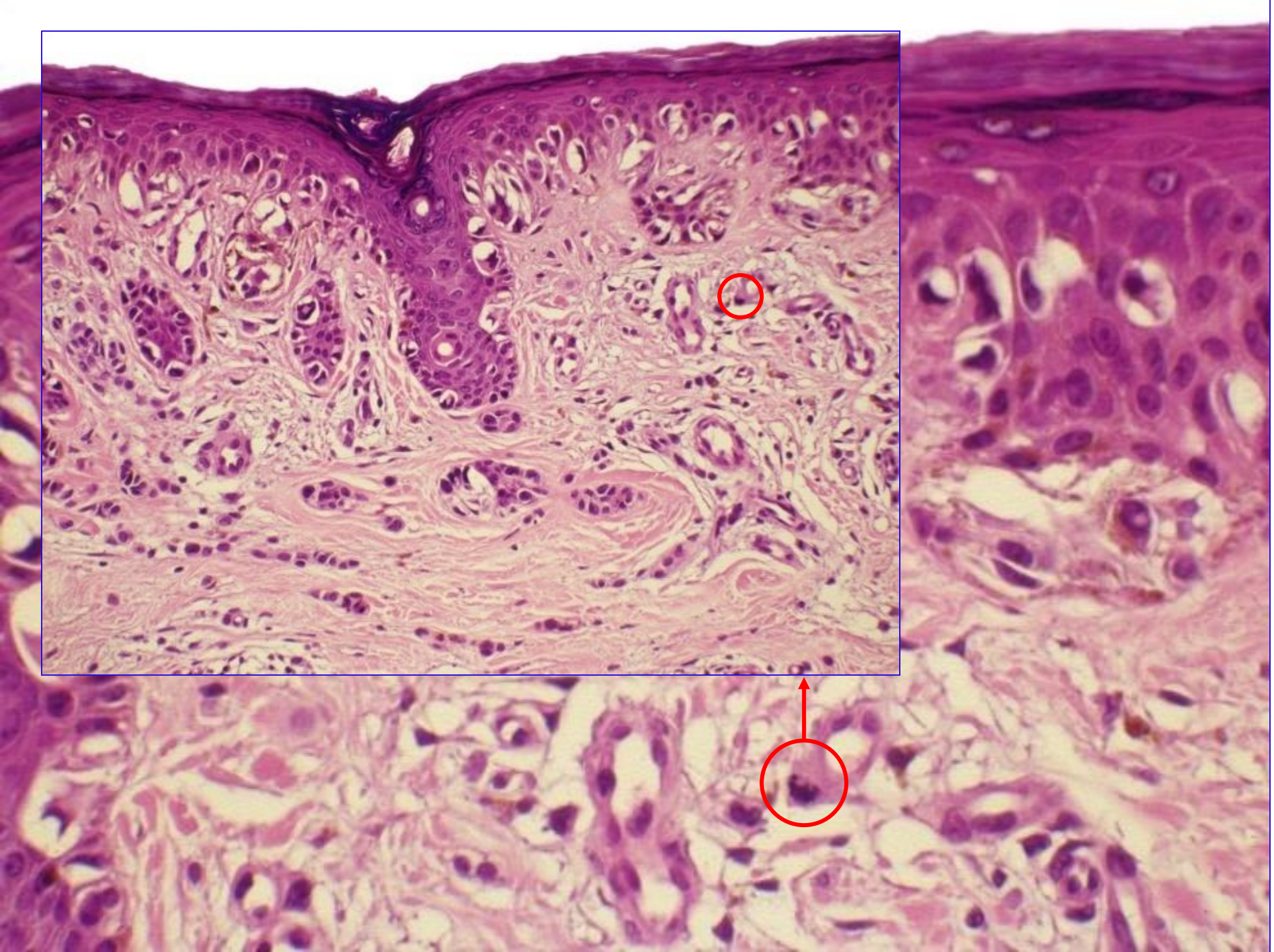
if a melanoma has a diameter of 1 cm, equal 10,000 µm, and the thickness of a histopathologic section is 5 µm, then one needs 10,000 through 5, equal 2000, sections to assess that lesion completely.

Of course, no pathologist can study 2000 sections thoroughly for presence of mitotic figures. Instead, a few sections are cut and large portions of the lesion are never examined.

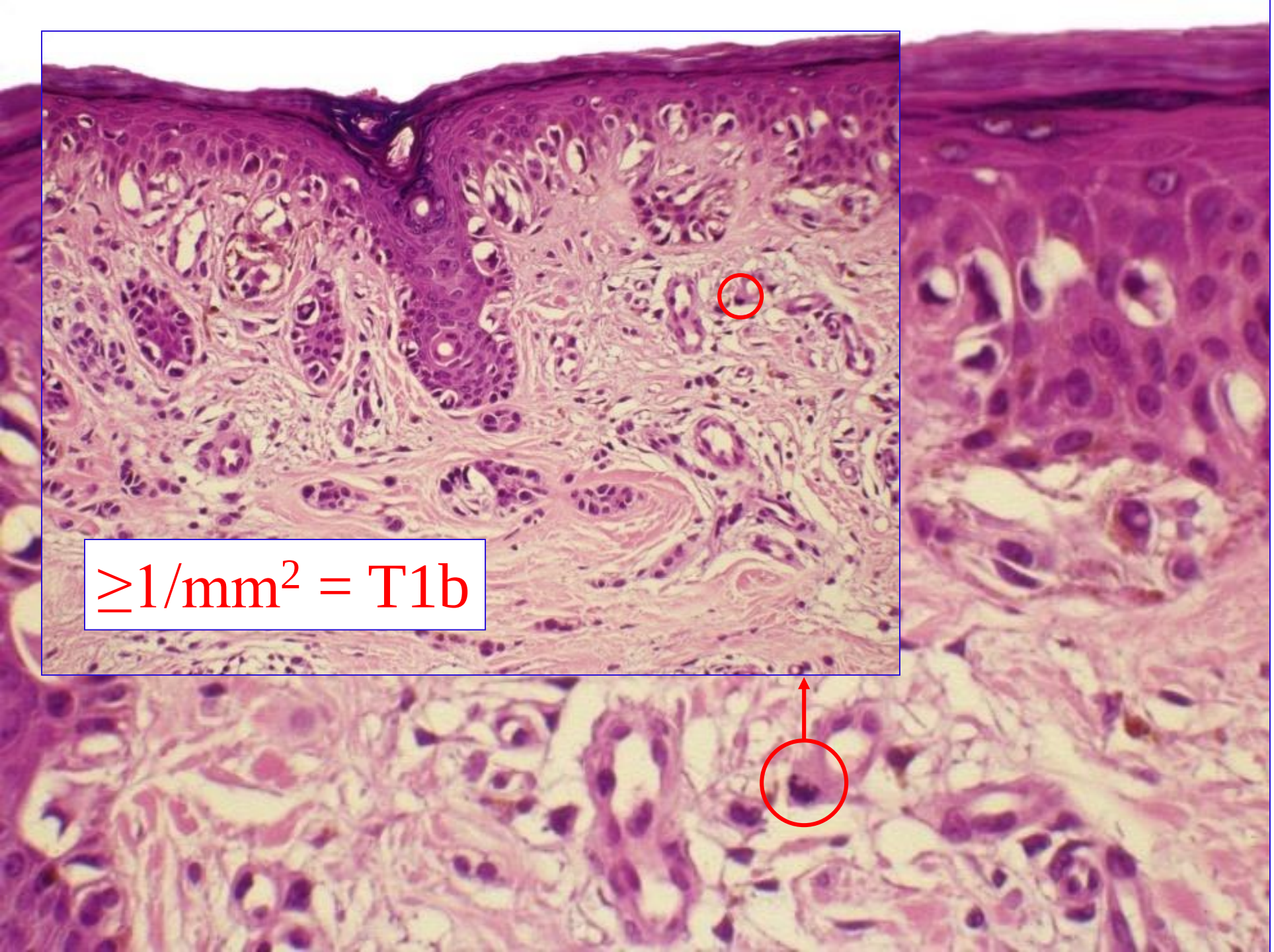


In those portions, one would always find mitoses because melanomas are proliferating neoplasms, and proliferation requires mitotic activity. This is what children learn in their basic biology class in school.

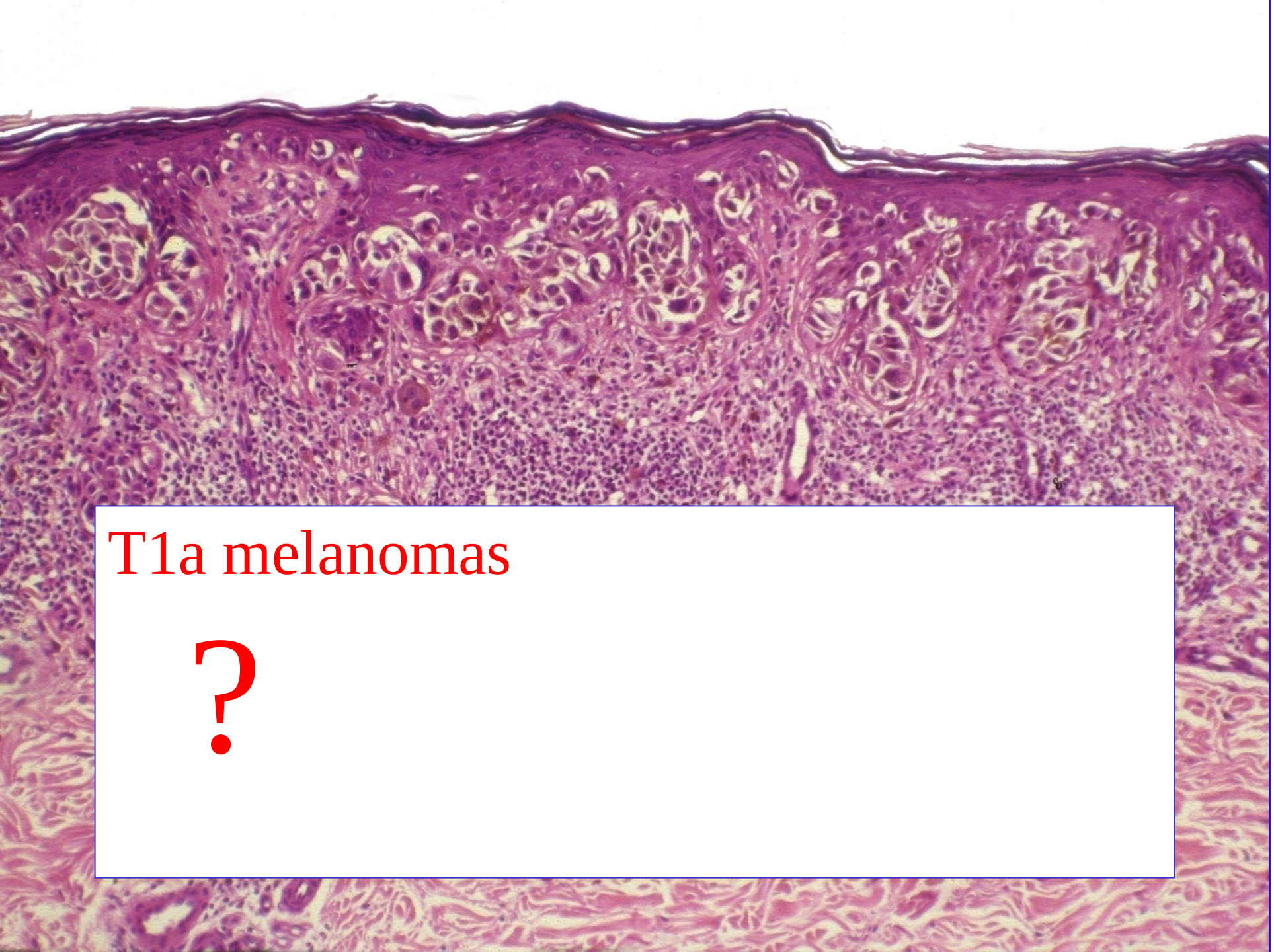
Detection of mitoses depends on how well they present themselves and on our diligence in searching for them. And if one really does not find a mitotic figure in 100 or 1000 sections, how can one be sure that it will not show up in section 1001?



And yet, if a single mitotic figure is found, it represents the “hot spot,”



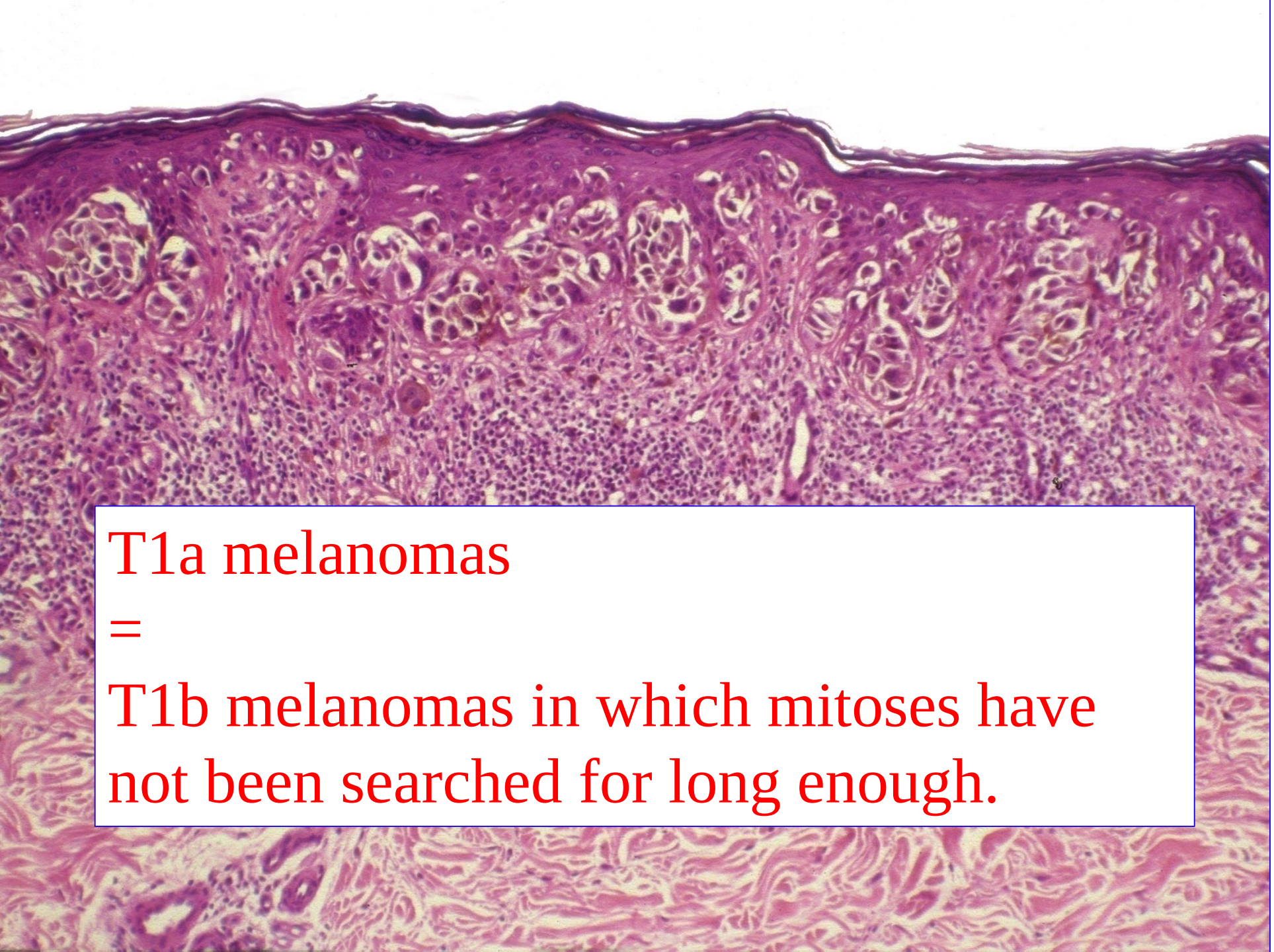
and if one finds no other mitoses in adjacent fields, the mitotic rate will automatically be ≥1/mm^2 and will thus fulfill criteria for stage T1b.



T1a melanomas

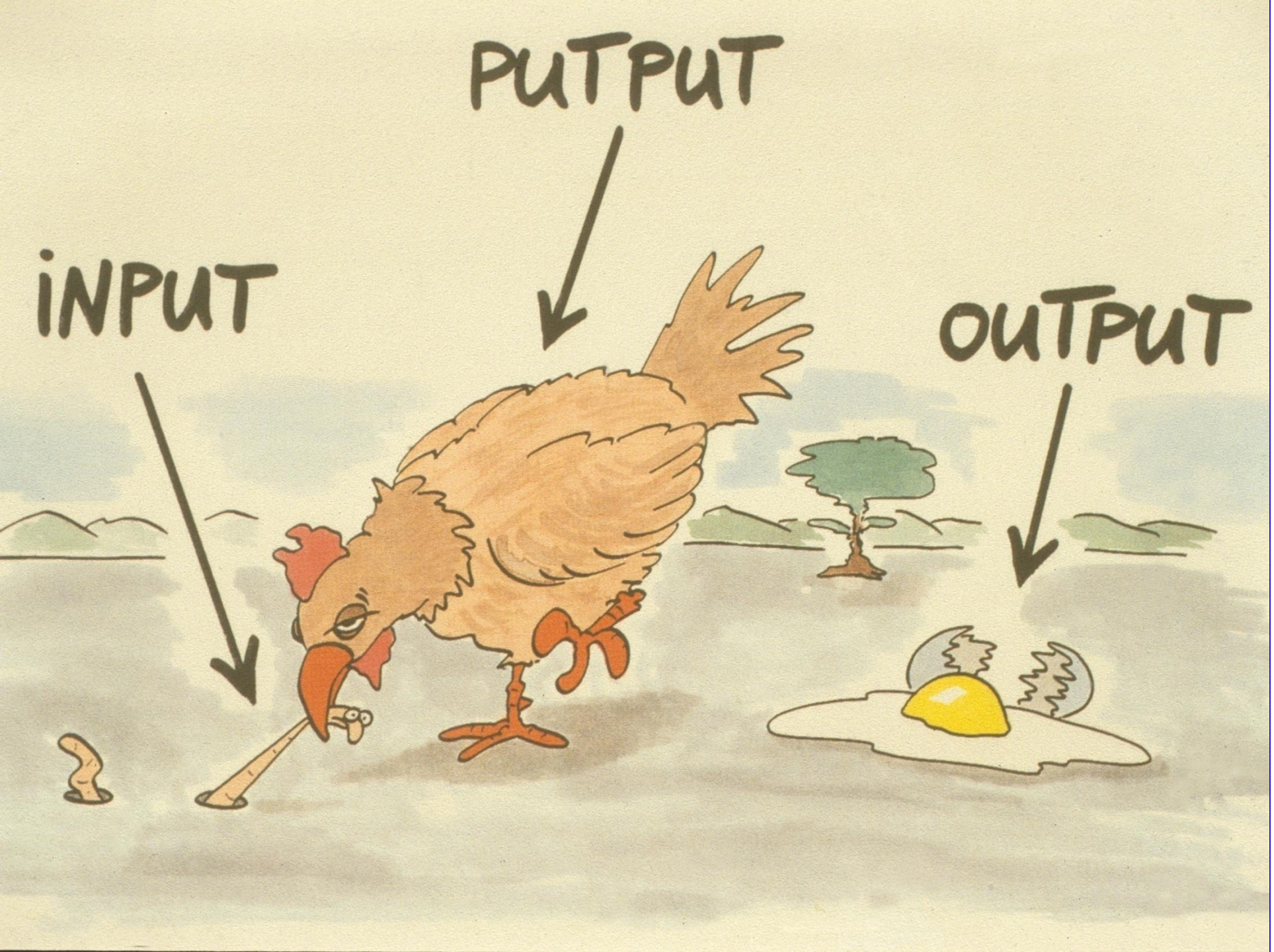
?

And what are T1a melanomas?



T1a melanomas
=
T1b melanomas in which mitoses have not been searched for long enough.

There is a synonym for them, namely, *“T1b melanomas in which mitoses have not been searched for long enough.”*



In short, the AJCC failed to consider the input before switching on its computer, and the output is a rotten egg.

Curiously, the committee did not even notice the foul smell.

Its members were completely blind to the fact that, by following the recommended “hot spot approach,” their own definition of T1b melanomas would be fulfilled by demonstration of a single mitotic figure.

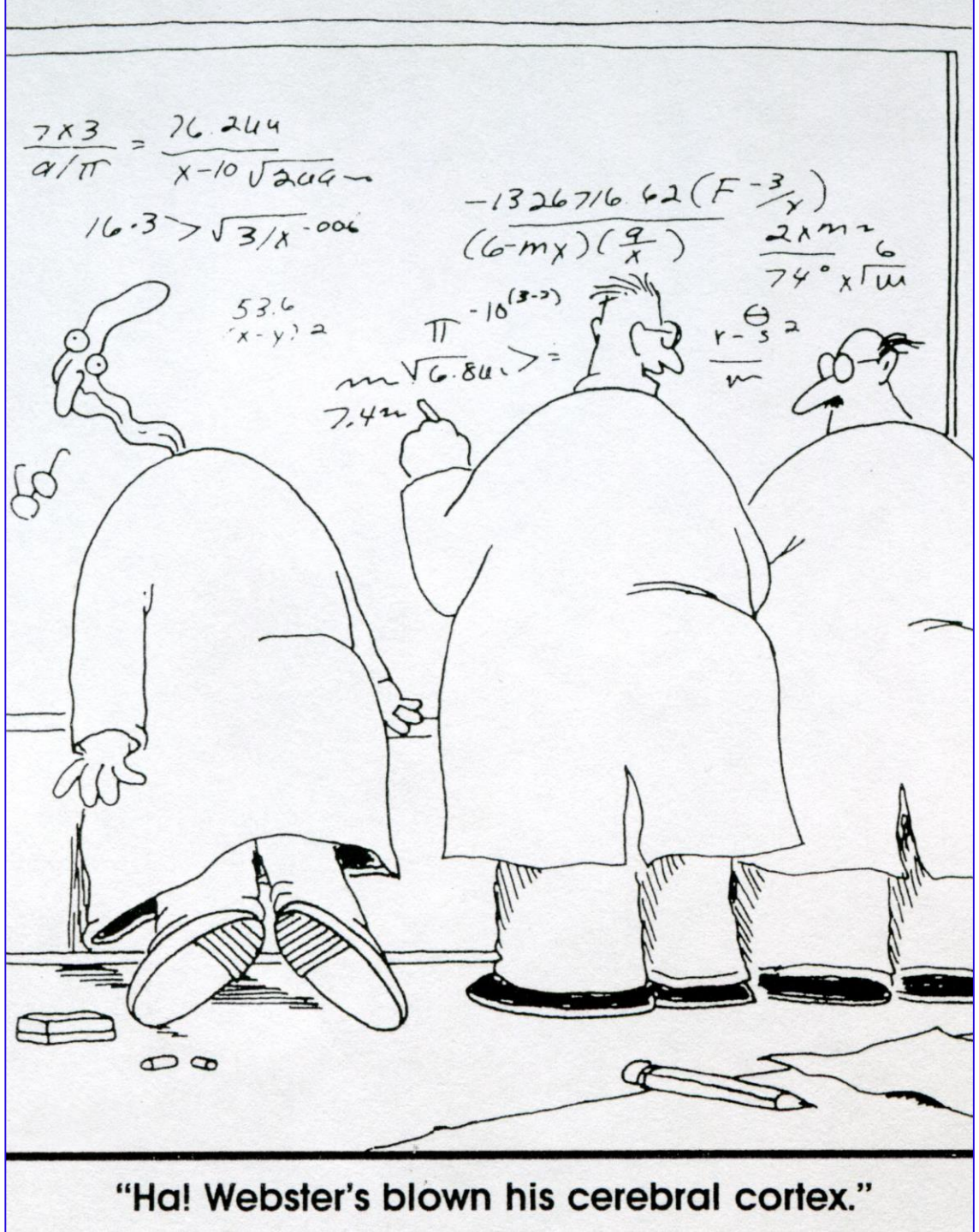
Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis $< 1/mm^2$ b: With ulceration or mitoses $\geq 1/mm^2$

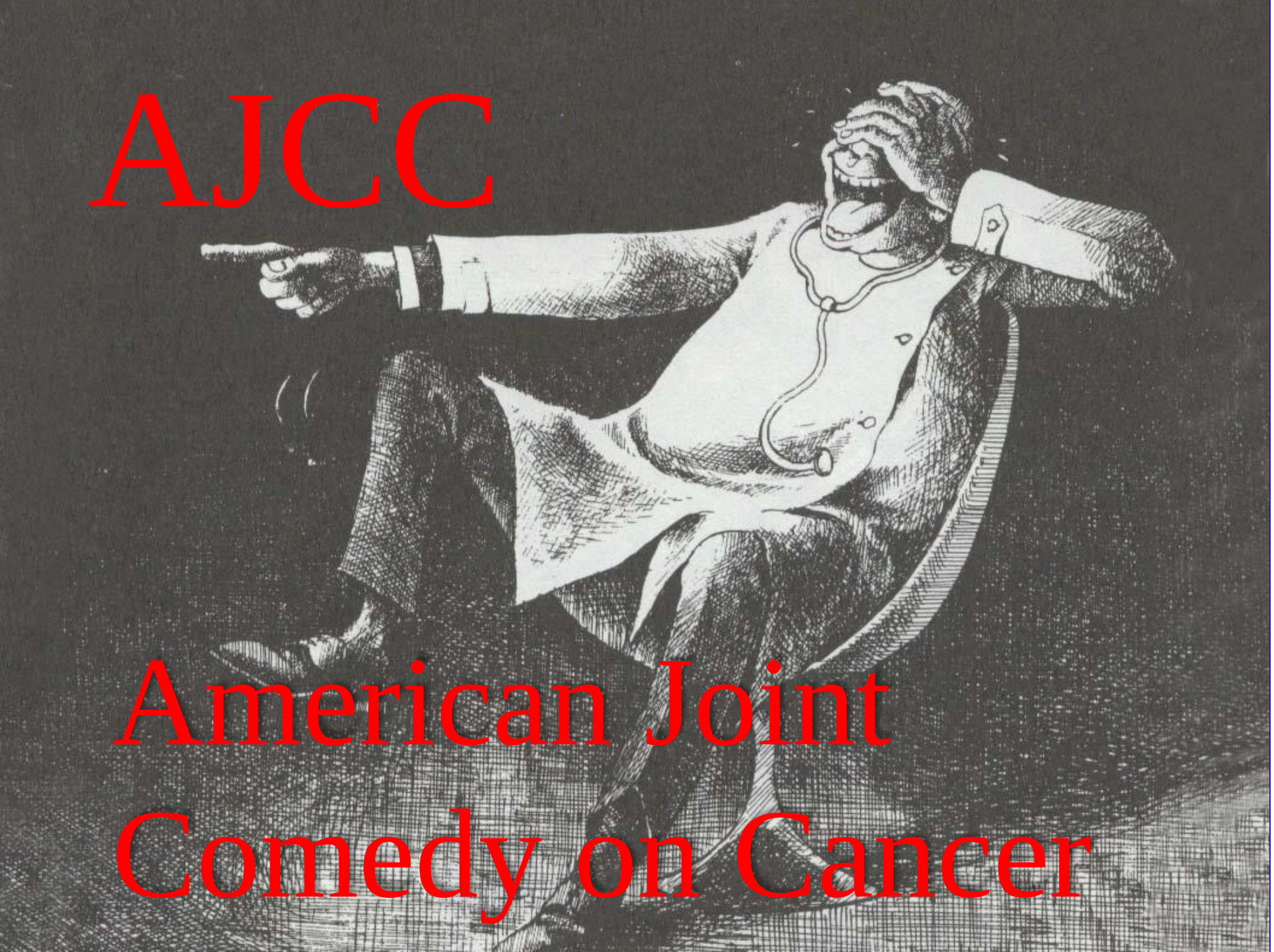
publication.[1] Mitotic rate was examined for the first time in this analysis. The Melanoma Staging Committee recommended that mitotic rate be determined by the "hot spot" approach and expressed as the number of mitoses per square millimeter of primary tumor.[3] Statistical analyses of the AJCC Melanoma

T4	> 4.00	a: Without ulceration b: With ulceration

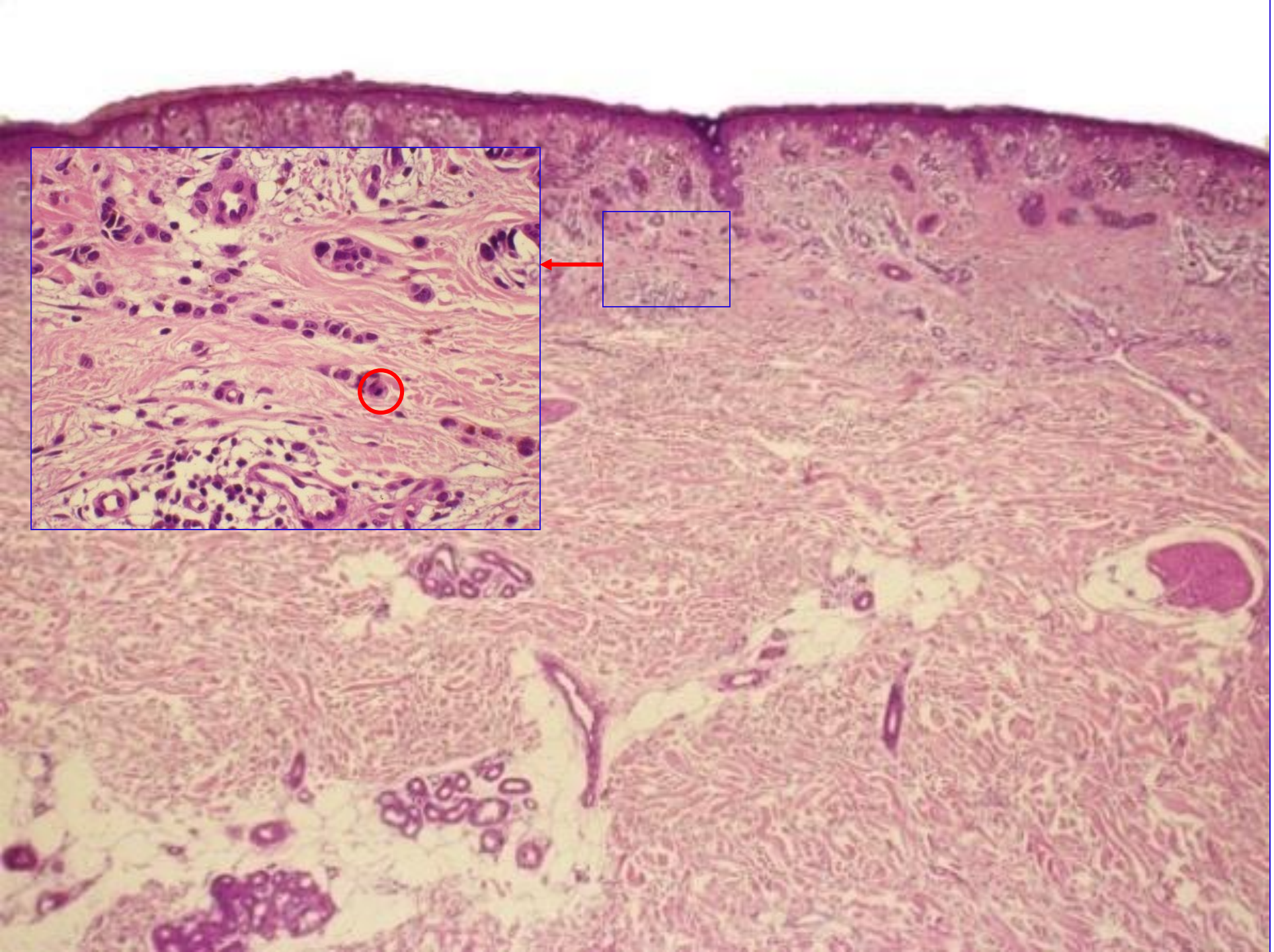
This is evidenced by the fact that they continue to speak of *"mitotic rate"* and *"hot spot approach,"* although there is no need to follow that approach in order to classify a melanoma as T1a or T1b. Once a mitotic figure is found, the work is done.



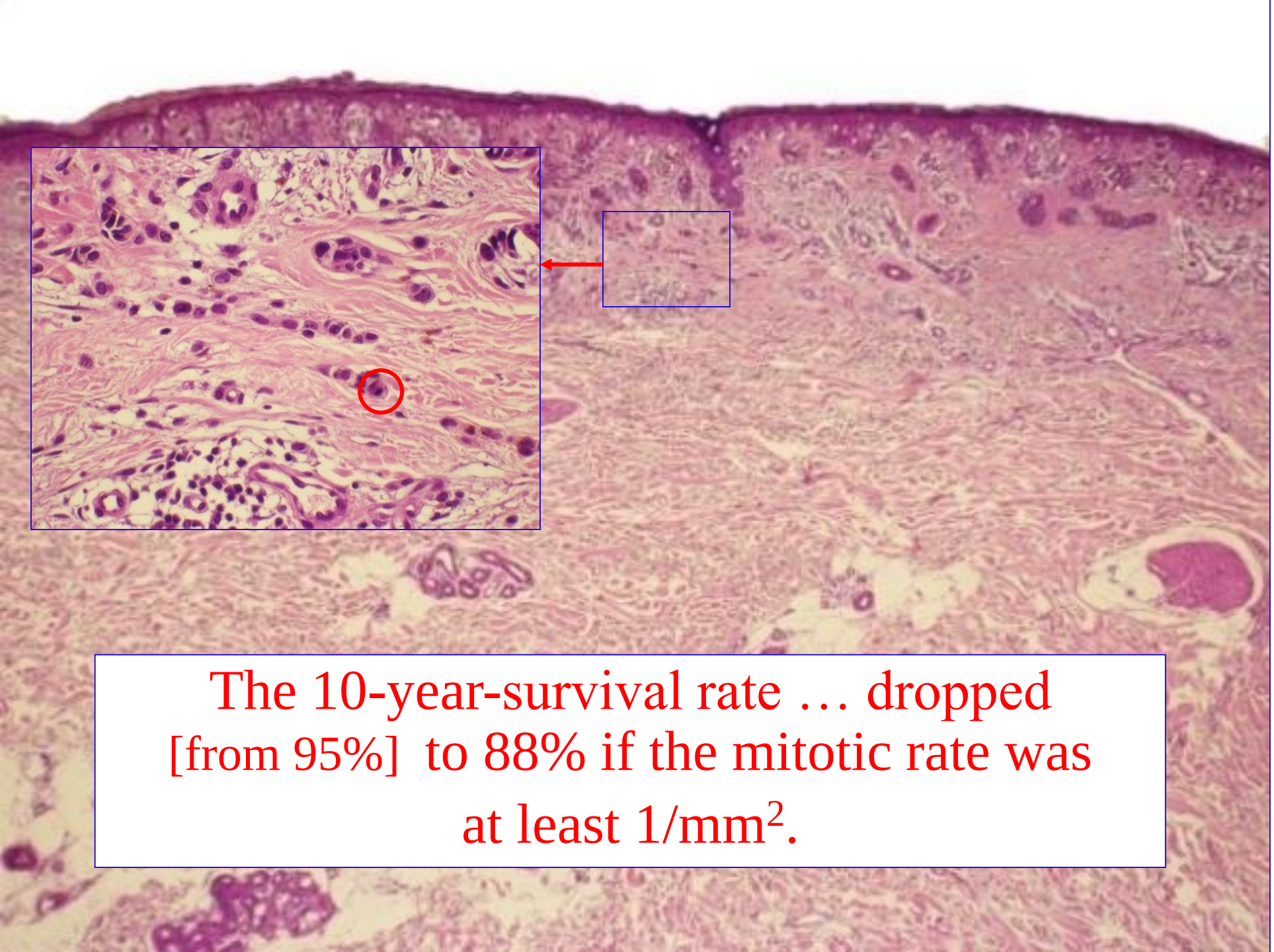
That this was never considered demonstrates how easy it is to blow one's cerebral cortex by attaching too much trust to the magic of numbers.



With the new melanoma classification, the AJCC has proved itself as a genuine American Joint Comedy on Cancer.

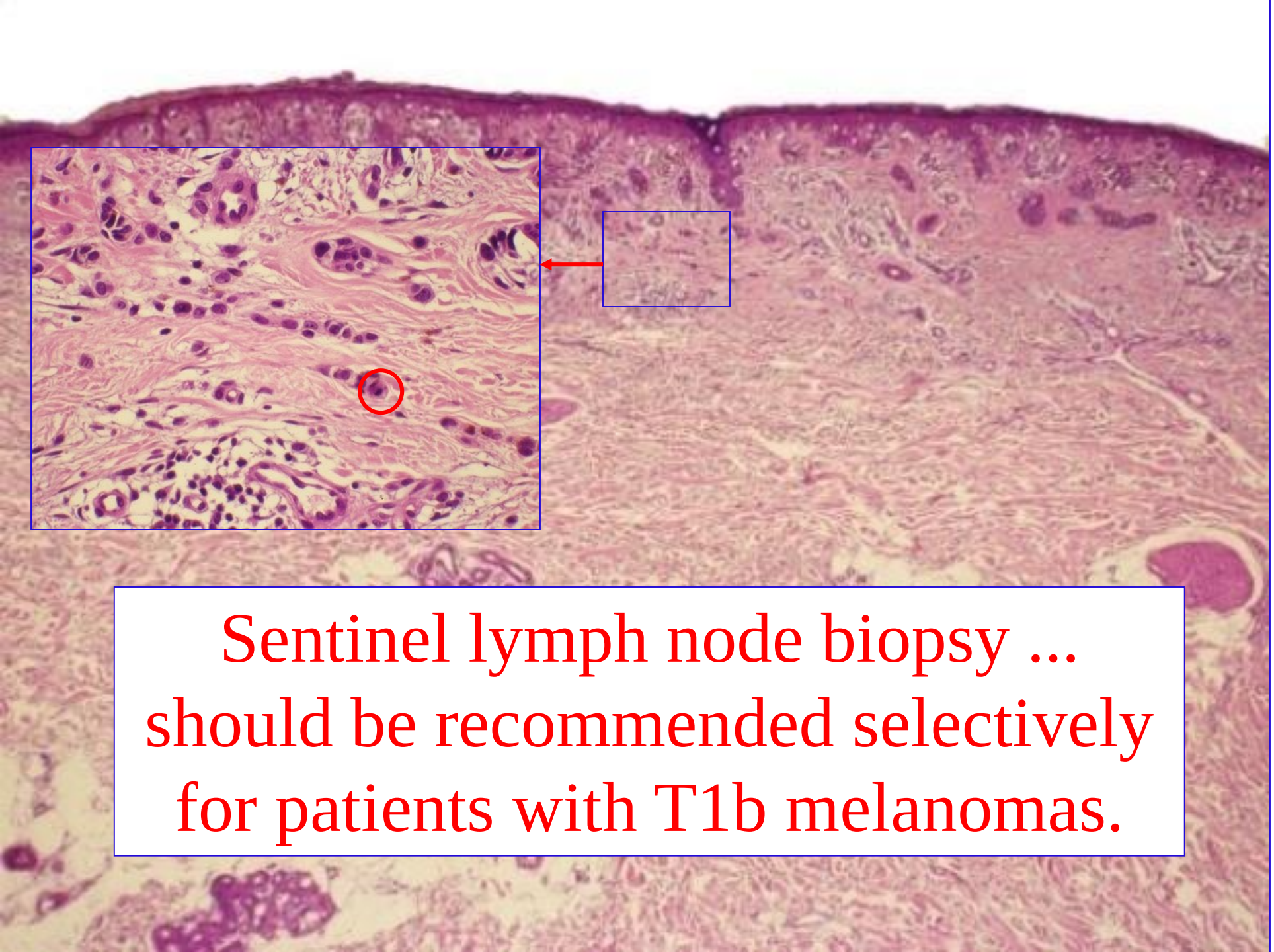


There are aspects, however, that are not so funny. The new classification may have serious consequences for patients with thin melanomas. With demonstration of a single mitotic figure, they are in stage T1b.



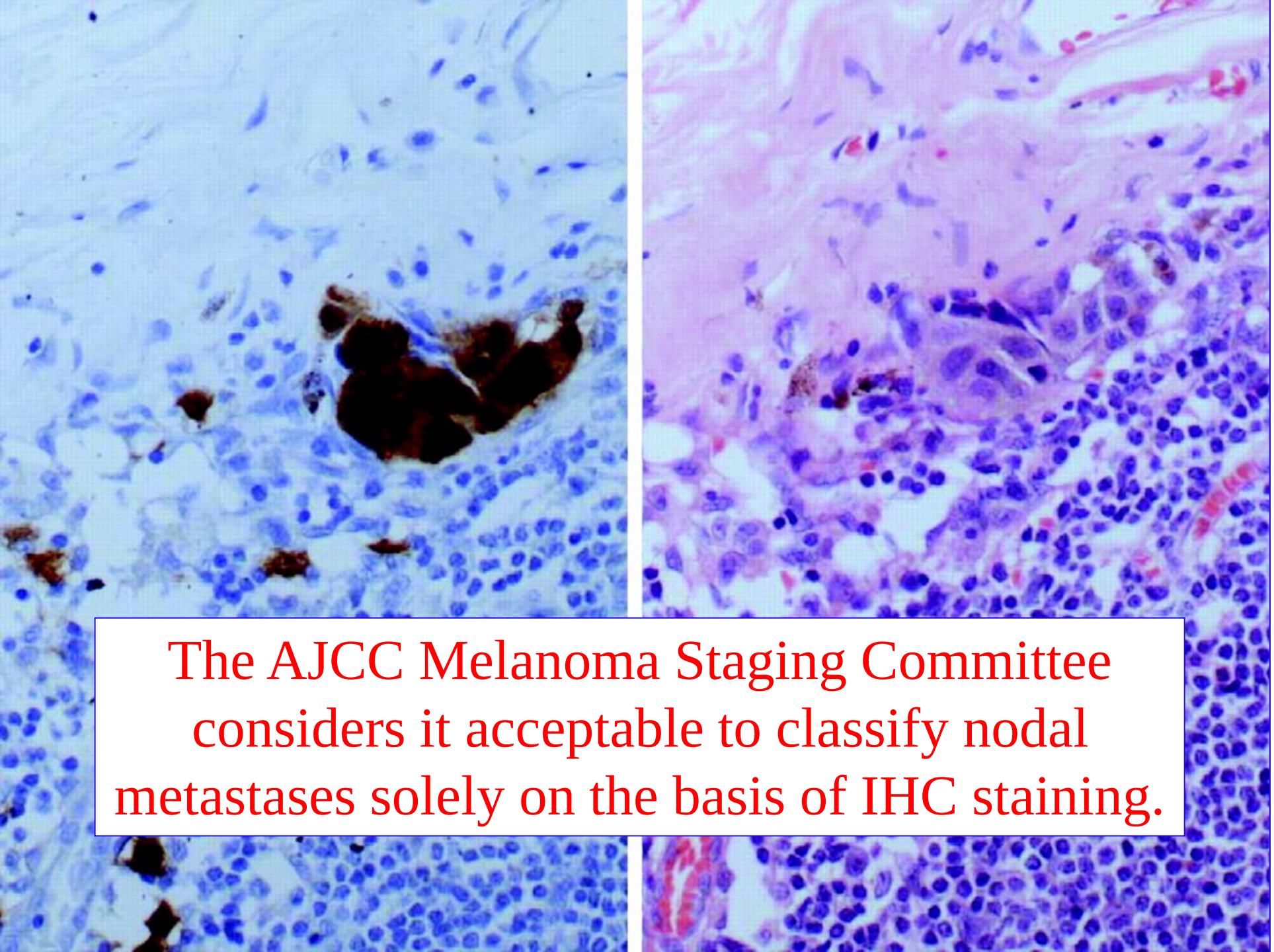
The 10-year-survival rate … dropped [from 95%] to 88% if the mitotic rate was at least 1/mm^2.

According to the AJCC, this means that the 10 year-survival rate drops from 95 to 88%.



Sentinel lymph node biopsy … should be recommended selectively for patients with T1b melanomas.

As a consequence, sentinel lymph node biopsies are *"recommended selectively for patients with T1b melanomas,"* and criteria for evaluation of them have also been changed.



The AJCC Melanoma Staging Committee considers it acceptable to classify nodal metastases solely on the basis of IHC staining.

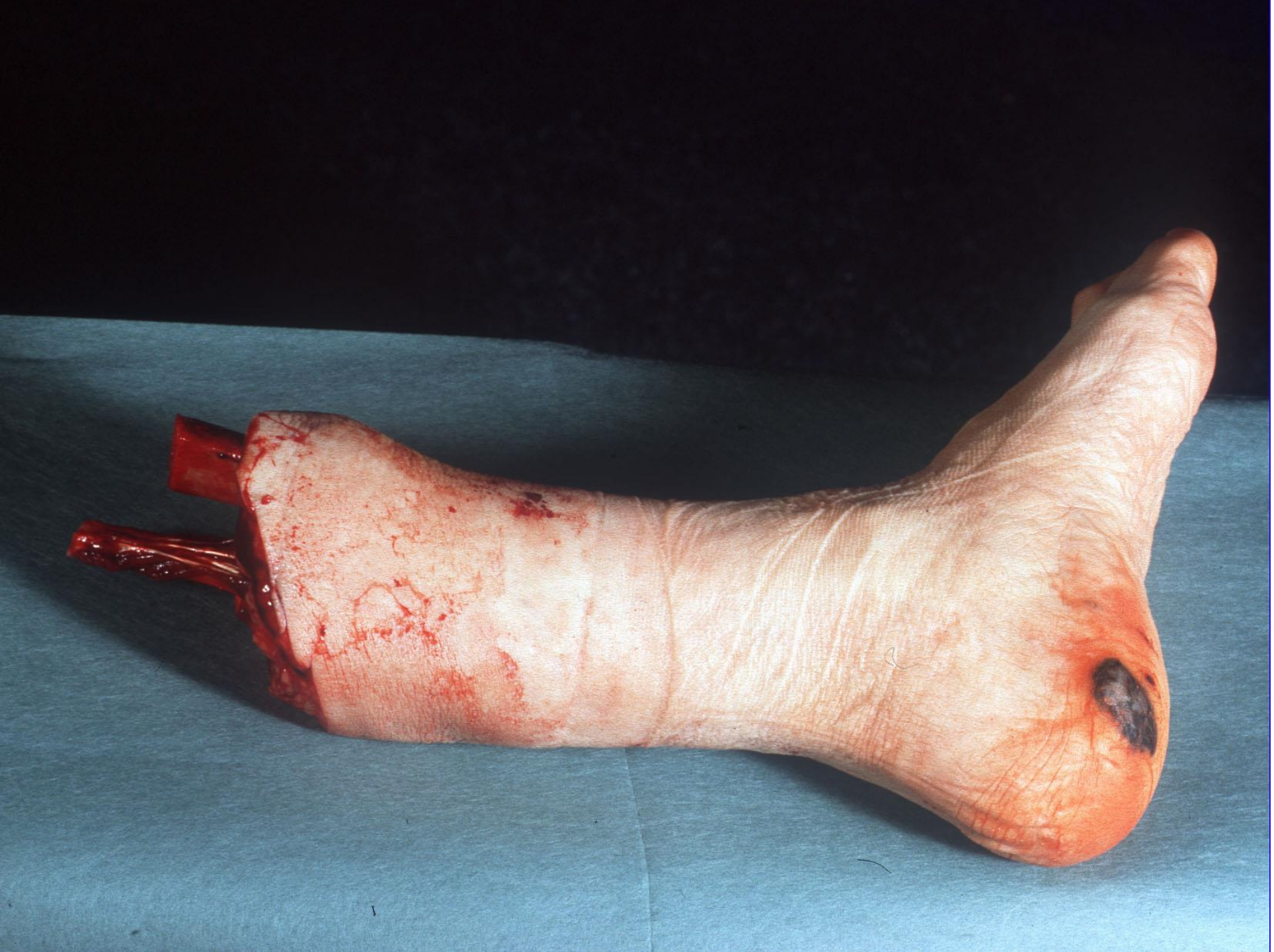
Since 2009, *"the AJCC melanoma staging committee considers it acceptable to classify nodal metastases solely on the basis of IHC staining."* In other words, a few Melan-A positive cells suffice for diagnosis of nodal micrometastasis,

Table 1. TNM Staging Categories for Cutaneous Melanoma

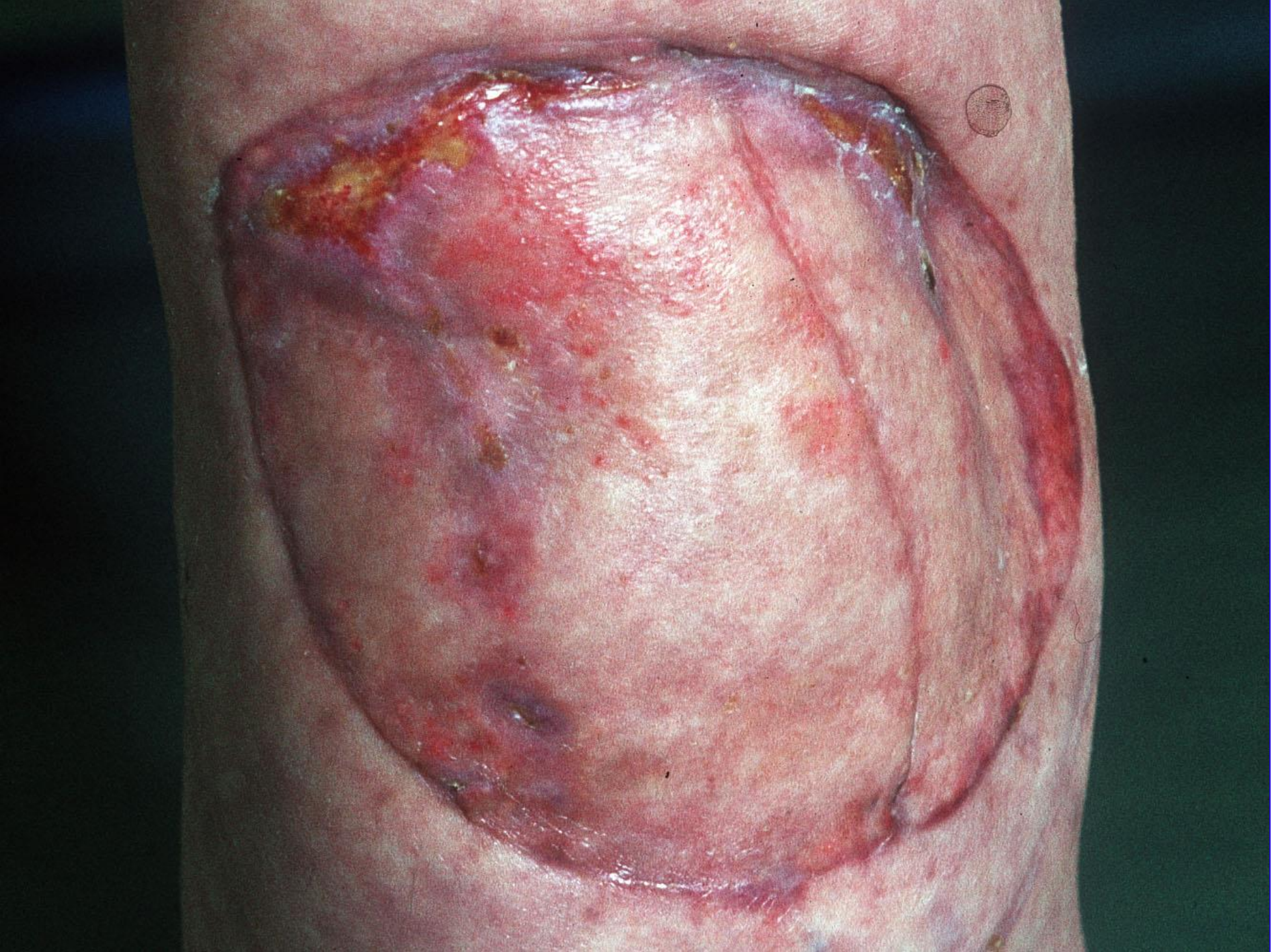
Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	**No. of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

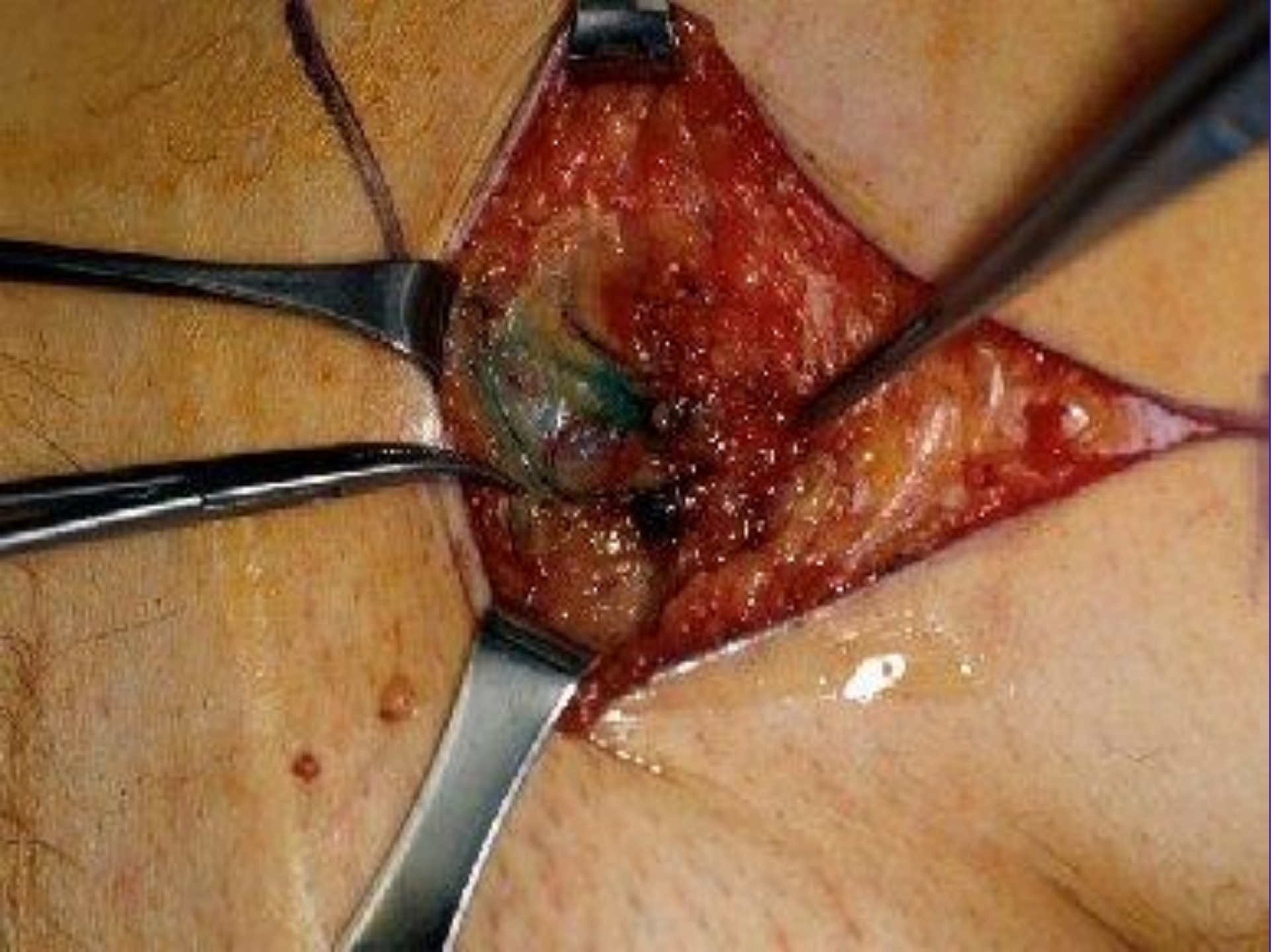
and once the patient is in stage N1, complete lymph node dissections are commonly performed, the only benefit being a psychological advantage, not for patient, but for the physician. Of course, oncologists are aware of terrible cases of melanoma, and they do not want to confront them empty-handed. It is comforting to be able to “offer” something to the patient.



In the not too distant past, this was amputation. If the patient died nonetheless, one had at least done everything possible.



Then came excision with wide margins under the pretext that removal of a scar and healthy skin might be beneficial.



Today, sentinel lymph node biopsies are recommended and, if positive, often supplemented by complete lymph node dissections

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JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Therapeutic Effect of Sentinel Lymph Node Biopsy in Melanoma Remains an Open Question

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Frank Yoon, *Department of Statistics, The Wharton School, University of Pennsylvania, Philadelphia, PA*
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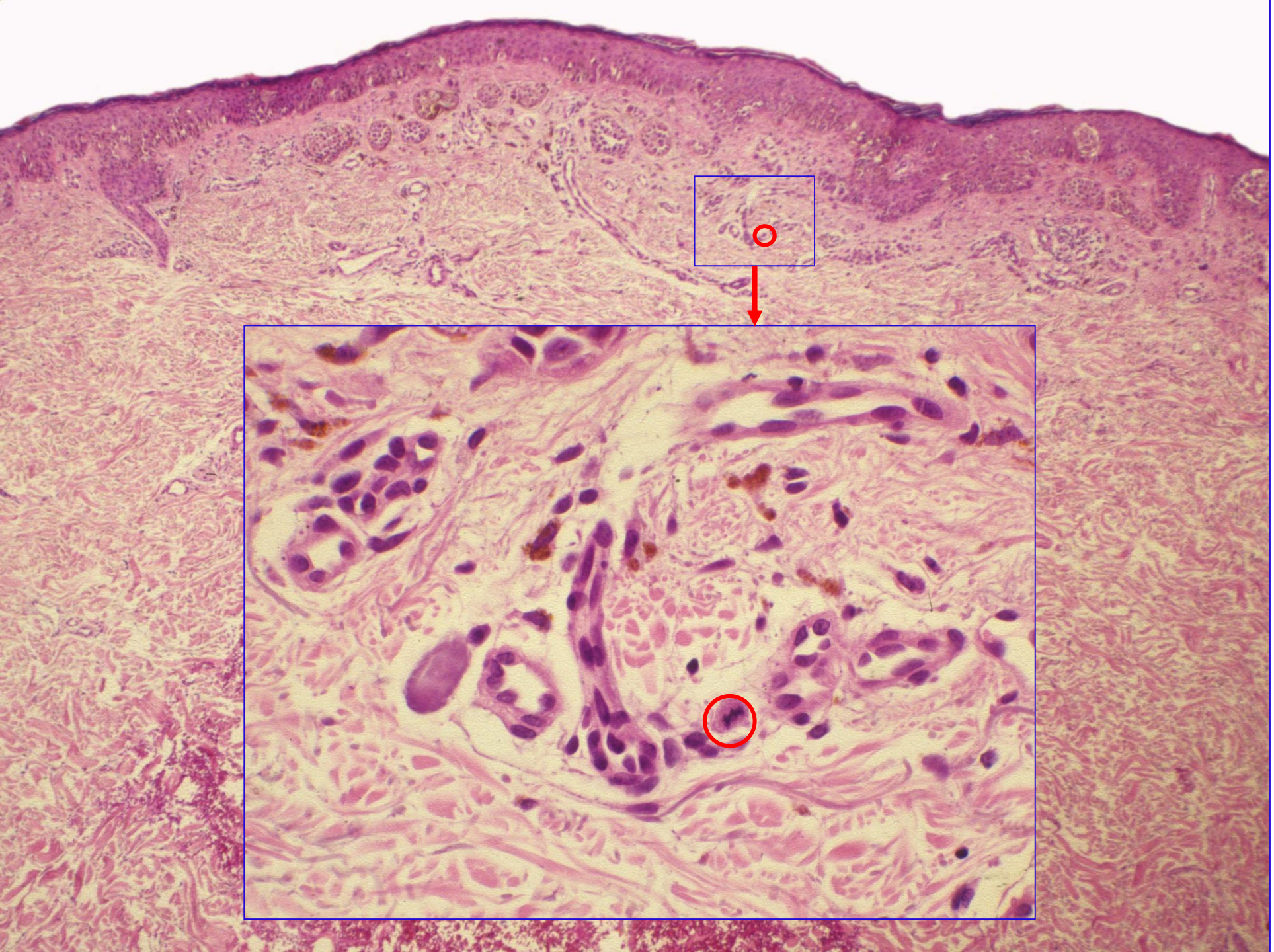
DuPont Guerry, *Department of Medicine, University of Pennsylvania, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

BACKGROUND

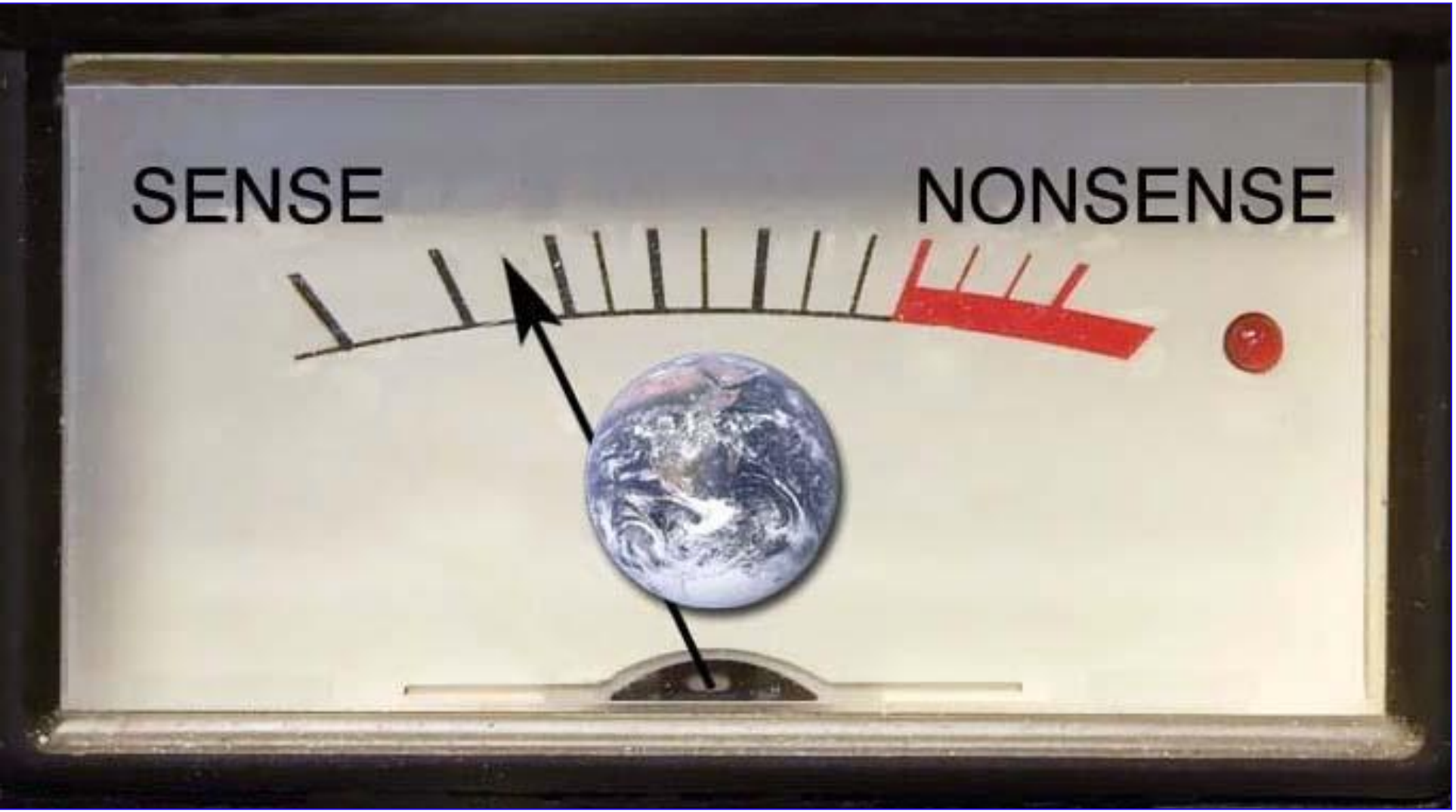
Whether sentinel lymph node biopsy (SLNB) in melanoma improves survival remains an open question. During the past two decades there have been five randomized controlled trials (RCTs) investigating the therapeutic effect of dissection of clinically uninvolved regional lymph nodes at the time of definitive surgery at the primary site. Four of these RCTs[1-4] examined the impact on disease-specific survival of having a prophylactic lymph node dissection (PLND; Table 1). In all but one of these RCTs there was no evidence in the primary analyses of a survival benefit for those who received PLND. The fourth trial[3] demonstrated a significant effect—the survival rate was 62% among those who

benefit of the procedure in patients with intermediate thickness melanomas.[5] MSLT enrolled 1,269 such patients between 1994 and 2002. In this trial, 769 patients were randomly assigned to receive SLNB, with immediate lymphadenectomy if nodal micrometastases were detected, and 500 were randomly assigned to observation, with subsequent lymphadenectomy if nodal relapse occurred. The effect size for the difference in 5-year survival rates corresponding to 80% power for the sample sizes in this clinical trial can be computed. Assuming 5-year melanoma-specific survival rates of 50% to 90% in the control group, the corresponding effect sizes for 5-year melanoma-specific survival rate would be 8.2% to 4.5%, corresponding to odds ratios of 1.4 to 1.9. In the report of the trial's primary outcome, based on data where all

although a therapeutic effect of sentinel lymph node biopsy has never been demonstrated.



In brief, detection by chance of a single mitotic figure in the dermis may result in great efforts and costs, not to mention unnecessary anxiety on the part of patient. Hence, if there really is a mitotic figure in the few sections of melanoma being examined, the patient can only hope that it is overlooked by the pathologist.



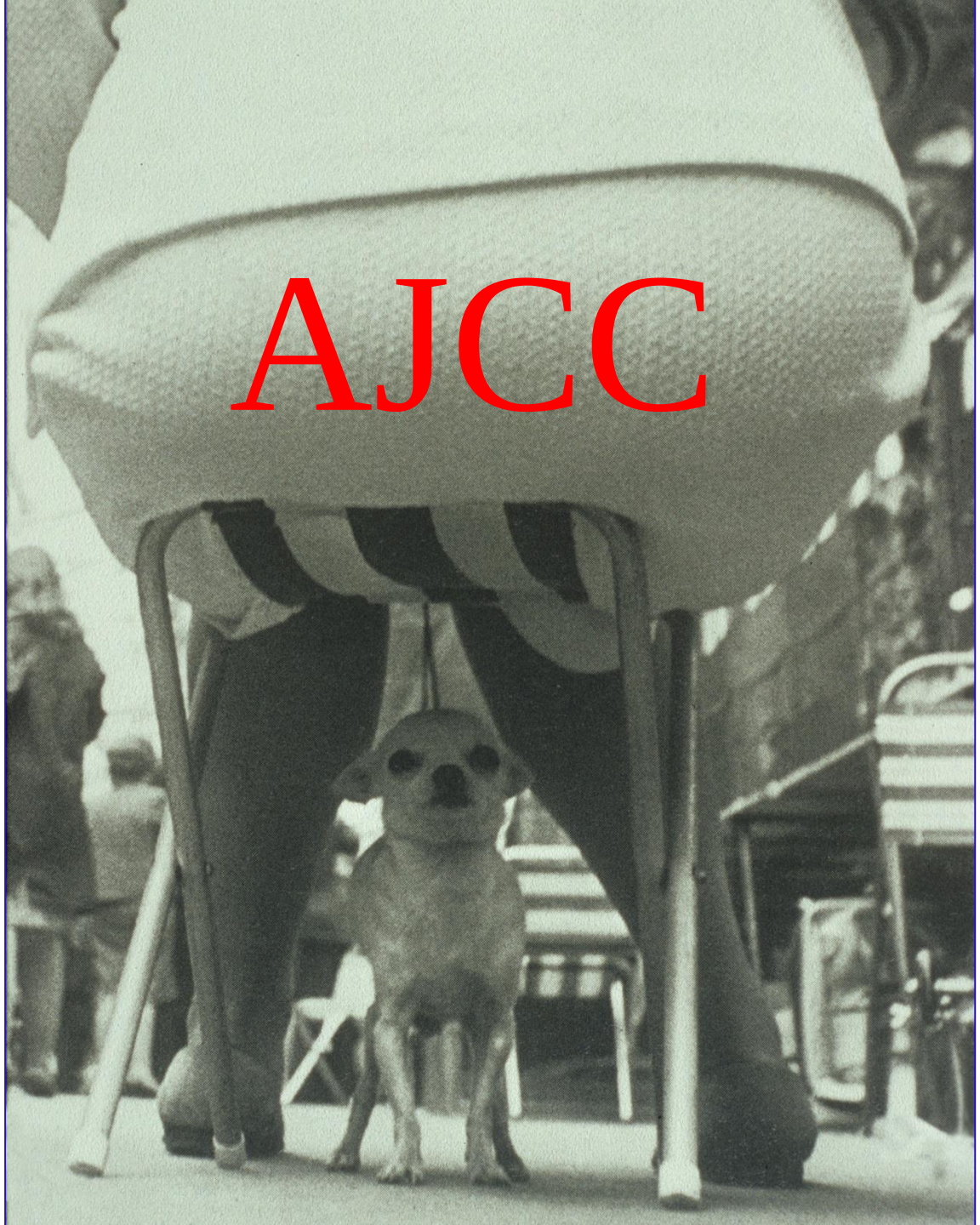
In the modern world, making sense is not enough. There is a great tendency to rely exclusively on numbers.

People love computations, the more complicated, the better,

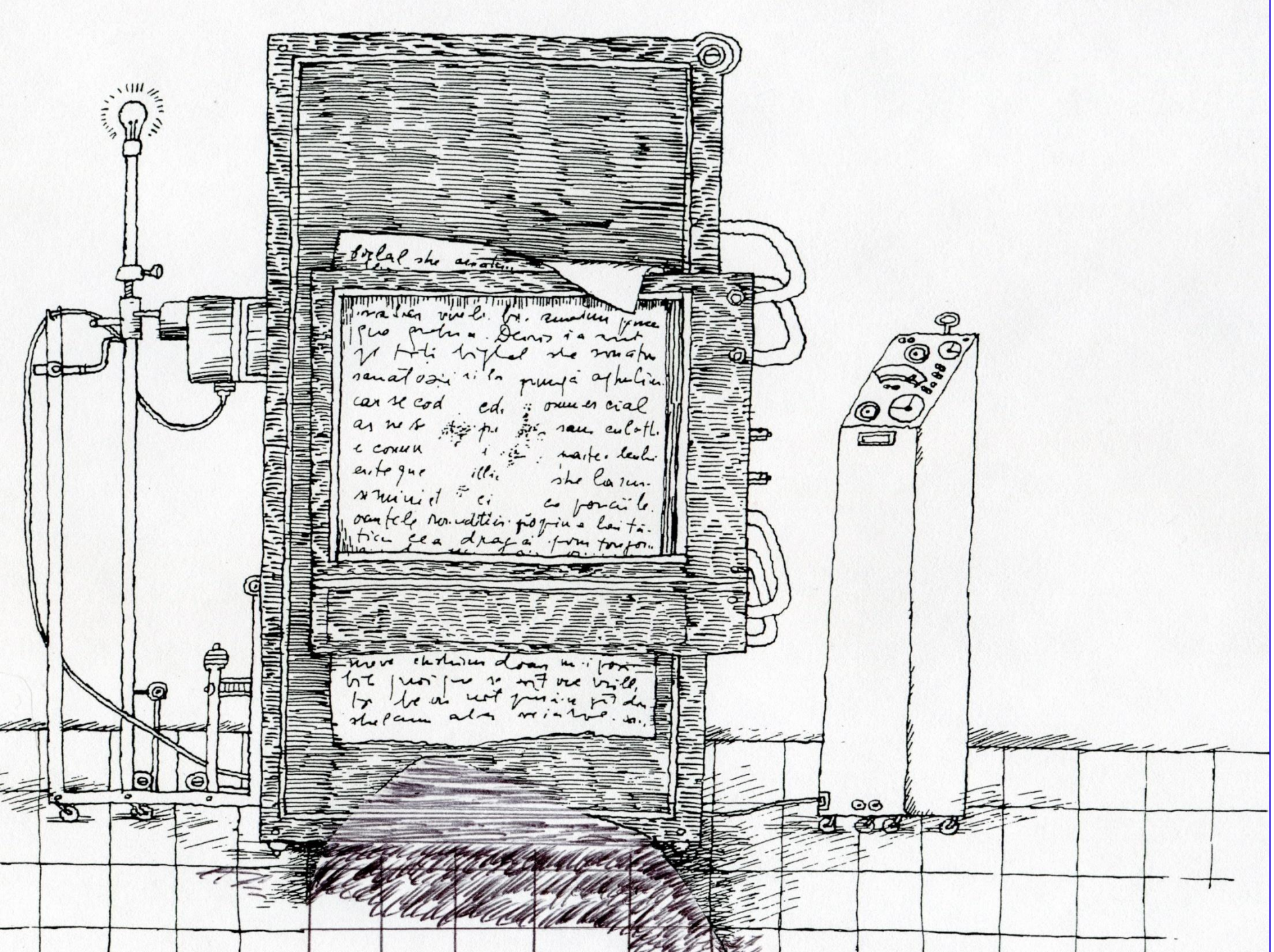
and modern meat choppers of statistics, such as the Cox proportional hazard model, look beautiful. For good hamburgers, however, one needs good meat. If the latter is rotten, even the most beautiful chopper won’t work.

The statisticians of the AJCC announced proudly that their database includes *"30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma,"* but they were oblivious to the fact that most of the meat was rotten.

They claimed to have produced something great, whereas, in truth,

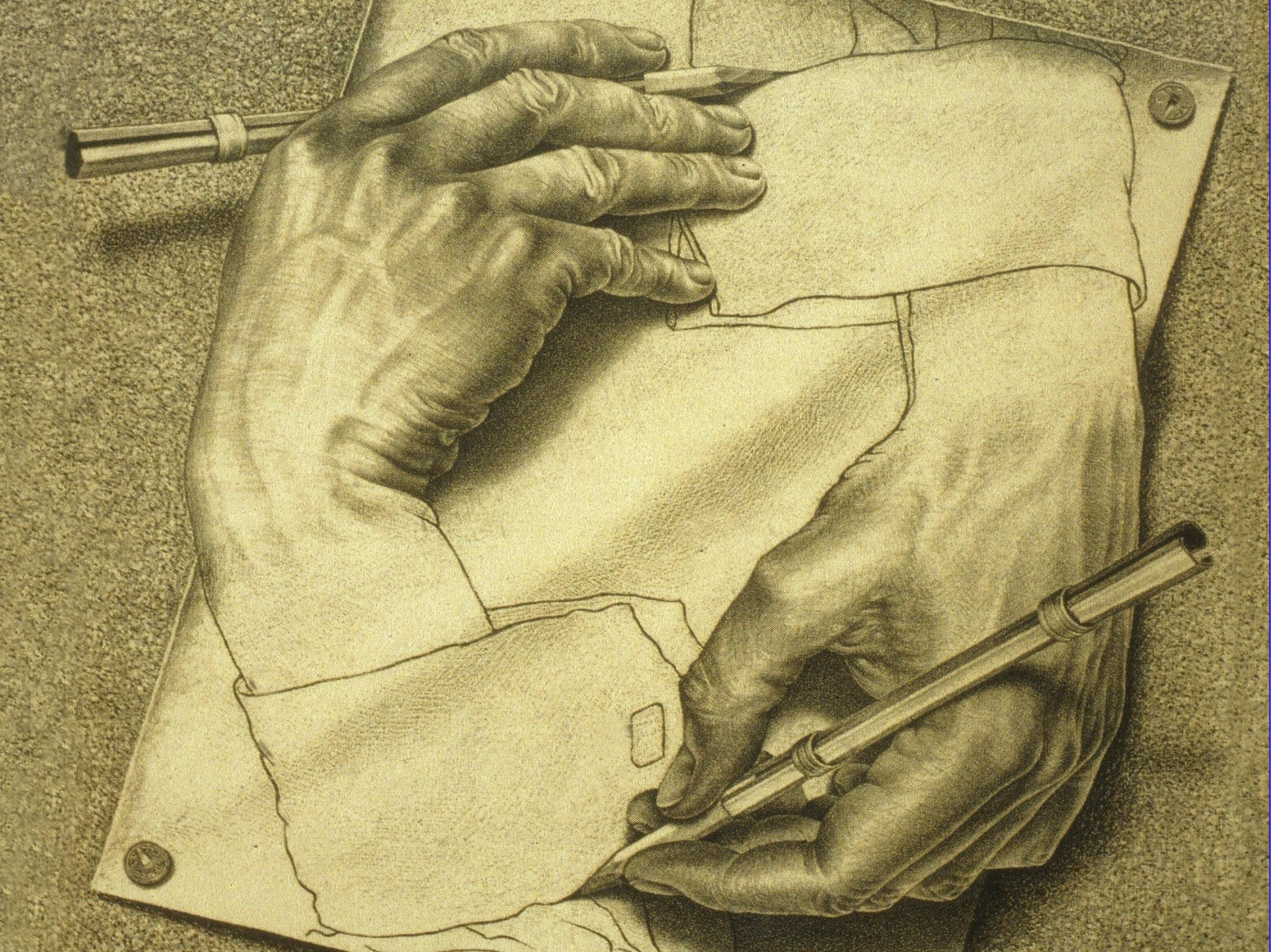


their product is a miserable creature that can survive only because it is sheltered by a big ass, the ass of the AJCC. What can this ass achieve?



A lot, because it belongs to a powerful organization. Once the new classification had been published, the printing press was put in full gear

and countless articles appeared, twisting the subject again and again,



one quoting the other, and as result, the new classification has been implemented worldwide.

BAD GUIDELINES

BJD
British Journal of Dermatology

Revised U.K. guidelines for the management of cutaneous melanoma 2010

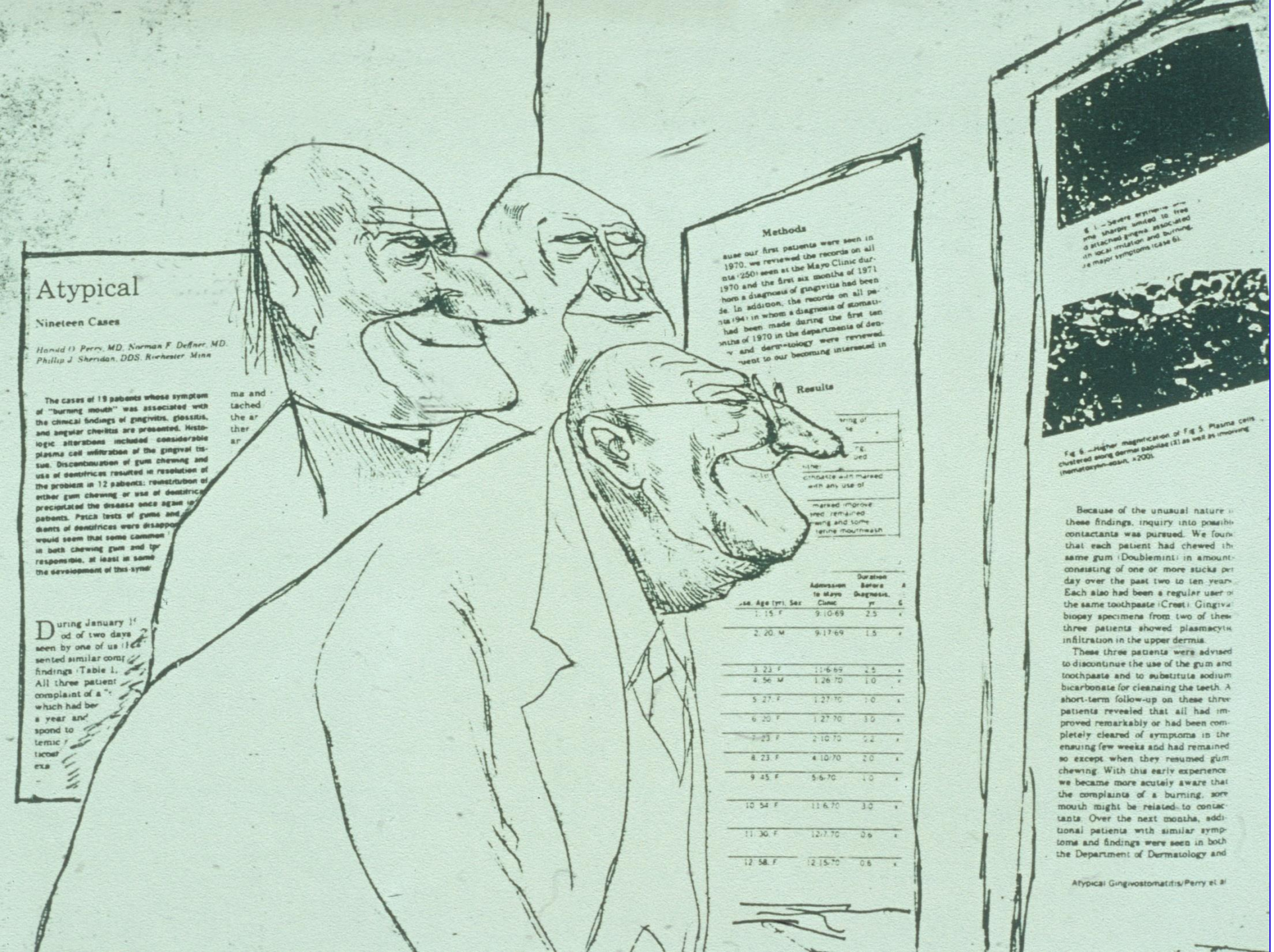
J.R. Marsden, J.A. Newton-Bishop,* L. Burrows,† M. Cook,‡ P.G. Corrie,§ N.H. Cox,¶ M.E. Gore,** P. Lorigan,†† R. MacKie,‡‡ P. Nathan,§§ H. Peach,¶¶ B. Powell*** and C. Walker

University Hospital Birmingham, Birmingham B29 6JD, U.K.
*University of Leeds, Leeds LS9 7TF, U.K.
†Salisbury District Hospital, Salisbury SP2 8BJ, U.K.
‡Royal Surrey County Hospital NHS Trust, Guildford GU2 7XX, U.K.
§Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 2QQ, U.K.
¶Cumberland Infirmary, Carlisle CA2 7HY, U.K.
**Royal Marsden Hospital, London SW3 6JJ, U.K.
††The Christie NHS Foundation Trust, Manchester M20 4BX, U.K.
‡‡University of Glasgow, Glasgow G12 8QQ, U.K.
§§Mount Vernon Hospital, London HA6 2RN, U.K.
¶¶St James's University Hospital, Leeds LS9 7TF, U.K.
***St George's Hospital, London SW17 0QT, U.K.

Br J Dermatol 2010; 163: 238

For example, it was readily adopted by the British Association of Dermatologists although the BAD at least acknowledged that these were "BAD guidelines." Nevertheless, they found general acceptance.

The whole world sucks from the breast of the AJCC,



Atypical

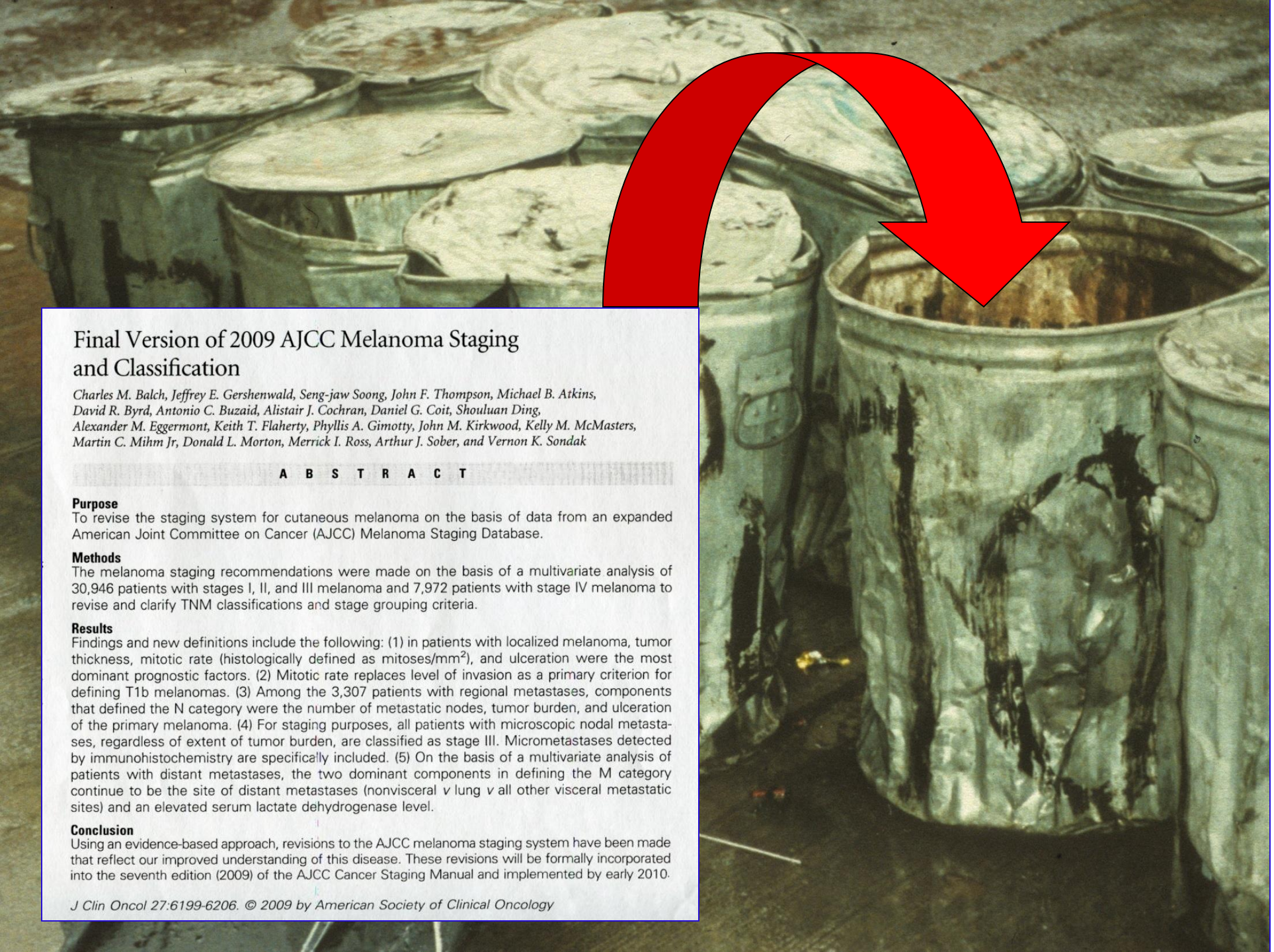
Nineteen Cases

Methods

Results

but instead of accepting everything with a broad smile,

the new classification deserves to be criticized harshly.



Final Version of 2009 AJCC Melanoma Staging and Classification

Charles M. Balch, Jeffrey E. Gershenwald, Seng-jaw Soong, John F. Thompson, Michael B. Atkins, David R. Byrd, Antonio C. Buzaid, Alistair J. Cochran, Daniel G. Coit, Shouluan Ding, Alexander M. Eggermont, Keith T. Flaherty, Phyllis A. Gimotty, John M. Kirkwood, Kelly M. McMasters, Martin C. Mihm Jr, Donald L. Morton, Merrick I. Ross, Arthur J. Sober, and Vernon K. Sondak

A B S T R A C T

Purpose
To revise the staging system for cutaneous melanoma on the basis of data from an expanded American Joint Committee on Cancer (AJCC) Melanoma Staging Database.

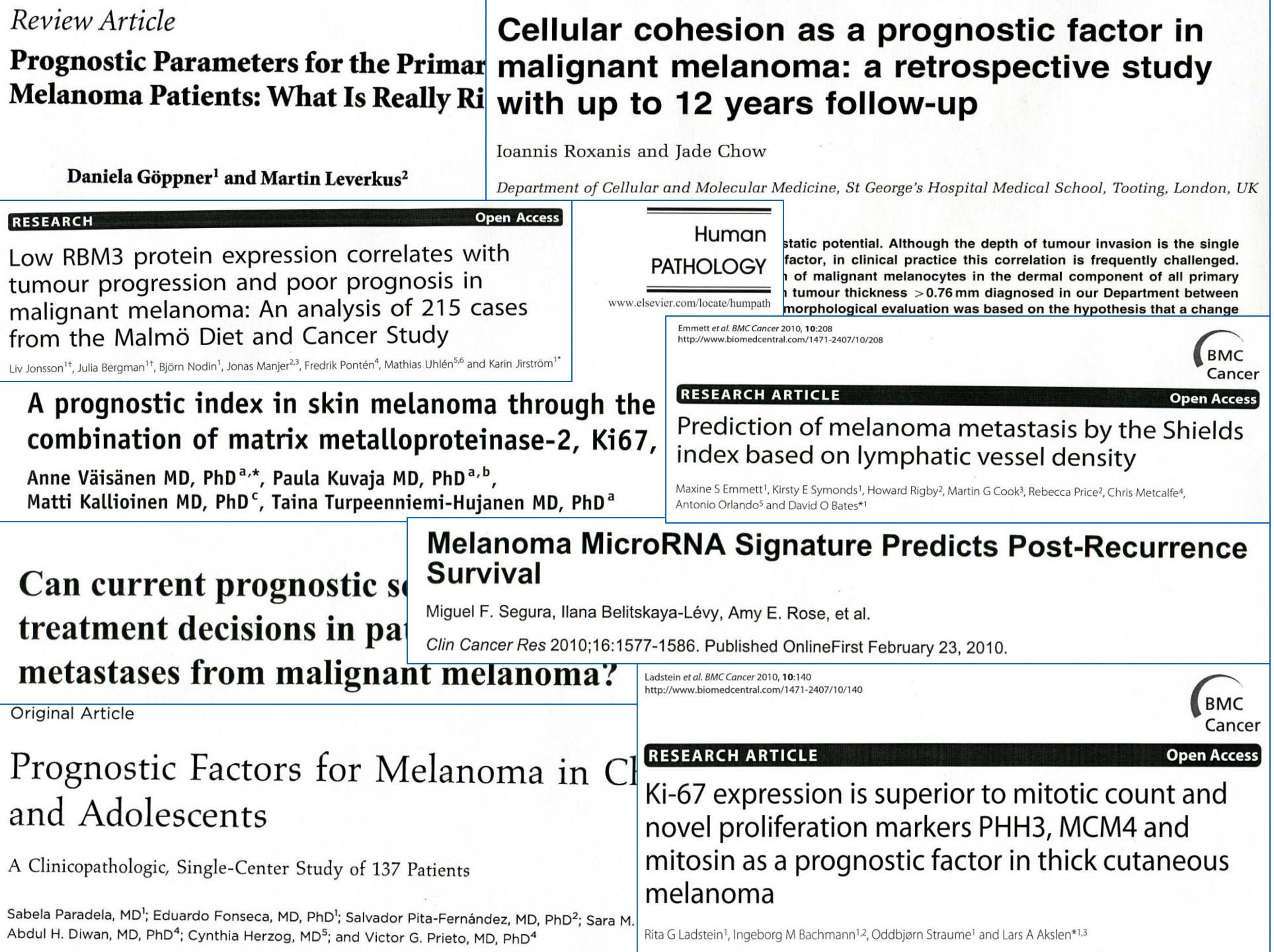
Methods
The melanoma staging recommendations were made on the basis of a multivariate analysis of 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma to revise and clarify TNM classifications and stage grouping criteria.

Results
Findings and new definitions include the following: (1) in patients with localized melanoma, tumor thickness, mitotic rate (histologically defined as mitoses/mm^2), and ulceration were the most dominant prognostic factors. (2) Mitotic rate replaces level of invasion as a primary criterion for defining T1b melanomas. (3) Among the 3,307 patients with regional metastases, components that defined the N category were the number of metastatic nodes, tumor burden, and ulceration of the primary melanoma. (4) For staging purposes, all patients with microscopic nodal metastases, regardless of extent of tumor burden, are classified as stage III. Micrometastases detected by immunohistochemistry are specifically included. (5) On the basis of a multivariate analysis of patients with distant metastases, the two dominant components in defining the M category continue to be the site of distant metastases (nonvisceral *v* lung *v* all other visceral metastatic sites) and an elevated serum lactate dehydrogenase level.

Conclusion
Using an evidence-based approach, revisions to the AJCC melanoma staging system have been made that reflect our improved understanding of this disease. These revisions will be formally incorporated into the seventh edition (2009) of the AJCC Cancer Staging Manual and implemented by early 2010.

J Clin Oncol 27:6199-6206.

There is only one place for it, the trash can.



Review Article

Prognostic Parameters for the Primar
Melanoma Patients: What Is Really Ri

Daniela Göppner[1] and Martin Leverkus[2]

Cellular cohesion as a prognostic factor in malignant melanoma: a retrospective study with up to 12 years follow-up

Ioannis Roxanis and Jade Chow

Department of Cellular and Molecular Medicine, St George's Hospital Medical School, Tooting, London, UK

tatic potential. Although the depth of tumour invasion is the single factor, in clinical practice this correlation is frequently challenged. of malignant melanocytes in the dermal component of all primary tumour thickness >0.76 mm diagnosed in our Department between morphological evaluation was based on the hypothesis that a change

RESEARCH Open Access

Low RBM3 protein expression correlates with tumour progression and poor prognosis in malignant melanoma: An analysis of 215 cases from the Malmö Diet and Cancer Study

Liv Jonsson[1†], Julia Bergman[1†], Björn Nodin[1], Jonas Manjer[2,3], Fredrik Pontén[4], Mathias Uhlén[5,6] and Karin Jirström[1*]

Human PATHOLOGY

www.elsevier.com/locate/humpath

A prognostic index in skin melanoma through the combination of matrix metalloproteinase-2, Ki67,

Anne Väisänen MD, PhD[a,*], Paula Kuvaja MD, PhD[a,b], Matti Kallioinen MD, PhD[c], Taina Turpeenniemi-Hujanen MD, PhD[a]

Emmett *et al. BMC Cancer* 2010, **10**:208
http://www.biomedcentral.com/1471-2407/10/208

BMC Cancer

RESEARCH ARTICLE Open Access

Prediction of melanoma metastasis by the Shields index based on lymphatic vessel density

Maxine S Emmett[1], Kirsty E Symonds[1], Howard Rigby[2], Martin G Cook[3], Rebecca Price[2], Chris Metcalfe[4], Antonio Orlando[5] and David O Bates*[1]

Melanoma MicroRNA Signature Predicts Post-Recurrence Survival

Miguel F. Segura, Ilana Belitskaya-Lévy, Amy E. Rose, et al.

Clin Cancer Res 2010;16:1577-1586. Published OnlineFirst February 23, 2010.

Can current prognostic s
treatment decisions in pa
metastases from malignant melanoma?

Original Article

Prognostic Factors for Melanoma in C
and Adolescents

A Clinicopathologic, Single-Center Study of 137 Patients

Sabela Paradela, MD[1]; Eduardo Fonseca, MD, PhD[1]; Salvador Pita-Fernández, MD, PhD[2]; Sara M. Abdul H. Diwan, MD, PhD[4]; Cynthia Herzog, MD[5]; and Victor G. Prieto, MD, PhD[4]

Ladstein *et al. BMC Cancer* 2010, **10**:140
http://www.biomedcentral.com/1471-2407/10/140

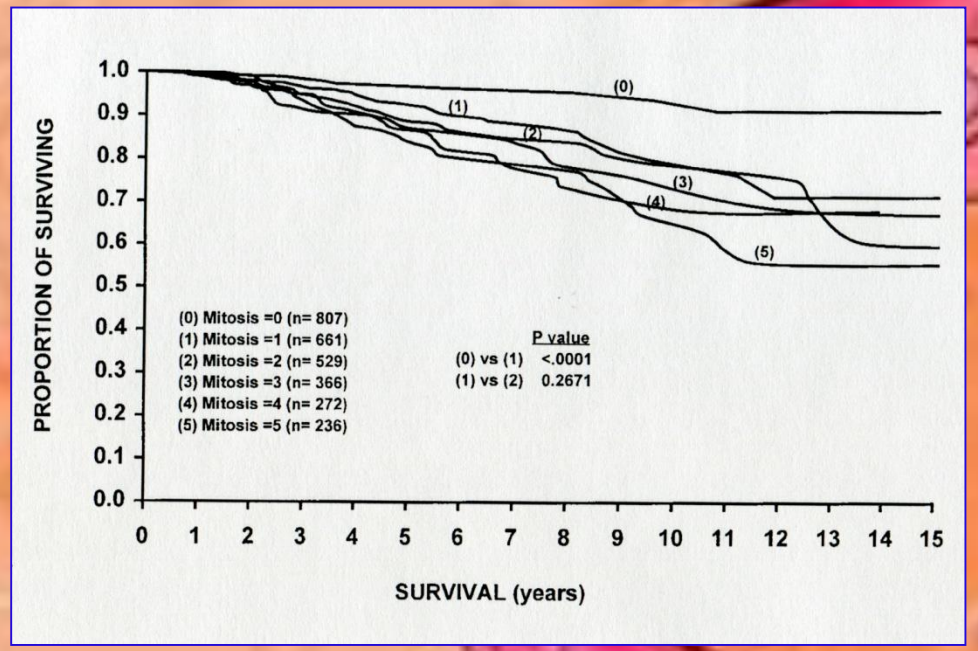
BMC Cancer

RESEARCH ARTICLE Open Access

Ki-67 expression is superior to mitotic count and novel proliferation markers PHH3, MCM4 and mitosin as a prognostic factor in thick cutaneous melanoma

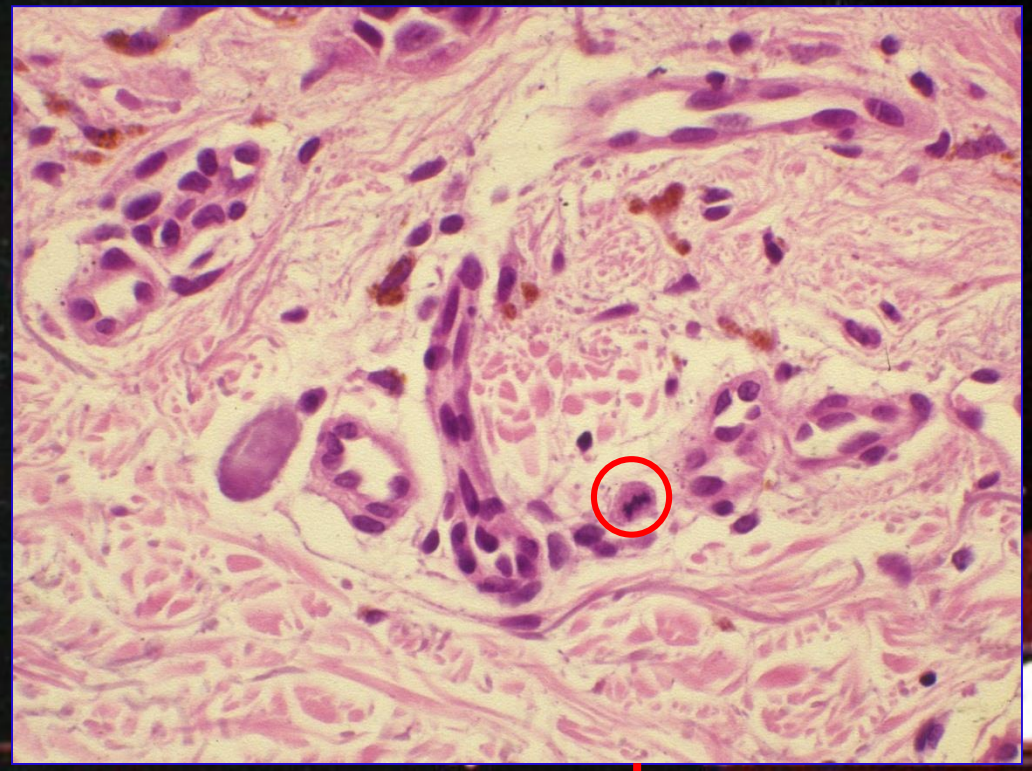
Rita G Ladstein[1], Ingeborg M Bachmann[1,2], Oddbjørn Straume[1] and Lars A Akslen*[1,3]

The problem, however, is not only this classification. In general, the ever increasing emphasis on prognostication needs to be re-considered. Our job is diagnosis, not prognosis. Nonetheless, prognostication often occupies more space than diagnosis in journals and textbooks of oncology, especially in regard to melanoma.



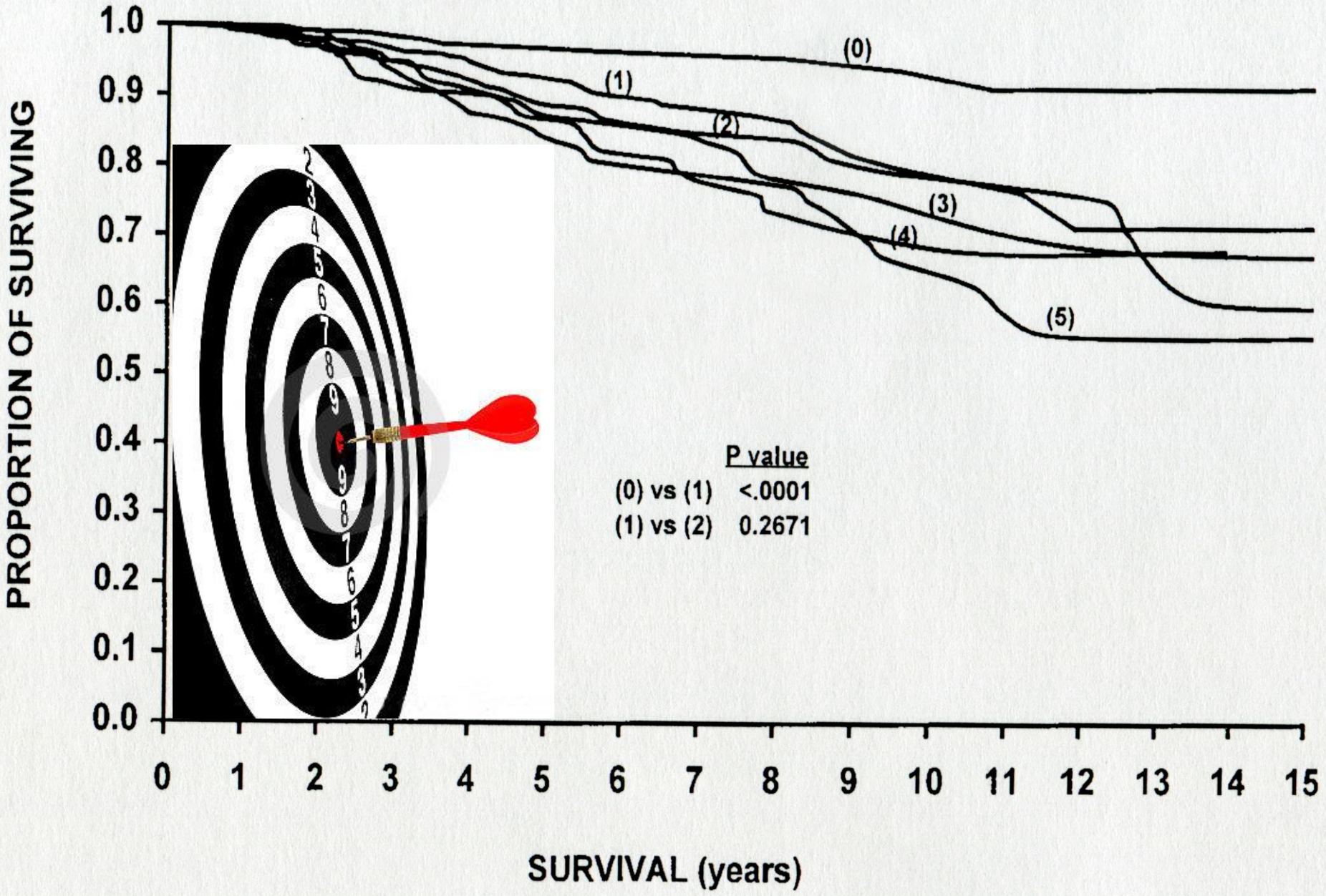
It is clear why pathologists love prognosis.

For a wrong diagnosis, they may go to court, but in regard to prognosis, any nonsense goes,



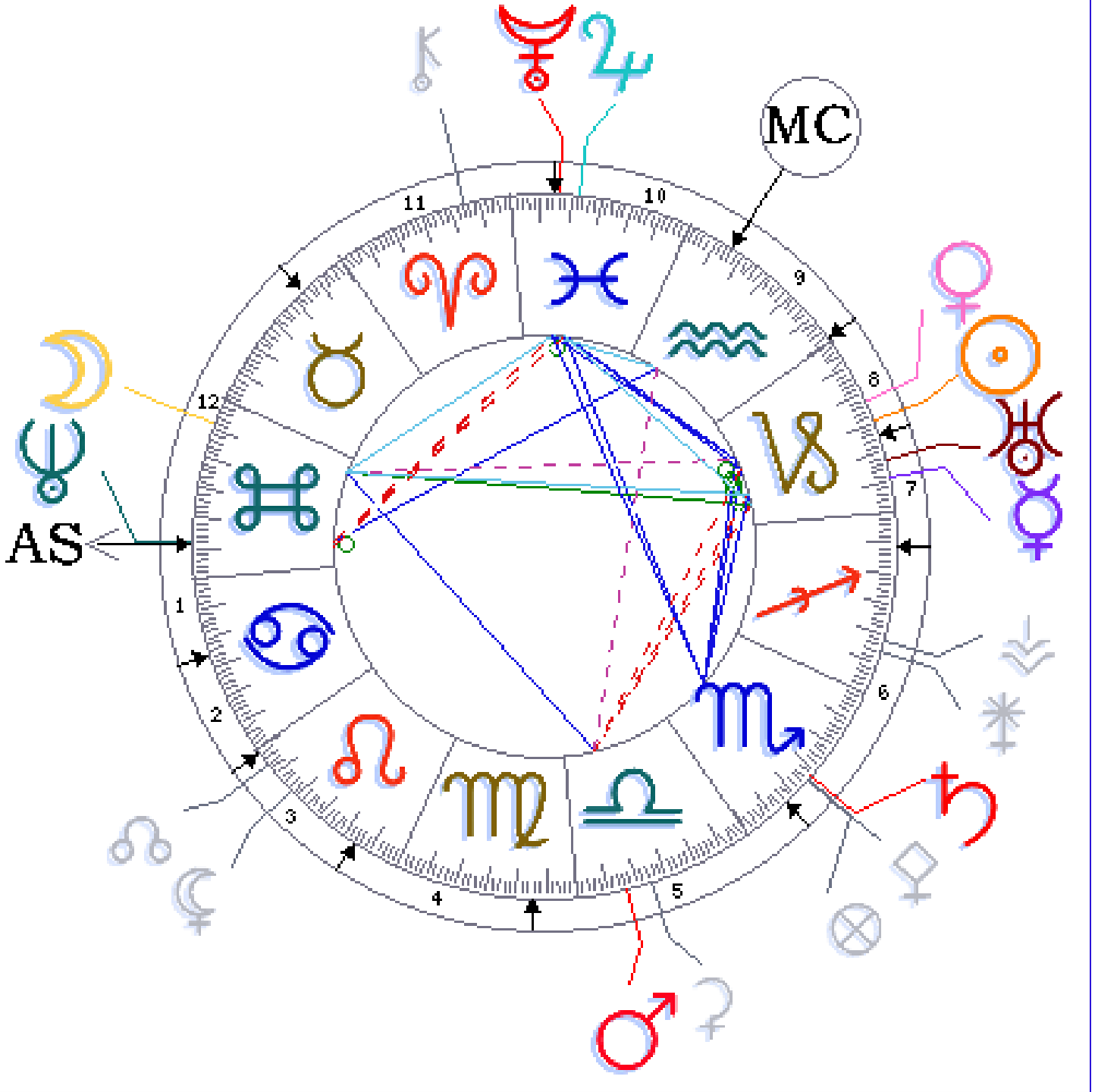
The 10-year-survival rate … dropped [from 95%] to 88% if the mitotic rate was at least 1/mm^2.

even the notion that a single mitotic figure causes the 10-year-survival rate of thin melanomas to drop to 88%. If patients remain free of disease despite presence of several mitotic figures, this is the expected outcome; if they develop metastases in the absence of mitotic figures, they belong to the unlucky 5%!



The prognosis, however, was on target! It is always right, one cannot err with prognosis.

The same is true for astrology. If one phrases one’s predictions careful enough, one cannot err, and like oncologists,



astrologists like to play with numbers in order to attach a scientific apparel to their prognostications,

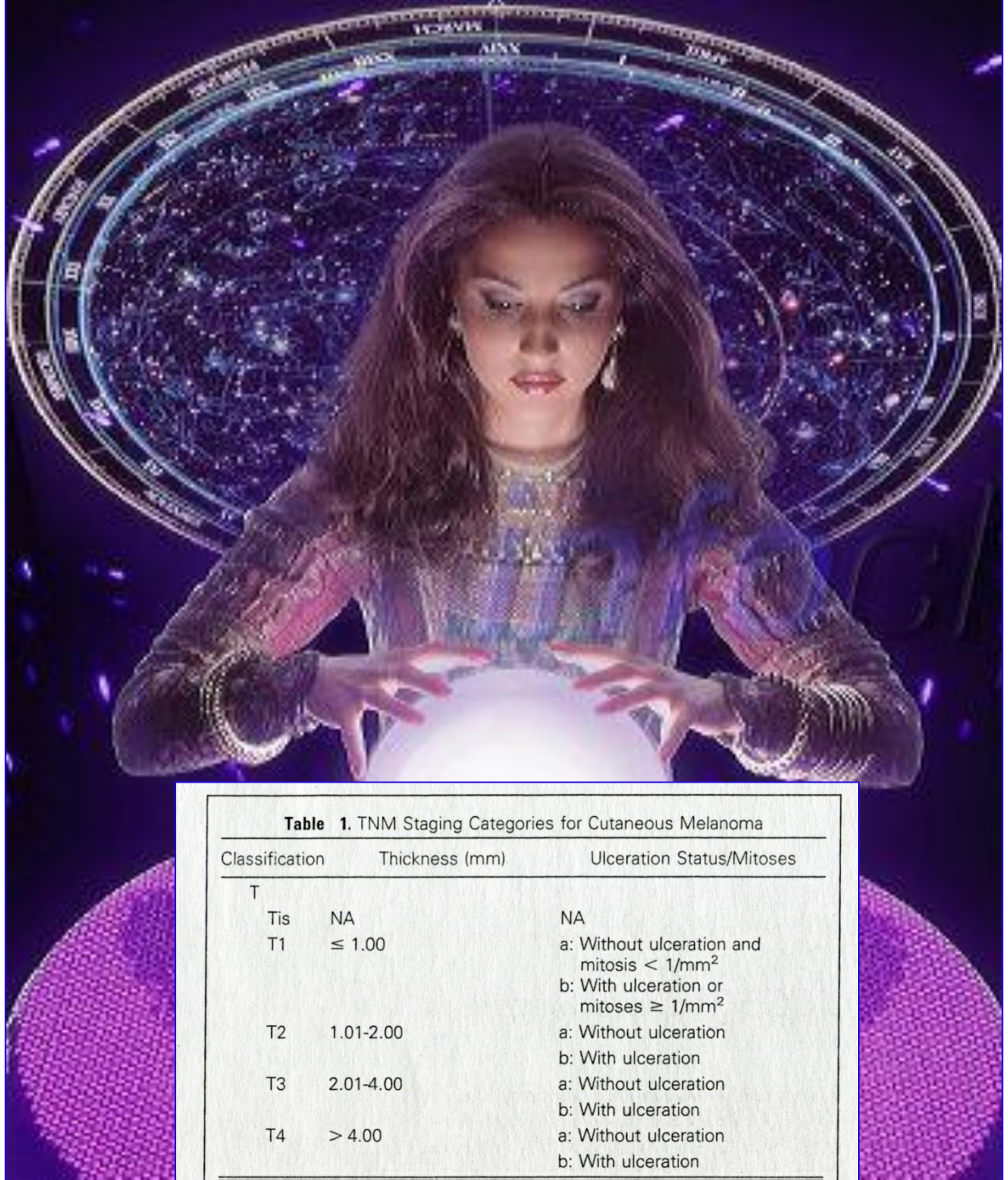
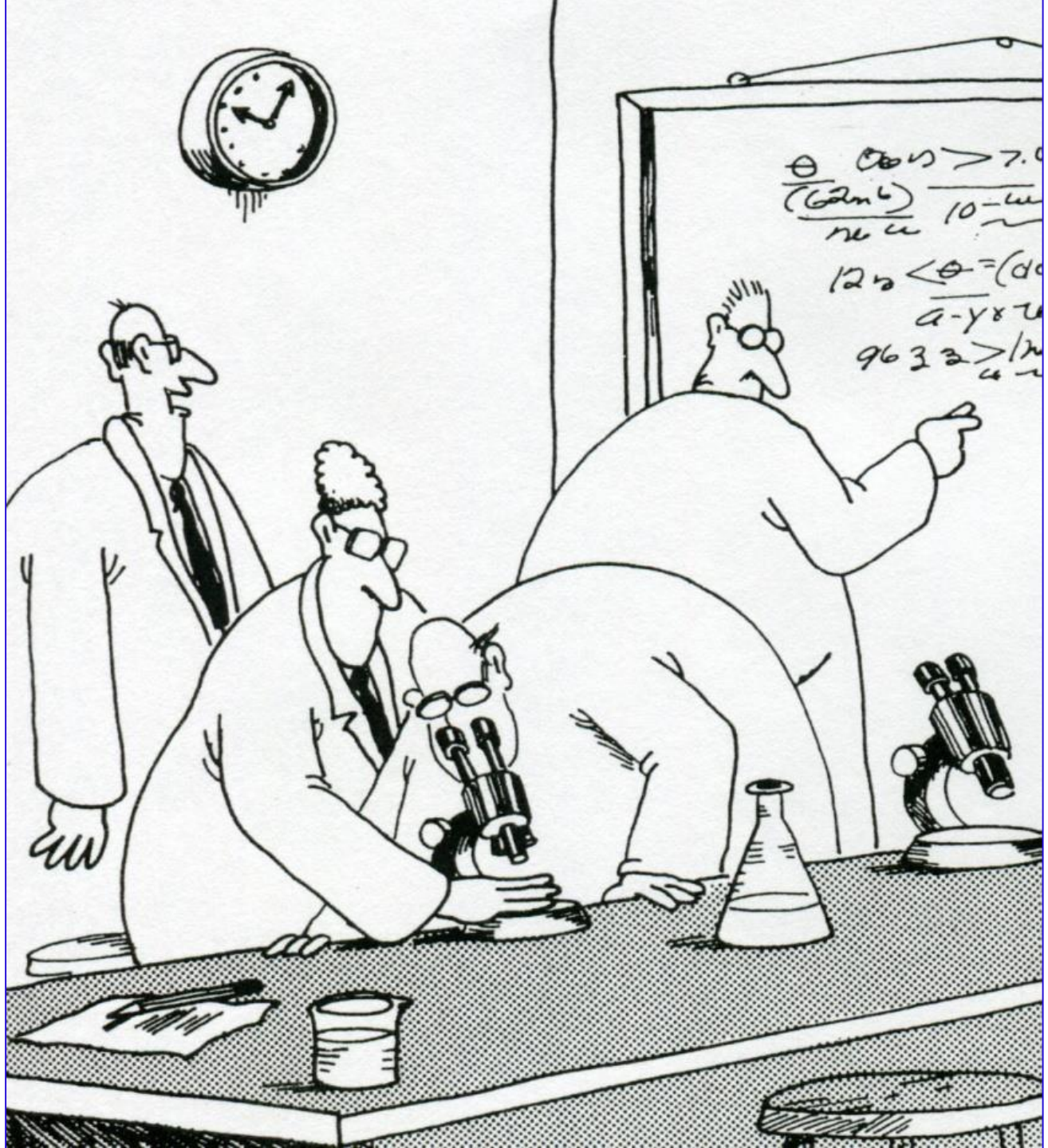


Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2
		b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration
		b: With ulceration
T3	2.01-4.00	a: Without ulceration
		b: With ulceration
T4	> 4.00	a: Without ulceration
		b: With ulceration

but the constellation of stars and other data entering into them are unreliable. The same is true for most parameters used to predict prognosis in melanoma.

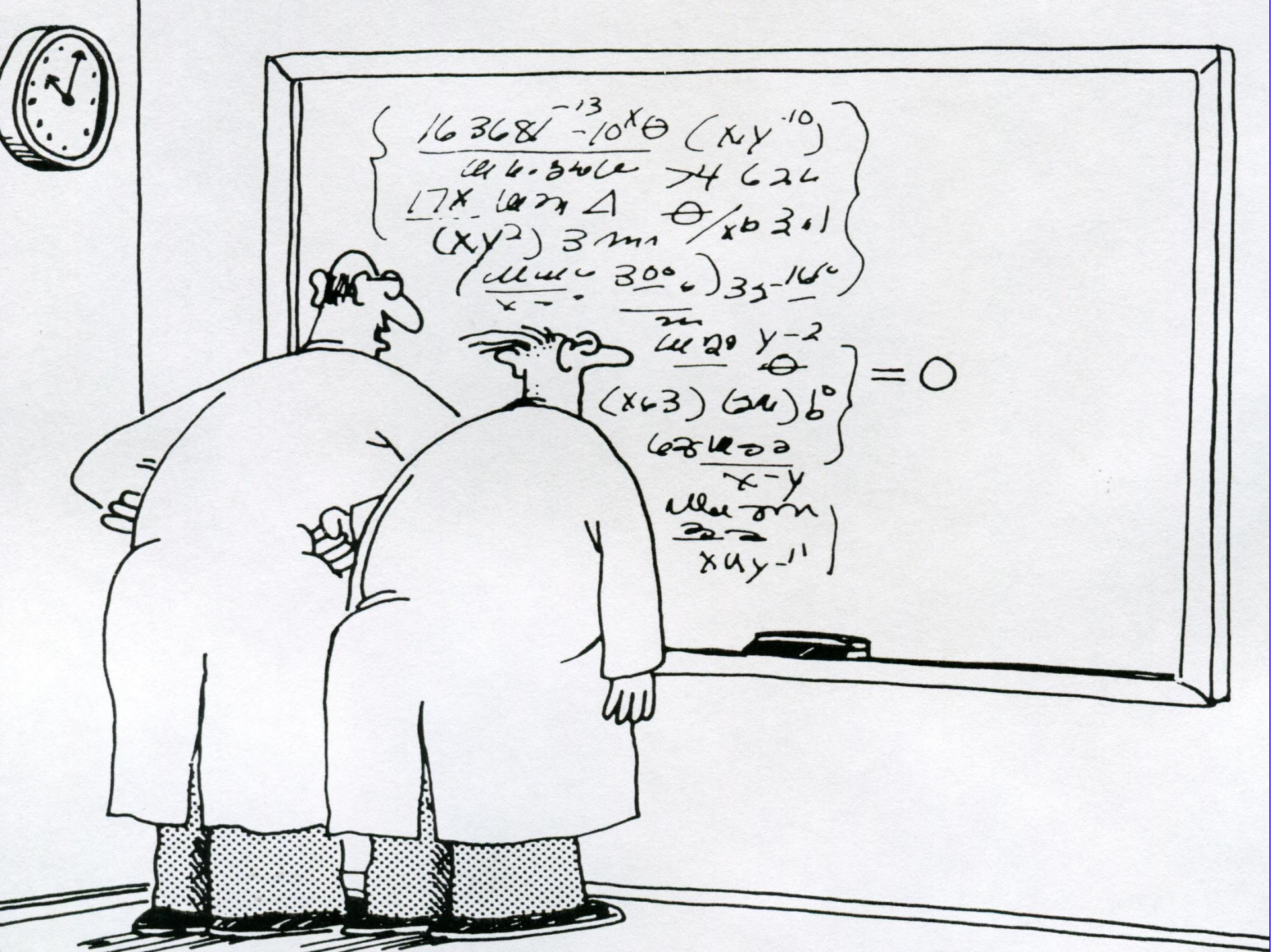
Factors such as thickness that reflect the stage of development of a lesion, whether it is a puppy or a full grown melanoma, have some value.



More sophisticated attempts to translate histopathologic findings into numbers

TUMOR THICKNESS SUBGROUP	PROGNOSTIC MODEL	DEFINITION AND CODING OF THE COVARIATE (X_i) WITHIN THE TUMOR THICKNESS SUBGROUP
<0.76 mm	$\hat{S}_1(t) = [\hat{S}_{10}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -1.11316(X_1 - 0.55769) + 0.73644(X_2 - 0.40247)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (level of invasion) = 0, if level II; = 1, if other levels.
0.76–1.49 mm	$\hat{S}_2(t) = [\hat{S}_{20}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -1.02481(X_1 - 0.90731) - 0.78450(X_2 - 0.55459) + 1.21636(X_3 - 0.89395)$	X_1 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_2 (lesion location) = 0, if axial; = 1, if extremity. X_3 (level of invasion) = 0, if level II; = 1, if other levels.
1.50–2.49 mm	$\hat{S}_3(t) = [\hat{S}_{30}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.61149(X_1 - 0.52813) - 0.58611(X_2 - 0.66705) - 0.79938(X_3 - 0.49024)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_3 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.
2.50–3.99 mm	$\hat{S}_4(t) = [\hat{S}_{40}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.35556(X_1 - 0.50000) - 0.33959(X_2 - 0.56157) - 0.38754(X_3 - 0.41791) - 0.46234(X_4 - 0.54851)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_3 (sex) = 0, if male; = 1, if female. X_4 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.
4.00–7.99 mm	$\hat{S}_5(t) = [\hat{S}_{50}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.56653(X_1 - 0.41690) + 0.54407(X_2 - 0.81690) - 0.76193(X_3 - 0.45352)$	X_1 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_2 (level of invasion) = 0, if levels II, III; = 1, if levels IV, V. X_3 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.

and to create a mathematical formula for prognosis of melanoma, however, are bound to fail. The complicated equations used by oncologists to calculate the future of melanoma patients may produce awe,



but they are pseudo-science, and in the end, they add up to zero.