The Fallacy of the Concept of Invasion

W. Weyers
Center for Dermatopathology, Freiburg, Germany

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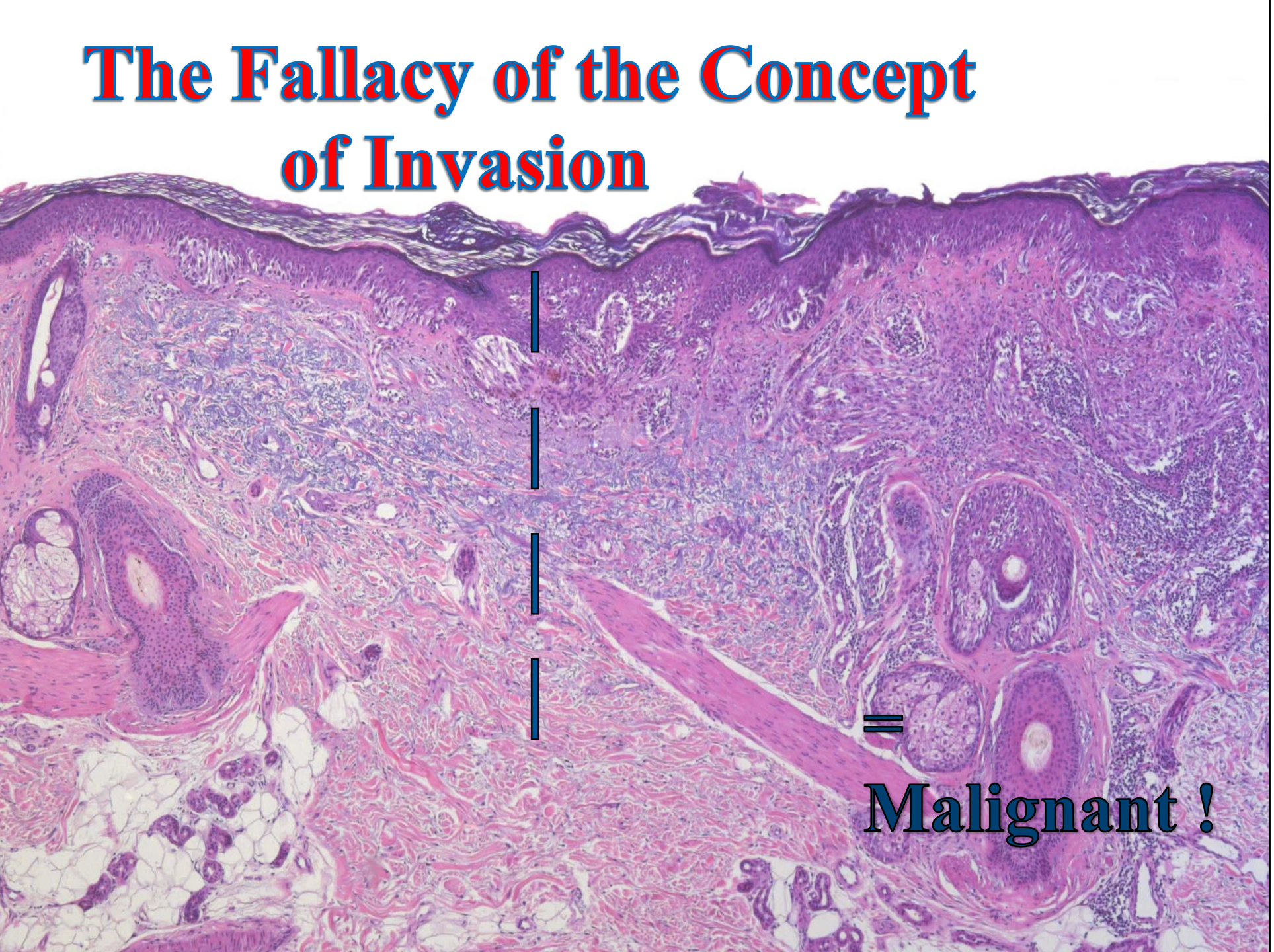
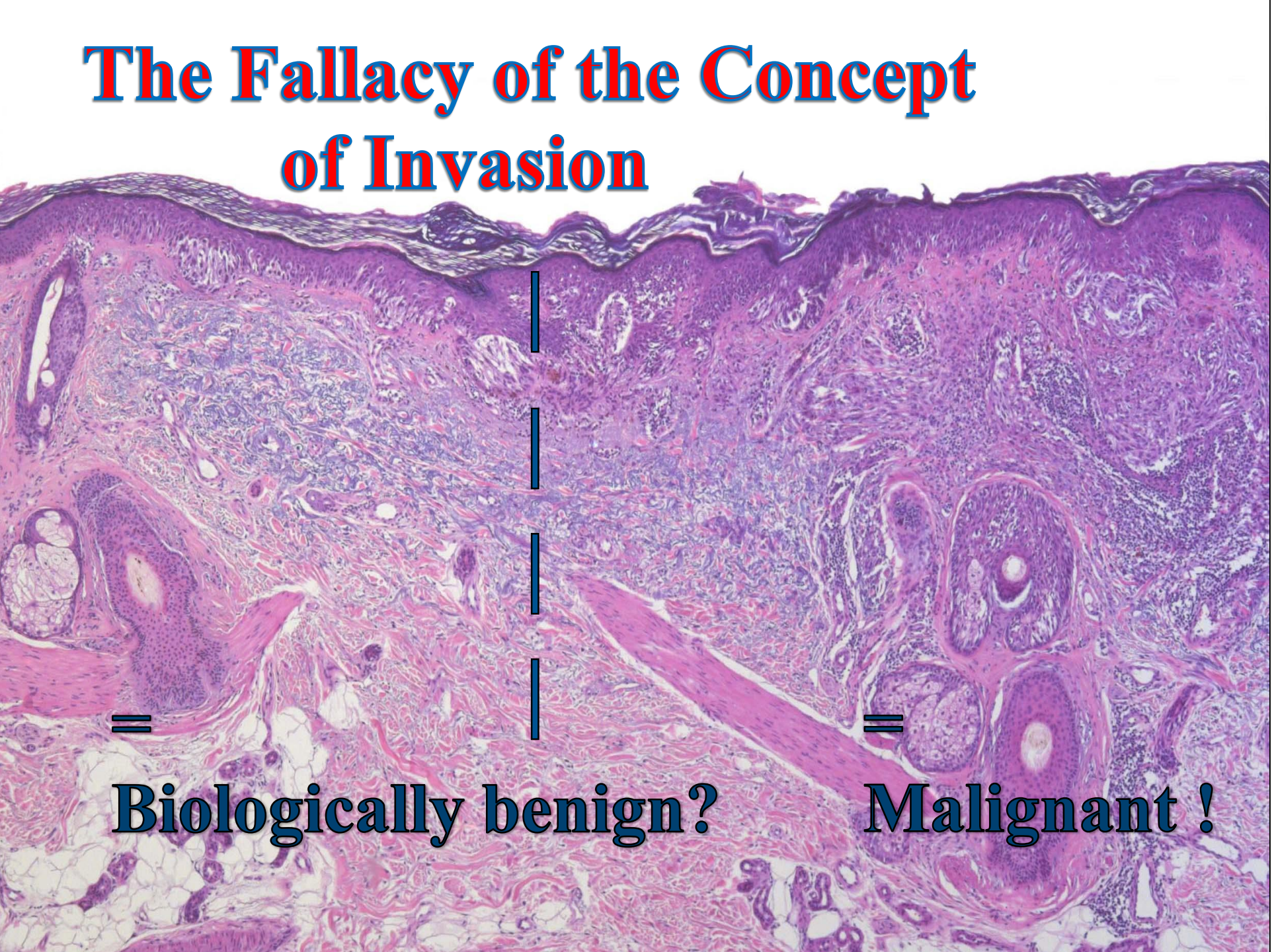
The most important task of histopathologists is diagnosis of malignancy at an early stage. In order to accomplish that task, one needs to have a clear concept of malignancy. Unfortunately, the latter is blurred by the concept of invasion.

The Fallacy of the Concept of Invasion

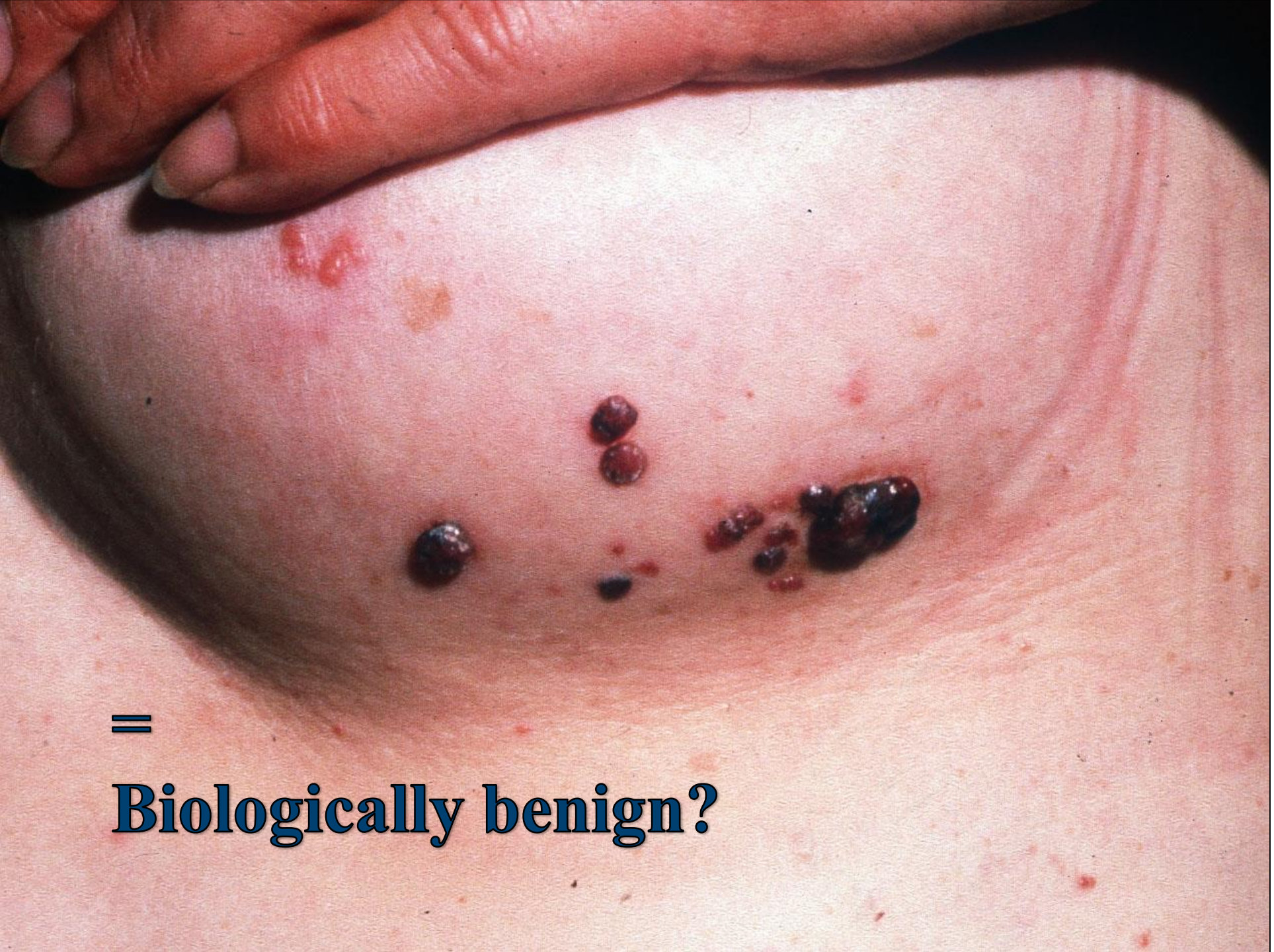


Many authors consider invasion to be a prerequisite for diagnosis of malignancy, arguing that, when still confined to the epithelium,

The Fallacy of the Concept of Invasion



a neoplasm is “biologically benign.” By the same token, however, one might argue



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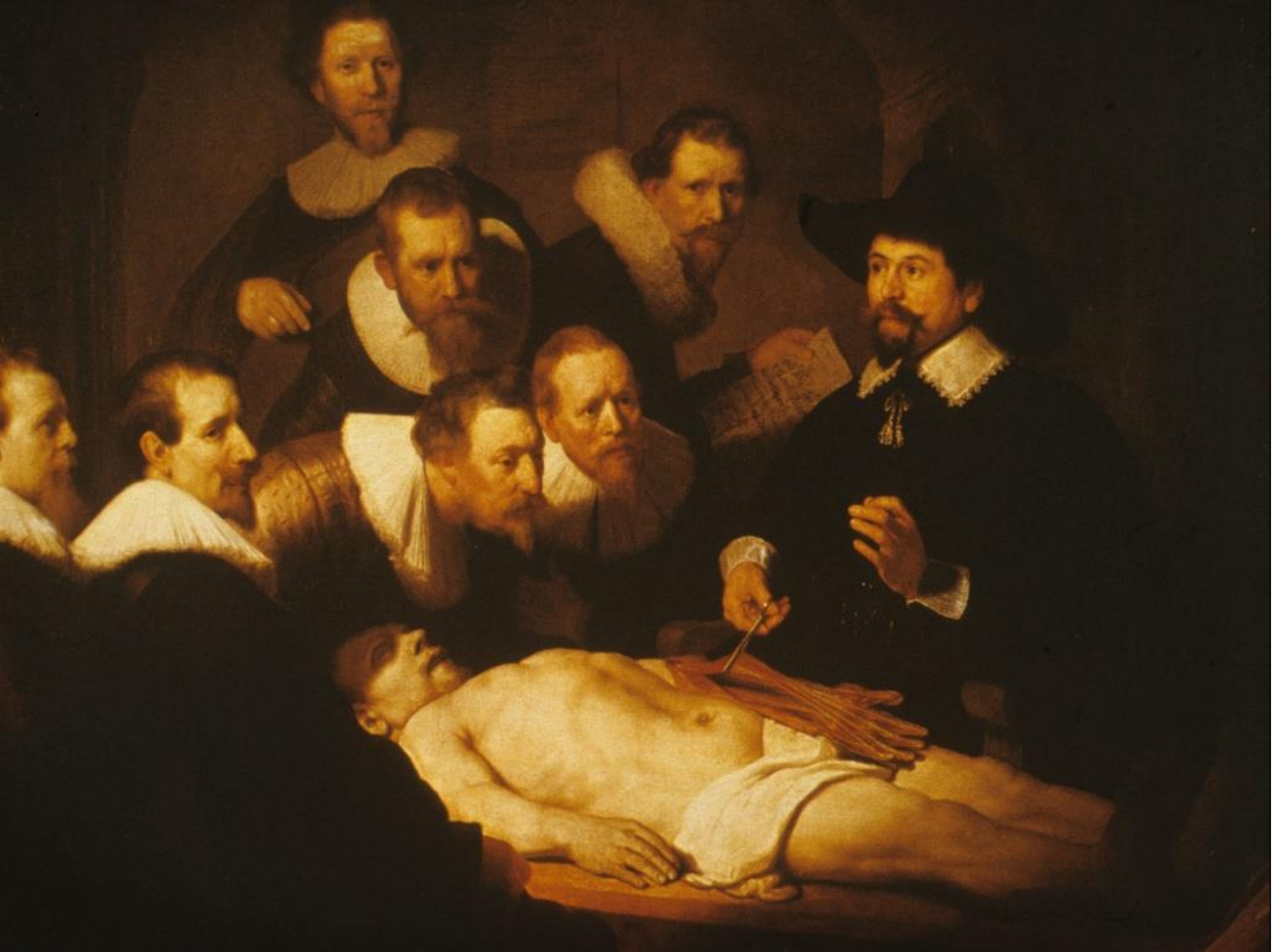
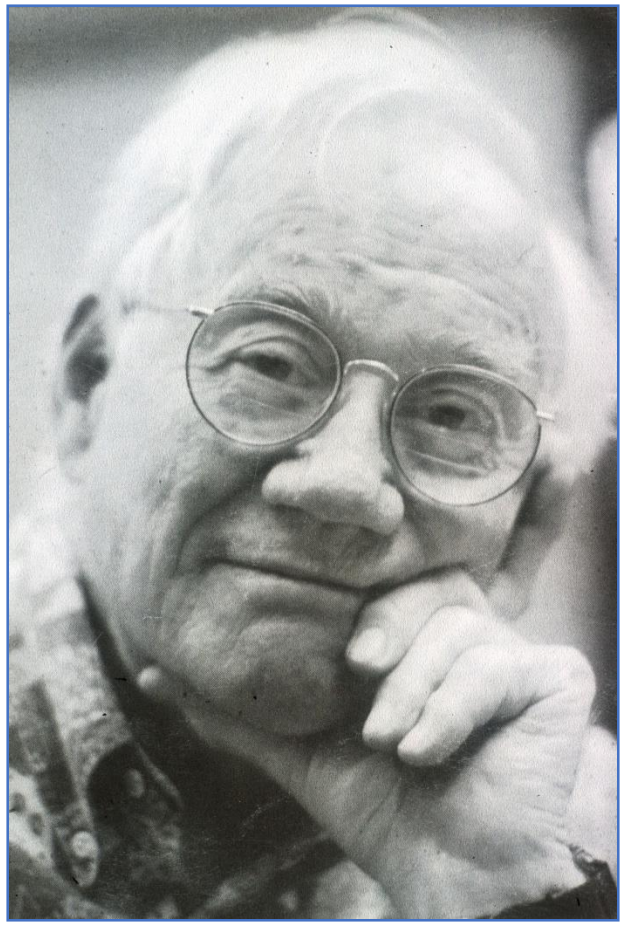
Biologically benign?

that a metastasizing neoplasm is “biologically benign” as long as it does not compromise the patient. This, obviously, makes no sense. Malignancy must be defined by the potential of a lesion, not by realization of that potential, namely,



death of the patient. A neoplasm is malignant long before the patient is dead, it is malignant from the outset if it has

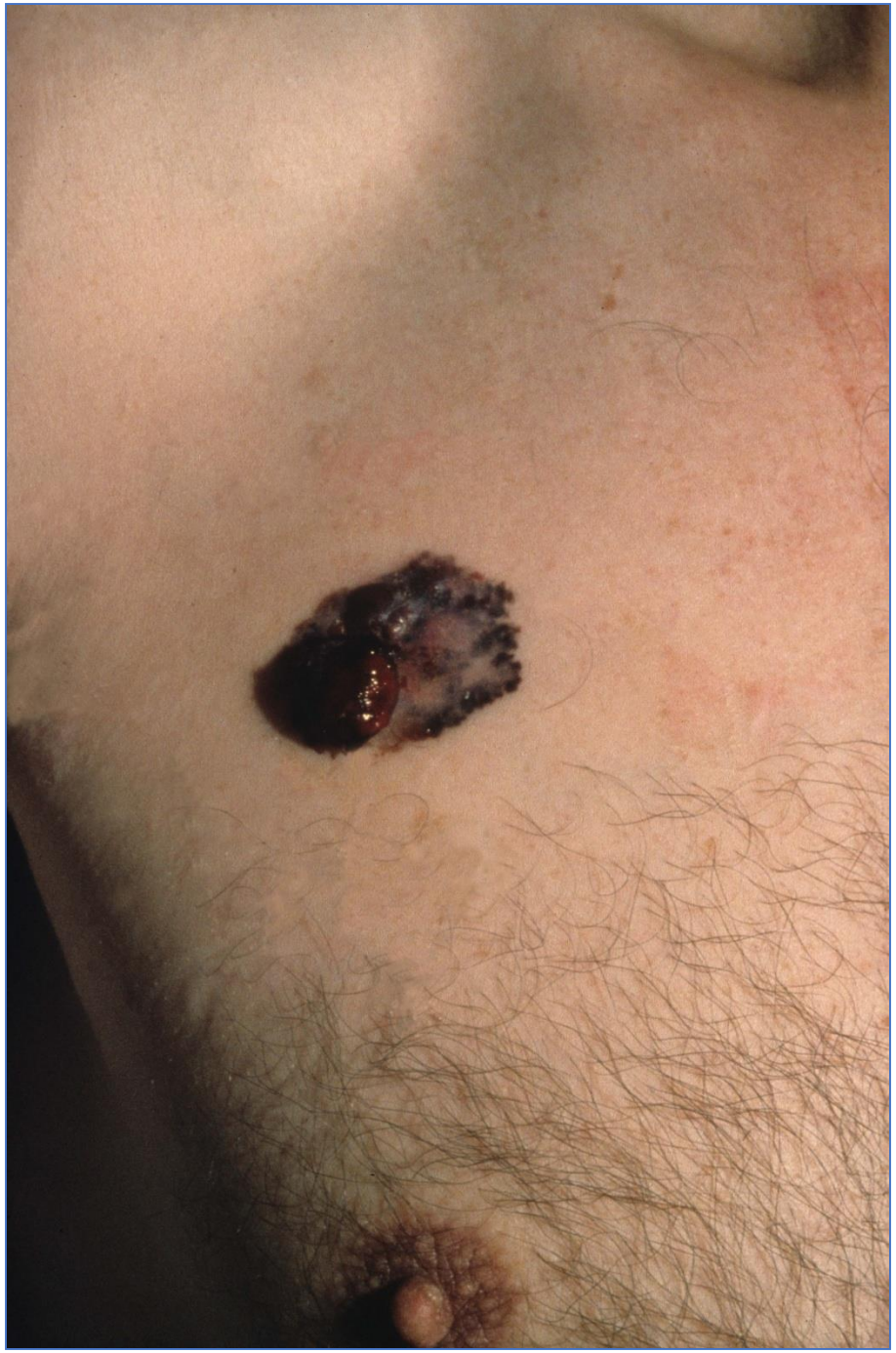
the *"potential to kill by destruction locally or by metastases widely."*
This brief, clear definition of malignancy was given by Bernard Ackerman in 1993. Compare it to another definition

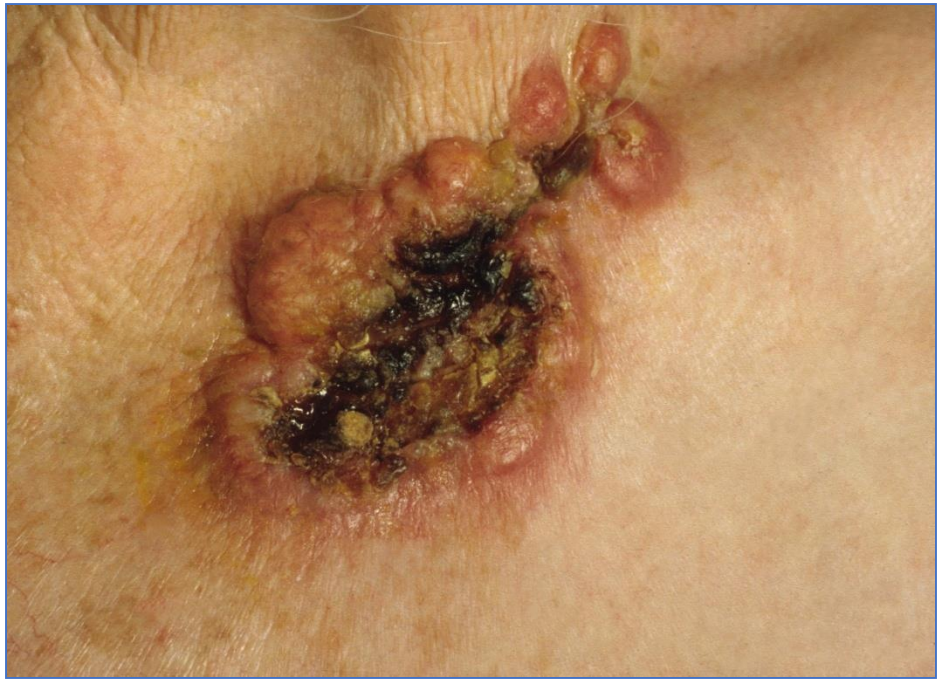


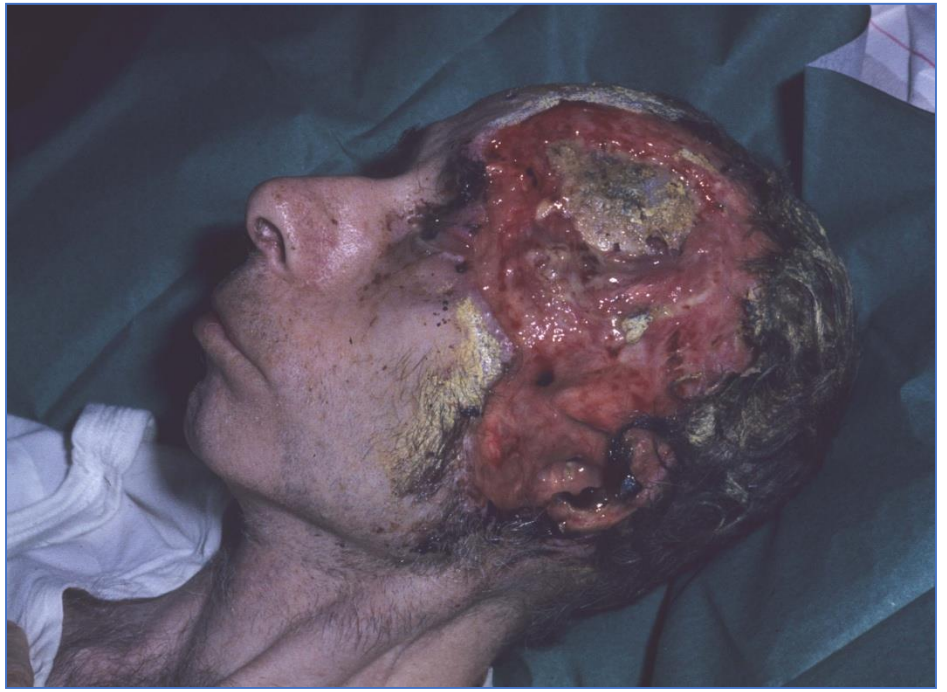
Cancer is a population of abnormal cells showing temporarily unrestricted growth preference … over normal cells. Such abnormal cells invade surrounding tissues, traverse at least one basement membrane zone, grow in the mesenchyme at the primary site, and may metastasize to distant sites. It is the totality of properties that determines whether a given lesion should be diagnosed as a cancer.

Wallace H. Clark, Jr., 1990

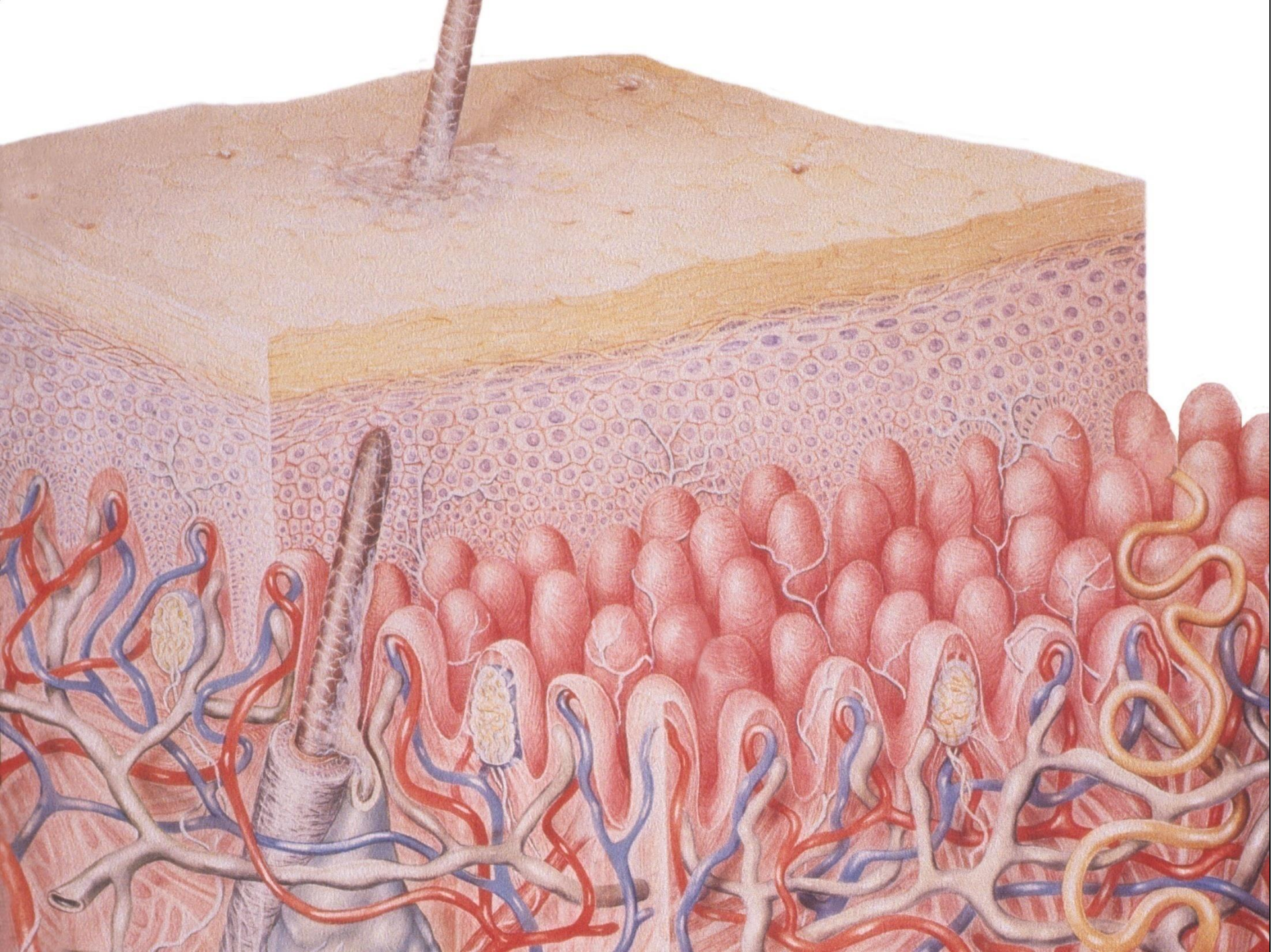
given at about the same time by Wallace H. Clark, Jr.: *"Cancer is a population of abnormal cells showing temporarily unrestricted growth preference … over normal cells. Such abnormal cells invade surrounding tissues, traverse at least one basement membrane zone, grow in the mesenchyme at the primary site, and may metastasize to distant sites. It is the totality of properties that determines whether a given lesion should be diagnosed as a cancer."* Obviously, this definition is very different. Instead of considering the potential of a lesion, a smorgasbord of aspects is presented, and the claim that *"the totality of properties"* must be fulfilled for a lesion to qualify as cancer means, literally,



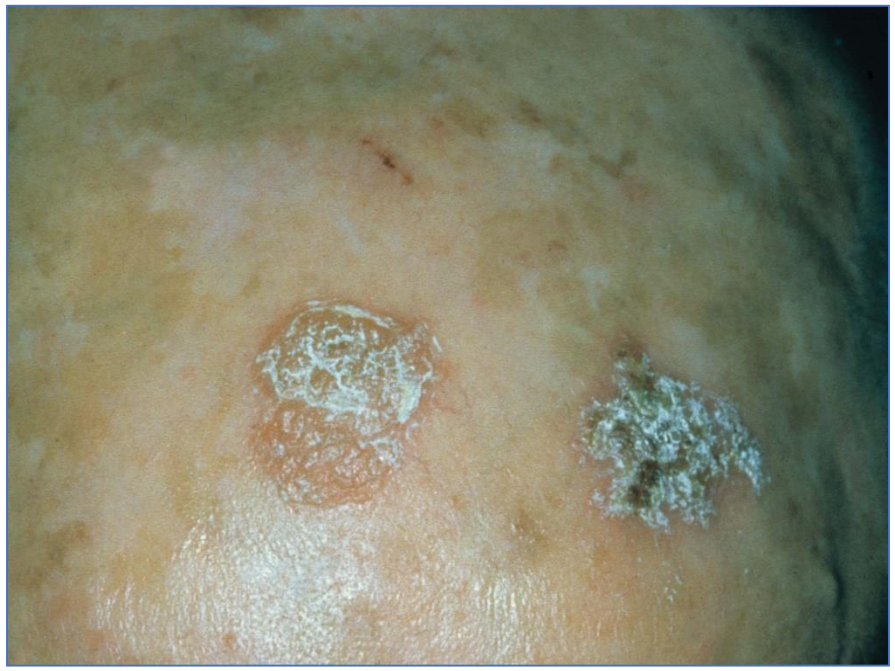


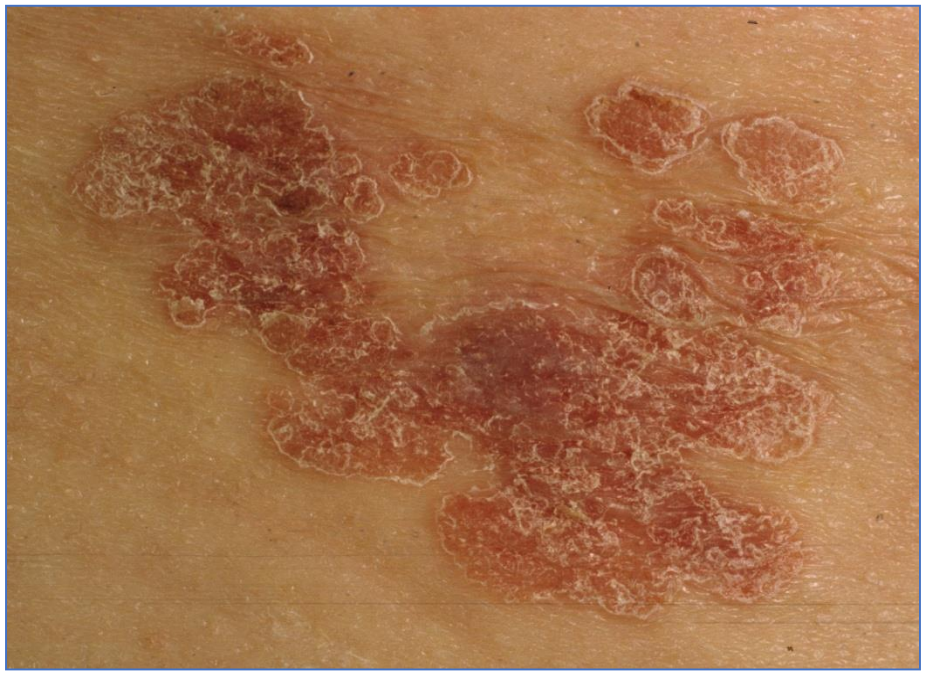


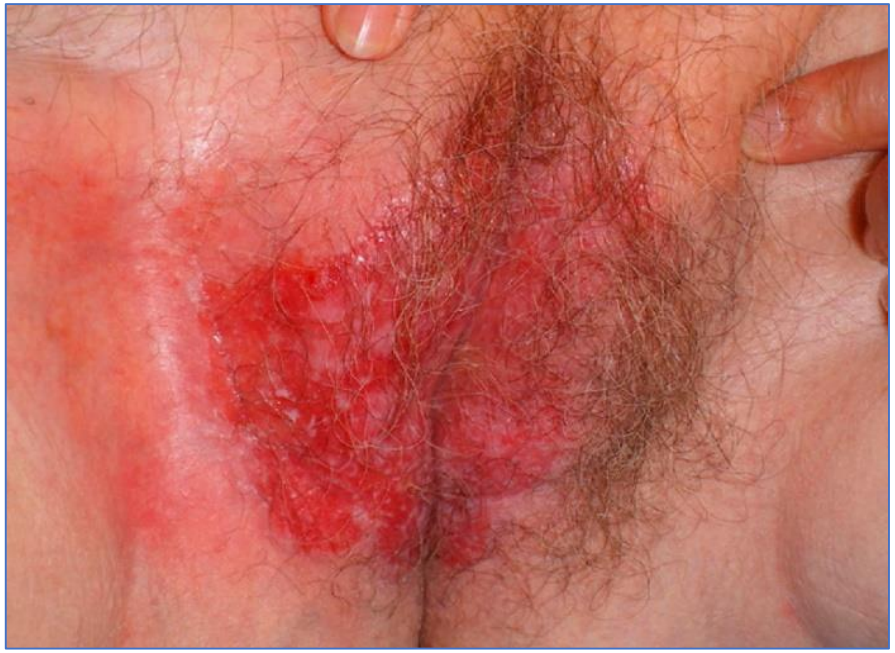
that lesions such as these could not be dubbed malignant in the absence of metastases. In order to fight cancer, however, one cannot wait for metastases but must recognize and name a lesion early in its course, when it is still restricted to the site from where it originates.

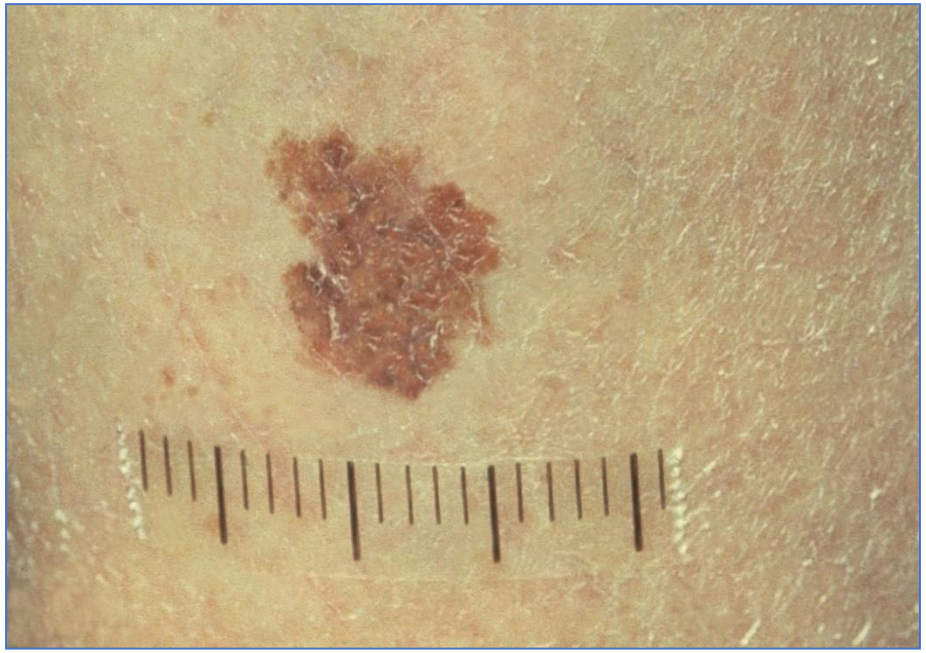


Physiologically, epithelial cells and melanocytes are situated in the epithelium. That is where neoplasms of those cells arise and where they should be diagnosed.
But can they be diagnosed when still confined to the epithelium?

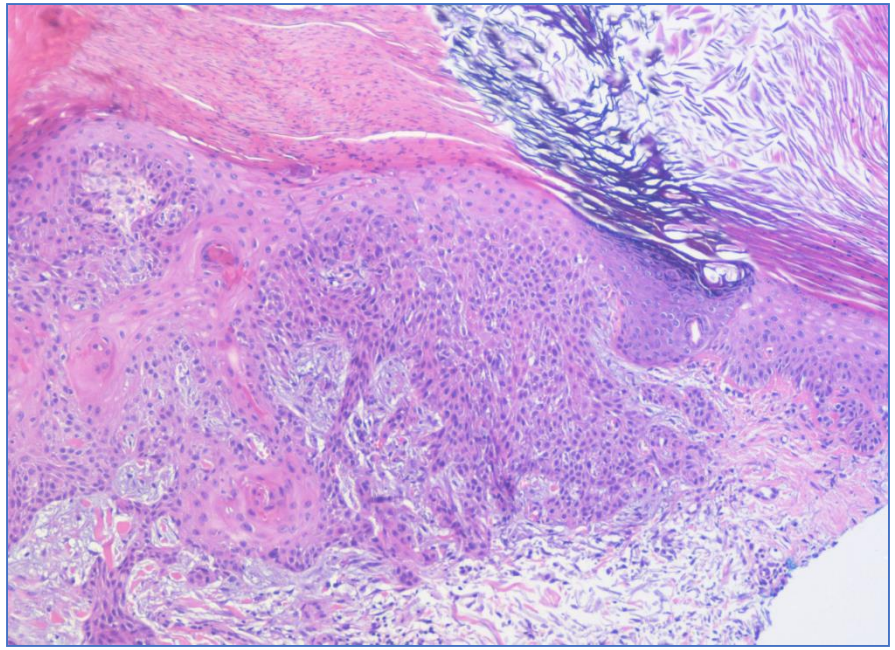


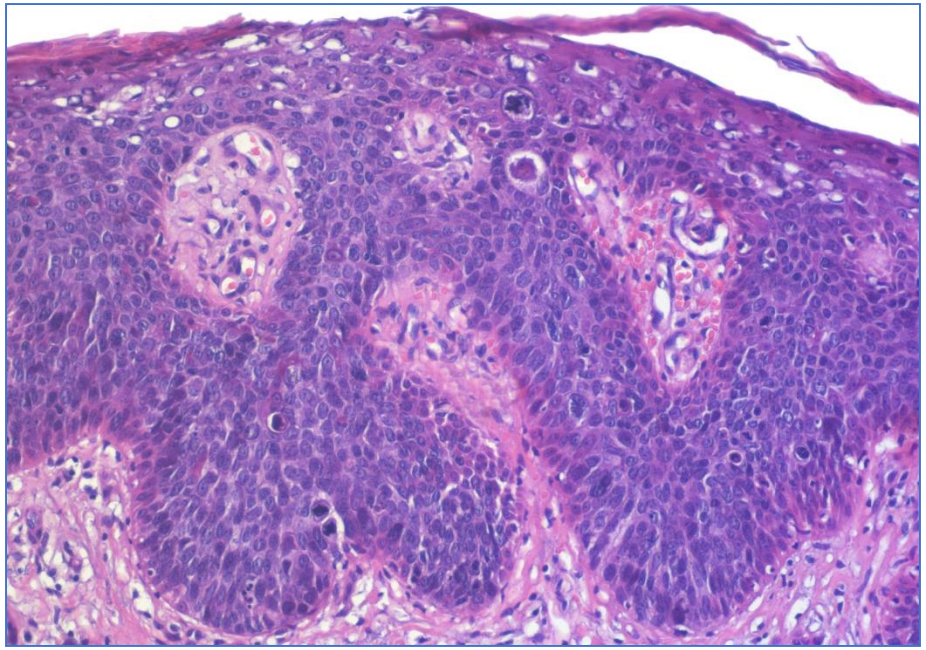


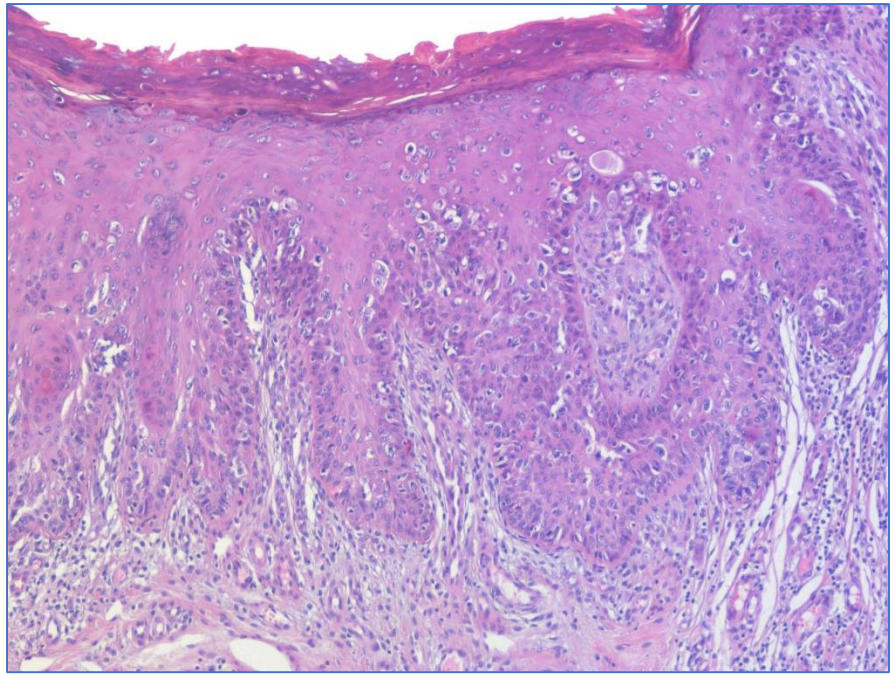


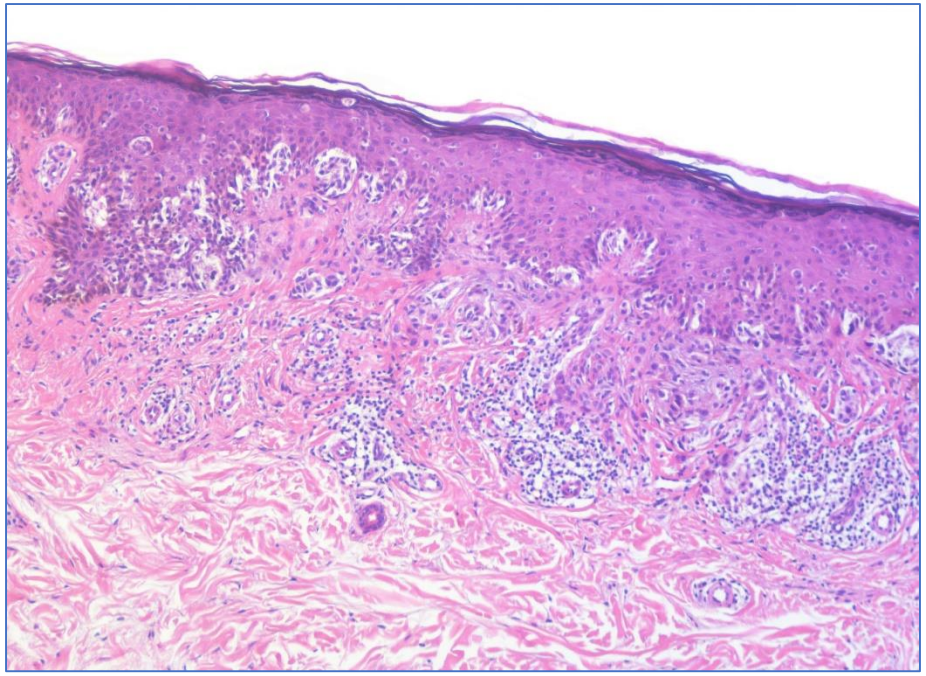


Of course they can, and clinicians do it all the time. In large, irregularly shaped lesions such as these, the clinical diagnosis of solar keratosis, Bowen's disease, extramammary Paget's disease, and melanoma is fairly easy

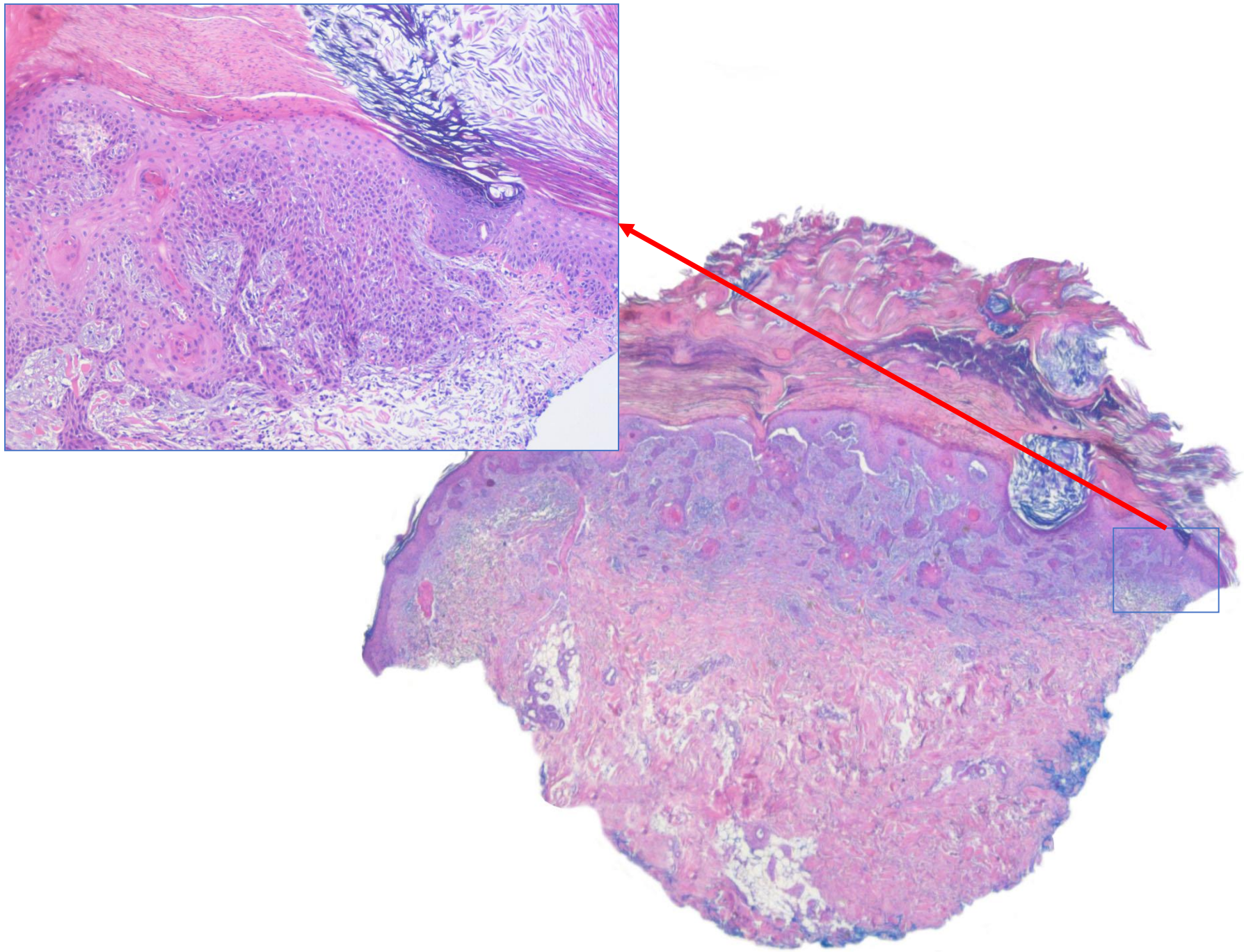




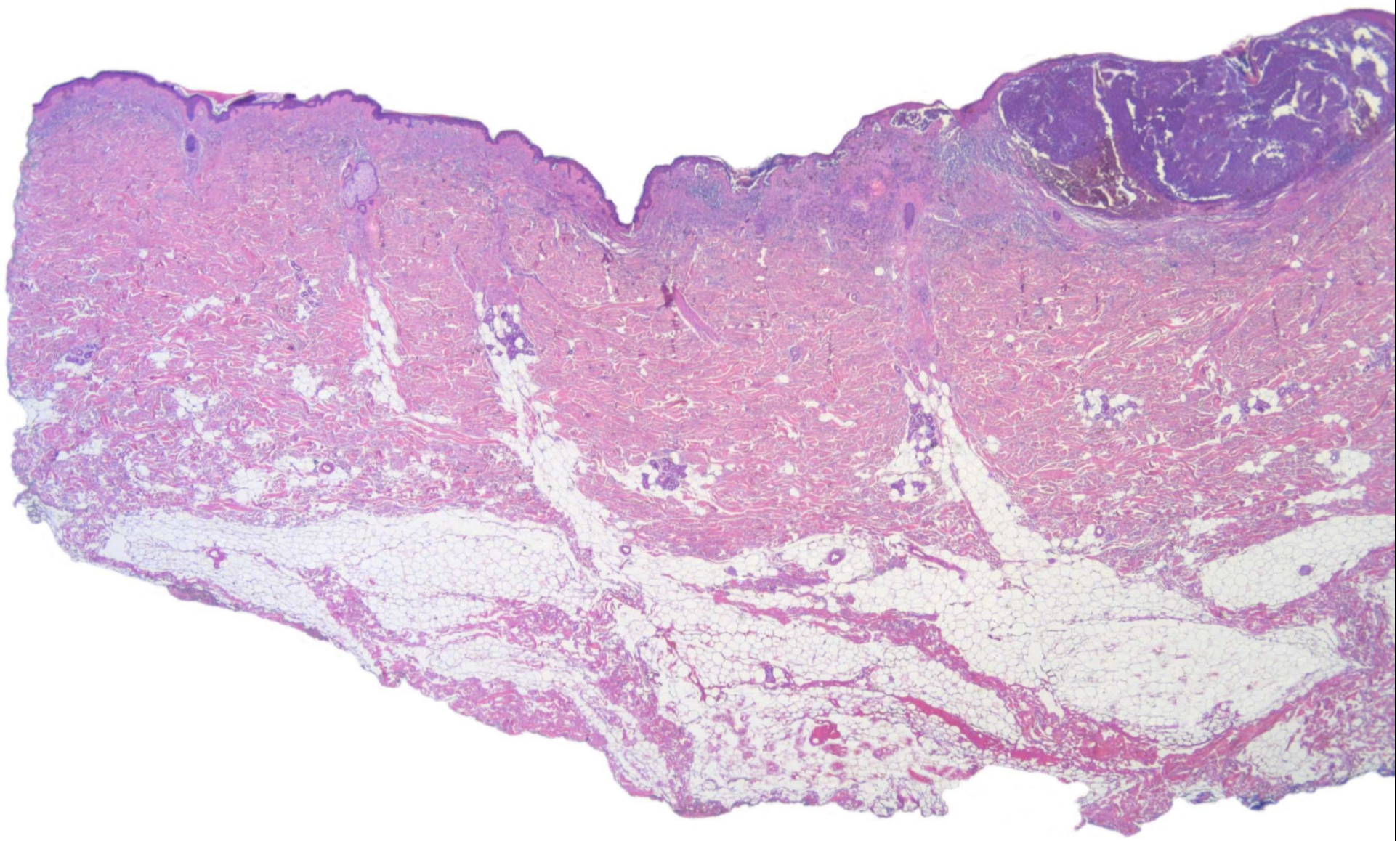




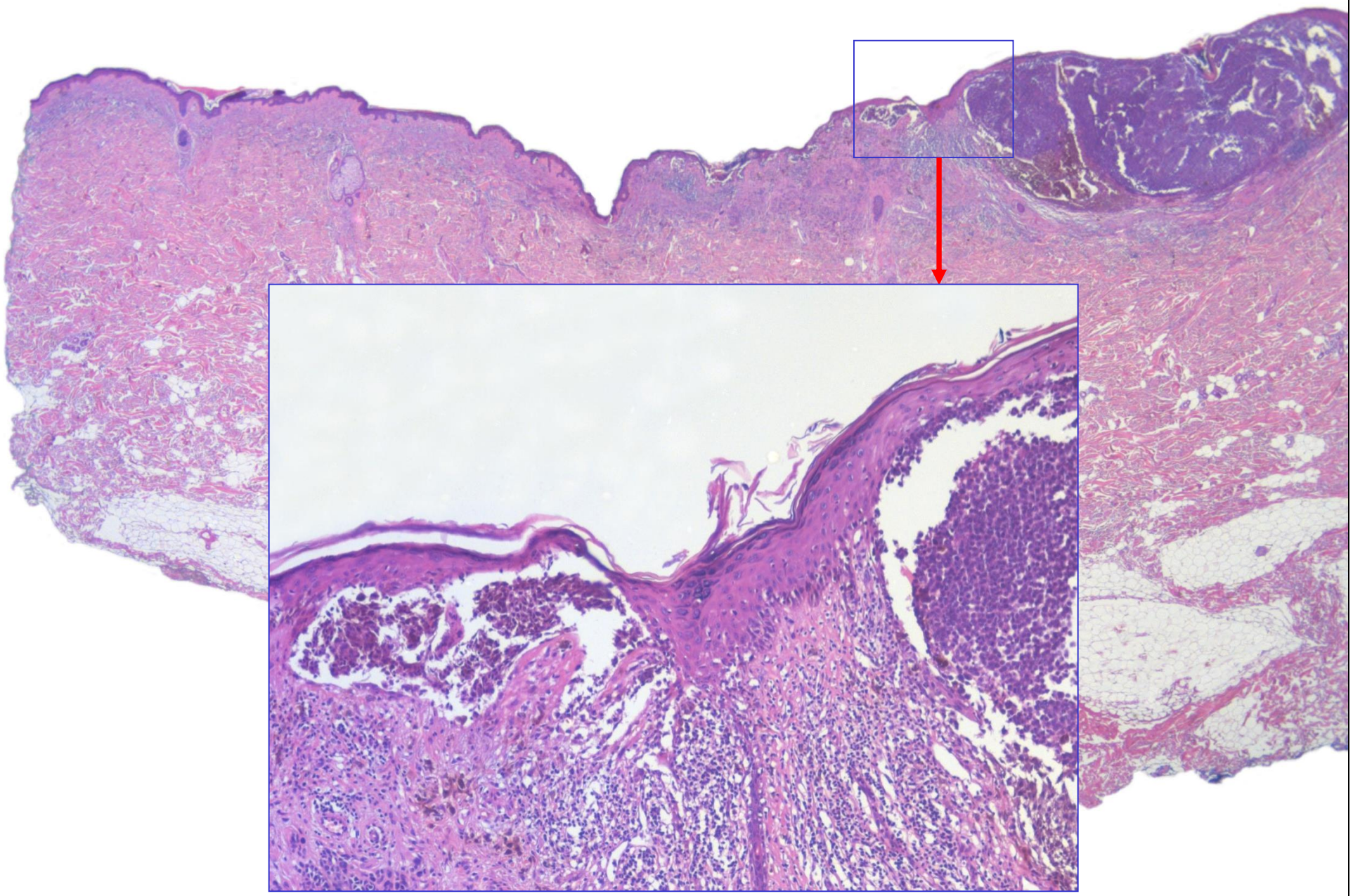
and can be confirmed readily by histopathologic examination. The changes seen in early in-situ lesions



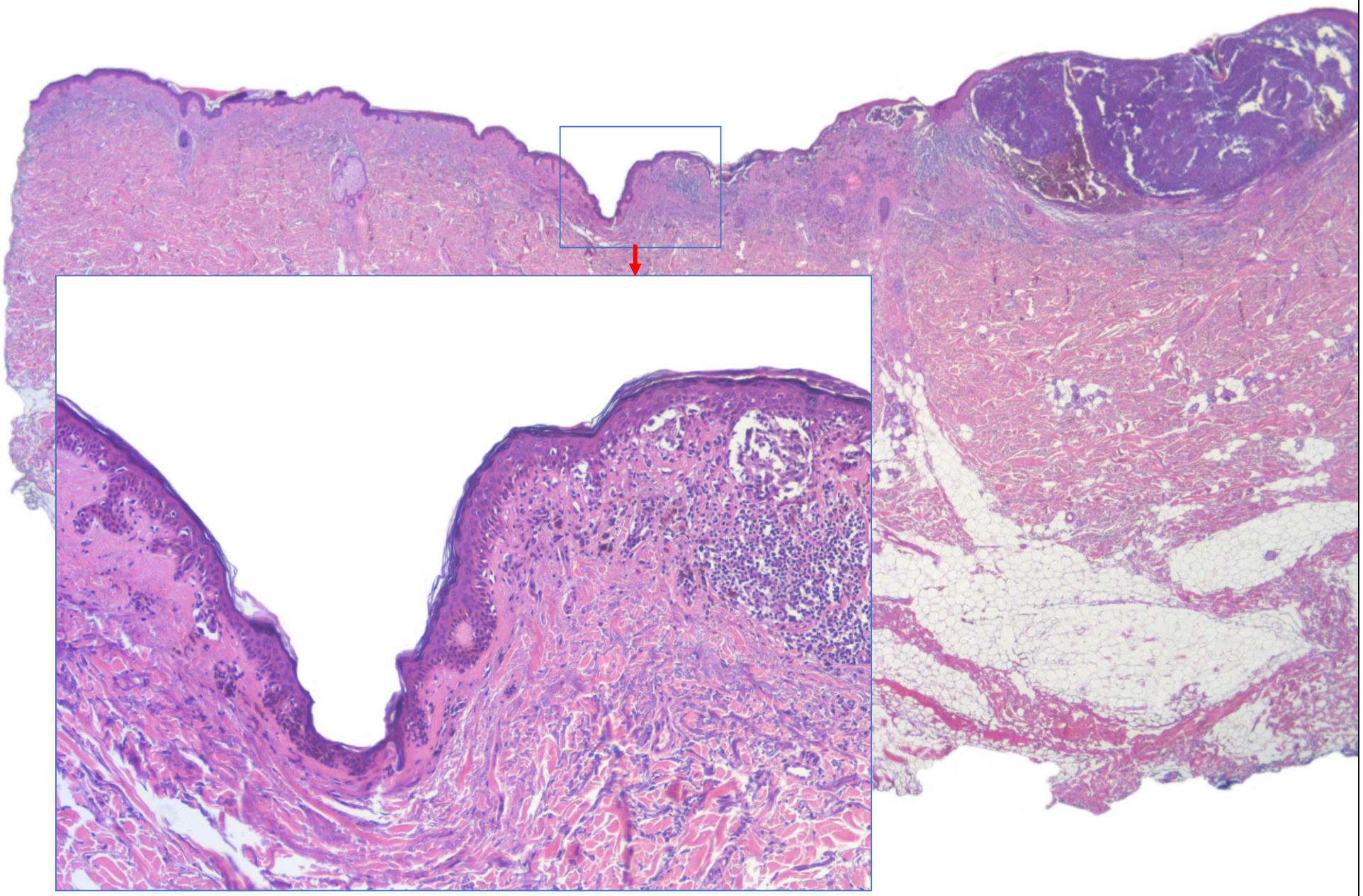
are the same as those at the edge of more advanced lesions, such as signs of solar keratosis with sparing of adnexal structures at the edge of this infiltrating squamous-cell carcinoma.



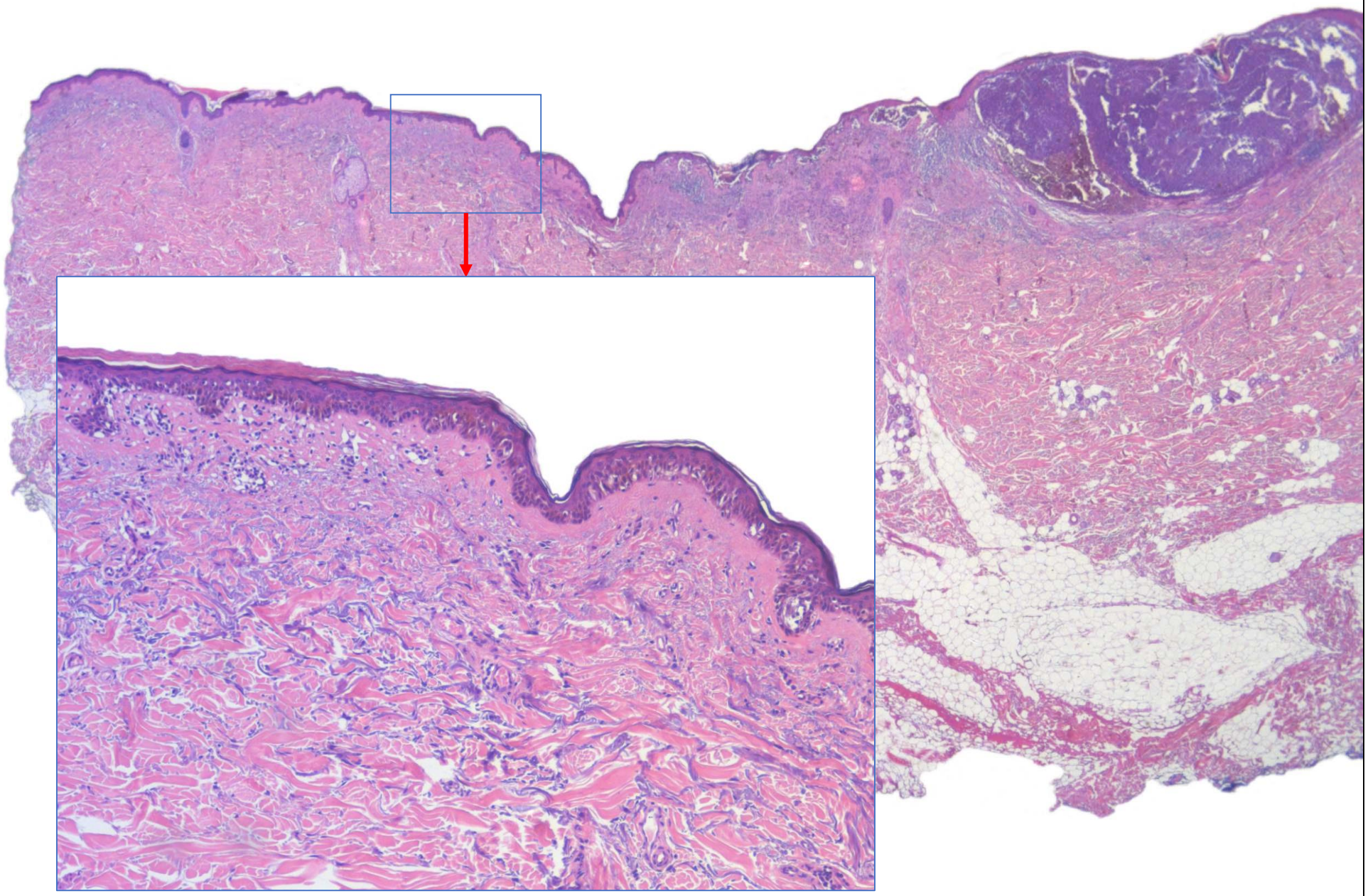
Likewise, the edge of this advanced melanoma reveals findings at progressively earlier stages when moving from the nodule to the periphery.



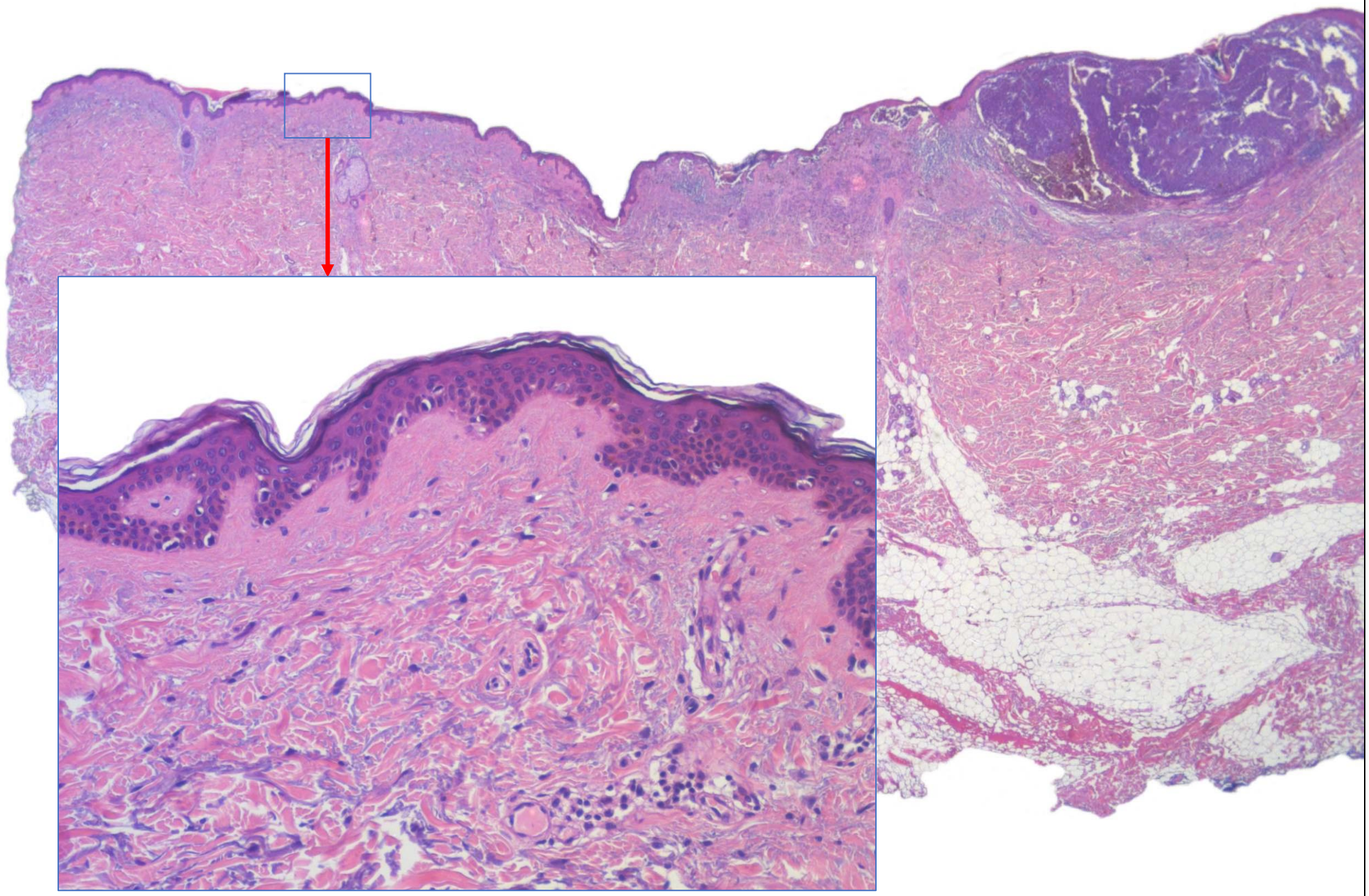
All those features – nests that are large, confluent and irregularly shaped,



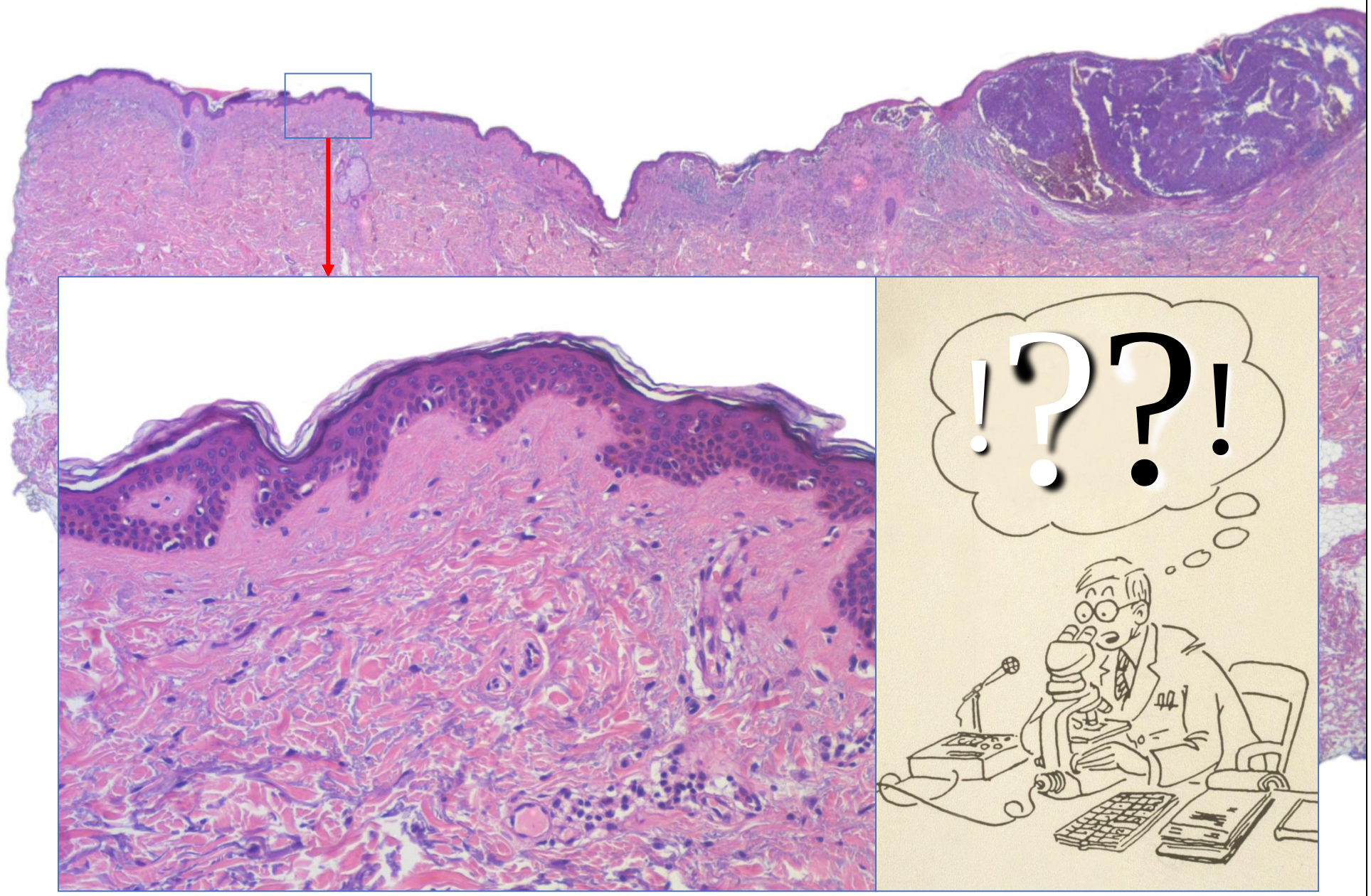
nests varying markedly in distance from one another, single melanocytes predominating over nests,



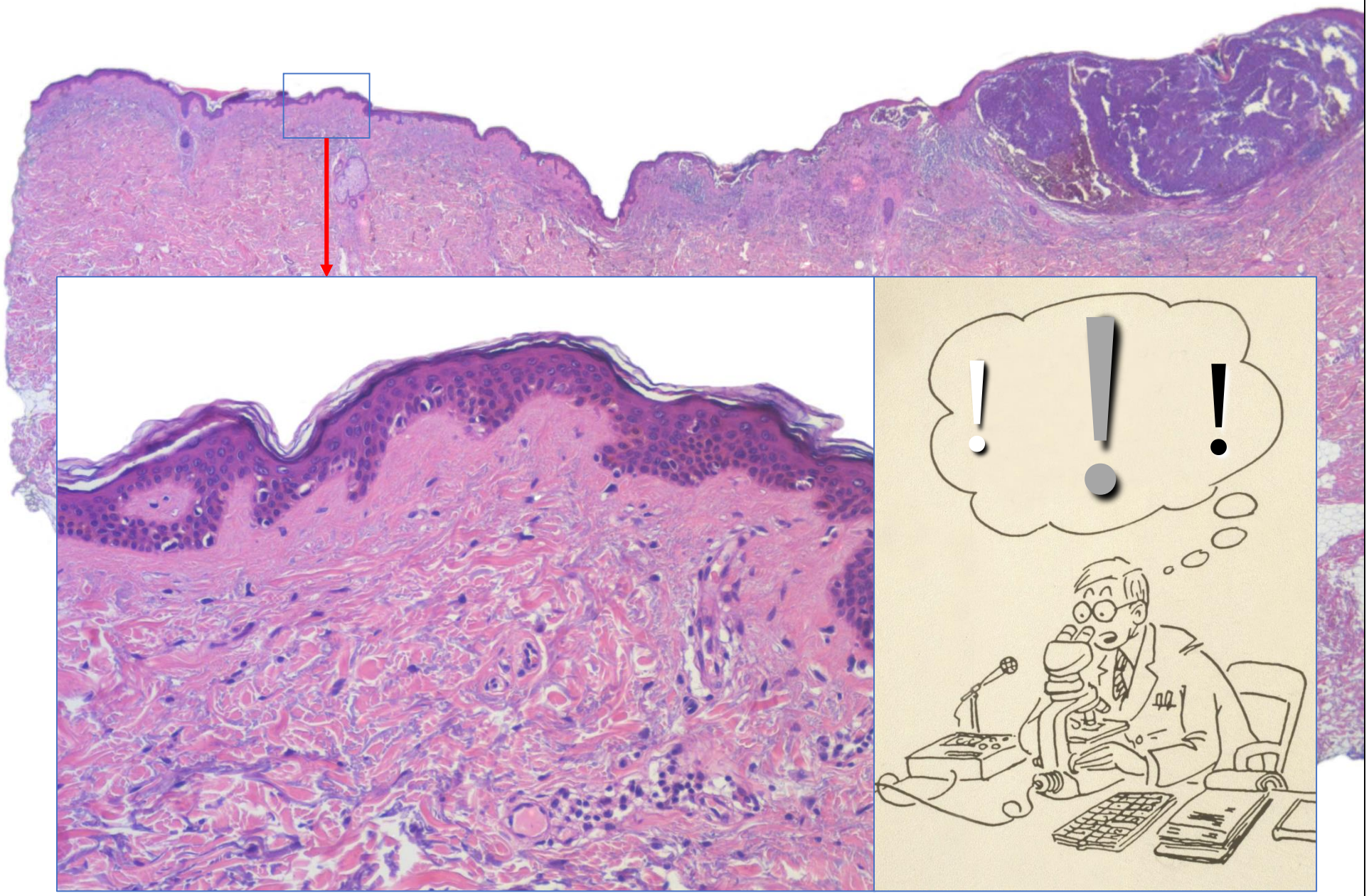
melanocytes in the upper reaches of the epidermis – distinguish melanoma from a nevus and still allow a definite diagnosis to be made until, eventually,



a stage is reached in which one simply cannot be sure, and a distinction between benign and malignant,



white and black, cannot be made with certainty. Those limitations in diagnostic acumen should be acknowledged forthrightly, but pathologists do not like to do that. Instead, they make believe that the diagnosis is clear and that the uncertainty rests with the lesion. They claim that the latter is neither black nor white



but grey, that it is borderline not only morphologically, but also biologically, and they refer to it by non-specific terms that start off as a description but eventually come to be regarded as a diagnosis.

A SURVEY OF THE ACTUALITIES AND POTENTIALITIES OF EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS *

By George N. Papanicolaou, M.D., *New York, N. Y.*

In 1925, when for the first time I had occasion to discuss with the late Dr. James Ewing, then Professor of Pathology in our School at Cornell, the possibility of using the vaginal smear as an aid in the diagnosis of uterine cancer, he asked me whether this method could be applied to endometrial as well as to cervical carcinomas. It was his opinion that such a method might prove to be of greater value in the diagnosis of adenocarcinomas of the endometrium than in carcinomas of the cervix, for which everyone would most likely resort to the well established and more dependable method of biopsy.

At that time my knowledge of the cytologic method was very limited and I was in no position to state whether a differential diagnosis between carcinomas of the cervix and adenocarcinomas of the fundus on a cytologic basis was possible. Nor did I know then that the diagnosis of carcinomas of the cervix by the smear method would be possible at an early asymptomatic stage, making it useful in detecting unsuspected lesions, which might still be invisible.

Now that the method has been tested by general use over a number of years our knowledge has been advanced to a point where we are able to differentiate with a fair degree of accuracy between lesions affecting different parts of the female genital tract, as well as between various cell types and smear patterns. We are now in a position to make a clearer distinction between the squamous cell type carcinomas of the cervix and the adenocarcinomas of the endometrium, in which the abnormal cells are of the glandular type. It is even possible at times to make a differentiation between an adenocarcinoma of the endometrium and one of the cervix, in which the abnormal cells are of the endocervical type.

Metaplasias of the endocervix and of the endometrium may also be recognized occasionally when clusters of endocervical or endometrial cells are present, in which some of the cells show a change toward the parabasal squamous type. In metaplasia of the endometrium one often encounters rosette-like clusters of cells in which there is marked enlargement and vacuolization of some of the more peripherally located cells. Endocervical or endometrial polypoid hyperplasias may be revealed by small polypoid fragments of the endocervical or endometrial mucosa found in endocervical or endometrial smears.

* Presented as a Morning Lecture, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 30, 1949.
The original work referred to in this paper has been aided by the Commonwealth Fund and by the National Cancer Institute.
From Cornell University Medical College.

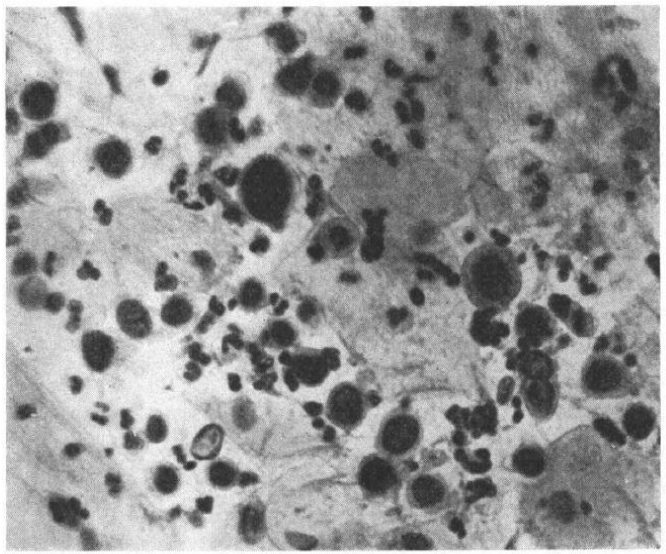


Fig. 3, *b*. Cervical parabasal cells characteristic of parabasal cell dyskaryosis. × 400.

The term "intermediate or navicular cell dyskaryosis" is used to indicate the prevalence of abnormal cells deriving from the intermediate or navicular zone (figures 2a, 2b). This type of dyskaryosis is rather rare and thus far we have had only two clear-cut cases of it.

An example is the term "dysplasia" that was introduced by Papanicolaou in 1949. When studying cervical smears for signs of cancer, he had to deal with cases not unequivocally diagnostic,

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G.N. Papanicolaou,
Ann Intern Med 1949; 31: 661-674.

and *“the term ‘dysplasia’ was proposed to specify such cytologic changes as would be suggestive of but not conclusive for malignancy.”* In other words, the term “dysplasia” was used as a synonym for “I don’t know.” Although not defined morphologically, it was embraced by pathologists as an astute method to conceal uncertainty

DYSPLASIA OF THE UTERINE CERVIX

Incidence of Regression, Recurrence, and Cancer

ELIZABETH STERN, M.D.,* AND PETER M. NEELY, PH.D.†

DYSPLASIA OF THE CERVIX IS A LESION THAT is morphologically similar to cancer in

very few were found in the much larger fraction of the population who had not shown
ia. Further, individuals with dysplasia
cervix detected during mass screening
ncer and then kept under observation
uted a high-risk group for cervical
6

Carcinoma-in-situ and Dysplasia of the Cervix *

LAMAN A. GRAY, M.D., MALCOLM L. BARNES, M.D., JOSEPH J. LEE, M.D.**

From the Department of Obstetrics and Gynecology, and Department of Pathology, University of Louisville, School of Medicine, and Norton Memorial Infirmary, Louisville, Kentucky

SINCE 1896 atypical changes in the squamous epithelium of the cervix uteri have been noted, and precancerous lesions have been discussed at length.[2] Schottländer and Kermauner[8] in 1912, described surface cancer surrounding invasive squamous cell carcinoma of the cervix as *Oberflächenbelag* or *Randbelag*. Rubin,[6] a student of Schottländer, in 1910, described three cases of incipient carcinoma of the cervix. The first two evidently represented the present day concept of carcinoma-in-situ with gland invasion. Schiller[7] in 1927, described beginning or noninvasive carcinoma of the cervix, and developed his iodine test in 1928 which indicates non-glycogen-containing areas for biopsy. Broders[1] introduced the term *carcinoma-in-situ* in 1932. In 1934, Schiller visited this country and stimulated Novak and many others. In that

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Received for publication Sept. 24, 1963.

OBSTETRICS and GYNECOLOGY *Journal of*

THE AMERICAN COLLEGE OF OBSTETRICIANS and GYNECOLOGISTS

Volume 38 December 1971 Number 6

Diagnosis and Prognosis of Cervical Dysplasia

UMBERTO VILLA SANTA, MD, FACOG

serve cells characteristic of dysplasia.
Study of the pattern of variability in a

and came to be accepted as a diagnosis, the "diagnosis of cervical dysplasia." Of course, "dysplasia" could not be distinguished from incipient carcinoma because it was carcinoma in most cases.

J Clin Pathol 1982;**35**:1-13

Review article

Cervical intraepithelial neoplasia

CH BUCKLEY, EB BUTLER, H FOX

From the Departments of Pathology, University of Manchester and St Mary's Hospital, Manchester

SUMMARY The theoretical and practical reasons for replacing the terms "cervical dysplasia" and "cervical carcinoma in situ" by the single diagnostic entity of "cervical intraepithelial neoplasia" are reviewed and the advantages and drawbacks of this newer terminology discussed. The histological characteristics and cytological features of the various grades of cervical intraepithelial neoplasia are described and the differential diagnosis of this lesion is considered.

In 1969 Govan and his colleagues gave a detailed account of the classification, nomenclature, histological features, and cytological characteristics of those various abnormalities of cervical squamous epithelium which fall short of a frankly invasive carcinoma.[1] This paper has served well as a guideline, and reference text, for many pathologists and cytologists but in the intervening years our knowledge of cervical pathology has expanded and our understanding and interpretation of cervical epithelial abnormalities has altered. One result of this changing appreciation of cervical lesions has been the introduction of a new terminology: this change has been welcomed by some, but resisted by, and indeed proved unacceptable to, others, with the result that whilst some pathologists and cytologists are currently couching their reports in terms of the new nomenclature others are still using the older and better established terminology. The concurrent use of two systems of nomenclature for cervical lesions is unsatisfactory and prone to cause confusion and misunderstanding.

As advocates of the new system of terminology it is our aim in this paper to detail the conceptual and practical reasons for adopting a new nomenclature, to consider the possible objections to its use, and to redefine the histological and cytological features of abnormalities of the cervical squamous epithelium in terms of this nomenclature.

Nomenclature of cervical epithelial abnormalities

A fundamental division of cervical squamous epithelial abnormalities can be made between those which lack any potential for evolving into an invasive squamous cell carcinoma and those in which there is a significant risk of progression to an invasive neoplasm. The first group of banal changes includes such entities as basal cell hyperplasia, reserve cell hyperplasia, immature squamous metaplasia, and mature squamous metaplasia, all of which are benign, indeed usually physiological, conditions unaccompanied by any increased risk of invasive carcinoma. Epithelial abnormalities that are potentially capable of progression into an invasive neoplasm have traditionally been categorised either as dysplasia or as carcinoma in situ, dysplastic changes within the epithelium being graded as of mild, moderate, or severe degree.

The new nomenclature applies only to those cervical epithelial abnormalities associated with an increased risk of invasive carcinoma, all of which are now put into the single diagnostic category of cervical intraepithelial neoplasia (CIN).[2, 3] Three grades of abnormality are recognised: CIN I which corresponds to mild dysplasia; CIN II which is equivalent to moderate dysplasia; and CIN III which encompasses both severe dysplasia and carcinoma in situ.

REASONS FOR THE CHANGE IN NOMENCLATURE

Firstly, it has to be recognised that there has been, and still is, considerable disagreement as to the definition of both dysplasia and carcinoma in situ. Thus in 1961, an International Committee on Histological Terminology defined a carcinoma in situ as "a lesion of the epithelium in which, throughout its thickness, no differentiation takes place."[4] This was also the view taken by Govan *et al* who insisted upon complete loss of stratification and of cellular differentiation as defining criteria.[1] There is no doubt that most histopathologists accept, and rely on, this definition but Burghardt[5] has maintained that there can be no theoretical objection to the concept of a differentiated carcinoma in situ, defining this

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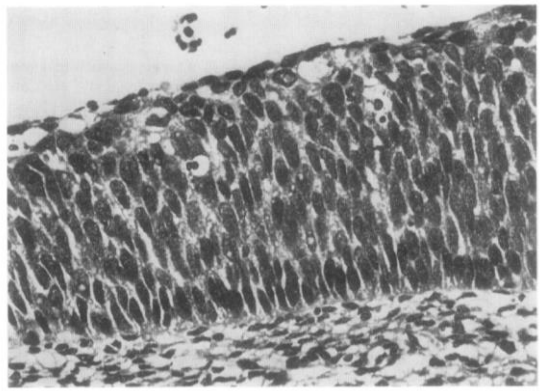

Fig. 3 *CIN III: undifferentiated cells of basaloid type occupy almost the full thickness of the epithelium. The constituent cells in this example are somewhat spindle-shaped. Haematoxylin and eosin × 350.*

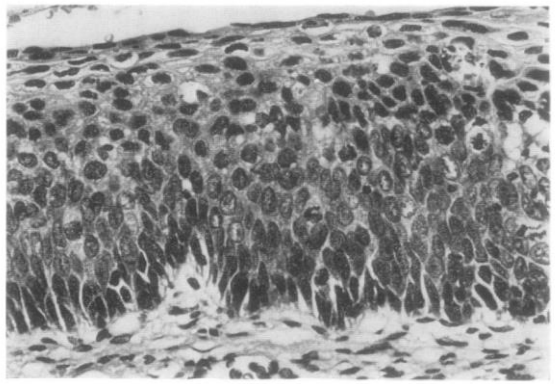

Fig. 2 *Squamous epithelium showing CIN II. Undifferentiated cells occupy less than two-thirds of the epithelial structure. Haematoxylin and eosin × 350.*

All cases of "dysplasia" …, irrespective of grade, [belong to] a spectrum of intraepithelial change which begins as a generally well differentiated neoplasm … and ends with invasive carcinoma.

All cases of CIN should be regarded as a single entity.

The identity led to the introduction of a new term, "cervical intraepithelial neoplasia," that was meant to replace *"the terms 'cervical dysplasia' and 'cervical carcinoma in situ' by a single diagnostic entity."* The authors emphasized that *"all cases of "dysplasia …, irrespective of grade, [belong to] a spectrum of intraepithelial change which begins as a generally well differentiated neoplasm … and ends with invasive carcinoma,"* and that *"all cases of CIN should be regarded as a single entity."* They did not explain, however, why they proposed a new term instead of simply referring to all cases as incipient carcinoma.

J Clin Pathol 1982;**35**:1-13

Review article

Cervical intraepithelial neoplasia

CH BUCKLEY, EB BUTLER, H FOX

From the Departments of Pathology, University of Manchester and St Mary's Hospital, Manchester

SUMMARY The theoretical and practical reasons for replacing the terms "cervical dysplasia" and "cervical carcinoma in situ" by the single diagnostic entity of "cervical intraepithelial neoplasia" are reviewed and the advantages and drawbacks of this newer terminology discussed. The histological characteristics and cytological features of the various grades of cervical intraepithelial neoplasia are described and the differential diagnosis of this lesion is considered.

In 1969 Govan and his colleagues gave a detailed account of the classification, nomenclature, histological features, and cytological characteristics of those various abnormalities of cervical squamous epithelium which fall short of a frankly invasive carcinoma.[1] This paper has served well as a guideline, and reference text, for many pathologists and cytologists but in the intervening years our knowledge of cervical pathology has expanded and our understanding and interpretation of cervical epithelial abnormalities has altered. One result of this changing appreciation of cervical lesions has been the introduction of a new terminology: this change has been welcomed by some, but resisted by, and indeed proved unacceptable to, others, with the result that whilst some pathologists and cytologists are currently couching their reports in terms of the new nomenclature others are still using the older and better established terminology. The concurrent use of two systems of nomenclature for cervical lesions is unsatisfactory and prone to cause confusion and misunderstanding.

As advocates of the new system of terminology it is our aim in this paper to detail the conceptual and practical reasons for adopting a new nomenclature, to consider the possible objections to its use, and to redefine the histological and cytological features of abnormalities of the cervical squamous epithelium in terms of this nomenclature.

Nomenclature of cervical epithelial abnormalities

A fundamental division of cervical squamous epithelial abnormalities can be made between those which lack any potential for evolving into an invasive squamous cell carcinoma and those in which there is a significant risk of progression to an invasive neoplasm. The first group of banal changes includes such entities as basal cell hyperplasia, reserve cell hyperplasia, immature squamous metaplasia, and mature squamous metaplasia, all of which are benign, indeed usually physiological, conditions unaccompanied by any increased risk of invasive carcinoma. Epithelial abnormalities that are potentially capable of progression into an invasive neoplasm have traditionally been categorised either as dysplasia or as carcinoma in situ, dysplastic changes within the epithelium being graded as of mild, moderate, or severe degree.

Accepted for publication 20 July 1981

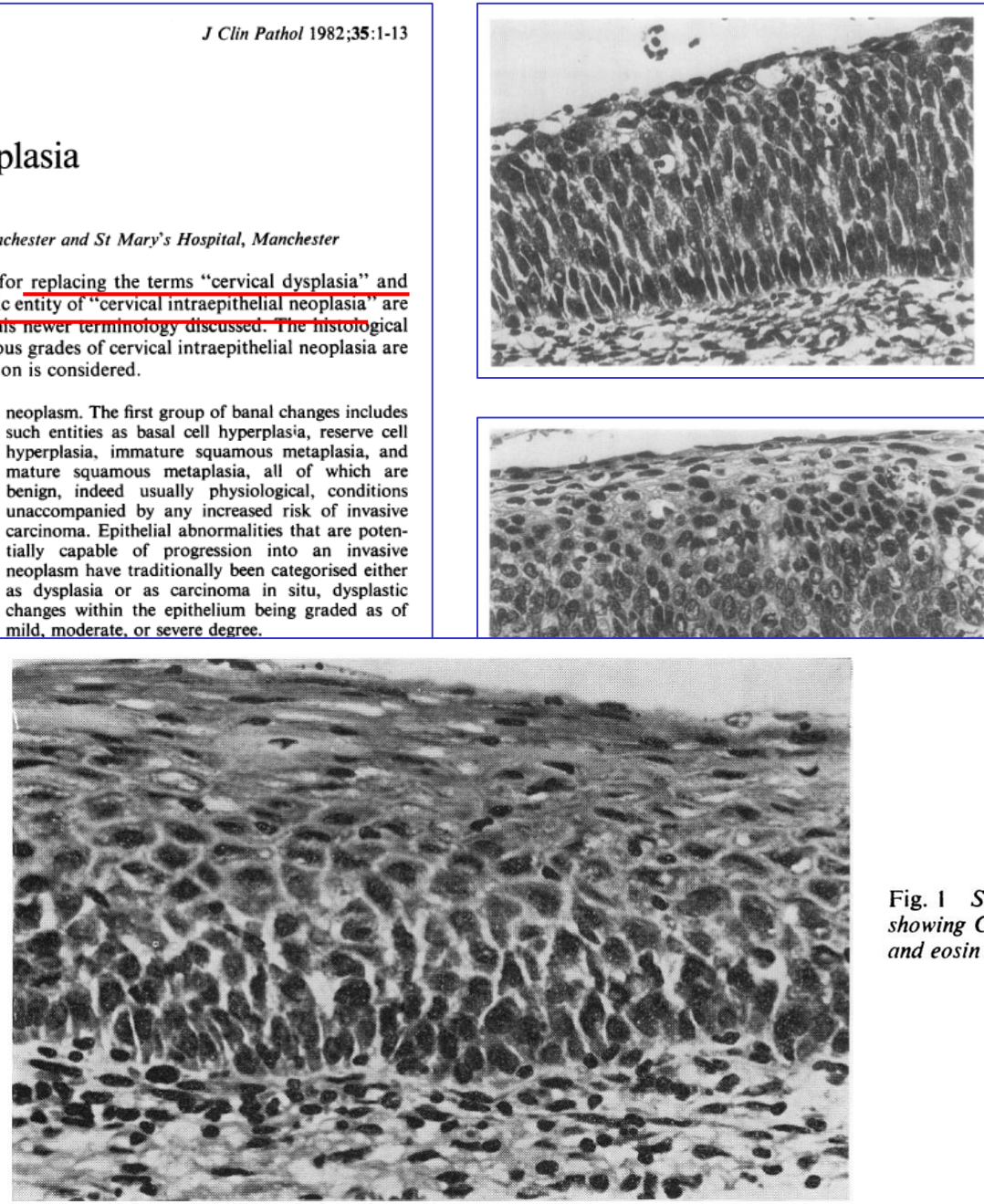

Fig. 1 *Squamous epithelium showing CIN I. Haematoxylin and eosin × 350*

Fig. 3 *CIN III: undifferentiated cells of basaloid type occupy almost the full thickness of the epithelium. The constituent cells in this example are somewhat spindle-shaped. Haematoxylin and eosin × 350.*

Fig. 2 *Squamous epithelium showing CIN II. Undifferentiated cells occupy less than two-thirds of the epithelial structure. Haematoxylin and eosin × 350.*

The tacit, yet obvious, reason was diagnostic uncertainty in regard to incipient changes designated as CIN 1 that could not be distinguished clearly from a reactive process. The authors faced a dilemma. On the one hand, they were aware that they were dealing with a single entity at different stages of development, and on the other hand, they hesitated to refer to incipient changes as "carcinoma in situ." Instead of acknowledging uncertainty, they resorted to the evasive designation of "cervical intraepithelial neoplasia."

That strategy was adopted for other organs, such as the prostate, stomach, and skin. However, because of dealing with a single process,

Prostate Cancer

High-Grade Prostatic Intraepithelial Neoplasia on a Prostate Biopsy—What Does It Mean?

Reviewed by Alan W. Partin, MD, PhD

Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD

[*Rev Urol.* 2002;4(3):157–158]

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EDITORIAL

Treatment strategy for gastric non-invasive intraepithelial neoplasia diagnosed by endoscopic biopsy

Tsutomu Nishida, Shusaku Tsutsui, Motohiko Kato, Takuya Inoue, Shunsuke Yamamoto, Yoshito Hayashi,

Aneuploidy and proliferation in keratinocytic intraepidermal neoplasias

Tim Smits[1], Diana Olthuis[1], Willeke A. M. Blokx[2], Marloes M. Kleinpenning[1], Peter C. M. van de Kerkhof[1] Piet E. J. van Erp[1] and Marie-Jeanne P. Gerritsen[1]

Departments of [1]Dermatology and [2]Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
Correspondence: T. Smits, MD, Department of Dermatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmeg
The Netherlands, Tel.: +31 24 3613724, Fax: +31 24 3541184, e-mail: t.smits@derma.umcn.nl

Accepted for publication 8 September 2006

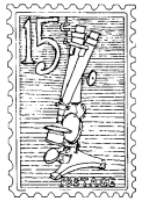
Abstract: Cutaneous squamous (pre)malignancies can be classified according to the keratinocytic intraepidermal neoplasia (KIN) classification. Aneuploidy can be seen as the result of chromosomal aberrations leading to altered DNA content and has been strongly associated with malignancy. Hyperproliferation is also strongly associated with tumorigenesis. The aim of the study was to analyse the presence and the amount of aneuploidy and proliferation in the progression from intraepithelial neoplasm to microinvasive carcinoma (miSCC). For this purpose, nuclei were isolated from 116 formalin-fixed KIN lesions from 68 patients in which DNA content was measured by flow cytometry. Proliferation was assessed by immunohistochemical staining for Ki67 as well as by flow cytometry. Aneuploidy was increasingly found in higher KIN lesions, but not in normal skin. However, in miSCC aneuploidy was relatively less frequently found. DN indices (mean ± SE) of KIN III-lesions (1.57 ± 0.05) were significantly lower compared with KIN I/II lesions (1.71 ± Ki67 expression was strongly positively correlated with KIN and proved to be a good adjunct in the classification of KI Thus, aneuploidy occurred more frequently in higher KIN indicating cumulative damage during KIN progression. Th frequency of aneuploidy in miSCC compared with KIN III point at alternative routes towards invasive carcinoma besi serial progression through all three KIN stages. Ki67 expres appears a valuable marker in the classification of KINs.

Key words: actinic keratosis – aneuploidy – Bowen's disea KIN – proliferation

Please cite this paper as: Aneuploidy and proliferation in keratinocytic intraepidermal neoplasias. Experimental Dermatology 2007; 16: 81–86.

The American Journal of Dermatopathology 9(1): 80–83, 1987

Letters to the Editor



Intraepithelial Melanocytic Neoplasia: A Classification by Pattern Analysis of Proliferations of Atypical Melanocytes

To the Editor:

The difficulty in classifying intraepithelial proliferations of atypical melanocytes is reflected in the confusing array of diagnostic terms used to describe them. When experts use names like atypical melanocytic hyperplasia, melanocytic dysplasia, active junctional nevus, and melanoma in situ, not only do they mean different things, but they often cannot agree on specific diagnoses (i.e., melanocytic nevi or malignant melanomas) (1).

Suggestions have been made for better methods of classification (2), but they have not included specific criteria for diagnosis. I propose here a simple classification for intraepithelial melanocytic proliferations of atypical melanocytes using pattern analysis, analogous to that already in use for cervical neoplasia, namely, intraepithelial melanocytic neoplasia (IMN).

This classification does not imply all malignant melanomas must progress from IMN-I through IMN-III in preparation for descent into the dermis, although this may often be the case. IMN-I, IMN-II, and IMN-III should be treated by simple conservative adequate excisions.

Dermatologists and pathologists are urged to adopt this classification because: (a) It is easy to use; (b) it avoids imprecise terms like "melanocytic dysplasia," "active junctional nevus," and "atypical melanocytic hyperplasia"; (c) it enables circumvention of the term "melanoma in situ," yet communicates the same information (i.e., IMN-III).

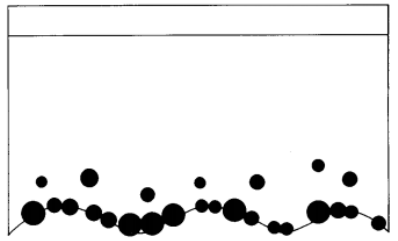


FIG. 2. In IMN-II, atypical melanocytes are present singly and in nests at the dermal–epidermal junction and within the lower one-third of the epithelium.

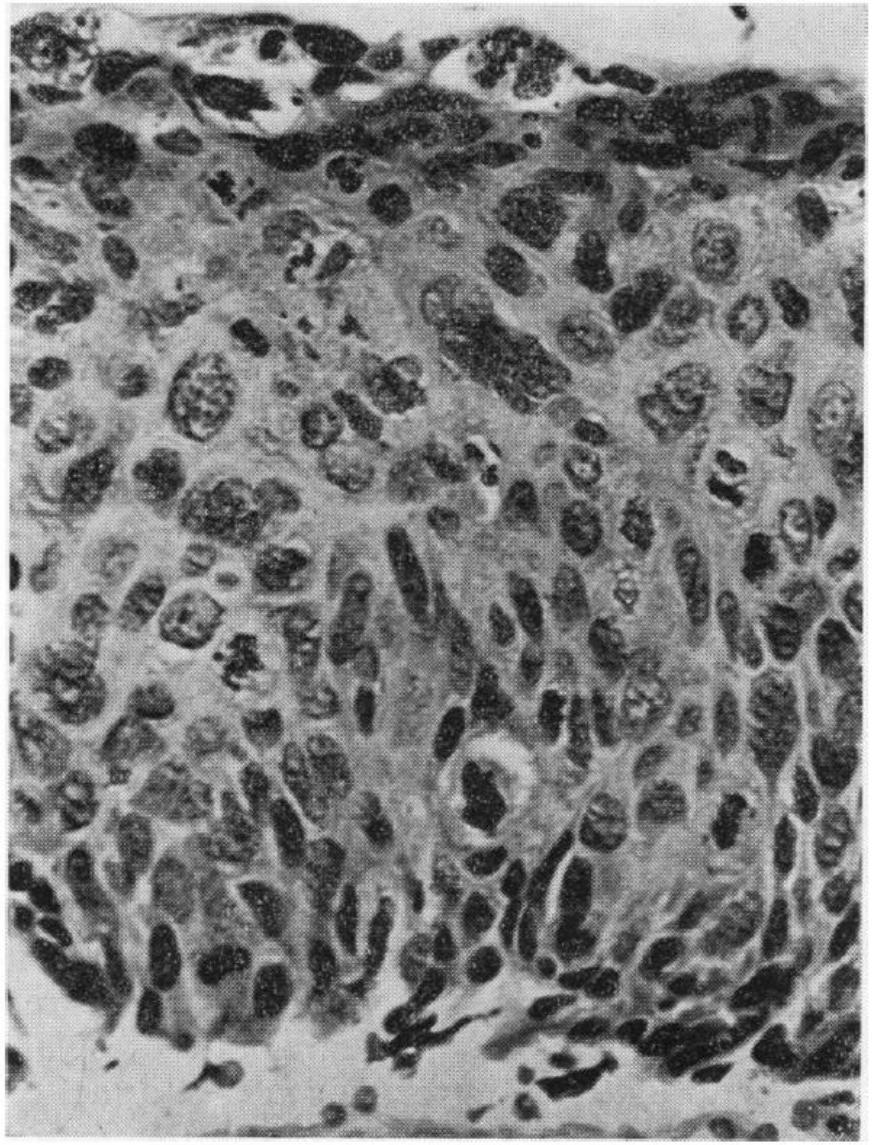


Fig. 5 *CIN III showing cytoplasmic maturation but a total lack of stratification; mitoses occur at all levels in the epithelium. Haematoxylin and eosin × 350.*

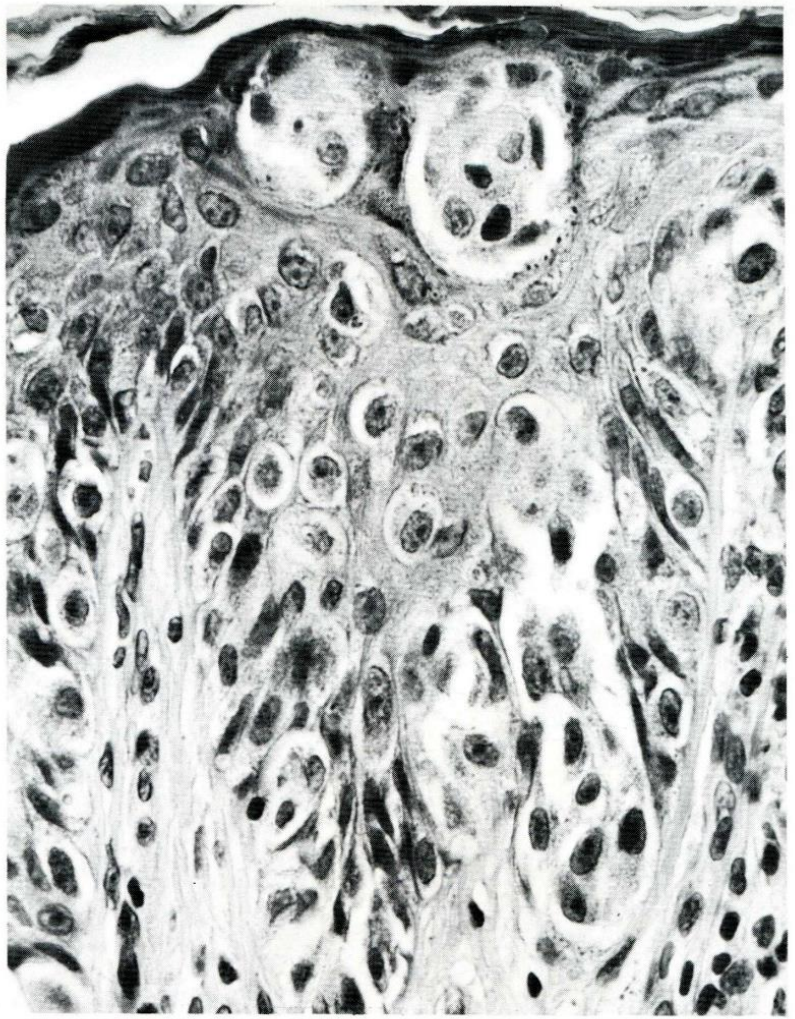


FIGURE 12. In this melanocytic dysplasia, the lesion in a small area shows a moderately severe dysplasia with pagetoid patterns of epidermal invasion. The cells in the basal portion of the epidermis and in the elongated rete ridges are distributed in lentiginous patterns. Rounded nests of cells are present near the granular layer. If this pattern were uniformly developed in the epidermis, the lesion would qualify as superficial spreading malignant melanoma. As a focal alteration in the epidermis in a moderate melanocytic dysplasia, it qualifies as focal, severe melanocytic dysplasia.

the evasive nomenclature, be it “CIN” or “melanocytic dysplasia,” was applied not only to incipient, but also to more advanced lesions that left no doubt concerning their malignancy. Naturally, at one point, the terminology needed to be changed in order to communicate the true nature of the lesion. Because there was no better option, the point of change was said to be invasion into the dermis.

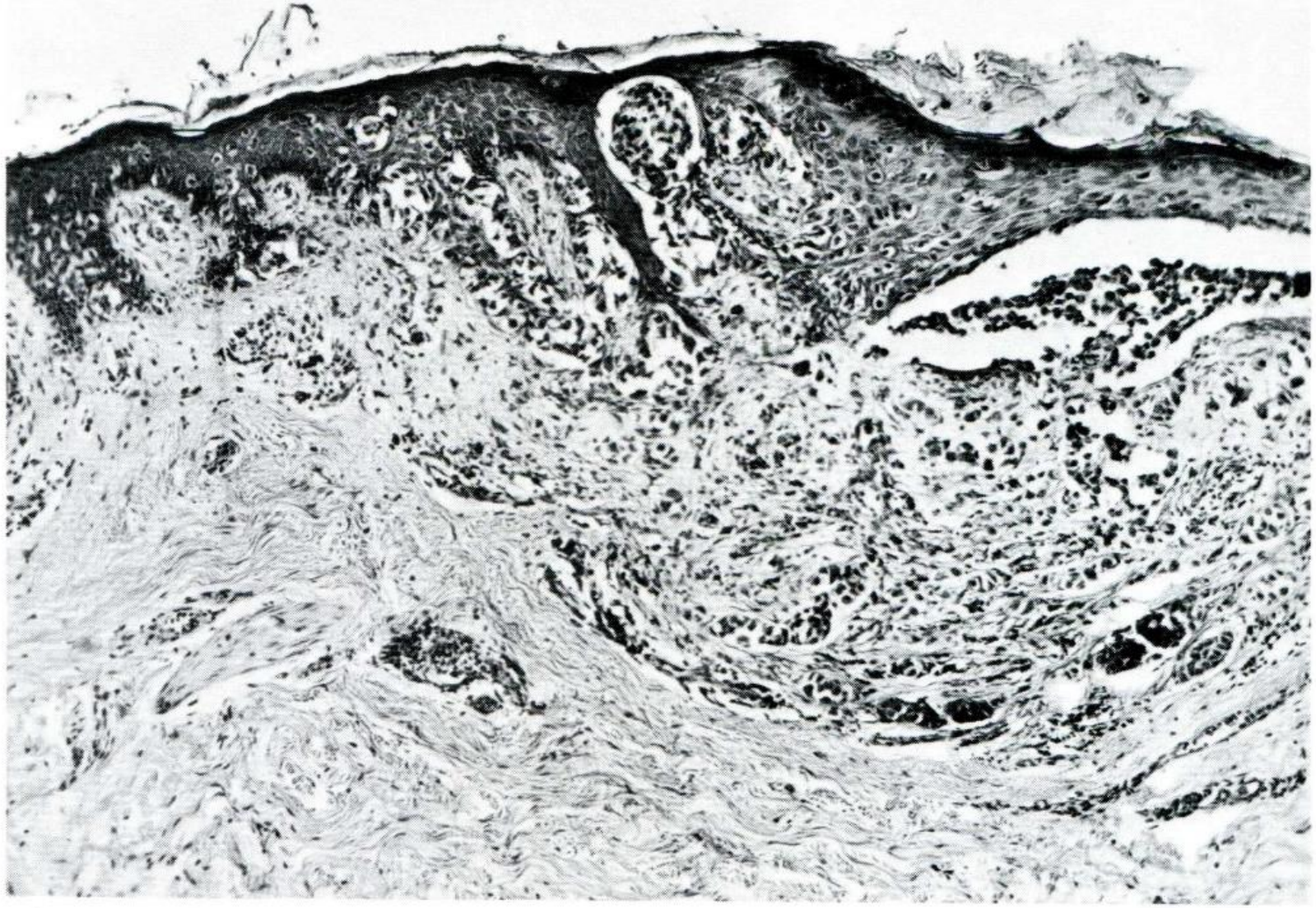


FIGURE 5. On the right, a nodule of atypical melanocytes has formed in a widened papillary dermis and a nest of comparably atypical cells is present at the dermal-epidermal interface. In the latter location, the cells show loss of cohesion. A radial growth component extends into the adjacent epidermis and shows moderate to moderately severe dysplastic changes. The nodule in the papillary dermis qualifies the lesion as an evolving malignant melanoma with thin, level III invasion. The changes in the adjacent epidermis provide a marker for a precursor melanocytic dysplasia.

Then lesions were suddenly accepted as carcinoma or melanoma, as in this example in which neoplastic cells in the epidermis and dermis are virtually identical; this is obviously one continuous process.

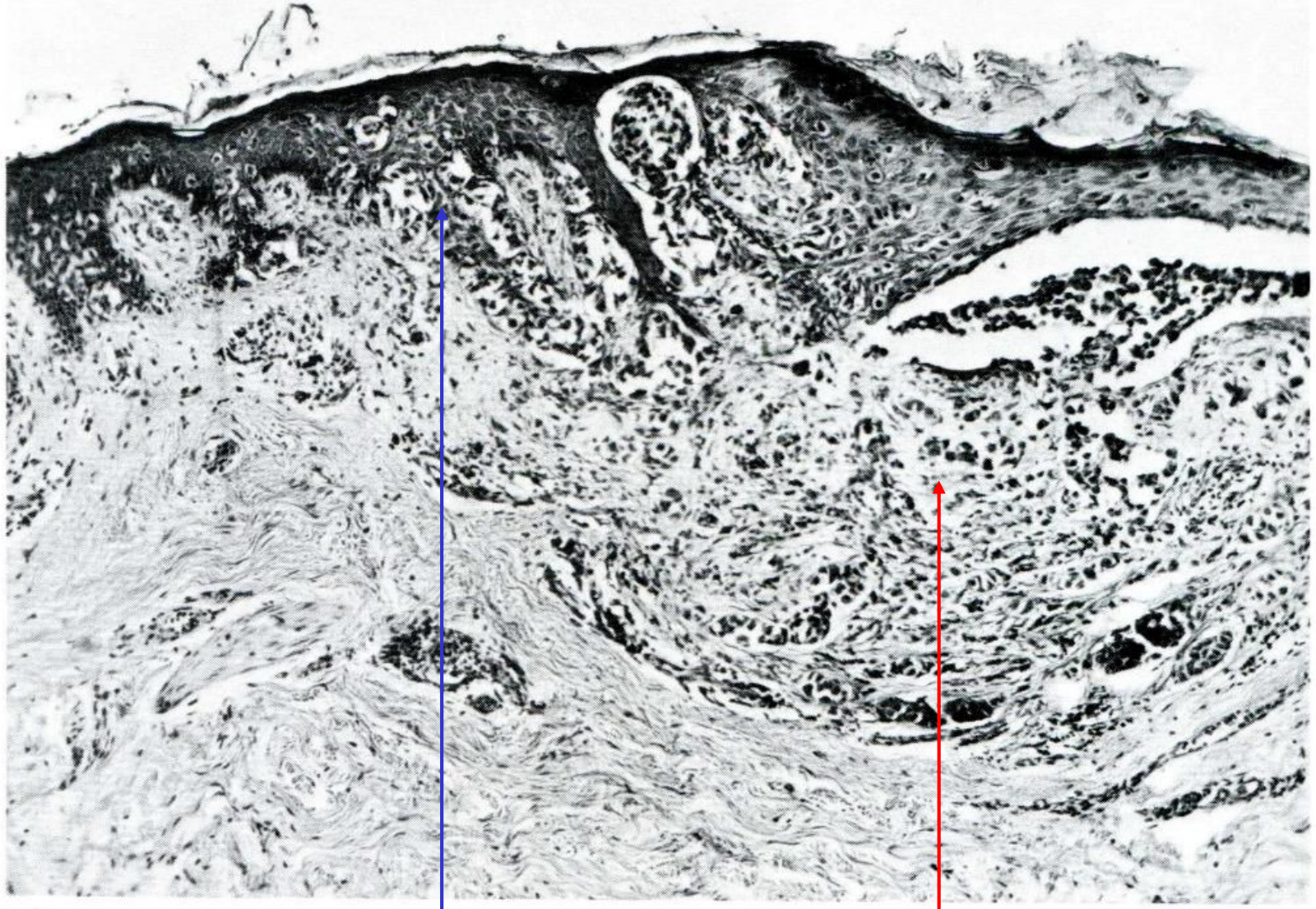
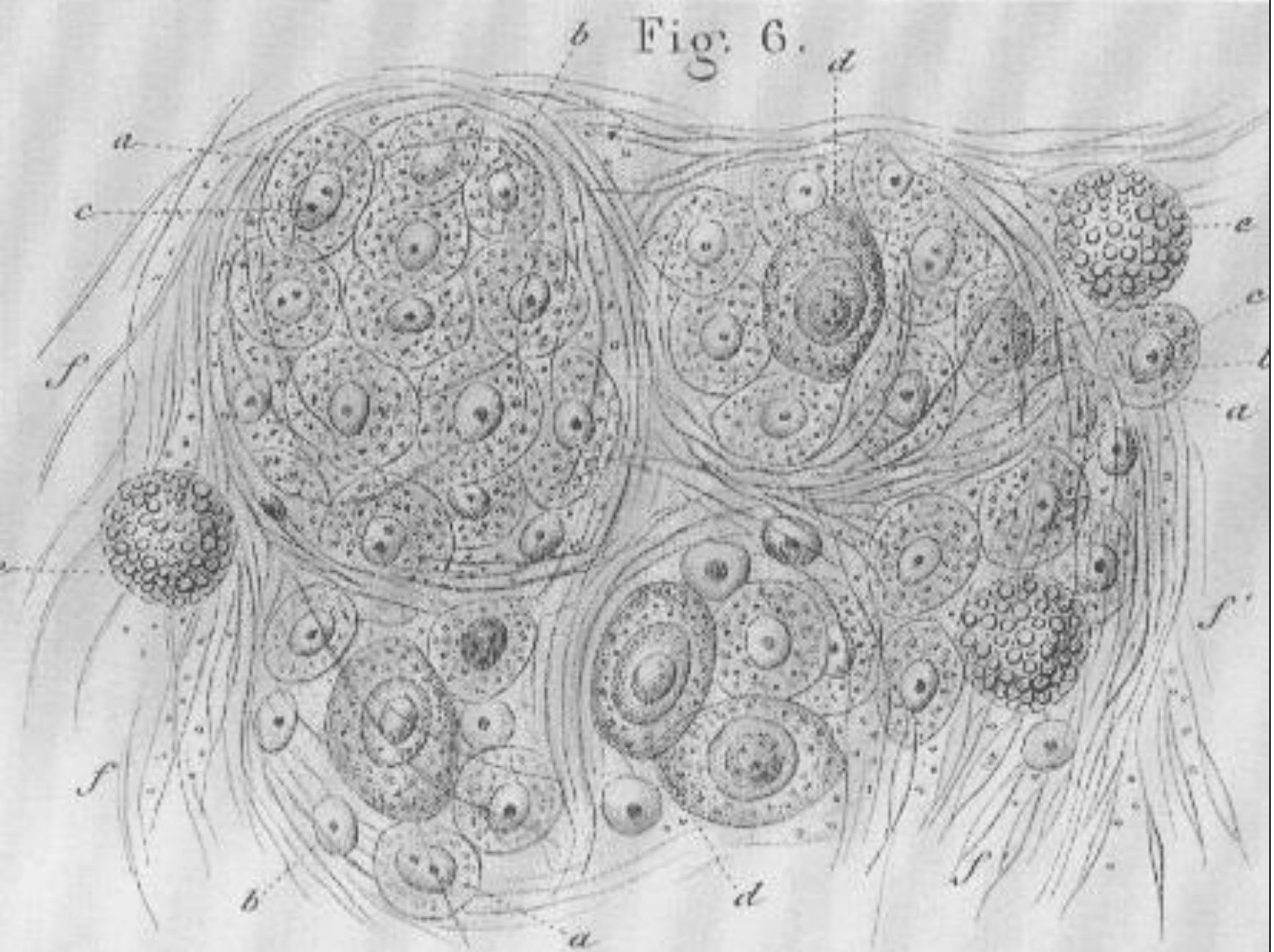


FIGURE 5. On the right, a nodule of atypical melanocytes has formed in a widened papillary dermis and a nest of comparably atypical cells is present at the dermal-epidermal interface. In the latter location, the cells show loss of cohesion. A radial growth component extends into the adjacent epidermis and shows moderate to moderately severe dysplastic changes. The nodule in the papillary dermis qualifies the lesion as an evolving malignant melanoma with thin, level III invasion. The changes in the adjacent epidermis provide a marker for a precursor melanocytic dysplasia.

Nevertheless, the authors claim that *"the nodule in the papillary dermis qualifies the lesion as an evolving malignant melanoma,"* whereas *"the changes in the adjacent epidermis"* are said to be a *"precursor melanocytic dysplasia,"* as if, with invasion, a new entity would suddenly spring into being.

This is exactly what proponents of the concept of invasion make believe: that malignancy starts in the dermis.



That concept originated in the 19th century when cancer was recognized and excised only in stages far advanced. As a consequence, pathologists saw large nodules of atypical cells in the dermis, often in the absence of changes in the surface epithelium.

Fig: 6.

The formation of cancer starts with the development of epithelium at an improper site and, therefore, proof of the impropriety of the site (heterotopia) is the first step to diagnosis.

Rudolf Virchow, 1888

Those findings prompted Rudolf Virchow to conclude that *"the formation of cancer starts with the development of epithelium at an improper site and, therefore, proof of the impropriety of the site (heterotopia) is the first step to diagnosis."*

Because of Virchow's powerful role in pathology, this concept became gospel worldwide and was defended tenaciously against all evidence accumulating against it.

DER

EPITHELIALKREBS

NAMENTLICH DER HAUT.

EINE ANATOMISCH-KLINISCHE UNTERSUCHUNG

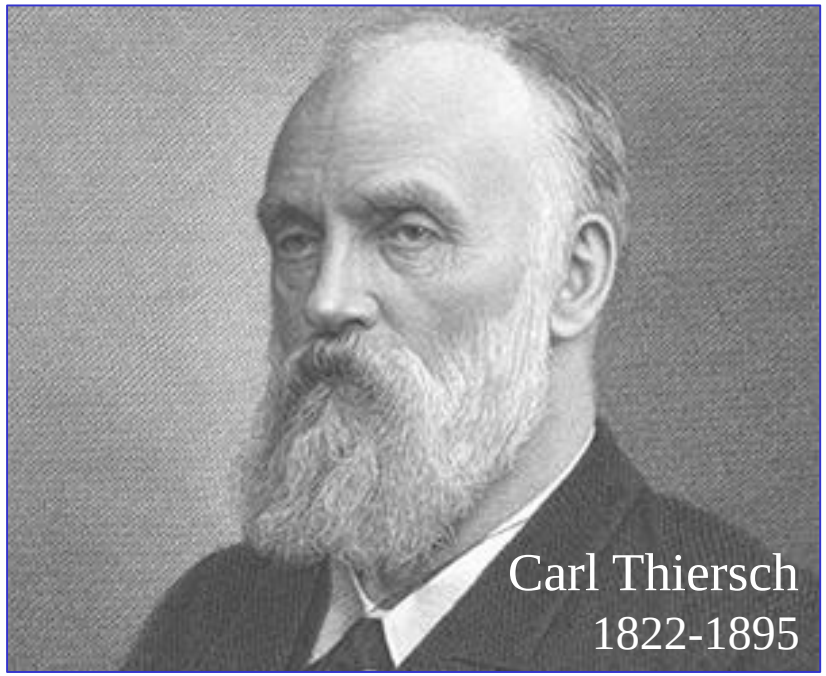
VON

DR. CARL THIERSCH,

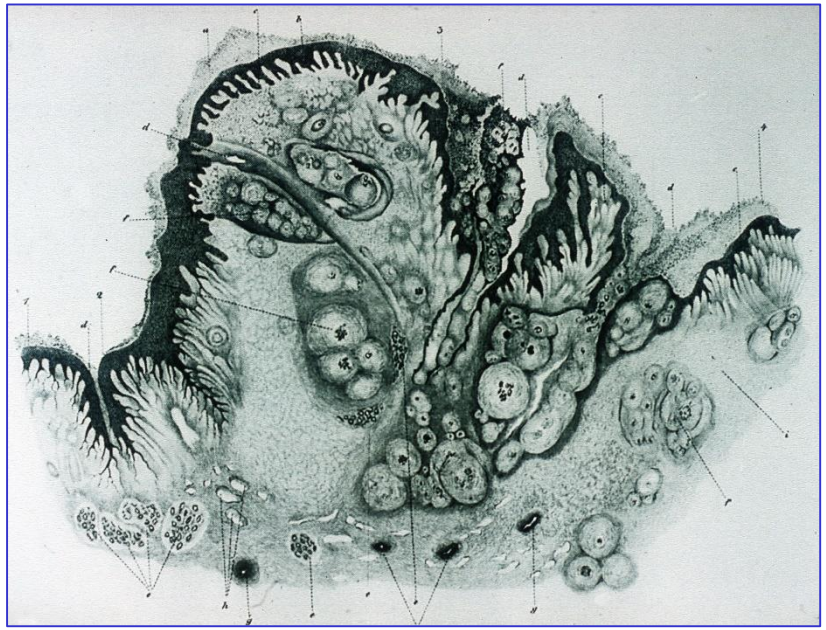
PROFESSOR DER CHIRURGIE AN DER UNIVERSITÄT ERLANGEN.

MIT EINEM ATLAS MIKROSKOPISCHER ABBILDUNGEN
VON 11 TAFELN.

LEIPZIG,
VERLAG VON WILHELM ENGELMANN.
1865.



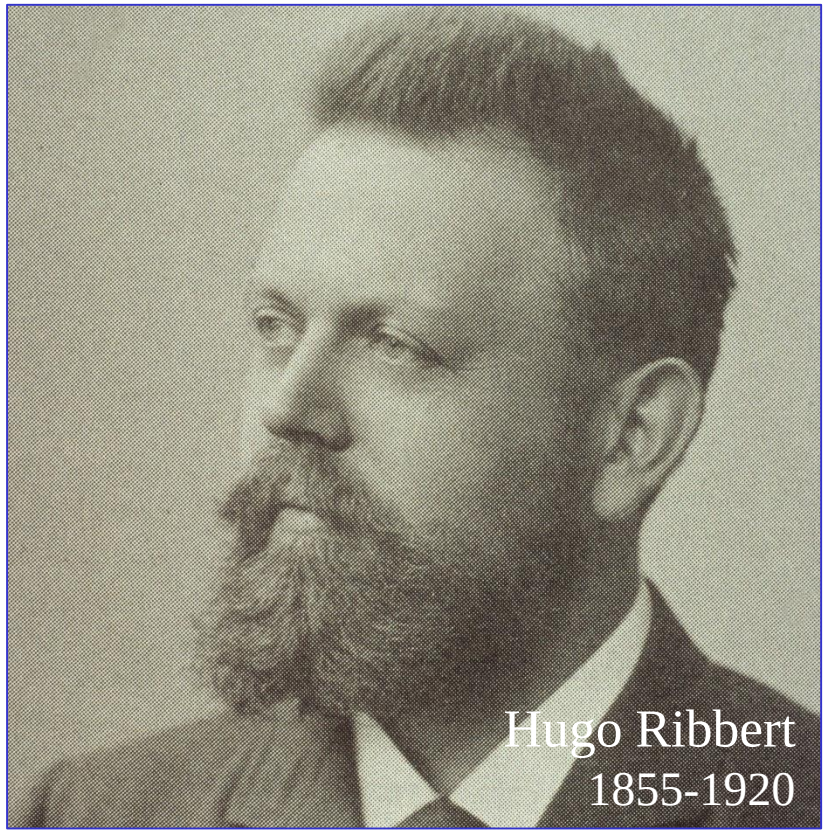
Carl Thiersch
1822-1895

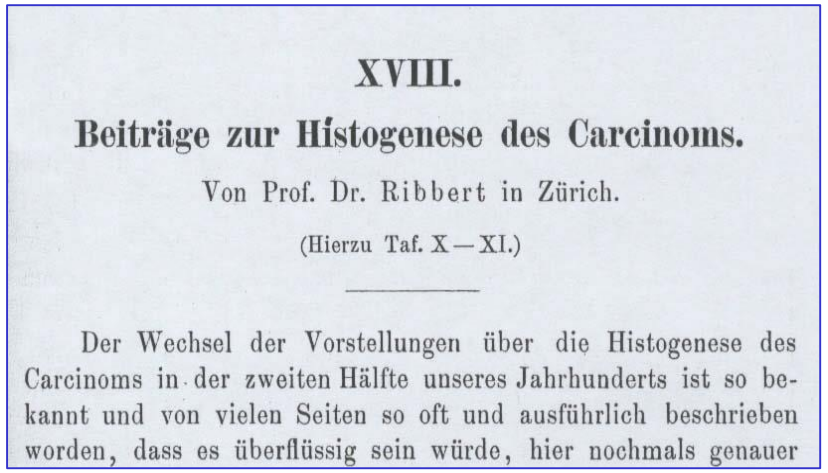


Even after the epithelial derivation of carcinomas had been demonstrated beyond doubt by Carl Thiersch in his monograph of 1865, “About Epithelial Cancer, Particularly of the Skin,” the connective tissue was implicated as the true site of carcinoma formation.

The development of carcinoma of the skin is initiated by a vivid proliferation of connective tissue … The expansion of epithelium into connective tissue is not caused by invasion of it into the depth but by exuberant growth of connective tissue into cones of epithelium whose cells become separated and isolated. From these elements of epithelial cells that have been displaced by newly formed connective tissue, the actual development of cancer begins.

Hugo Ribbert, 1894





XVIII.

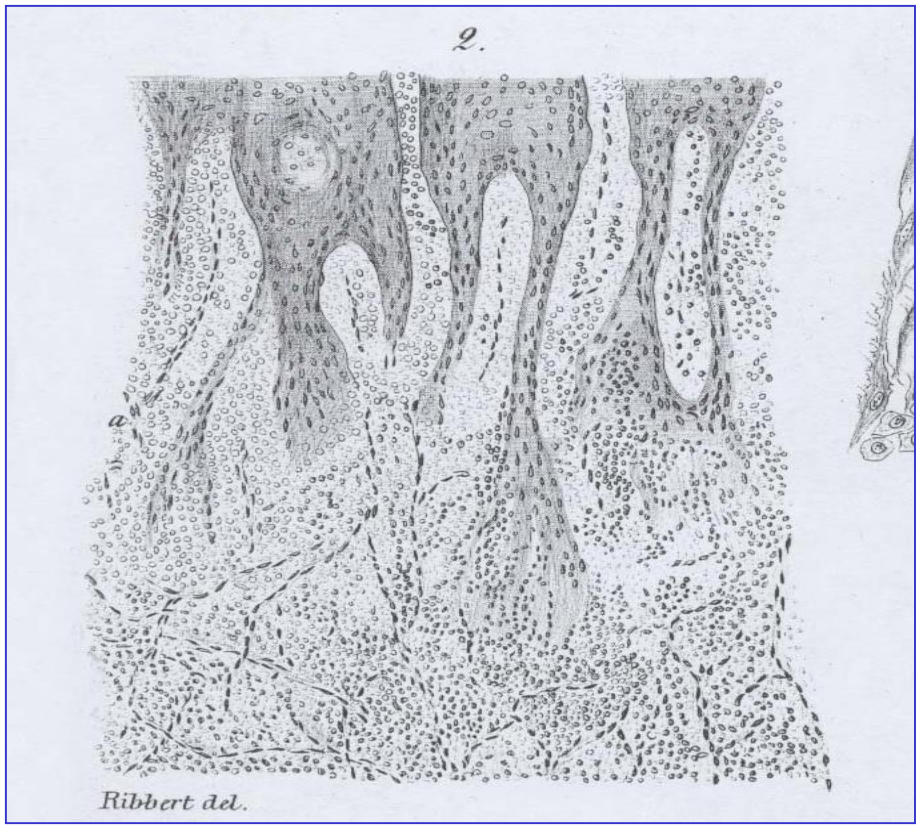
Beiträge zur Histogenese des Carcinoms.

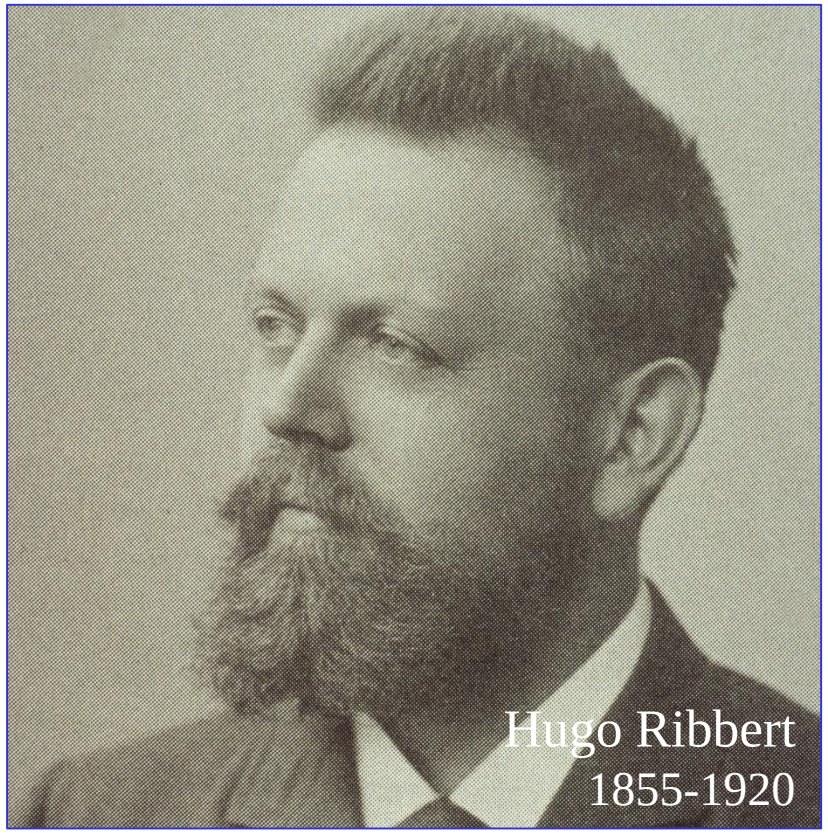
Von Prof. Dr. Ribbert in Zürich.

(Hierzu Taf. X—XI.)

Der Wechsel der Vorstellungen über die Histogenese des Carcinoms in der zweiten Hälfte unseres Jahrhunderts ist so bekannt und von vielen Seiten so oft und ausführlich beschrieben worden, dass es überflüssig sein würde, hier nochmals genauer

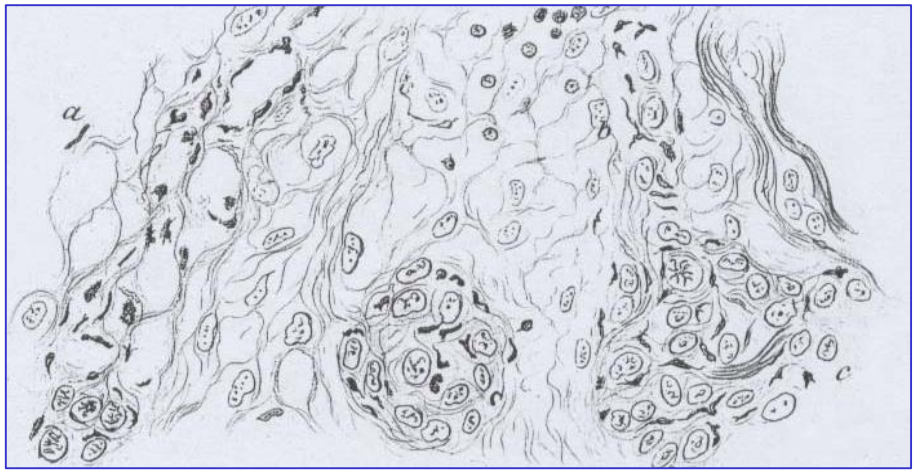
For example, Hugo Ribbert of Zurich claimed in an article about the "Histogenesis of Carcinoma" in 1894, that *"the development of carcinoma of the skin is initiated by a vivid proliferation of connective tissue … The expansion of epithelium into connective tissue is not caused by invasion of it into the depth but by exuberant growth of connective tissue into cones of epithelium whose cells become separated and isolated. From these elements of epithelial cells that have been displaced by newly formed connective tissue, the actual development of cancer begins."*

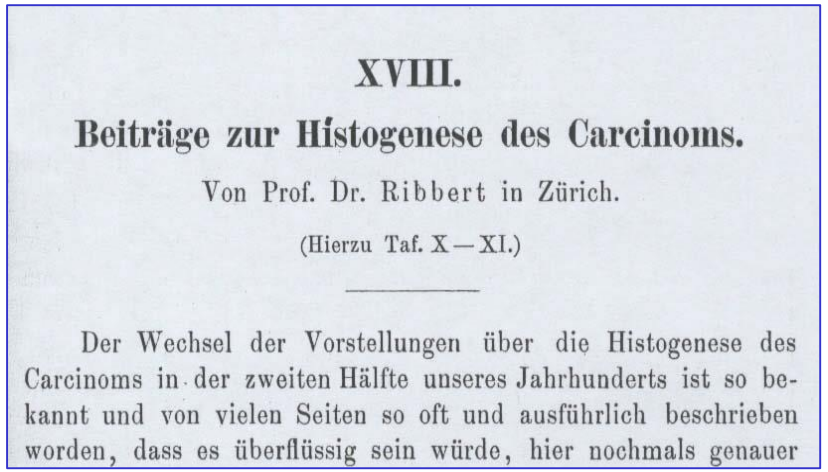




Ribbert illustrated his concept in drawings showing the encroachment of connective tissue on the epithelium and the displacement of innocuous epithelial cells into the dermis, where they began to be transformed and started to proliferate.

It took three more decades until the obvious fact that epithelial neoplasms originate in the epithelium was acknowledged.





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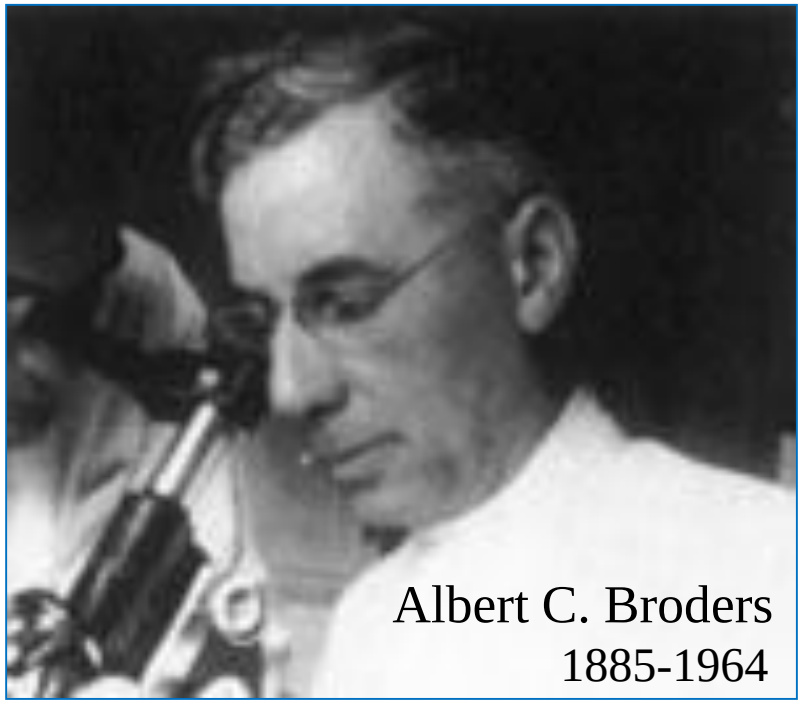
The entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and … all other phases or sequelae, although of great importance, are in reality of secondary nature ... the day has passed when epithelium can be considered noncarcinomatous or at the most only precarcinomatous because it is within the confines of the so-called basement membrane and, conversely, carcinomatous because it has penetrated beyond this barrier. It is therefore imperative that the microscopist take into consideration the character of the epithelial cells above everything else in order to arrive at a correct diagnosis.

Albert C. Broders, 1932



Albert C. Broders
1885-1964

CARCINOMA IN SITU CONTRASTED WITH BENIGN PENETRATING EPITHELIUM

ALBERT C. BRODERS, M.D.
ROCHESTER, MINN.

Before I undertake to point out the importance of bringing into the category of carcinoma certain so-called entities that for the most part have remained outside of this category and to exclude from this category epithelial hyperplasia that is not of carcinomatous nature, I believe it is essential to emphasize established facts. These are that the entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and that all other phases and sequelae, although of great importance, are in reality of secondary nature.

In 1932, Albert C. Broders of the Mayo Clinic introduced the term “carcinoma in situ” to emphasize the continuity of cancer development. He explained that *“the entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and … all other phases or sequelae, although of great importance, are in reality of secondary nature ... the day has passed when epithelium can be considered noncarcinomatous or at the most only precarcinomatous because it is within the confines of the so-called basement membrane and, conversely, carcinomatous because it has penetrated beyond this barrier.”*

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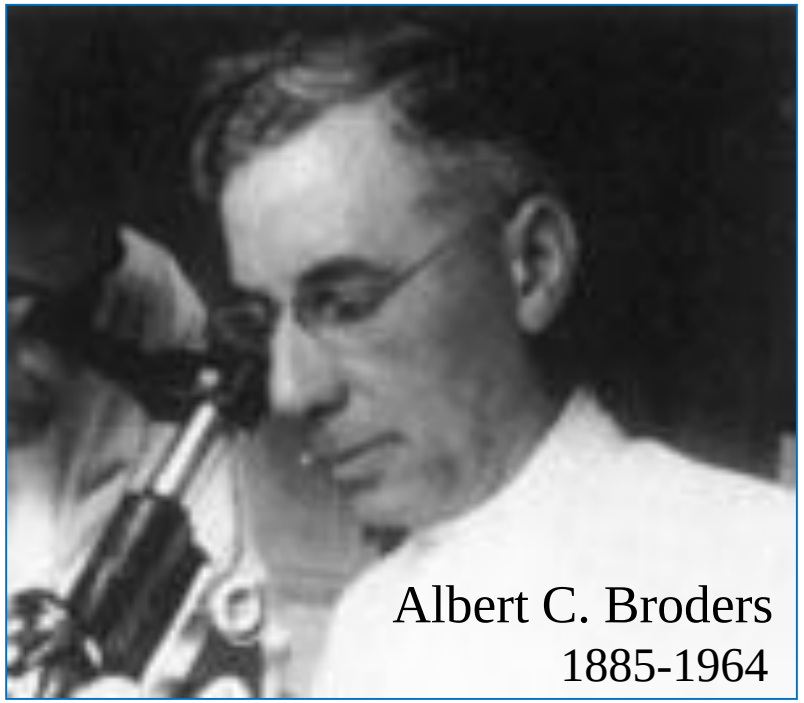

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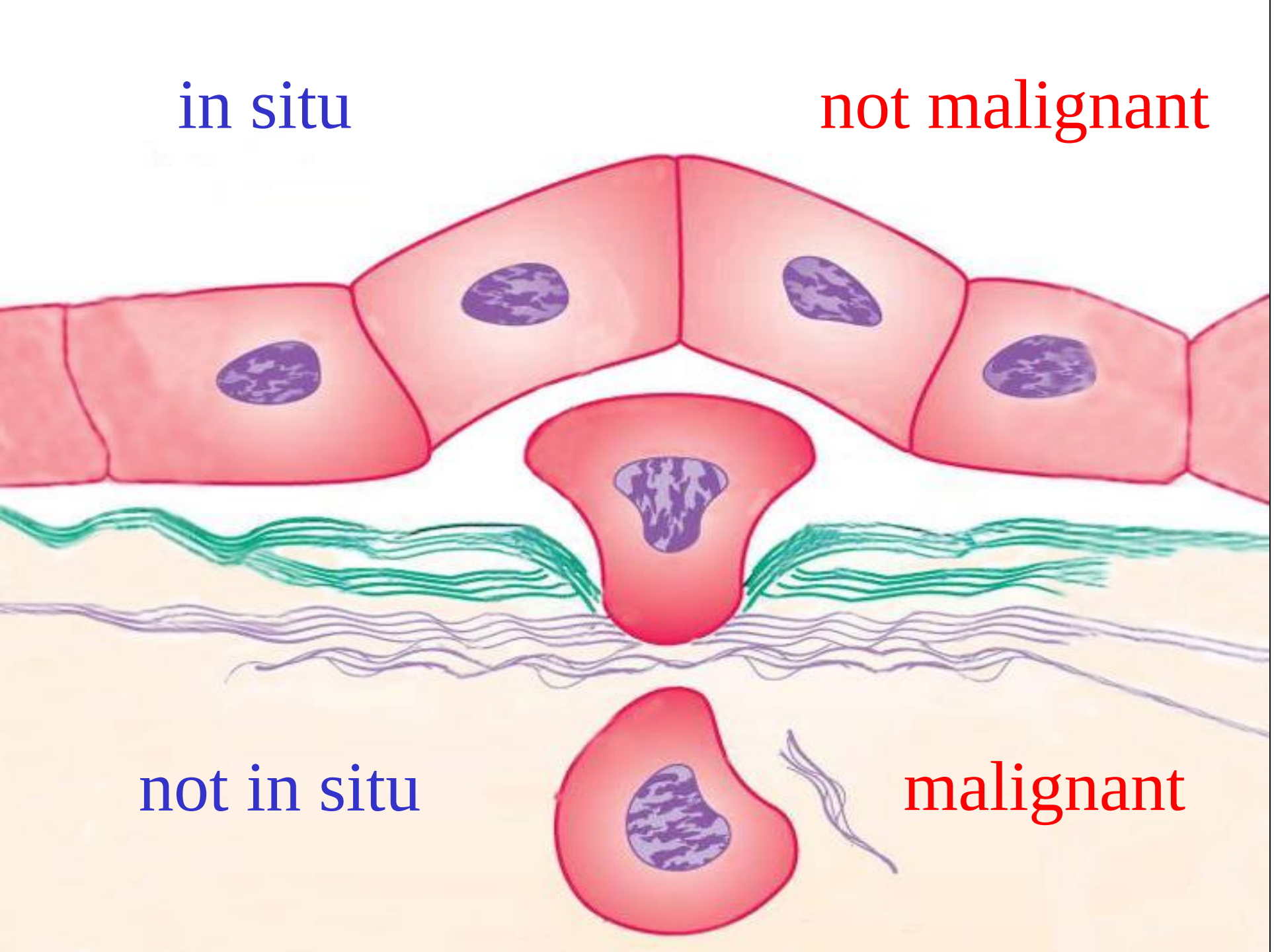
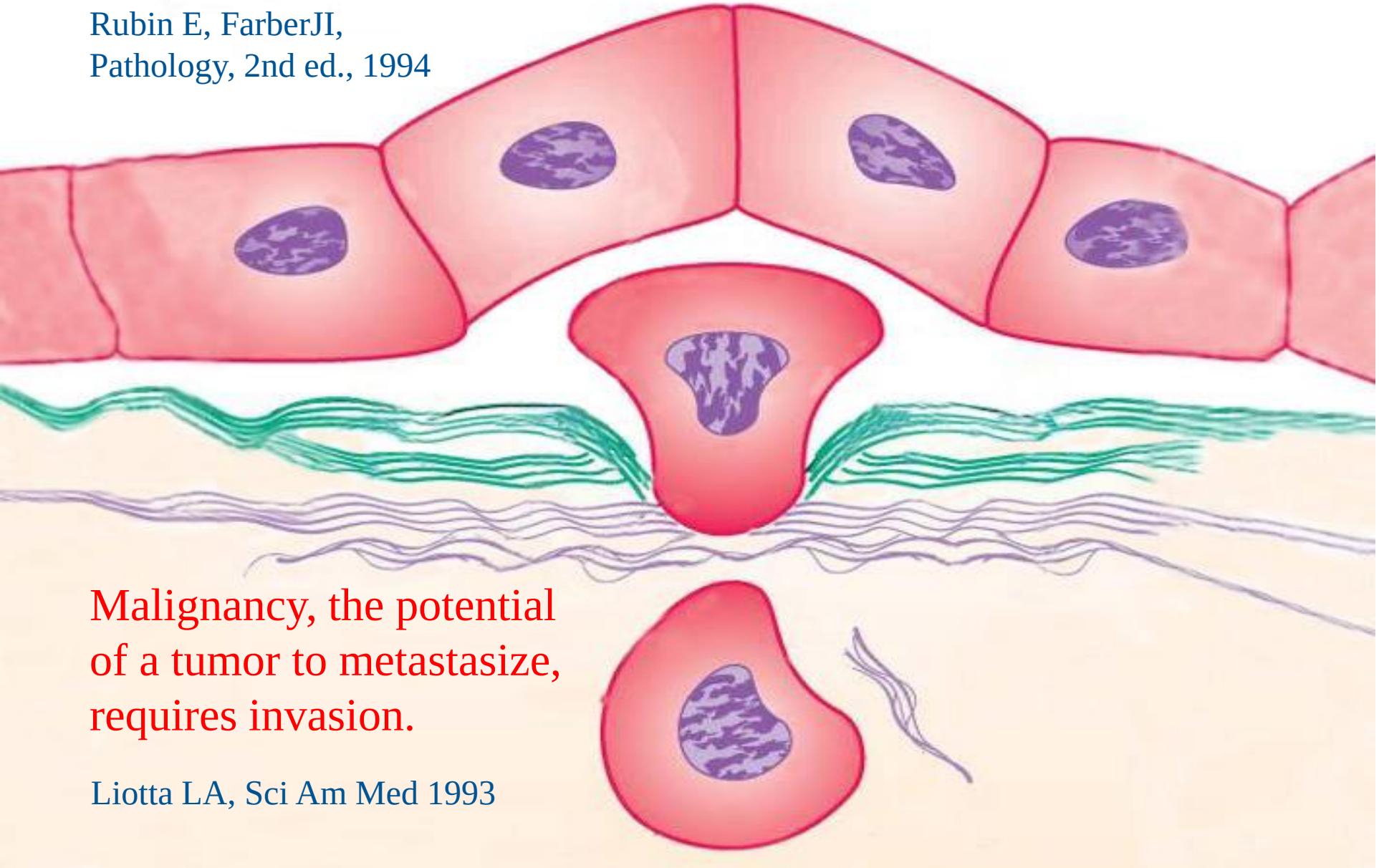


While all this was true, Borders' choice of the term "carcinoma in situ" was extremely unfortunate because it attached undue importance to the difference between "in situ" and "not in situ," though Broders tried to emphasize the opposite. As a consequence, the basement membrane continued to be regarded as the watershed of malignancy.

The two properties that are unique to cancer cells are the ability to invade locally and the capacity to metastasize to distant sites.

Rubin E, FarberJI,
Pathology, 2nd ed., 1994



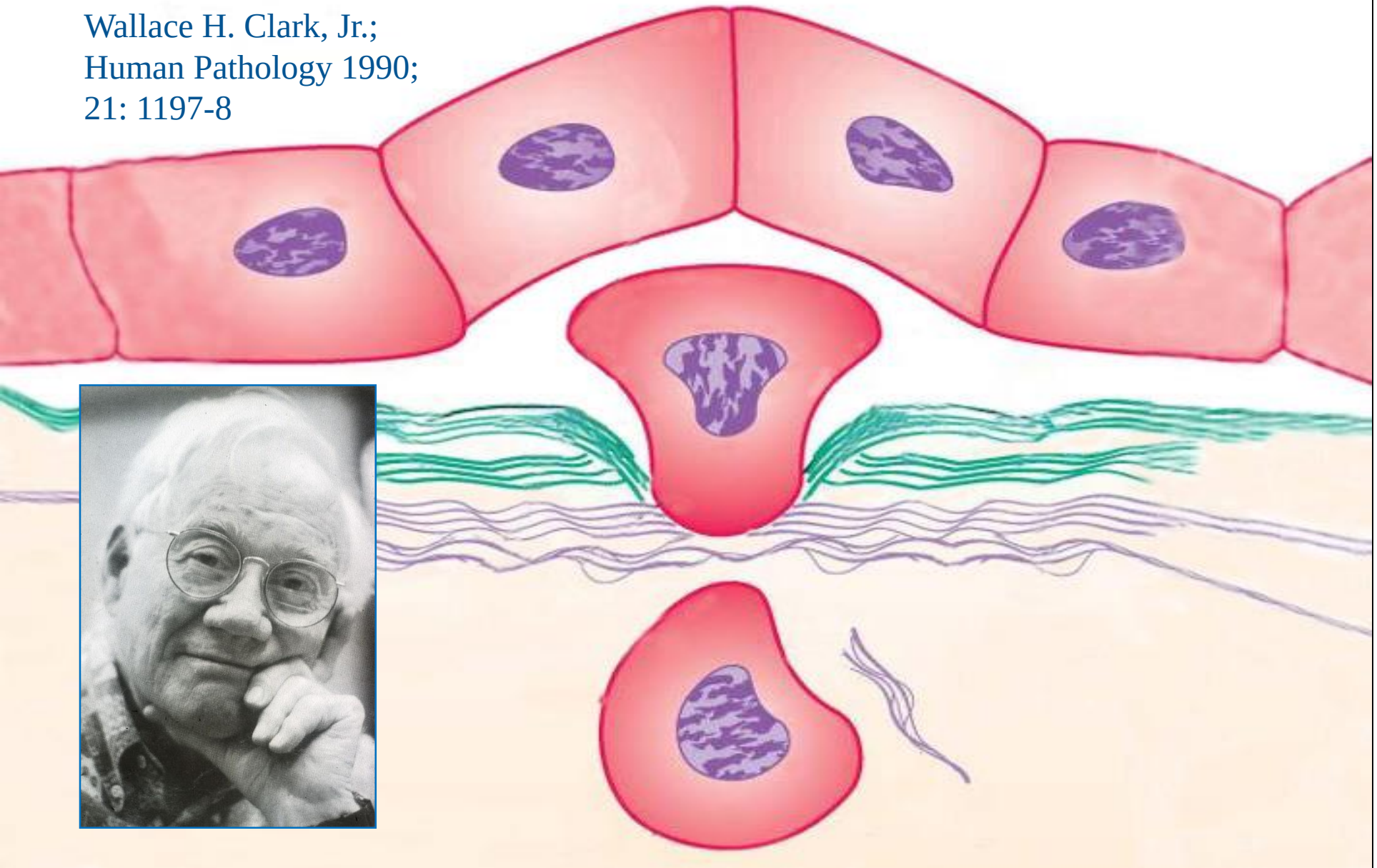
Malignancy, the potential of a tumor to metastasize, requires invasion.

Liotta LA, Sci Am Med 1993

Textbooks of general pathology emphasized that *"the two properties that are unique to cancer cells are the ability to invade locally and the capacity to metastasize to distant sites."* Many authors still claim that *"malignancy, the potential of a tumor to metastasize, requires invasion."*

The diagnosis of carcinoma in situ (melanoma in situ, malignancy in situ) is a contradiction in terms, the prototype of an oxymoron.

Wallace H. Clark, Jr.;
Human Pathology 1990;
21: 1197-8

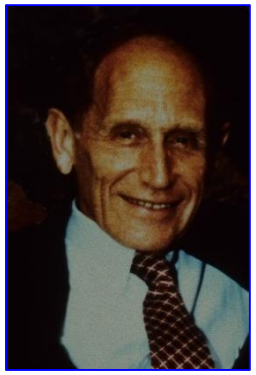


In 1990, Wallace H. Clark, Jr. stated that *"the diagnosis of carcinoma in situ (melanoma in situ, malignancy in situ) is a contradiction in terms, the prototype of an oxymoron."*

Those notions were based chiefly on the argument that, before invading the dermis, neoplastic cells are not capable of invasion and, therefore, not malignant.

The American Journal of Dermatopathology 11(4): 387–389, 1989

Malignant Melanoma in Light of the Multistep Theory of Neoplasia*



Arkadi M. Rywlin, M.D.

Malignant melanoma (MM) appears to be an experiment of nature that supports the multistep theory of neoplasia (1). According to this theory, the transformation of a normal cell to a malignant cell requires several steps. A cell can be considered completely transformed when it has acquired the capacity to invade surrounding tissue and to metastasize. Scientists working with tissue cultures de-

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the capacity to invade and metastasize is limited. The loss of fibronectin from the cell surface of carcinoma cells is one of several mechanisms that seems to be important (3).

Pathologists are fully aware that many epithelial malignant tumors represent the endstage of a continuum that starts with hyperplasia (reversible) and evolves to atypical hyperplasia (reversible), then to neoplasia in situ (irreversible), and finally to invasive neoplasia. By definition, hyperplasia is reversible whereas neoplasia is irreversible. This continuum of changes can be observed in the skin, oral mucous membrane, bronchial mucosa, vocal cords, breast, uterine cervix, endometrium, prostate, and other areas. From experimental pathology, it is

ders between hyperplasia and neoplasia in situ cannot be determined morphologically at the present state of our knowledge. The multistep theory of neoplasia makes the definition of a malignancy in situ easy. Malignancy in situ is a condition in which one or several cells have acquired the ability to invade and metastasize, but have not as yet exercised these options. The problem is that malignancy in situ, when defined as above, is not diagnosable because we cannot recognize these fully transformed cells until they actually invade the underlying tissue. We have no marker to inform us that all the genetic and epigenetic events that render a cell capable of invasion have occurred. The arbitrary definition of carcinoma in situ as atypia involving the full thickness of the epithelium is obviously not justified because a state of carcinoma in situ can occur before there is full-thickness atypia. This situation occurs when an invasive squamous cell carcinoma evolves in an actinic keratosis.

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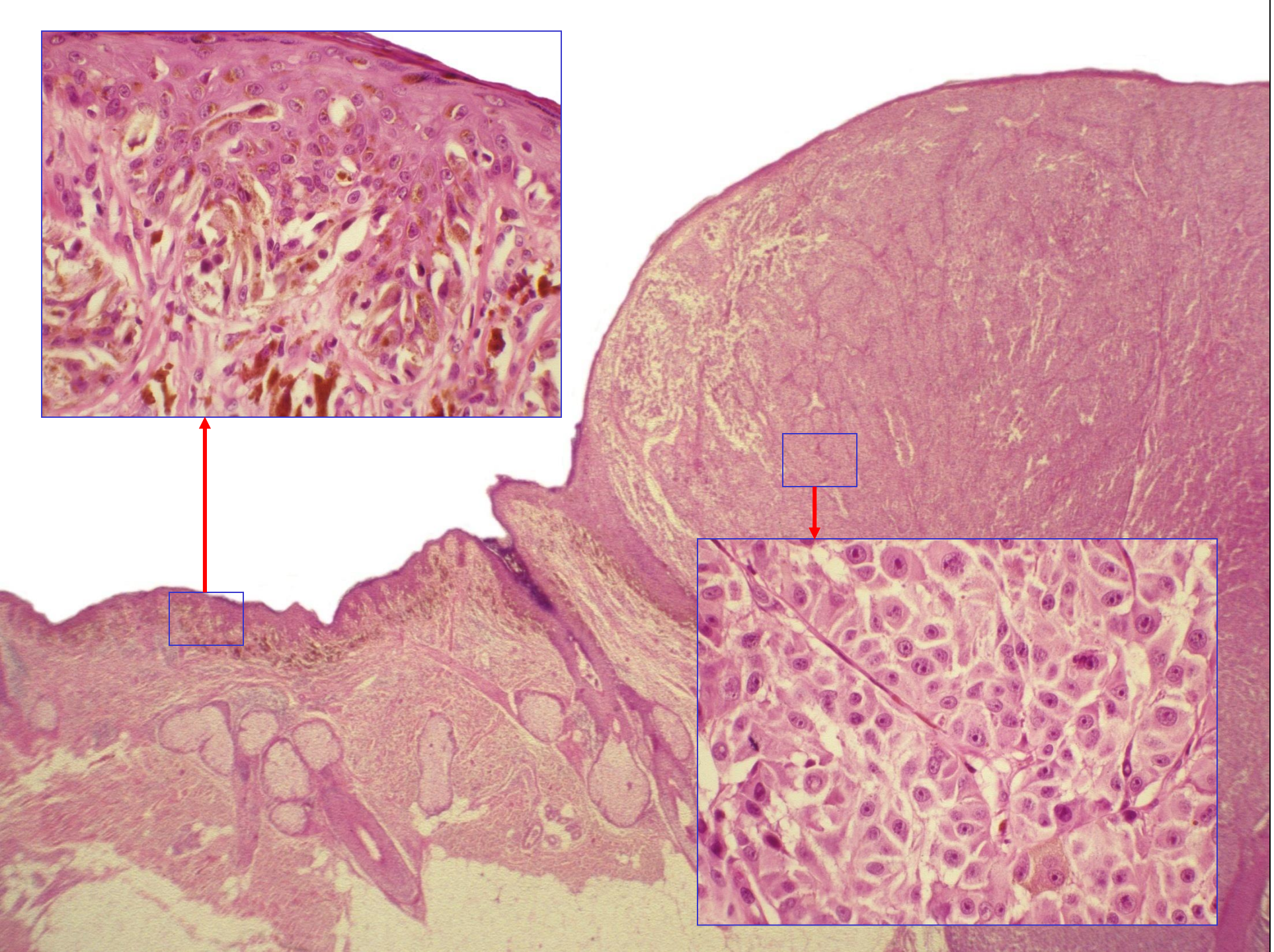
For example, when the late Arkadi Rywlin discussed "malignant melanoma in the light of the multistep theory of neoplasia," he argued that *"the transformation of a normal cell to a malignant cell requires several steps. … A cell can be considered completely transformed when it has acquired the capacity to invade surrounding tissue and to metastasize."* In his view, this was not the case in in-situ malignancies. *"The intraepithelial containment of the atypical cells … appears not to be due to surveillance by the immune system, but to the lack of complete transformation of cells."*



This speculation was based on the observation that, in some melanomas, cells in the intraepidermal and in the dermal component differ strikingly from one another morphologically, the former being relatively small and monomorphous, the latter large, pleomorphic, with ample cytoplasm and numerous mitotic figures. Because of those findings,

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.

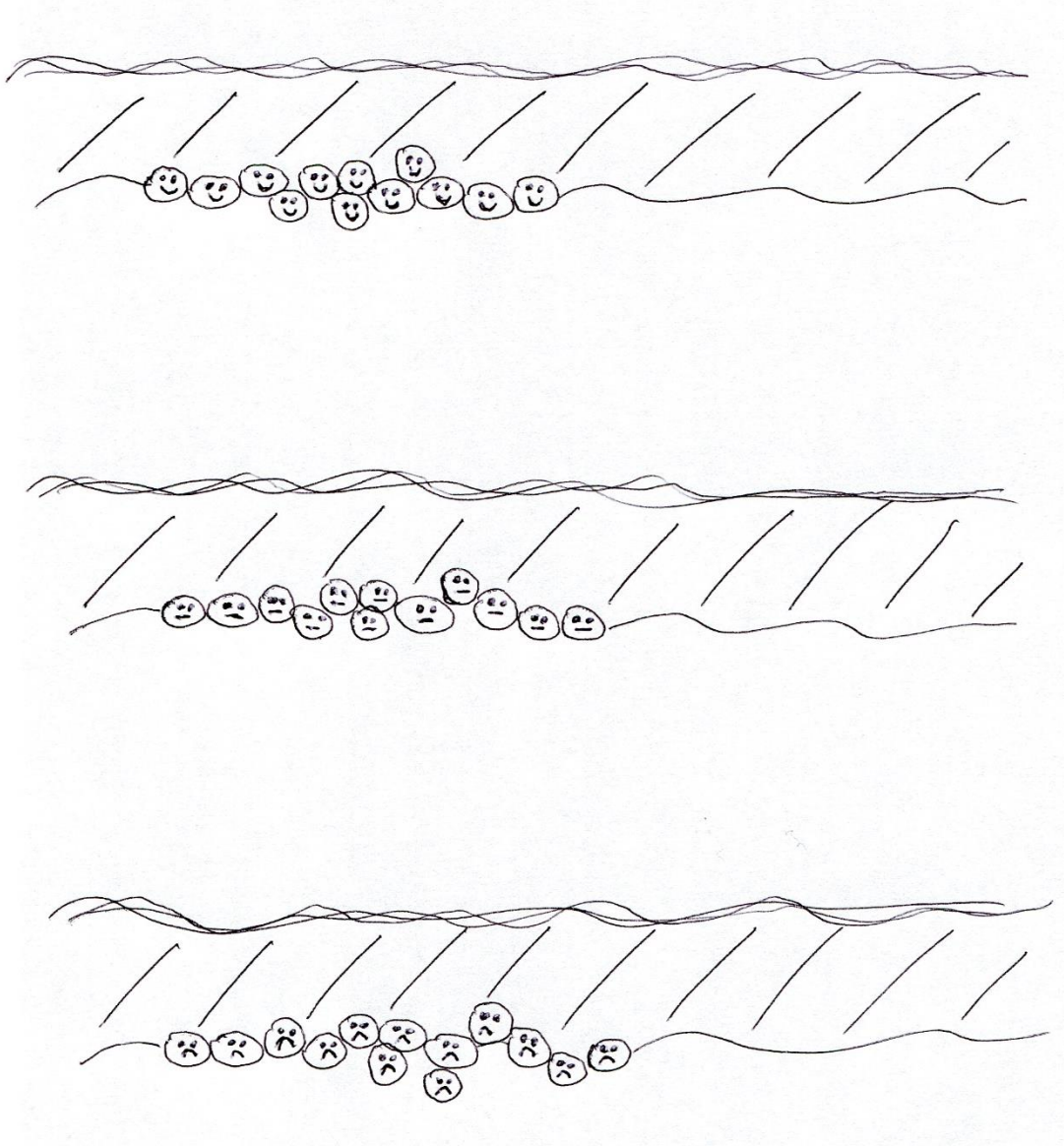
Six evident lesional steps of tumor progression form the neoplastic system that affects the human epidermal melanocyte: 1) the common acquired melanocytic nevus; 2) a melanocytic nevus with lentiginous melanocytic hyperplasia, i.e., aberrant differentiation; 3) a melanocytic nevus with aberrant differentiation 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.

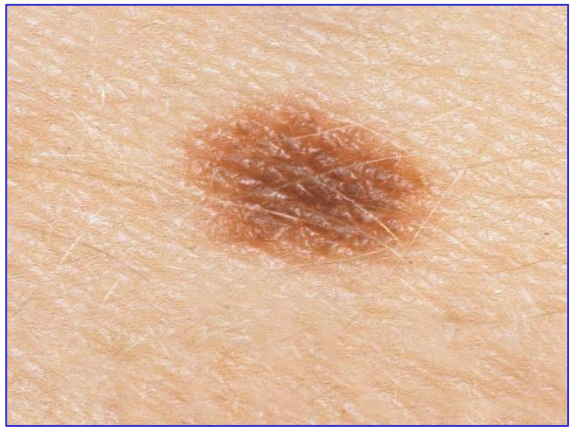
to the directional growth of the radial growth phase. As a rule, the cells of the vertical growth phase grow in an expansile fashion, expansile as a balloon expands: a growth form char-

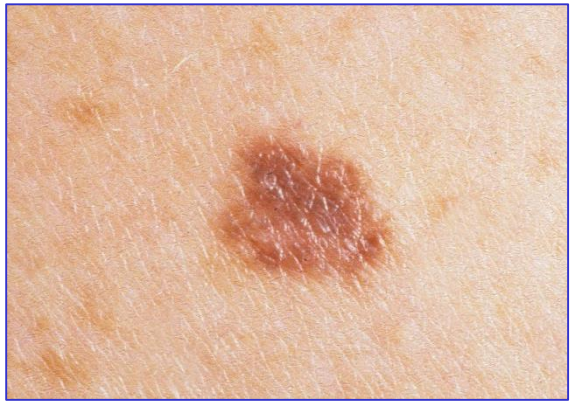
plasia is exemplified by the first evident lesion of the system: a focal proliferation in the basilar epidermal

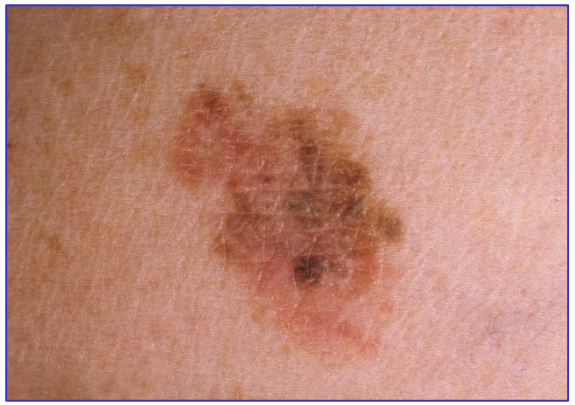
Clark considered melanoma to be a model for the hypothesis of multistep carcinogenesis and in 1984 advanced a concept of tumor progression with what he called *"six evident lesional steps,"* starting with a benign nevus and eventuating, via different steps of increasing dysplasia, to primary and metastatic melanoma.

However, there is no such thing as a gradual change in the dignity of an established neoplasm.

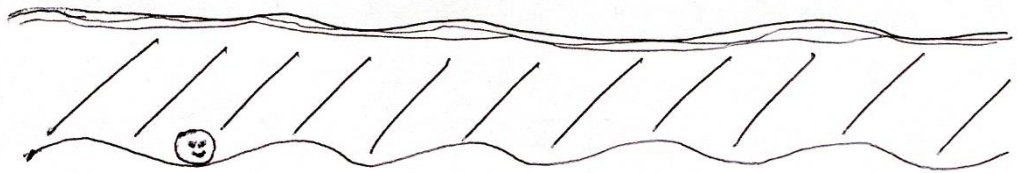


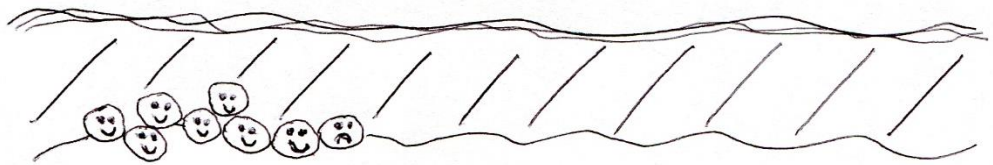


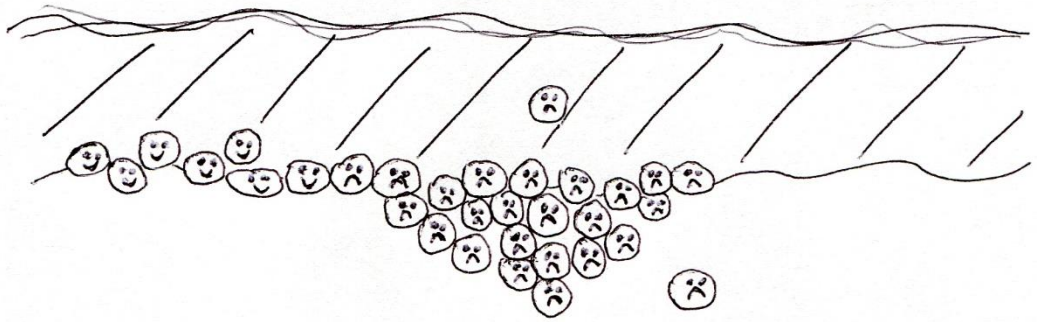


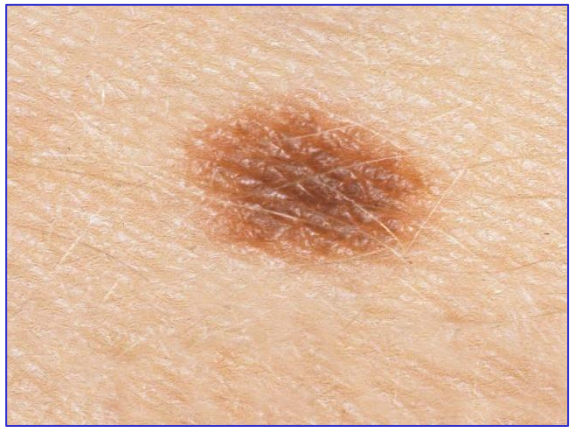


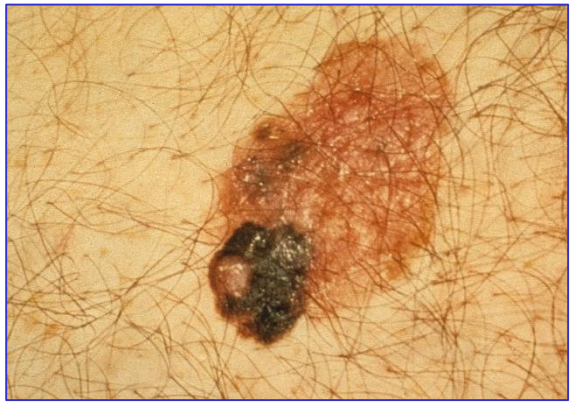
According to Clark's concept, the entire lesion changes its character, as if neoplastic cells constituting it transformed in synchrony from being happy and benign to being slightly upset and ultimately bad-tempered and malignant. But this is not the case.



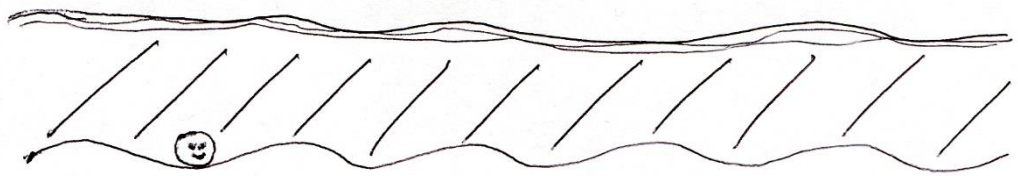


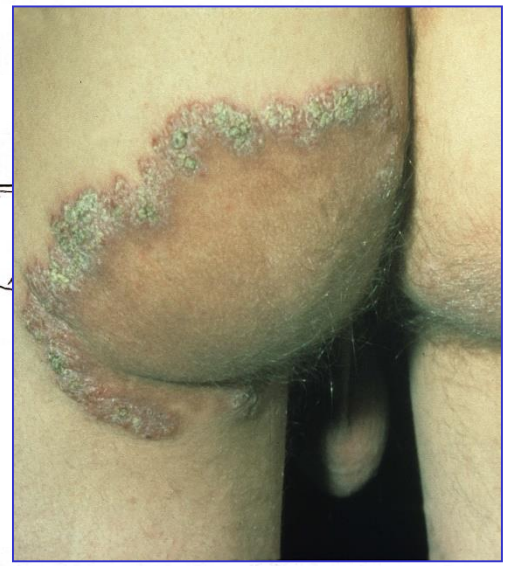


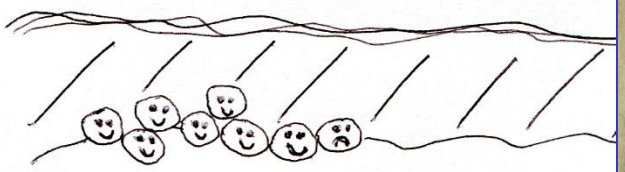


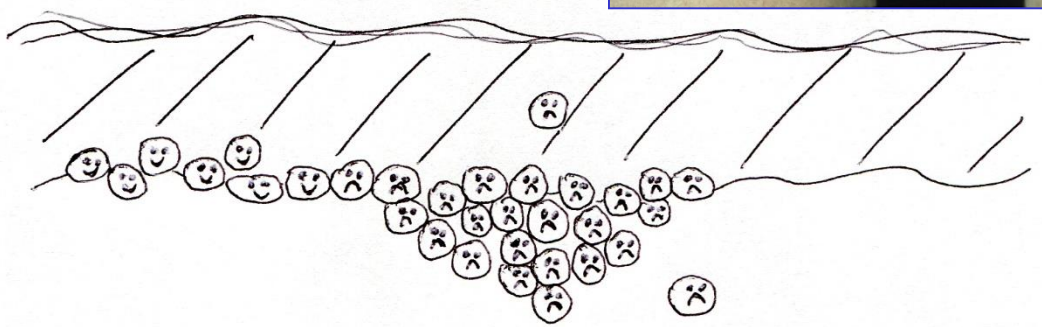


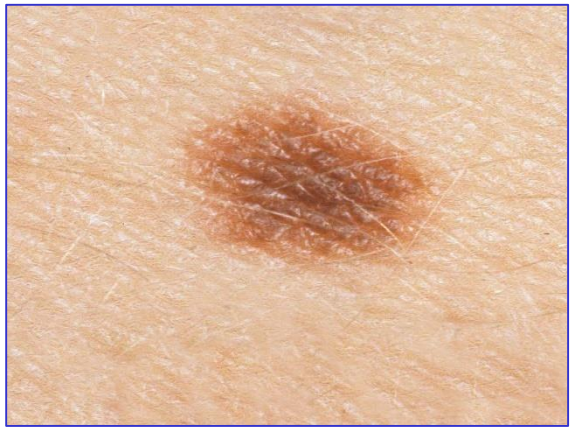
Neoplasms result from clonal proliferation. A benign cell may give rise to a benign neoplasm, and if one of its cells becomes malignant, a malignant neoplasm grows on top of the benign one. This is not a transformation,

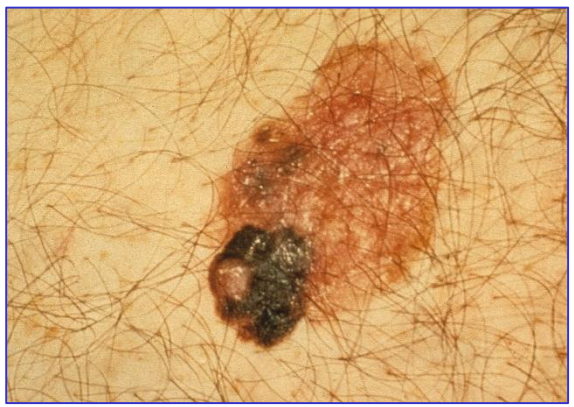




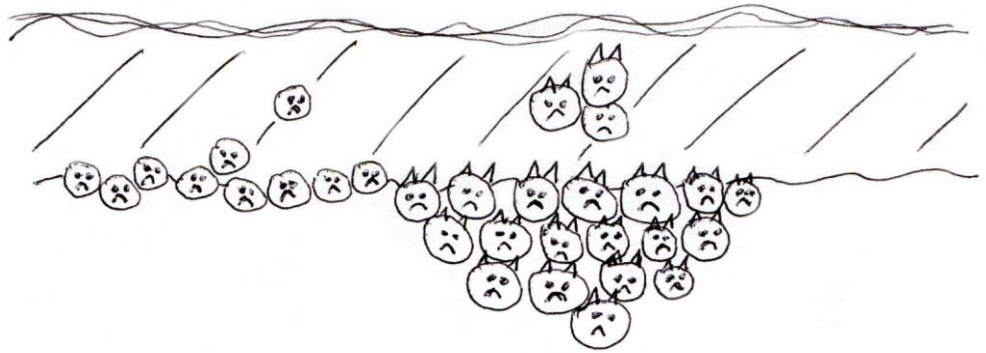


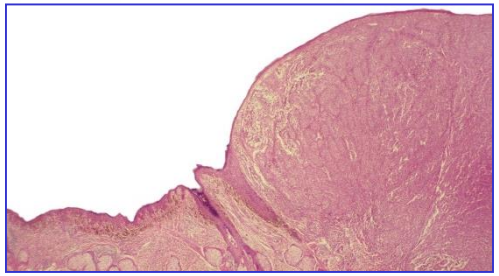


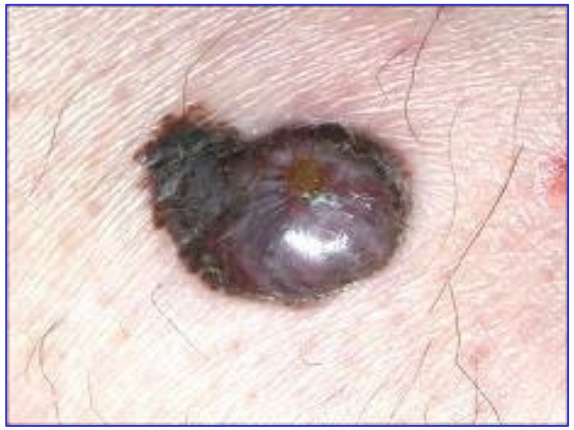




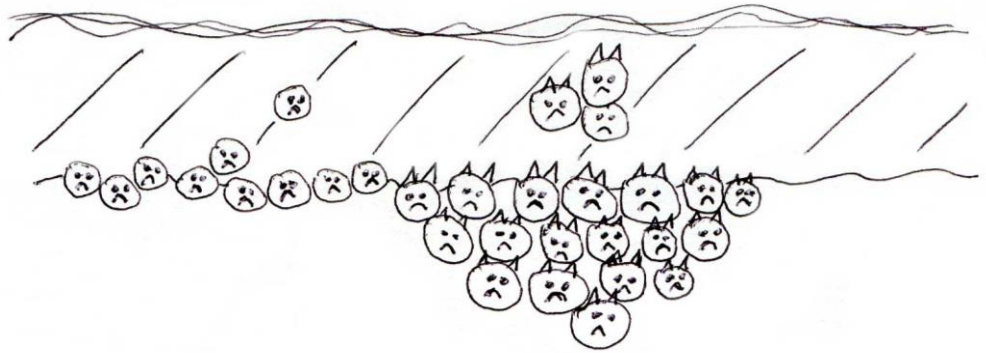
just as a man does not transform into a fungus only because a fungus grows on him. A melanoma arising on a nevus is a new, separate phenomenon, and that sequence of events is an exception rather than the rule.

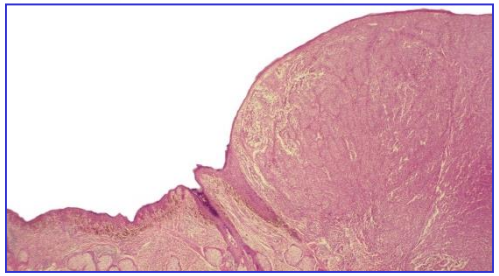


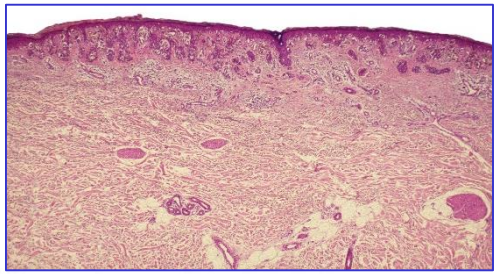


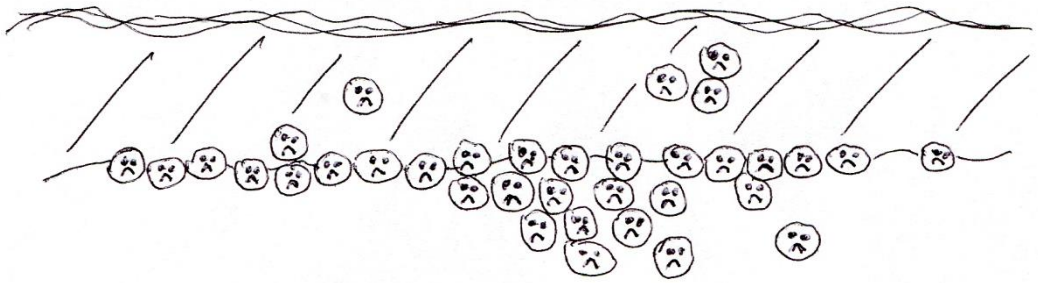


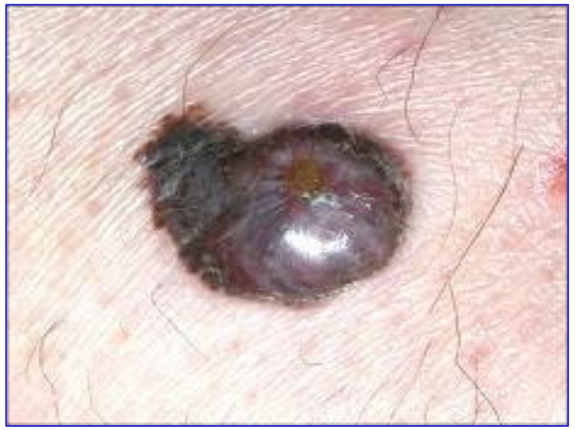
Likewise, a new and more malignant clone of cells may arise in an already established melanoma, cells turning from malignant to truly devilish. But this is also an exception usually seen only in lesions far advanced.

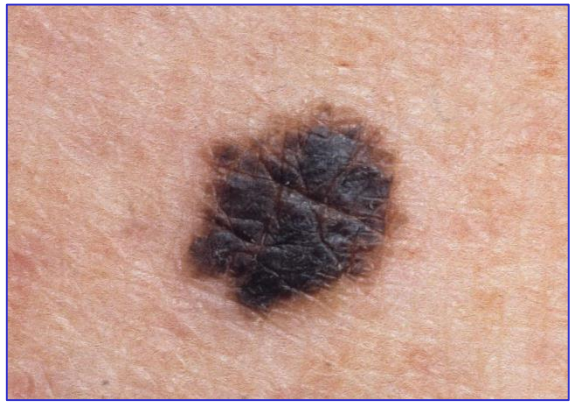




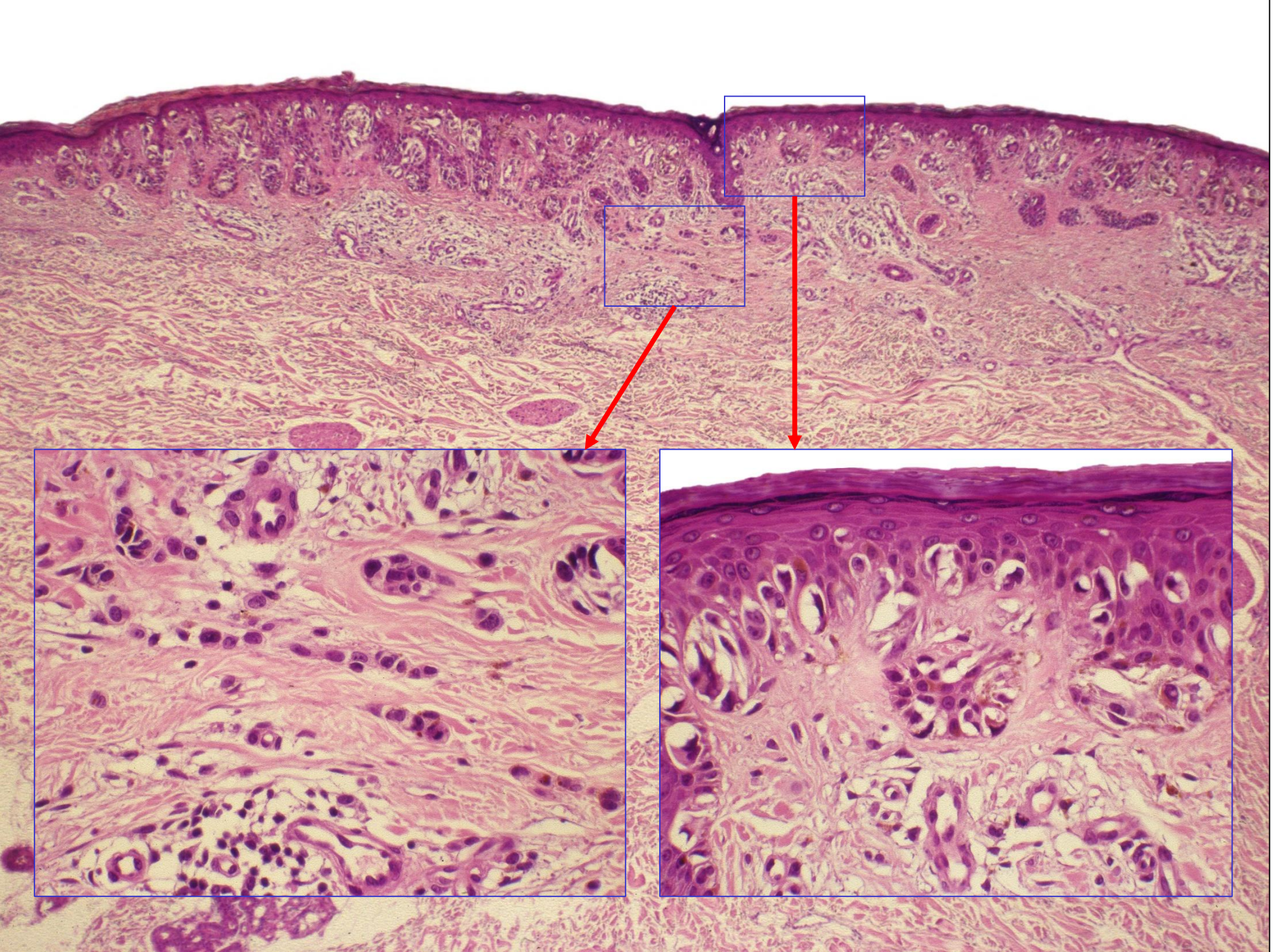








In general, melanomas grow relatively steadily, at least in the beginning, and cells within the epidermis and dermis do not differ strikingly from one another.



Whether located in the epidermis or in the dermis, they look more or less the same.

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

A. Hunter Shain, Ph.D., Iwei Yeh, M.D., Ph.D., Ivanka Kovalyshyn, D.O., Aravindhan Sriharan, M.D., Eric Talevich, Ph.D., Alexander Gagnon, B.A., Reinhard Dummer, M.D., Jeffrey North, M.D., Laura Pincus, M.D., Beth Ruben, M.D., William Rickaby, M.B., Ch.B., Corrado D'Arrigo, M.B., Ch.B., Ph.D., Alistair Robson, F.R.C.Path., and Boris C. Bastian, M.D.

ABSTRACT

BACKGROUND

The pathogenic mutations in melanoma have been largely catalogued; however, the order of their occurrence is not known.

METHODS

We sequenced 293 cancer-relevant genes in 150 areas of 37 primary melanomas and their adjacent precursor lesions. The histopathological spectrum of these areas included unequivocally benign lesions, intermediate lesions, and intraepidermal or invasive melanomas.

RESULTS

Precursor lesions were initiated by mutations of genes that are known to activate the mitogen-activated protein kinase pathway. Unequivocally benign lesions harbored *BRAF* V600E mutations exclusively, whereas those categorized as intermediate were enriched for *NRAS* mutations and additional driver mutations. A total of 77% of areas of intermediate lesions and melanomas in situ harbored *TERT* promoter mutations, a finding that indicates that these mutations are selected at an unexpectedly early stage of the neoplastic progression. Biallelic inactivation of *CDKN2A* emerged exclusively in invasive melanomas. *PTEN* and *TP53* mutations were found only in advanced primary melanomas. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong signature of the effects of ultraviolet radiation detectable at all evolutionary stages. Copy-number alterations became prevalent only in invasive melanomas. Tumor heterogeneity became apparent in the form of genetically distinct subpopulations as melanomas progressed.

CONCLUSIONS

Our study defined the succession of genetic alterations during melanoma progression, showing distinct evolutionary trajectories for different melanoma subtypes. It identified an intermediate category of melanocytic neoplasia, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features. Finally, our study implicated ultraviolet radiation as a major factor in both the initiation and progression of melanoma. (Funded by the National Institutes of Health and others.)

From the Departments of Dermatology and Pathology (A.H.S., I.Y., E.T., A.G., J.N., L.P., B.R., B.C.B.) and the Helen Diller Family Comprehensive Cancer Center (A.H.S., I.Y., E.T., A.G., B.C.B.), University of California, San Francisco (UCSF), San Francisco; the Departments of Dermatology and Pathology, Cleveland Clinic, Cleveland (I.K.); the Department of Pathology, Orlando Health, Orlando, FL (A.S.); the Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland (R.D.); and the Department of Dermatology, Dorset County Hospital, Dorchester (C.D.), and the Department of Dermatology, St. John's Institute of Dermatology, London (W.R., A.R.) — both in the United Kingdom. Address reprint requests to Dr. Bastian at the UCSF Dermatopathology Service, 1701 Divisadero St., Suite 280, San Francisco, CA 94115, or at boris.bastian@ucsf.edu.

N Engl J Med 2015;373:1926-36.
DOI: 10.1056/NEJMoa1502583

Nonetheless, Clark's outdated concept of tumor progression has been revived recently by studies pertaining to the *"genetic evolution of melanoma from precursor lesions."*

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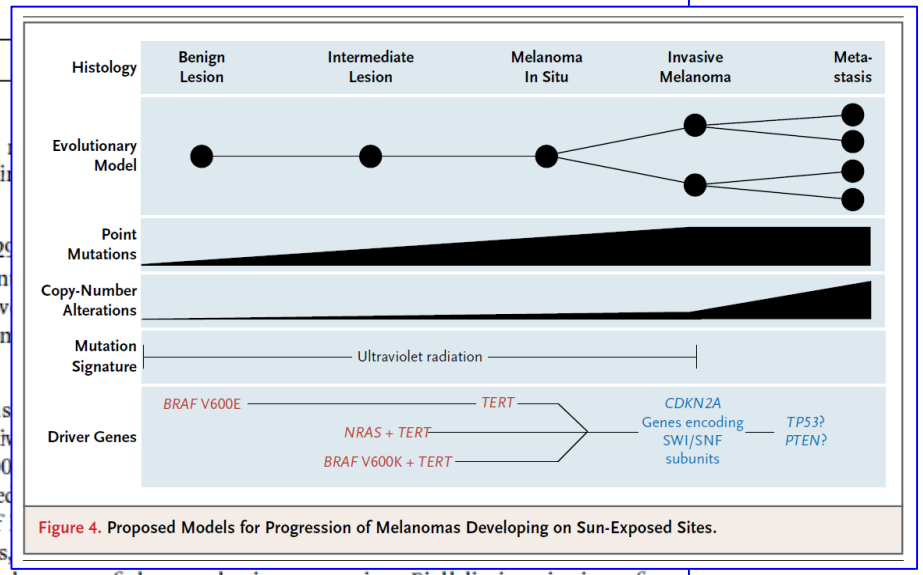

Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.

From the Departments of Dermatology and Pathology (A.H.S., I.Y., E.T., A.G., J.N., L.P., B.R., B.C.B.) and the Helen Diller Family Comprehensive Cancer Center (A.H.S., I.Y., E.T., A.G., B.C.B.), University of California, San Francisco (UCSF), San Francisco; the Departments of Dermatology and Pathology, Cleveland Clinic, Cleveland (I.K.); the Department of Pathology, Orlando Health, Orlando, FL (A.S.); the Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland (R.D.); and the Department of Dermatology, Dorset County Hospital, Dorchester (C.D.), and the Department of Dermatology, St. John's Institute of Dermatology, London (W.R., A.R.) — both in the United Kingdom. Address reprint requests to Dr. Bastian at the UCSF Dermatopathology Service, 1701 Divisadero St., Suite 280, San Francisco, CA 94115, or at boris.bastian@ucsf.edu.

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Because of an increasing load of mutations harbored by nevi, melanoma in situ, invasive melanoma, and melanoma metastases, the authors suggested a gradual evolution of established lesions, benign at first, then "intermediate," and then fully malignant.

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

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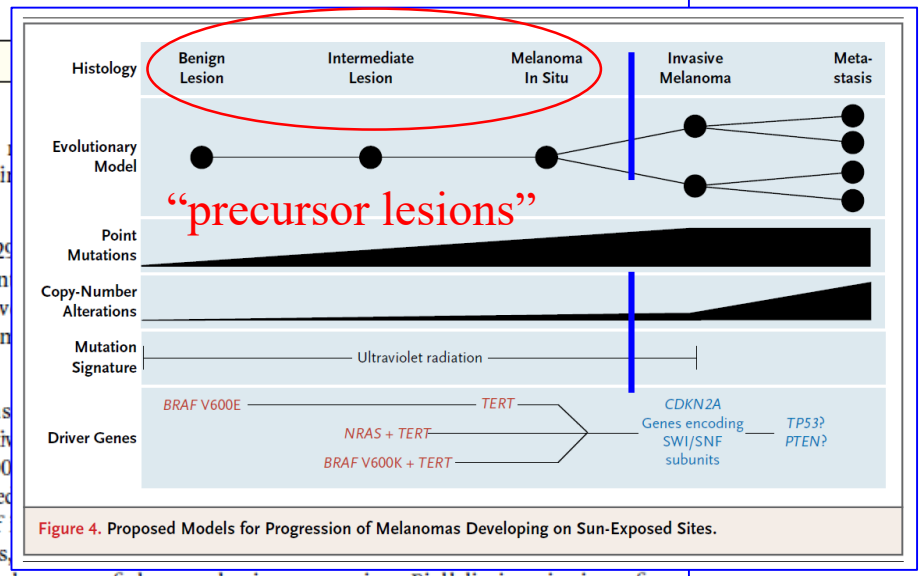

Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.

They also made a distinction between melanoma and so-called "precursor lesions," by which they referred to nevi, so-called "intermediate lesions", and melanoma in situ,

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

A. Hunter Shain, Ph.D., Iwei Yeh, M.D., Ph.D., Ivanka Kovalyshyn, D.O., Aravindhan Sriharan, M.D., Eric Talevich, Ph.D., Alexander Gagnon, B.A., Reinhard Dummer, M.D., Jeffrey North, M.D., Laura Pincus, M.D., Beth Ruben, M.D., William Rickaby, M.B., Ch.B., Corrado D'Arrigo, M.B., Ch.B., Ph.D., Alistair Robson, F.R.C.Path., and Boris C. Bastian, M.D.

From the Departments of Dermatology and Pathology (A.H.S., I.Y., E.T., A.G., J.N., L.P., B.R., B.C.B.) and the Helen Diller Family Comprehensive Cancer Center (A.H.S., I.Y., E.T., A.G., B.C.B.), University of California, San Francisco (UCSF), San Francisco; the Departments of Dermatology and Pathology, Cleveland Clinic, Cleveland (I.K.); the Department of Pathology, Orlando Health, Orlando, FL (A.S.); the Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland (R.D.); and the Department of Dermatology, Dorset County Hospital, Dorchester (C.D.), and the Department of Dermatology, St. John's Institute of Dermatology, London (W.R., A.R.) — both in the United Kingdom. Address reprint requests to Dr. Bastian at the UCSF Dermatopathology Service, 1701 Divisadero St., Suite 280, San Francisco, CA 94115, or at boris.bastian@ucsf.edu.

N Engl J Med 2015;373:1926-36.
DOI: 10.1056/NEJMoa1502583

BACKGROUND
The pathogenic
the order of their

METHODS
We sequenced 29
and their adjacen
included unequiv
invasive melanon

RESULTS
Precursor lesions
the mitogen-activ
bored *BRAF* V600
ate were enriched
77% of areas of
moter mutations.
unexpectedly early stage of the neoplastic progression. Biallelic inactivation of *CDKN2A* emerged exclusively in invasive melanomas. *PTEN* and *TP53* mutations were found only in advanced primary melanomas. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong signature of the effects of ultraviolet radiation detectable at all evolutionary stages. Copy-number alterations became prevalent only in invasive melanomas. Tumor heterogeneity became apparent in the form of genetically distinct subpopulations as melanomas progressed.

CONCLUSIONS
Our study defined the succession of genetic alterations during melanoma progression, showing distinct evolutionary trajectories for different melanoma subtypes. It identified an intermediate category of melanocytic neoplasia, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features. Finally, our study implicated ultraviolet radiation as a major factor in both the initiation and progression of melanoma. (Funded by the National Institutes of Health and others.)

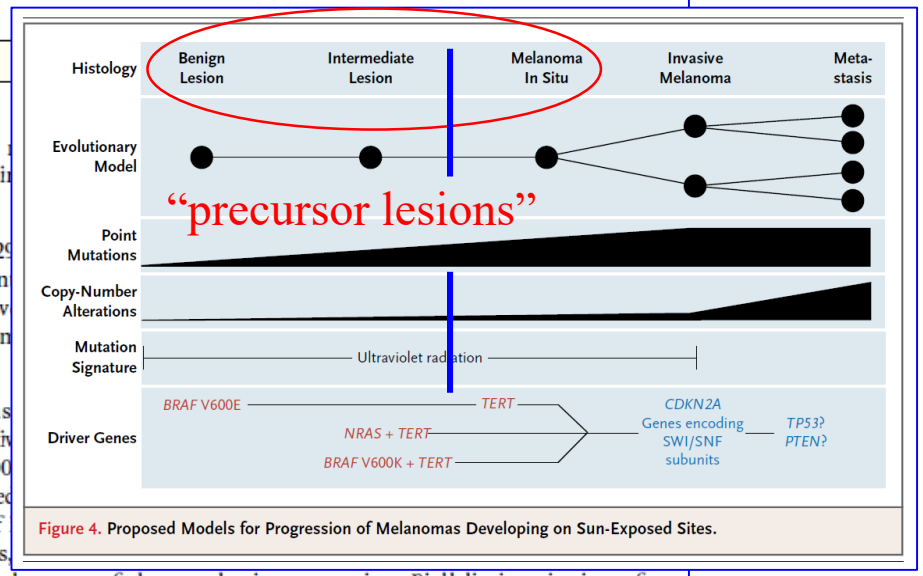

Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.

rather than drawing a line between malignant lesions and benign ones. The reason for that perplexing division

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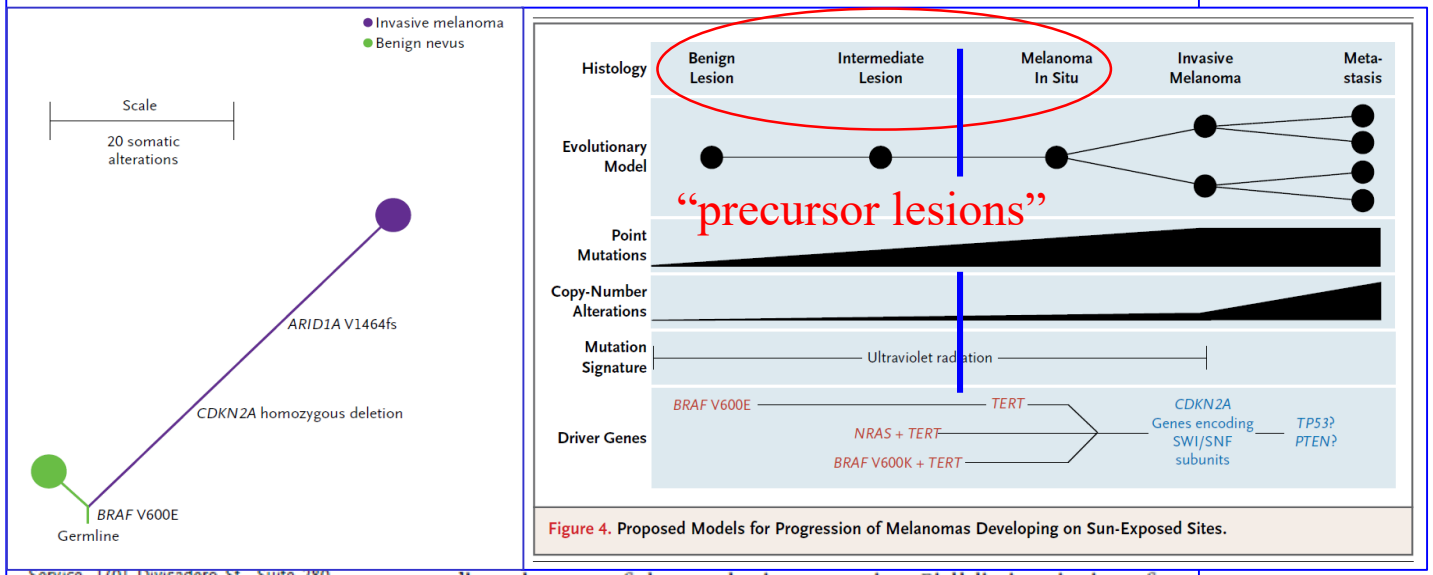

Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.

Service, 1701 Divisadero St., Suite 280, San Francisco, CA 94115, or at boris.bastian@ucsf.edu.

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unexpectedly early stage of the neoplastic progression. Biallelic inactivation of *CDKN2A* emerged exclusively in invasive melanomas. *PTEN* and *TP53* mutations were found only in advanced primary melanomas. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong signature of the effects of ultraviolet radiation detectable at all evolutionary stages. Copy-number alterations became prevalent only in invasive melanomas. Tumor heterogeneity became apparent in the form of genetically distinct subpopulations as melanomas progressed.

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was a mutation found exclusively in melanoma cells in the dermis, namely, *"biallelic inactivation of CDKN2A."* However, restriction of that defect to intradermal melanoma cells does not imply that it has anything to do with invasion, let alone being a prerequisite for it, as suggested by the authors. Melanocytes do not need a specific gene defect for entering the dermis,

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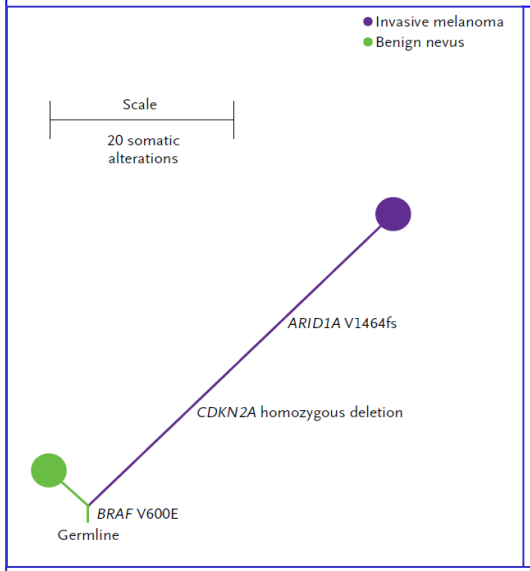


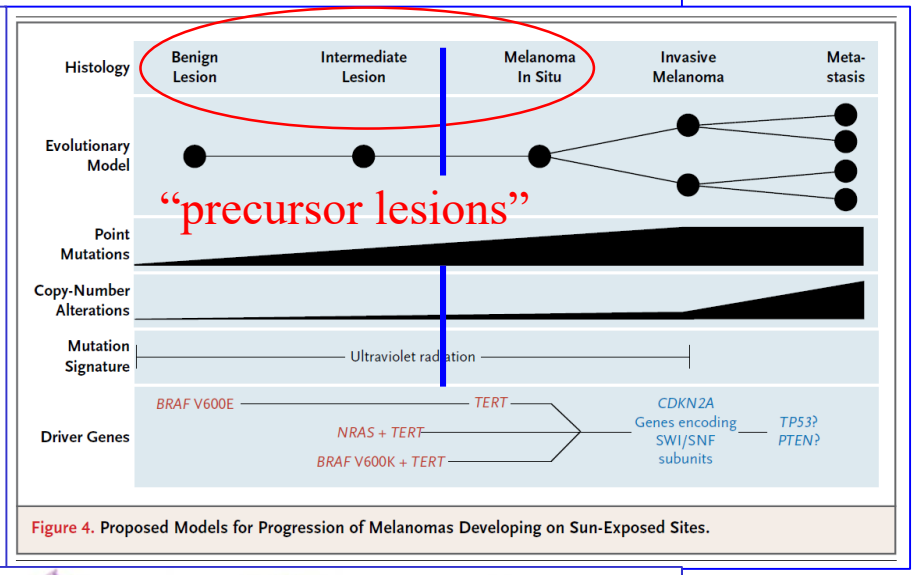
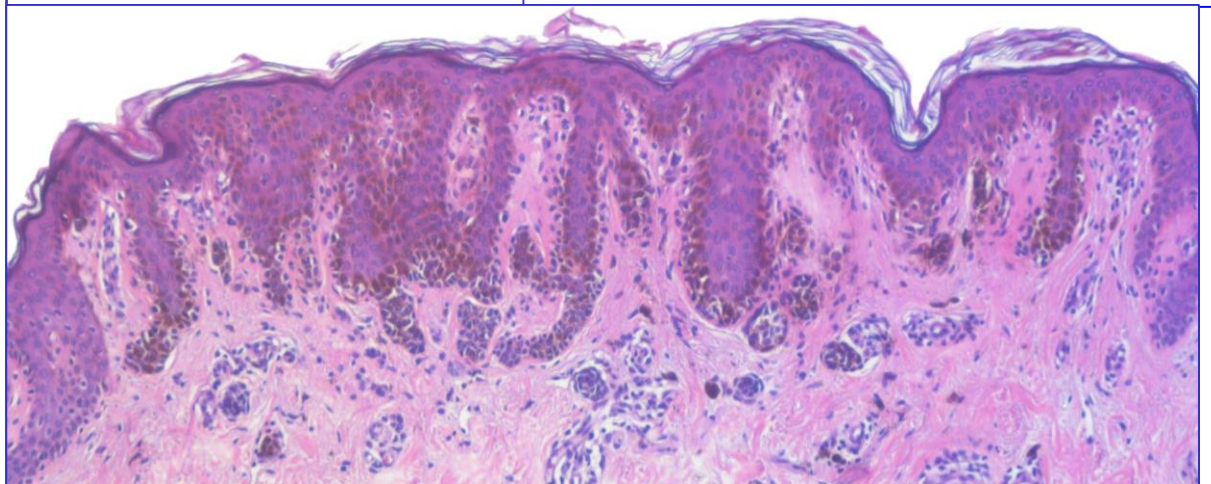


Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.



as demonstrated by any compound nevus.

Moreover, the claim of a "genetic evolution of melanoma from precursor lesions" has no substance. Although nevi and melanomas may share some genetic defects, there is no identifiable "precursor lesion" in the vast majority of melanomas.

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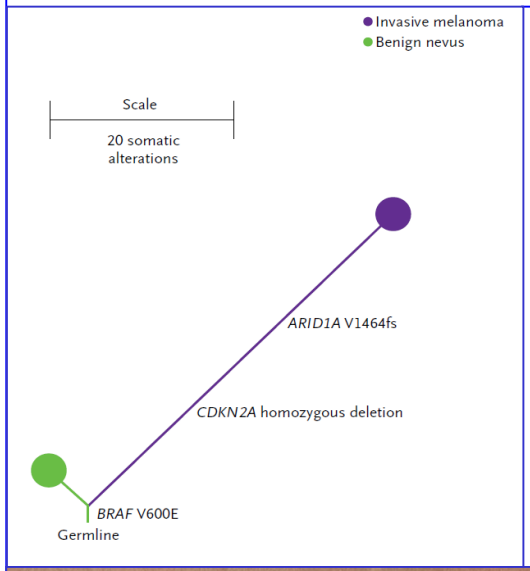


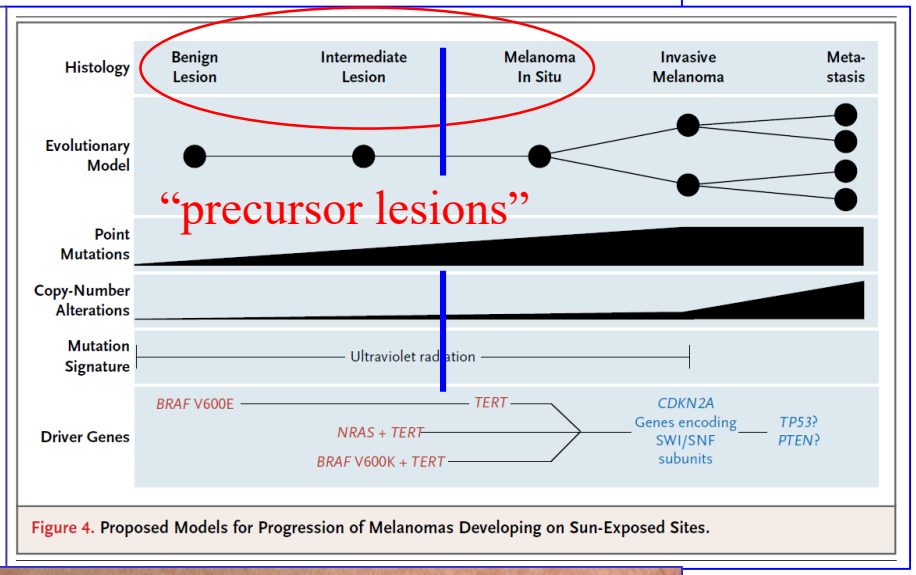
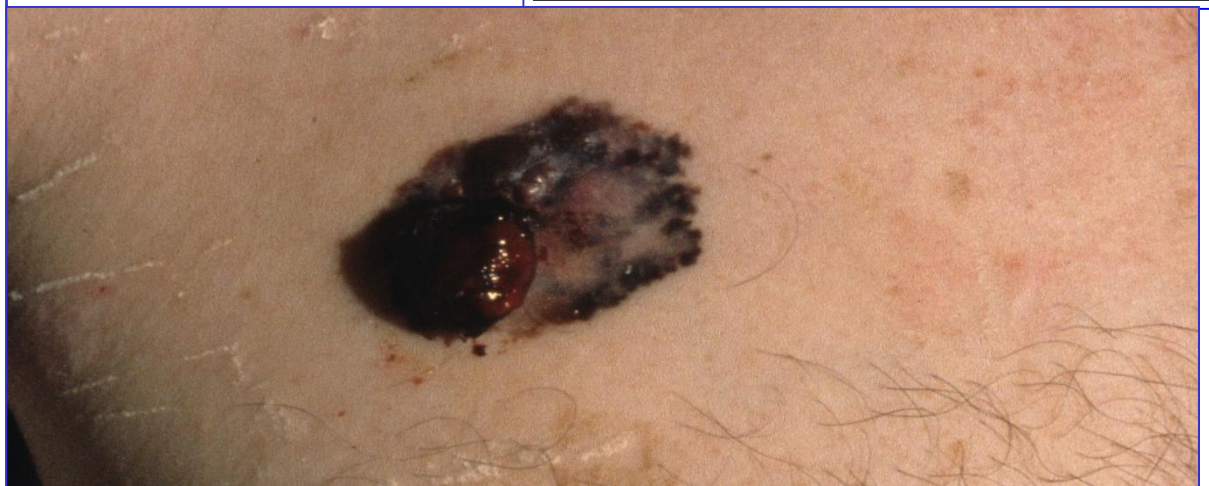
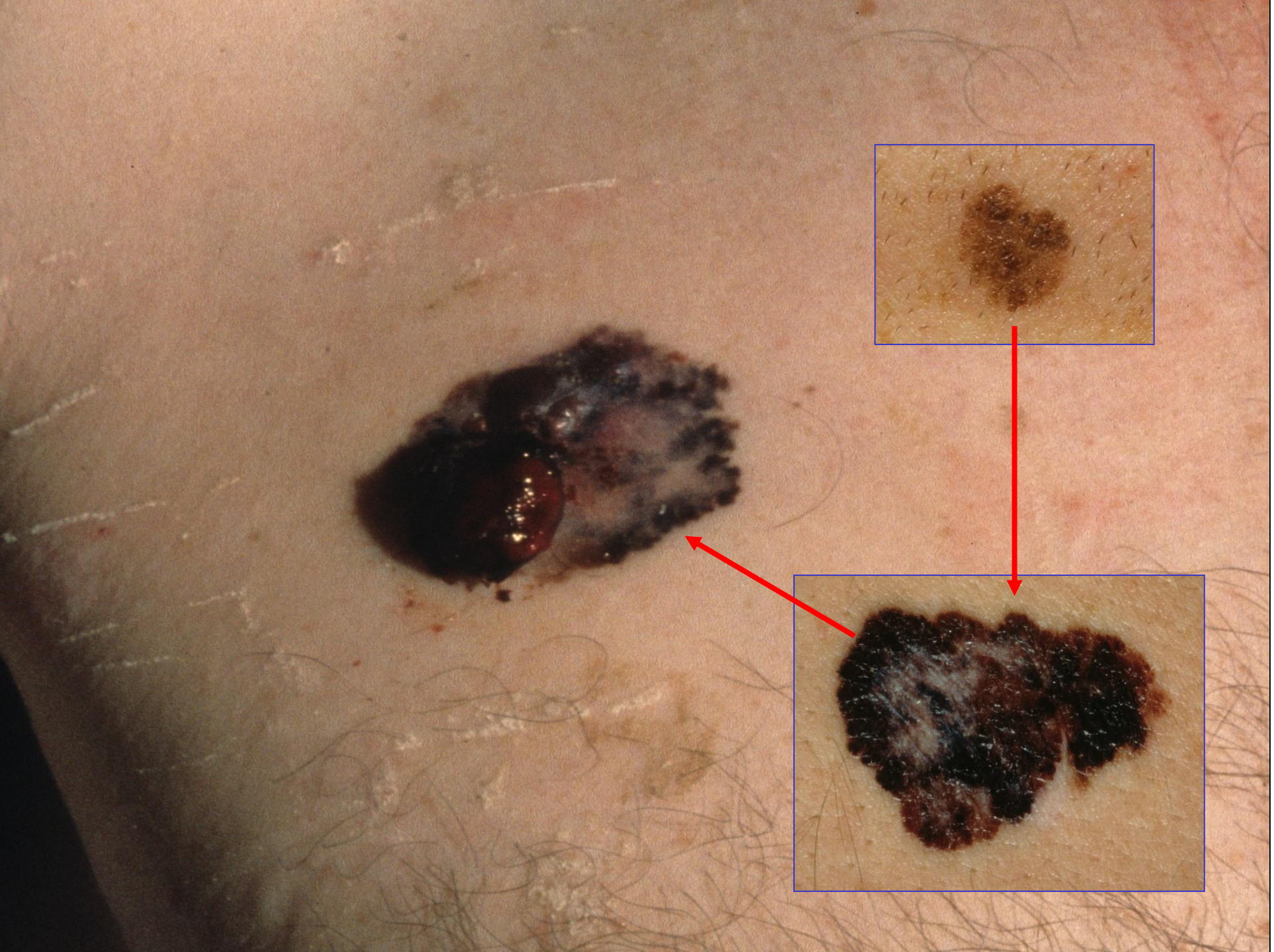


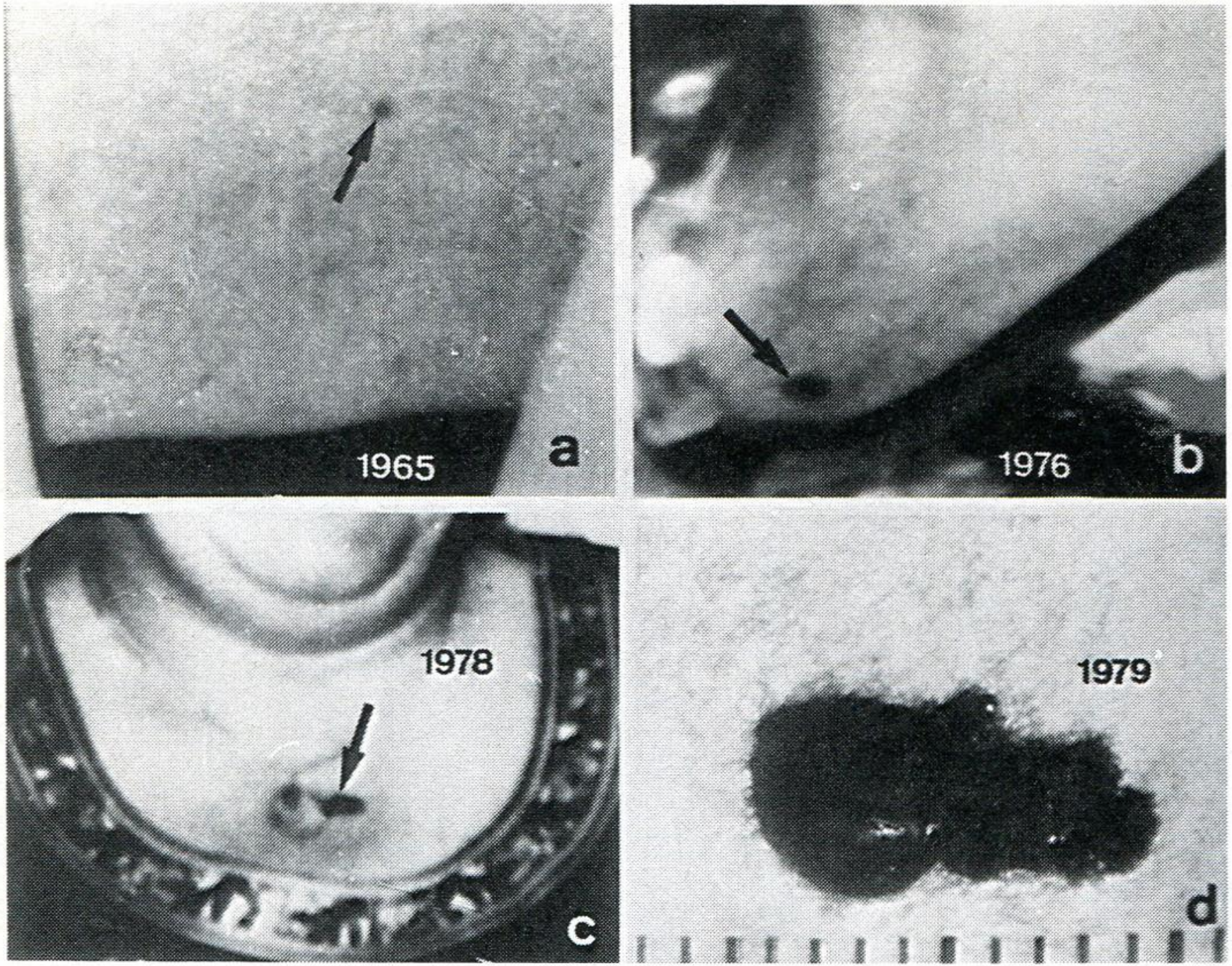
Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.



The flat portion formerly misinterpreted as pre-existing nevus fulfils criteria for malignancy, such as uneven pigmentation and irregular outline,



and those signs are usually visible early-on.



Photokatamnestic studies have demonstrated the slow, steady expansion of melanoma over decades, rather than sudden changes in quality.

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

Harold Kittler, MD,[a] Hubert Pehamberger, MD,[b] Klauss Wolff, MD, FRCP,[a] and Michael Binder, MD[a] *Vienna, Austria*

Background: Digital epiluminescence microscopy (DELM) has been reported to be a useful technique for the follow-up of melanocytic nevi. One of the promises of this technique is to identify modifications over time that indicate impending or incipient malignancy and to facilitate surveillance of melanocytic skin lesions, particularly in patients with multiple clinically atypical nevi.

Objective: Our purpose was to report on patterns of modifications over time observed in benign melanocytic skin lesions and melanoma.

Methods: A total of 1862 sequentially recorded DELM images of melanocytic lesions from 202 patients (mean age, 36.1 years; 54.0% female patients) with multiple clinically atypical nevi were included in the analysis. The median follow-up interval was 12.6 months. Melanocytic lesions with substantial modifications over time (enlargement, changes in shape, regression, color changes or appearance of ELM structures known to be associated with melanoma) were excised and referred to histopathologic examination.

Results: A total of 75 melanocytic skin lesions (4.0%) from 52 patients (mean age, 33.3 years; 63.5% female patients) showed substantial modifications over time and were excised and referred to histopathologic examination. Eight changing lesions were histologically diagnosed as early melanomas. These lesions frequently showed focal enlargement associated with a change in shape as well as appearance of ELM structures that are known to be associated with melanoma. In contrast, the majority of benign changing lesions (common and atypical nevi) showed symmetric enlargement without substantial structural ELM changes. Six of the 8 patients in whom melanoma developed were unaware of the fact that the lesion had changed over time.

Conclusion: We demonstrate that follow-up of melanocytic lesions with DELM helps to identify patterns of morphologic modifications typical for early melanoma. DELM may therefore serve as a useful tool to improve the surveillance of patients with multiple atypical nevi. (J Am Acad Dermatol 2000;43:467-76.)

Follow-up of melanocytic skin lesions with digital epiluminescence microscopy

Clark's nevus

Melanoma →

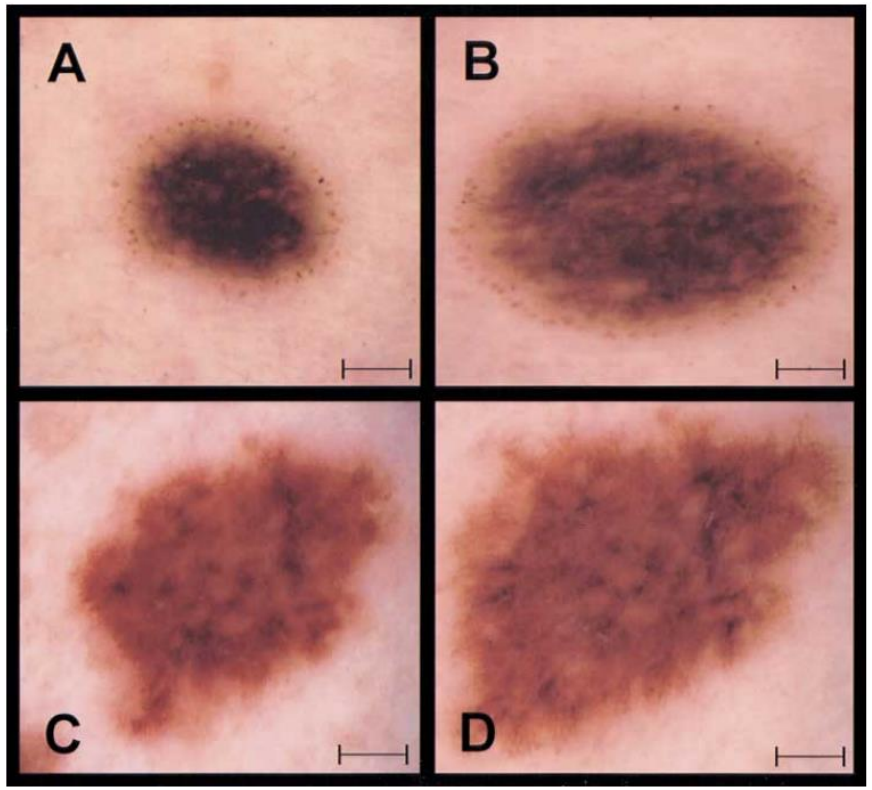


Fig 1. DELM images of two benign melanocytic skin lesions. **A** and **B,** Common nevus with symmetric enlargement without substantial structural modifications. *Right image* **(B)** was obtained 6 months after *left image*. Peripheral rim of brown globules **(A)** is a highly characteristic feature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

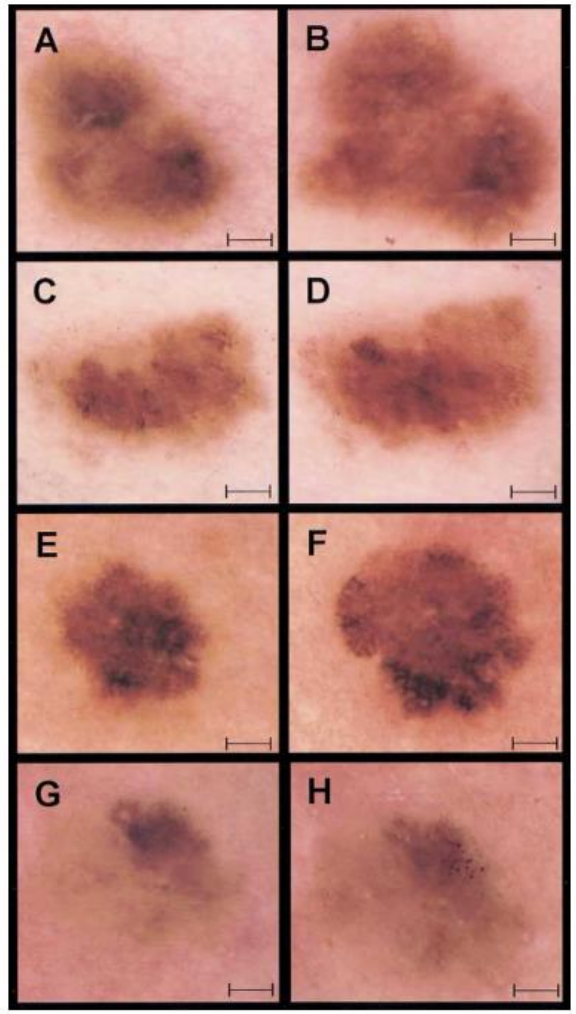
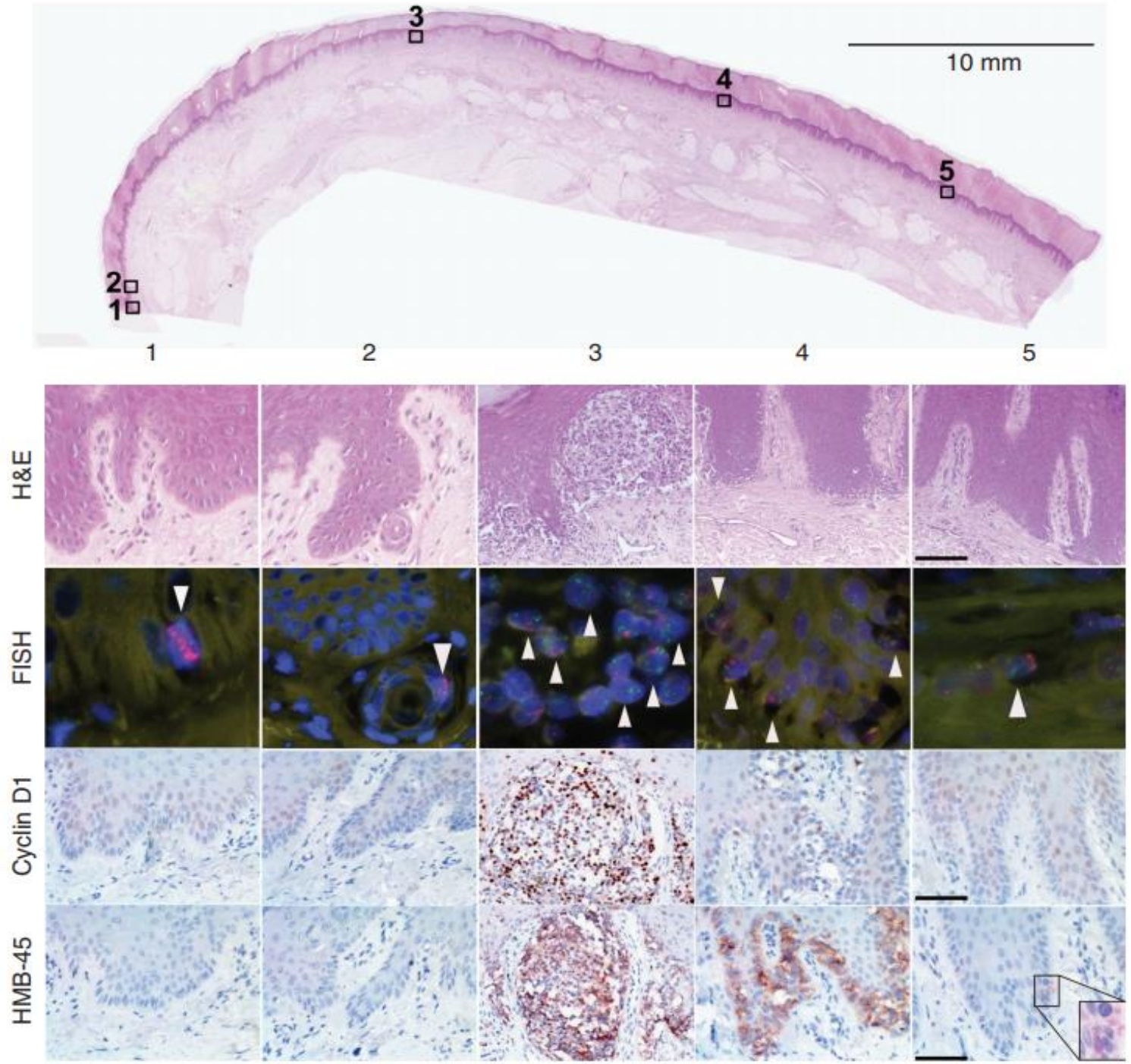


Fig 4. Four early melanomas with substantial morphologic modifications over time identified by follow-up with DELM. **A** and **B,** Superficial spreading melanoma (Breslow thickness, 0.55 mm; Clark level, II). **B,** This image was obtained 14 months after image shown in **A**. Melanoma shows focal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

revealed different patterns of growth in nevi and incipient melanomas separating both types of lesions from one another.



Genetic studies of melanomas revealed characteristic molecular alterations that were present in the early in-situ stage, even preceding the first identifiable histopathologic alterations. The authors referred to those cells

ORIGINAL ARTICLE

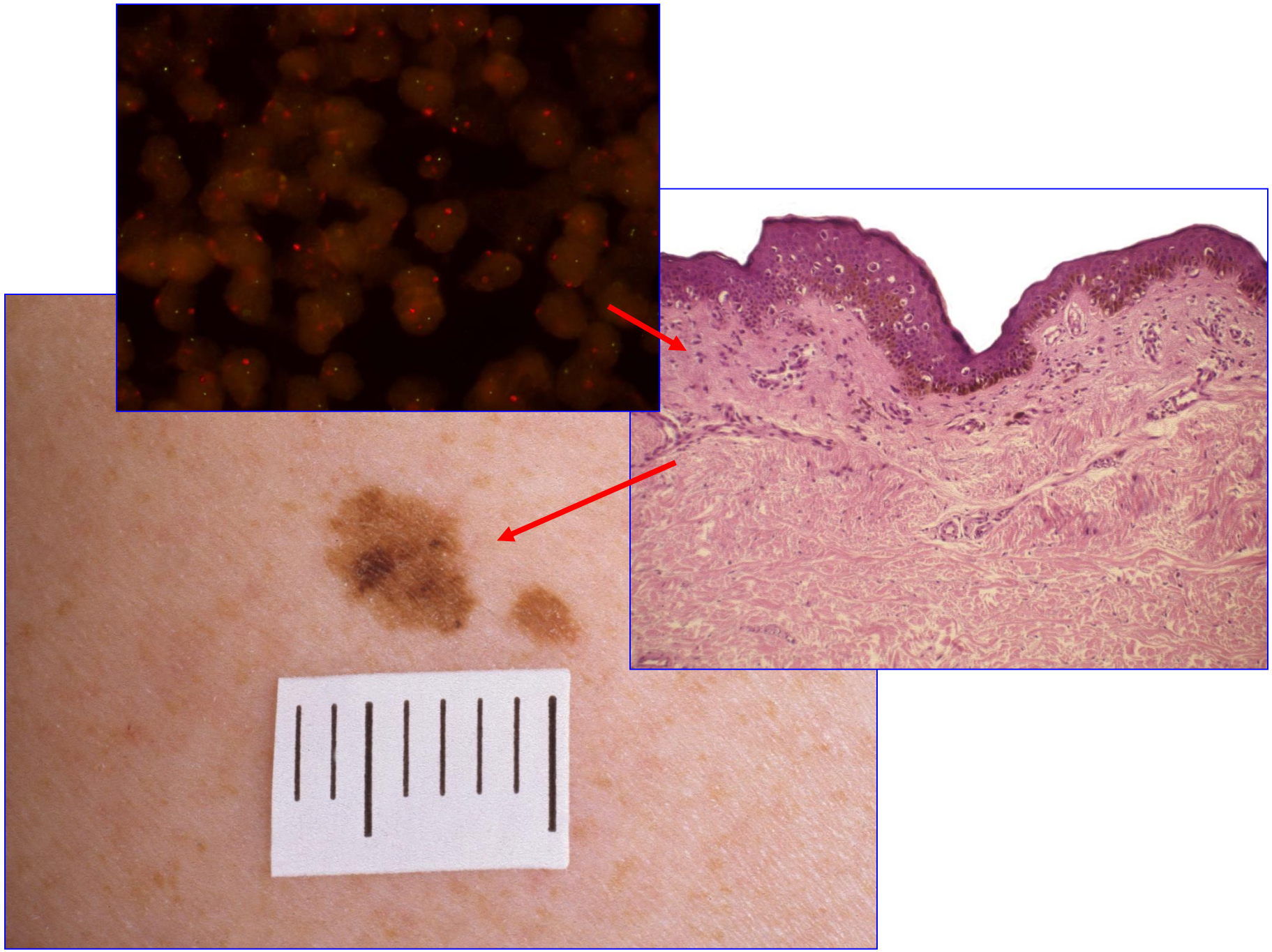
Distribution and Significance of Occult Intraepidermal Tumor Cells Surrounding Primary Melanoma

Jeffrey P. North[1,2], Toshiro Kageshita[3], Daniel Pinkel[4,5], Philip E. LeBoit[4,6] and Boris C. Bastian[4,6]

Primary melanoma can recur at the excision site if not excised with a safety margin of surrounding uninvolved skin. To characterize the nature of residual melanoma in the skin surrounding primary tumors targeted by safety margins, we used array comparative genomic hybridization and fluorescent *in situ* hybridization to detect and spatially map aberrations in the skin adjacent to acral melanomas. Melanocytic cells with genetic amplifications in histopathologically normal skin (field cells) were detected exclusively in the epidermis in 84% of 19 cases, with a mean extension of 6.1 mm (*in situ* melanomas) and 4.5 mm (invasive melanomas) beyond the histopathological margin. Genetic profiling of these field cells indicated that they represent an early phase of disease preceding melanoma *in situ*. The extent of field cells did not correlate with tumor depth or diameter, indicating that tumor depth is not suited to predict the extent of field cells. These results demonstrate that, on acral sites, melanoma field cells extend significantly into seemingly normal skin. These field cells provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision.

Journal of Investigative Dermatology (2008) **128,** 2024–2030; doi:10.1038/jid.2008.41; published online 6 March 2008

as *"an early phase of disease preceding melanoma in situ,"* but this is imprecise; in actuality they represent the early phase of melanoma in situ preceding the first visible manifestations of it.



Although melanoma results from a series of molecular alterations that accumulate in time because of genetic instability, its fundamental nature is usually established before there is a lesion, before the first histopathologic changes are detectable that, in turn, precede the first visible clinical changes. By the time a lesion is noted by the patient or physician, the decisive phase of multistep carcinogenesis is over, and criteria for malignancy are fulfilled.

TABLE I. *Criteria for the Histologic Diagnosis of Malignant Melanoma*

Architectural Pattern:
Wide lateral extent of the lesion, i.e., greater than 6 mm
Asymmetry of the lesion
Horizontal extension of atypical melanocytes within the epidermis, beyond the bulk of the intraepidermal and intradermal components of the neoplasm
Increased number of atypical melanocytes, singly and/or in nests, within the epidermis
Atypical melanocytes at all levels of the epidermis, even the cornified layer
Variation in sizes and shapes of nests of atypical melanocytes within the epidermis; shapes irregular
Confluence of nests of melanocytes within the epidermis and the dermis
Presence of atypical melanocytes in epithelial structures of adnexa
Failure of maturation of atypical melanocytes with progressive descent into the dermis (i.e., the nuclei do not become smaller)
Cytologic features:
Atypical melanocytes
Melanocytes in mitosis (some of them may be atypical)
Necrotic melanocytes

There are many such criteria, and nearly all of them pertain to changes in the epidermis and adnexal epithelium, rendering possible histopathologic diagnosis of melanoma at an in situ stage.

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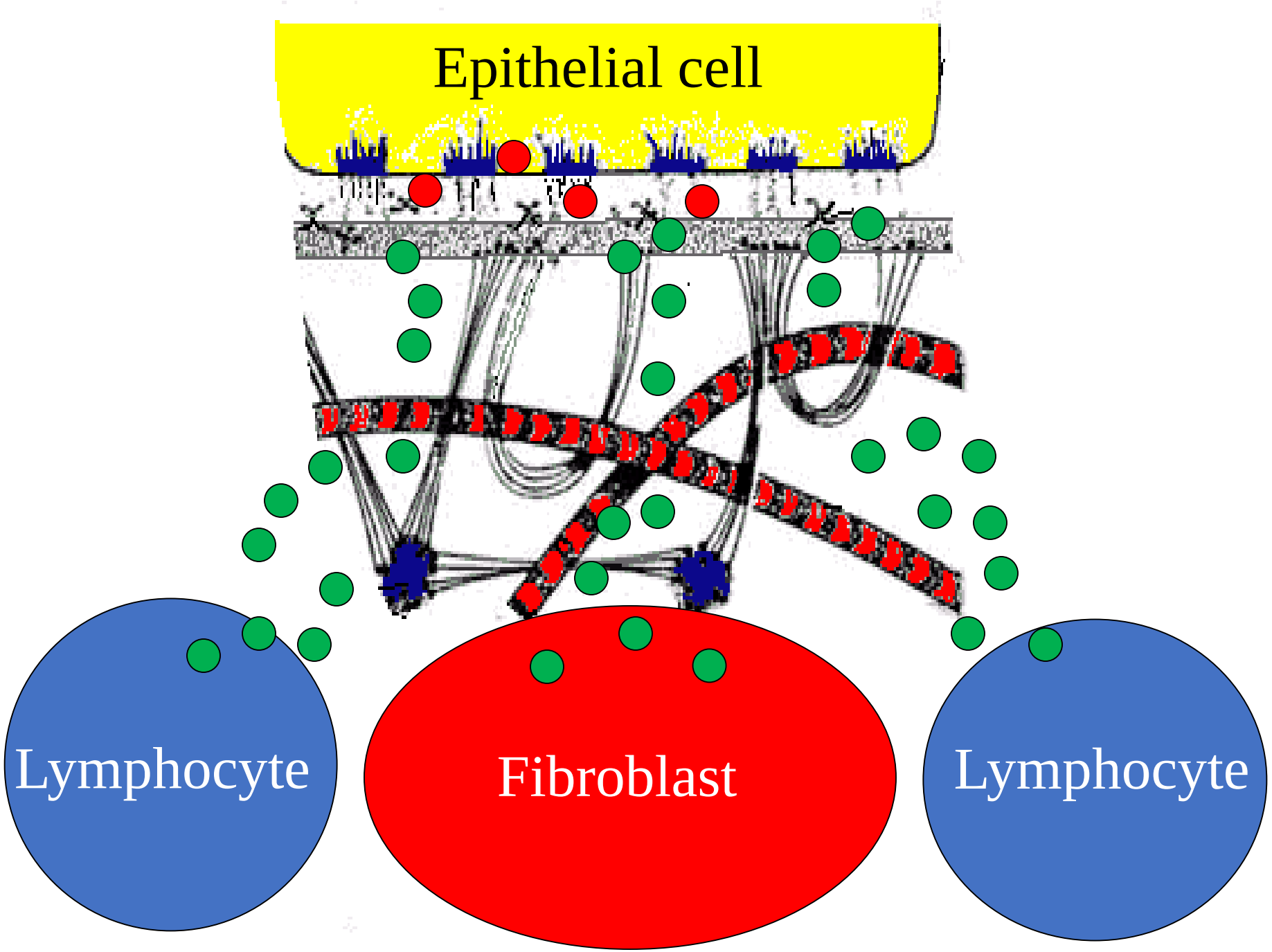
Failure of maturation of atypical melanocytes with progressive descent into the dermis (i.e., the nuclei do not become smaller)
Cytologic features:
Atypical melanocytes
Melanocytes in mitosis (some of them may be atypical)
Necrotic melanocytes

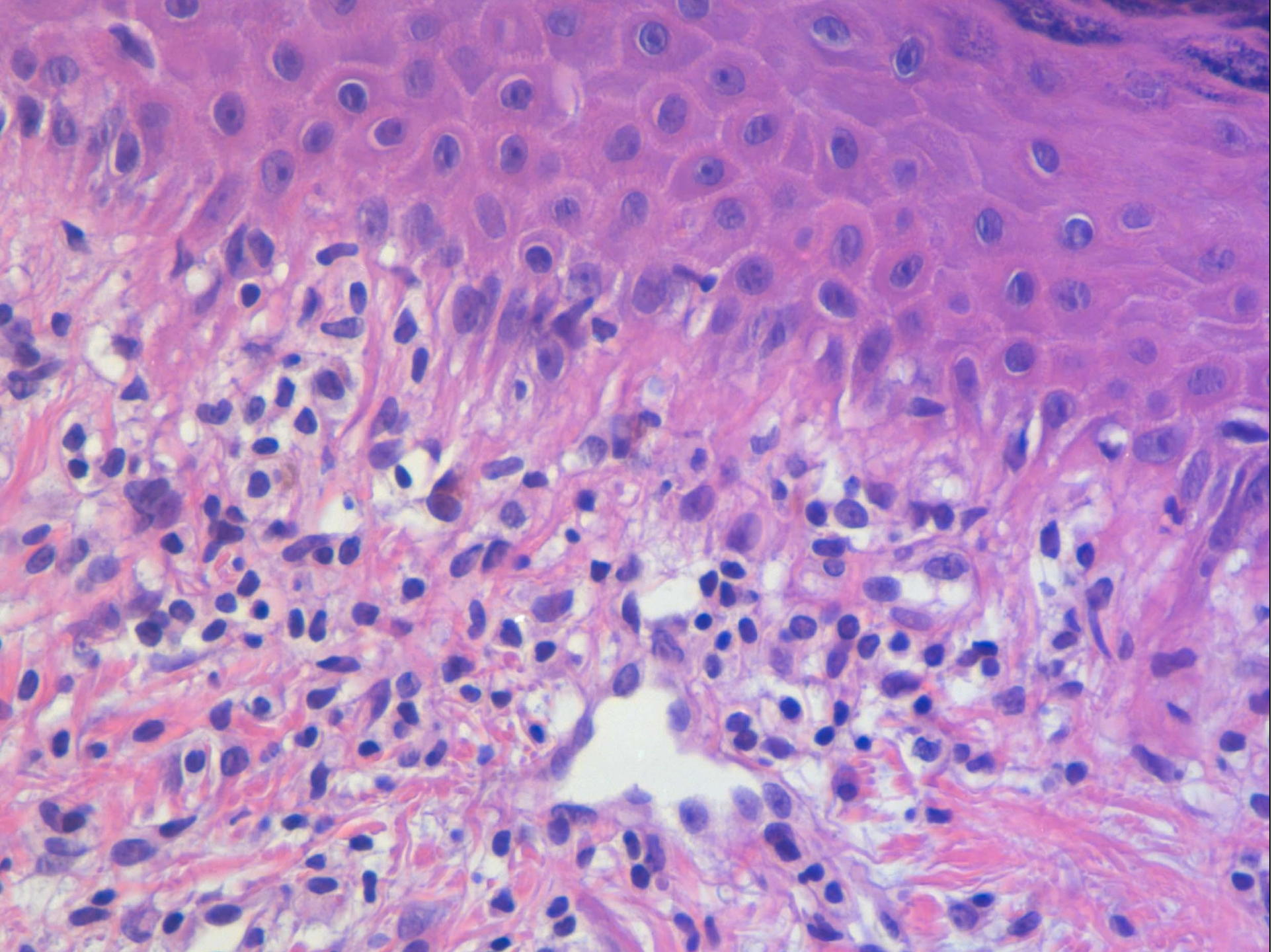
Only few criteria pertain to changes in the dermis, and "invasion" is not among them.

The reason is that the basement membrane is not the strictly guarded frontier as which it is presented in textbooks of oncology;

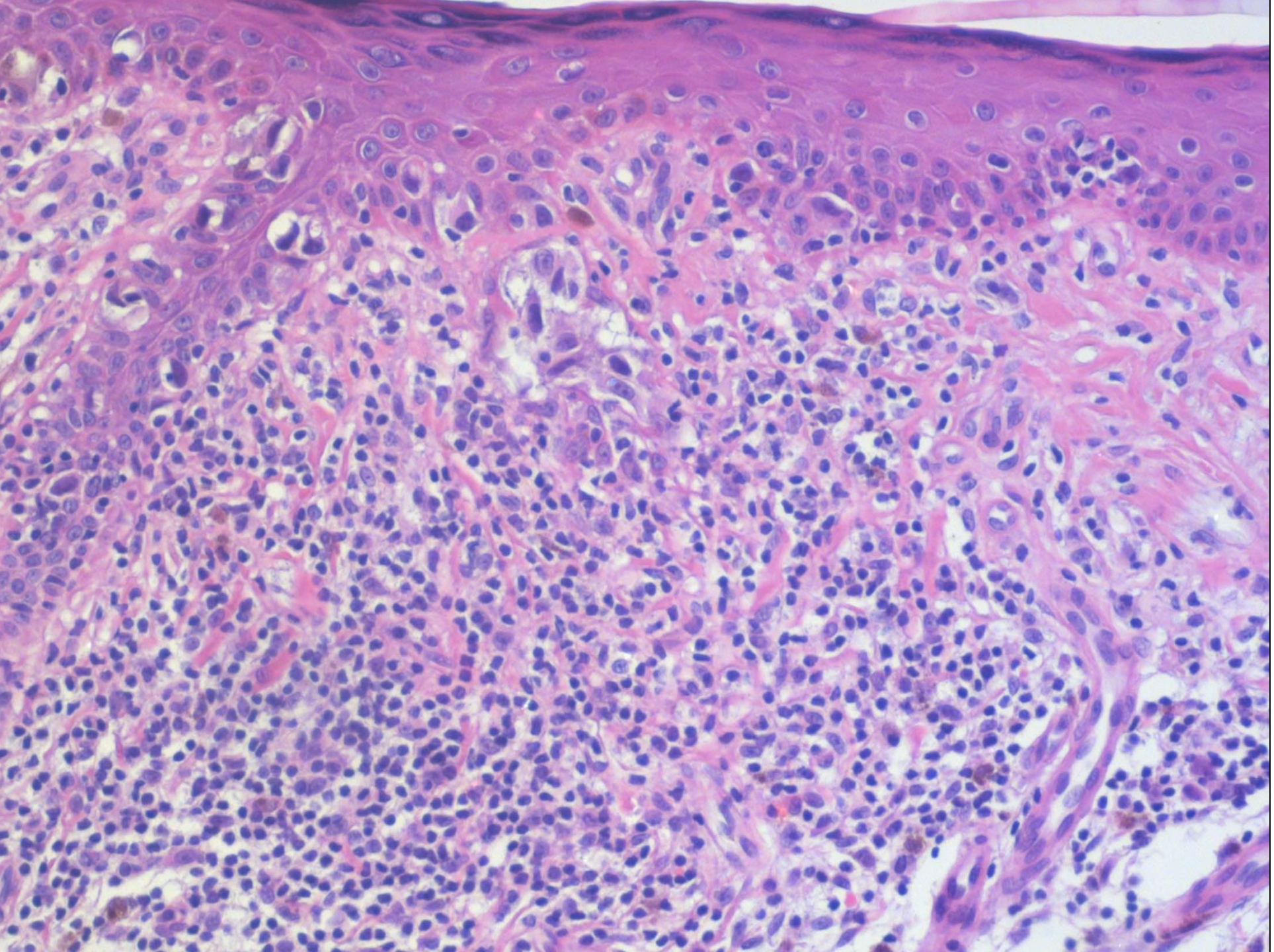
it is a relatively open border where the traffic is waived through.



The basement membrane undergoes continuous remodelling, being dissolved by proteases, especially matrix-metalloproteinases produced by epithelial cells, lymphocytes, and fibroblasts.



It is trespassed in all inflammatory processes affecting the epidermis, with lymphocytes moving up and pigment dropping down.



Inflammation, rather than properties of neoplastic cells, may also be responsible for the invasion of neoplastic cells.

Clin Cancer Res. 2015 March 1; 21(5): 962–968. doi:10.1158/1078-0432.CCR-13-3173.

Molecular Pathways: Linking Tumor Microenvironment to Epithelial–Mesenchymal Transition in Metastasis

Hae-Yun Jung[#1], **Laurent Fattet**[#1], and **Jing Yang**[1,2,*]

[1]Department of Pharmacology, University of California, San Diego, La Jolla, CA, USA

[2]Department of Pediatrics, University of California, San Diego, La Jolla, CA, USA

[#] These authors contributed equally to this work.

Abstract

During tumor development, tumor cells constantly communicate with the surrounding microenvironment through both biochemical and biophysical cues. In particular, the tumor microenvironment can instruct carcinoma cells to undergo a morphogenesis program termed epithelial-to-mesenchymal transition (EMT) to facilitate local invasion and metastatic dissemination. Growing evidence uncovered a plethora of microenvironmental factors in promoting EMT, including pro-inflammatory cytokines secreted by locally activated stromal cells, hypoxia conditions, extracellular matrix components, and mechanical properties. Here, we review various biochemical and biophysical factors in the tumor microenvironment that directly impinge upon the EMT program. Specifically, cytokines such as TGFβ, TNFα and IL6 and hypoxia are capable of inducing EMT in various tumors. Several extracellular matrix (ECM) proteins, including Collagen-I, Fibronectin, and Hyaluronan, and ECM remodeling via extracellular Lysyl oxidase are also implicated in regulating EMT. In preclinical studies and ongoing clinical trials, targeting these tumor microenvironmental signals has shown promises in halting tumor progression in various human cancers.

In recent years, the tumor microenvironment has been implicated with a decisive role in invasion, the *"plethora of microenvironmental factors including pro-inflammatory cytokines secreted by locally activated stromal cells, hypoxia conditions, extracellular matrix components, and mechanical properties."* In brief,

the whole concept of invasion as an aggressive act committed by neoplastic cells may be wrong.

That concept has been adopted from the military, and it was spawn at a time when warfare was clearly arranged.

A declaration of war was handed over with cordial regards,

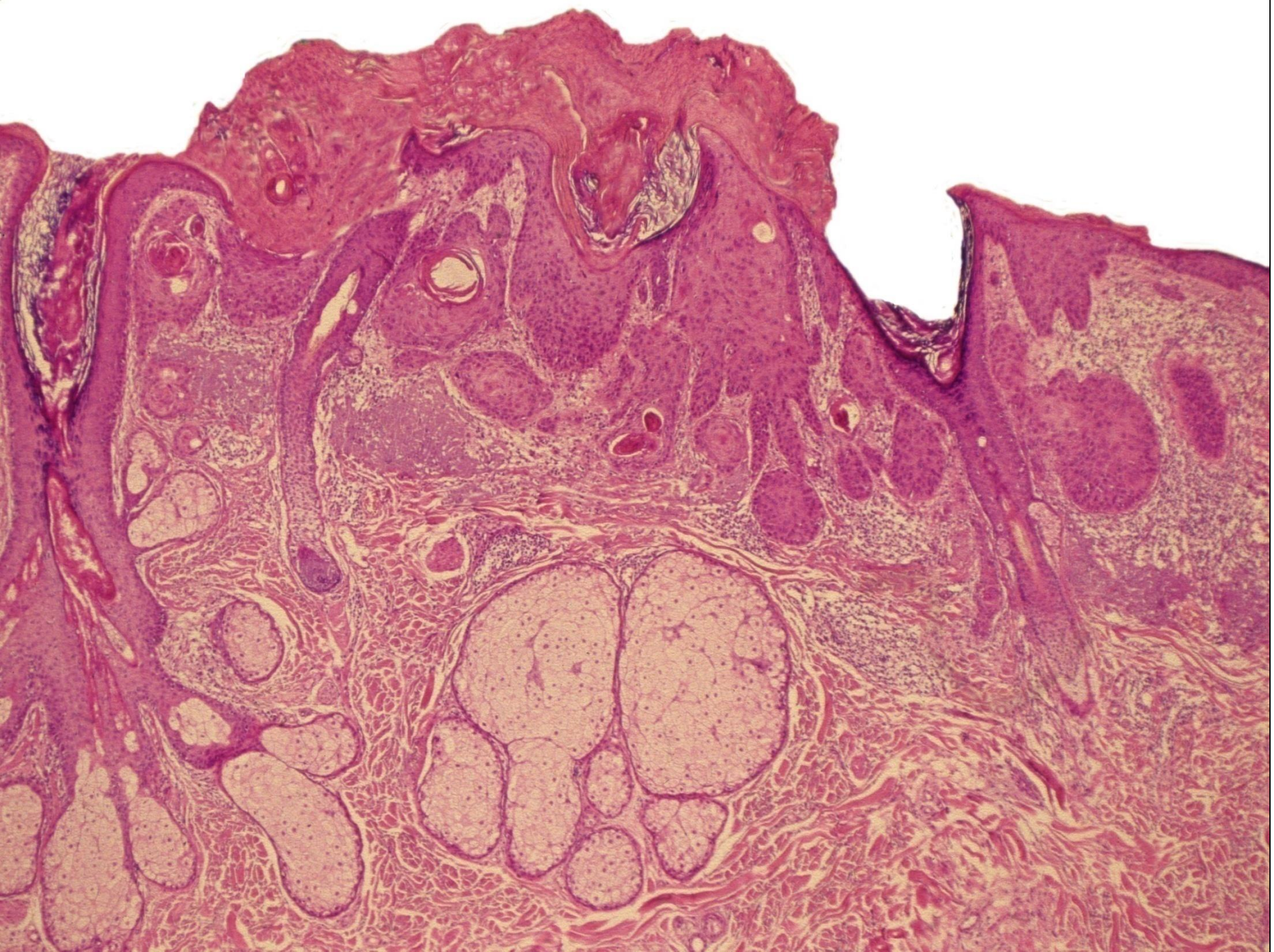
armies were set in motion, and, upon entering the battlefield,

they unfolded flags to notify their presence.

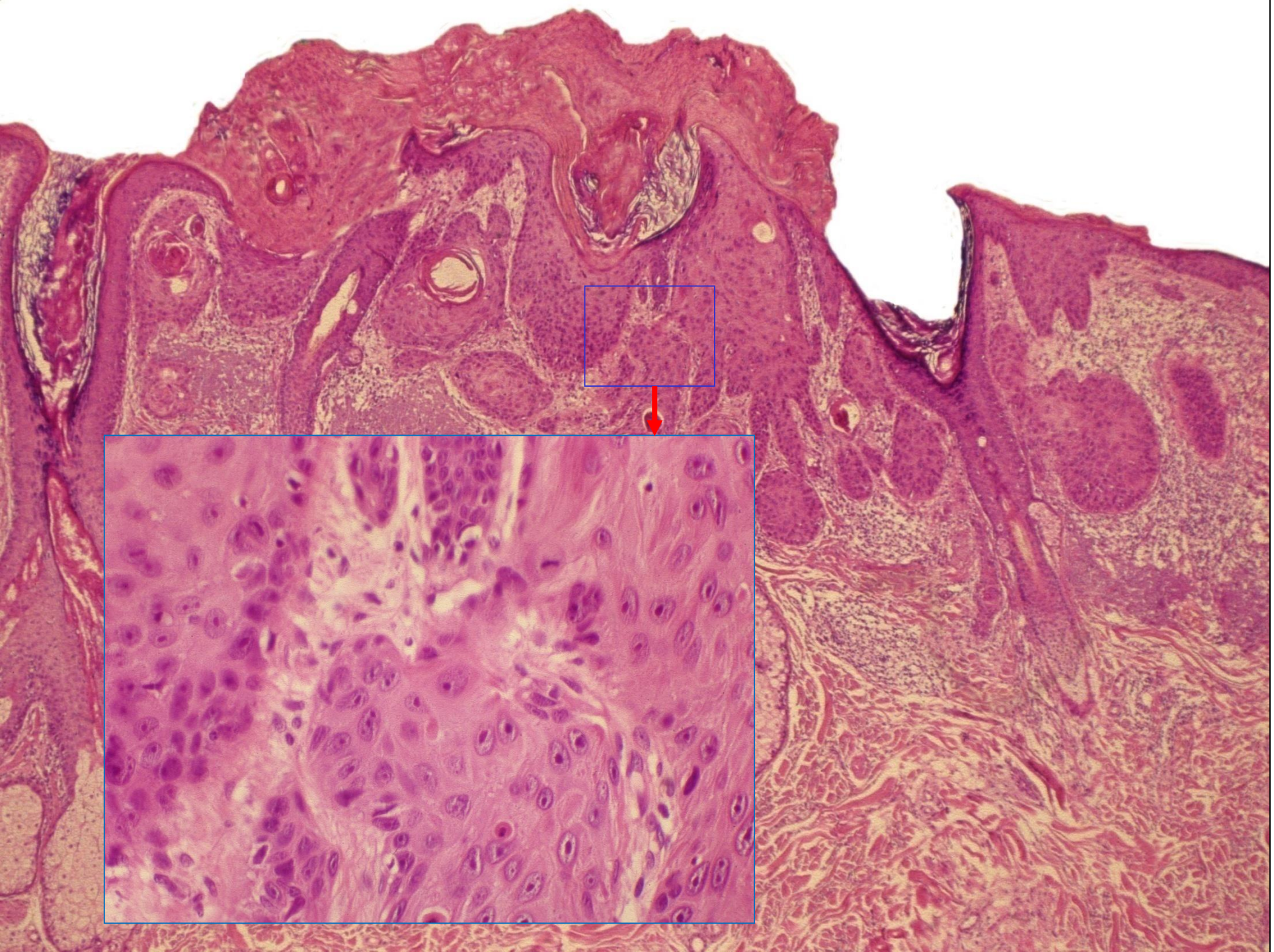
Modern wars are different, often starting without a declaration and sometimes long before being noticed, with enemies in one’s own country who remain invisible

until they strike.

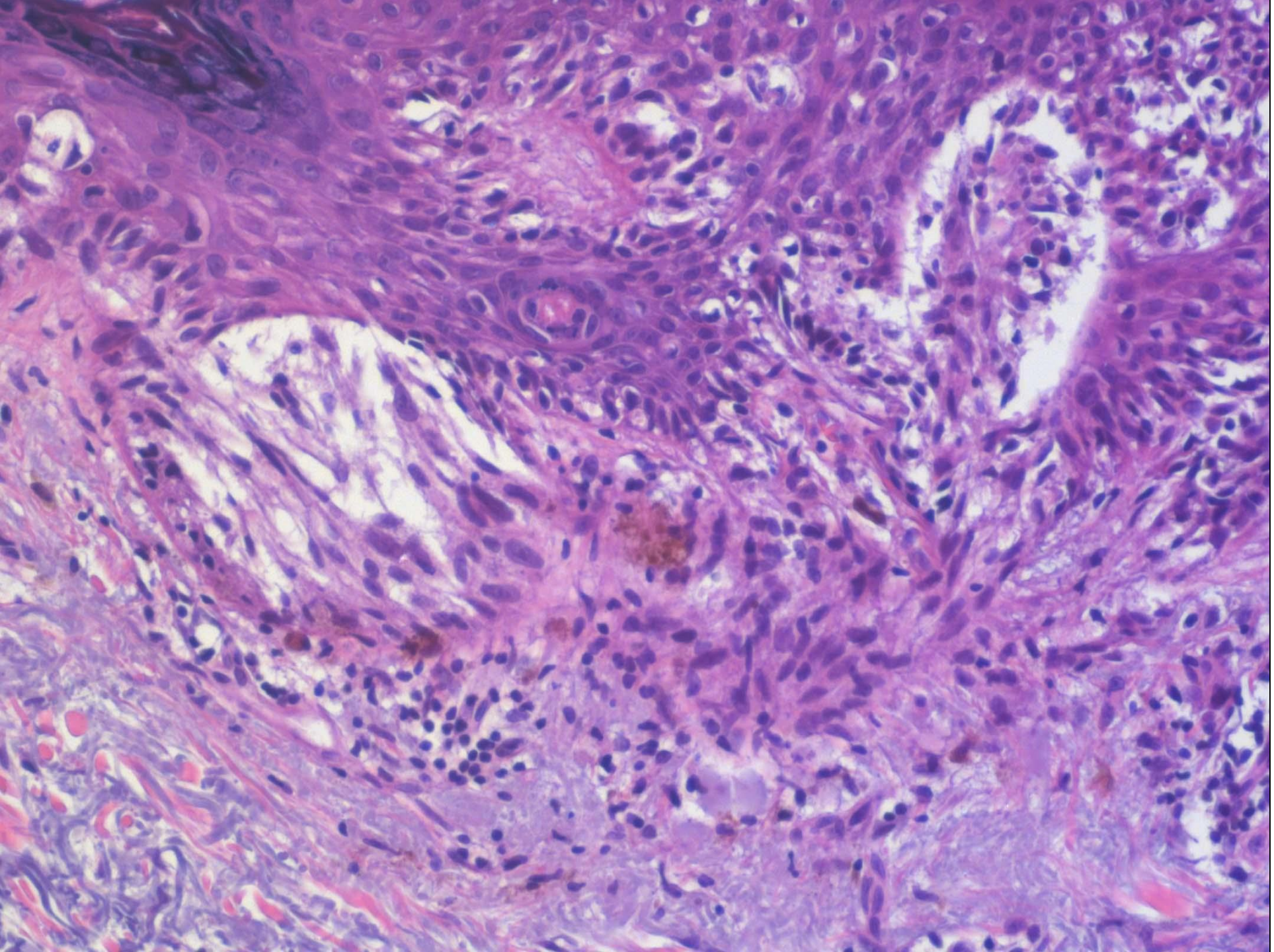
The battle of neoplasia resembles modern warfare. Dissemination of malignant cells starts imperceptibly,



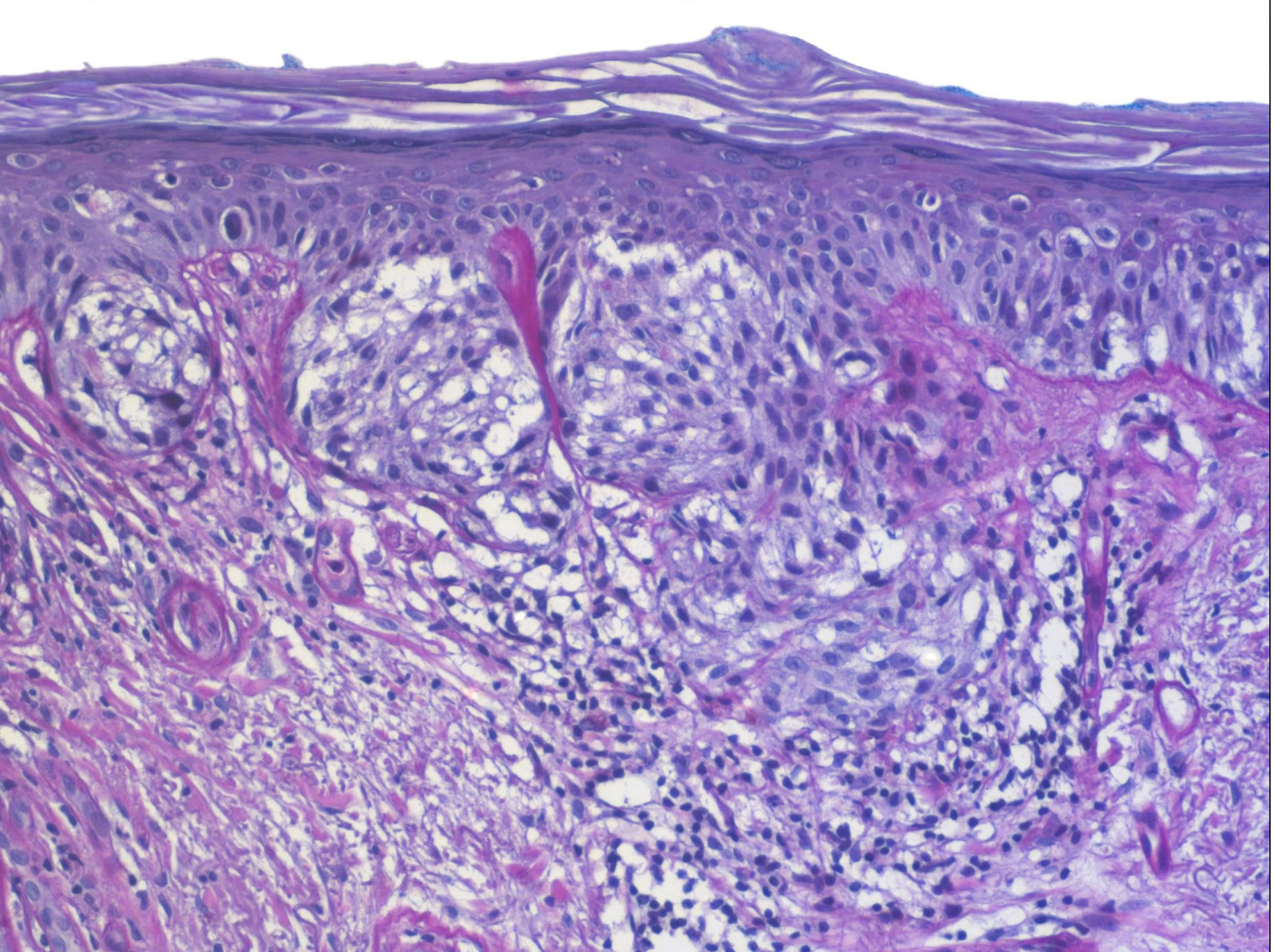
and in the beginning it is often impossible to decide whether or not invasion has occurred. What seem to be detached aggregations of neoplastic cells in the dermis may be connected to surface epithelium at another level,



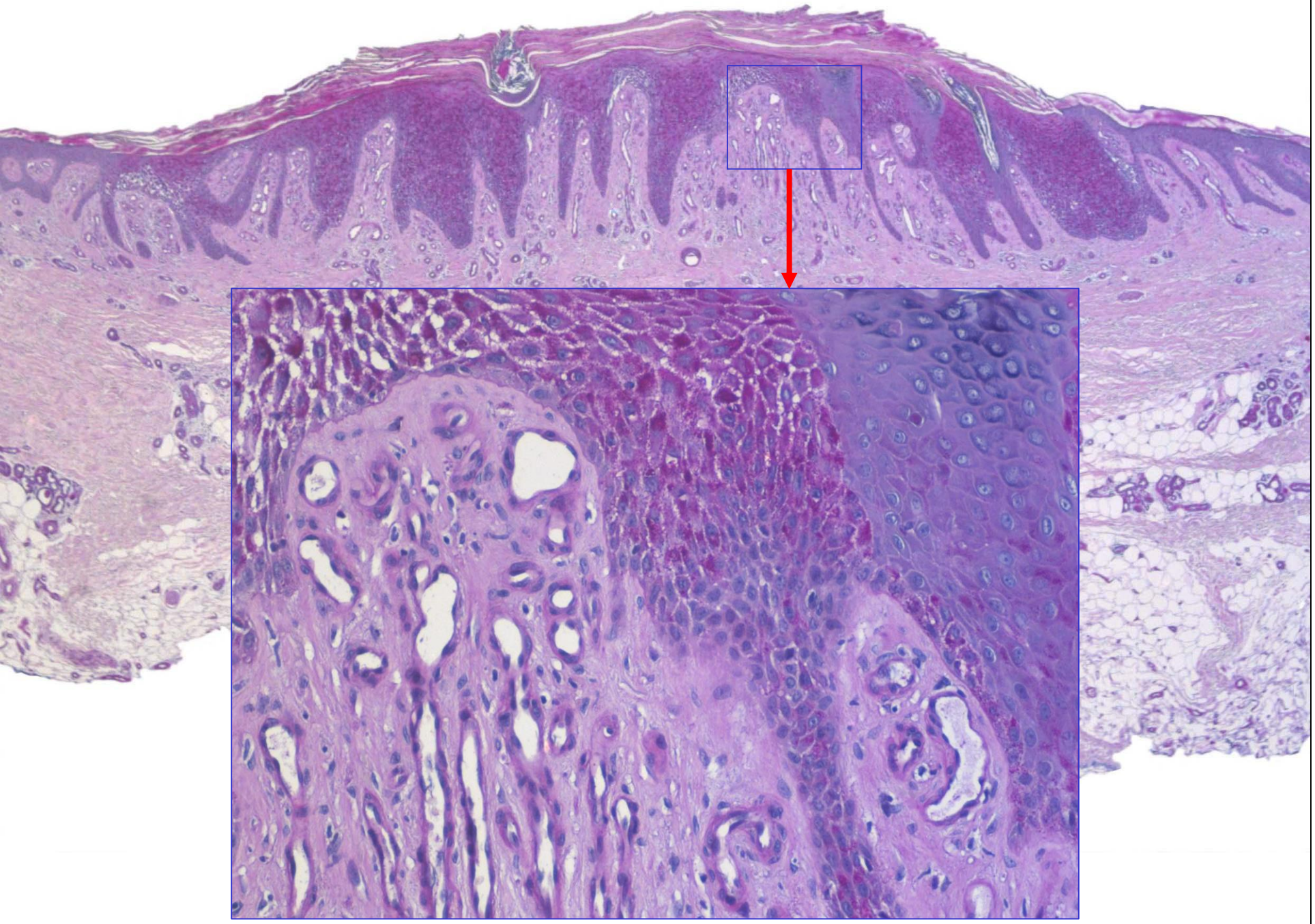
and these thin connections may no longer be visible in deeper sections.



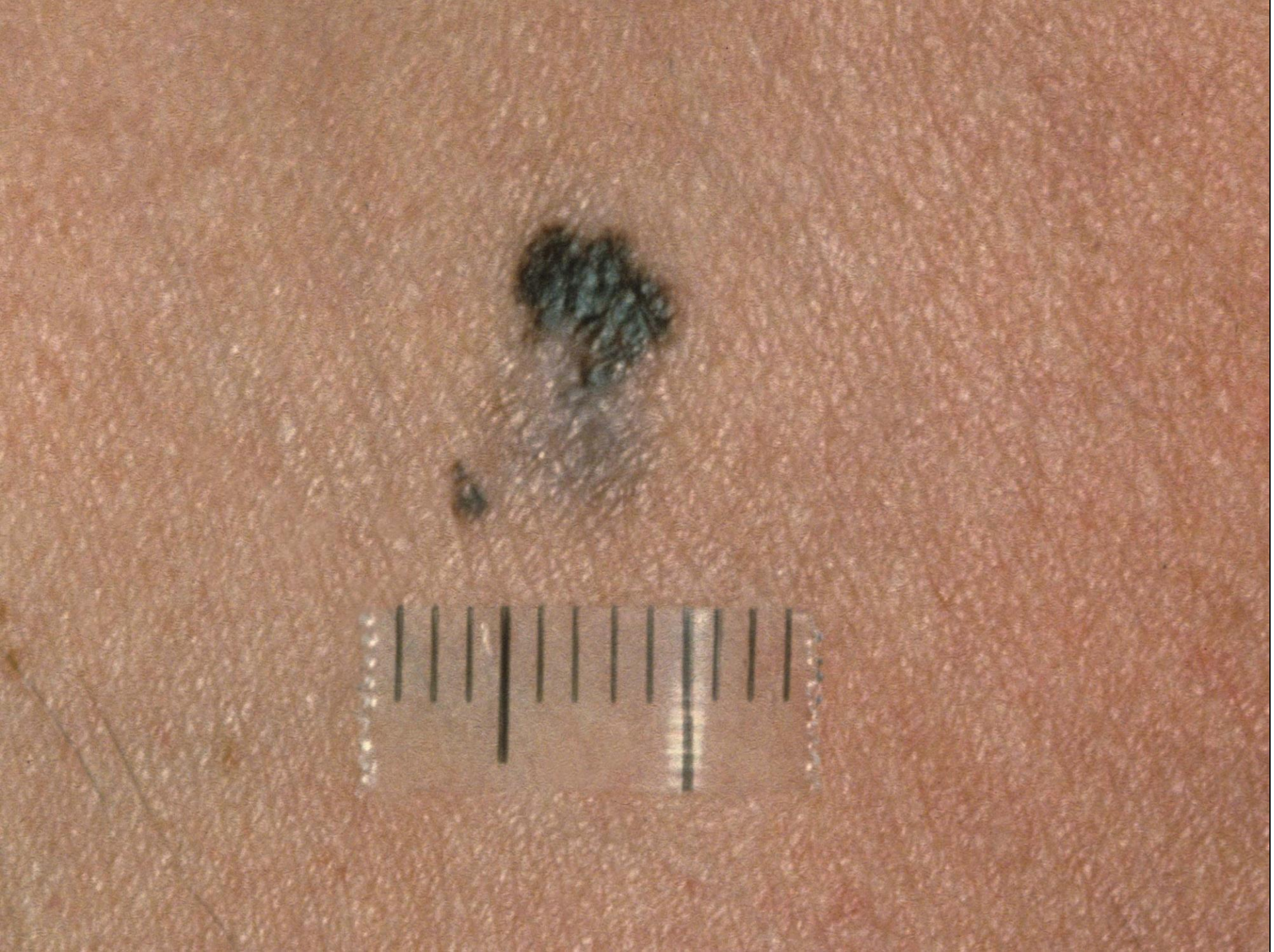
The same difficulties occur in melanocytic neoplasms. It has been claimed that focal loss of the basement membrane indicates invasion,



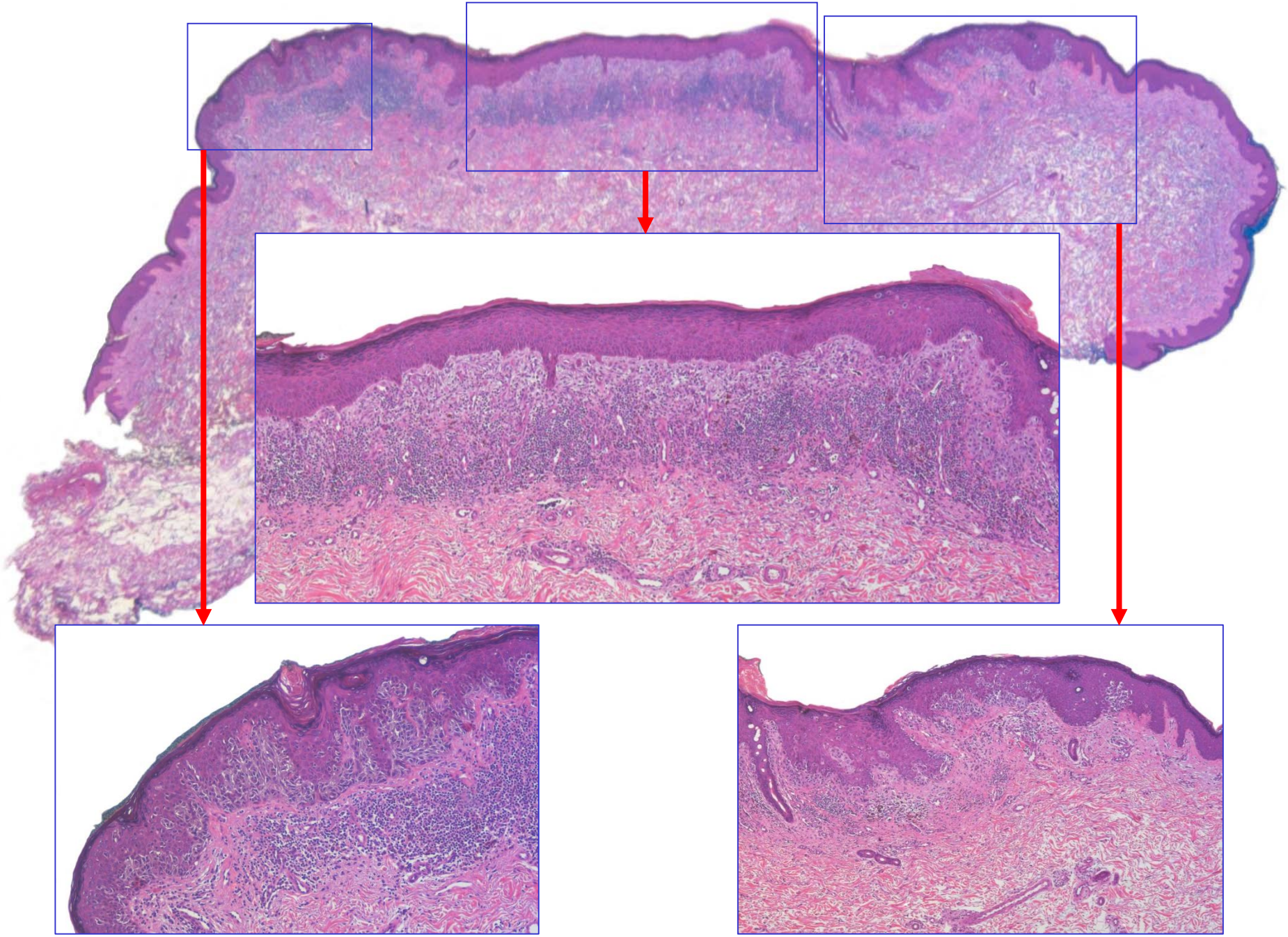
based on findings such as this one, with a detectable basement membrane in the periphery but not at the bottom of those nests. However, focal loss of the basement membrane can be seen in any inflammatory process affecting the epidermis



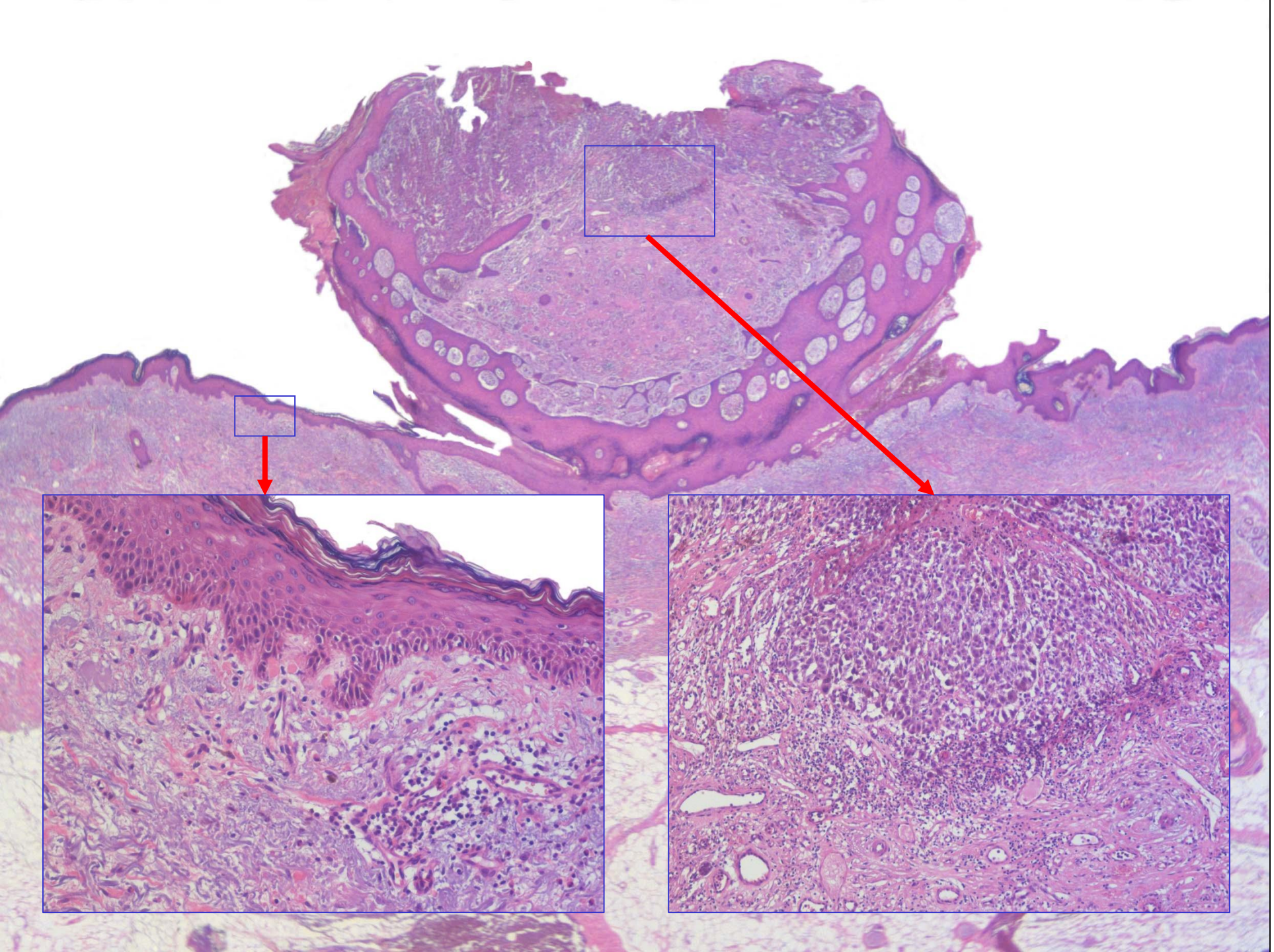
and in any benign epidermal neoplasm, as demonstrated by this case of pale cell acanthoma.



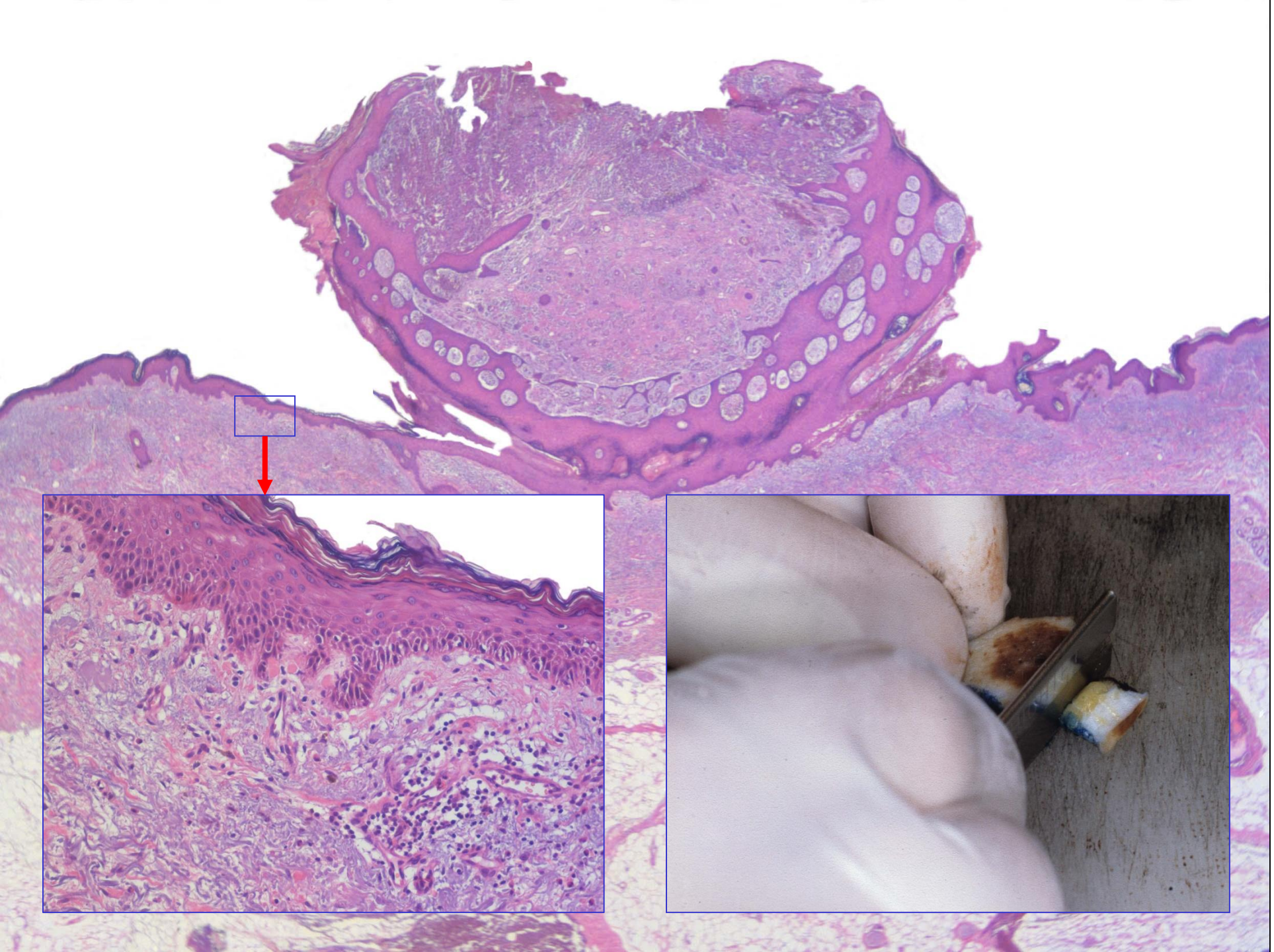
Another problem confounding invasion is the phenomenon of regression that is extremely common in epithelial and melanocytic neoplasms. It may be obvious clinically



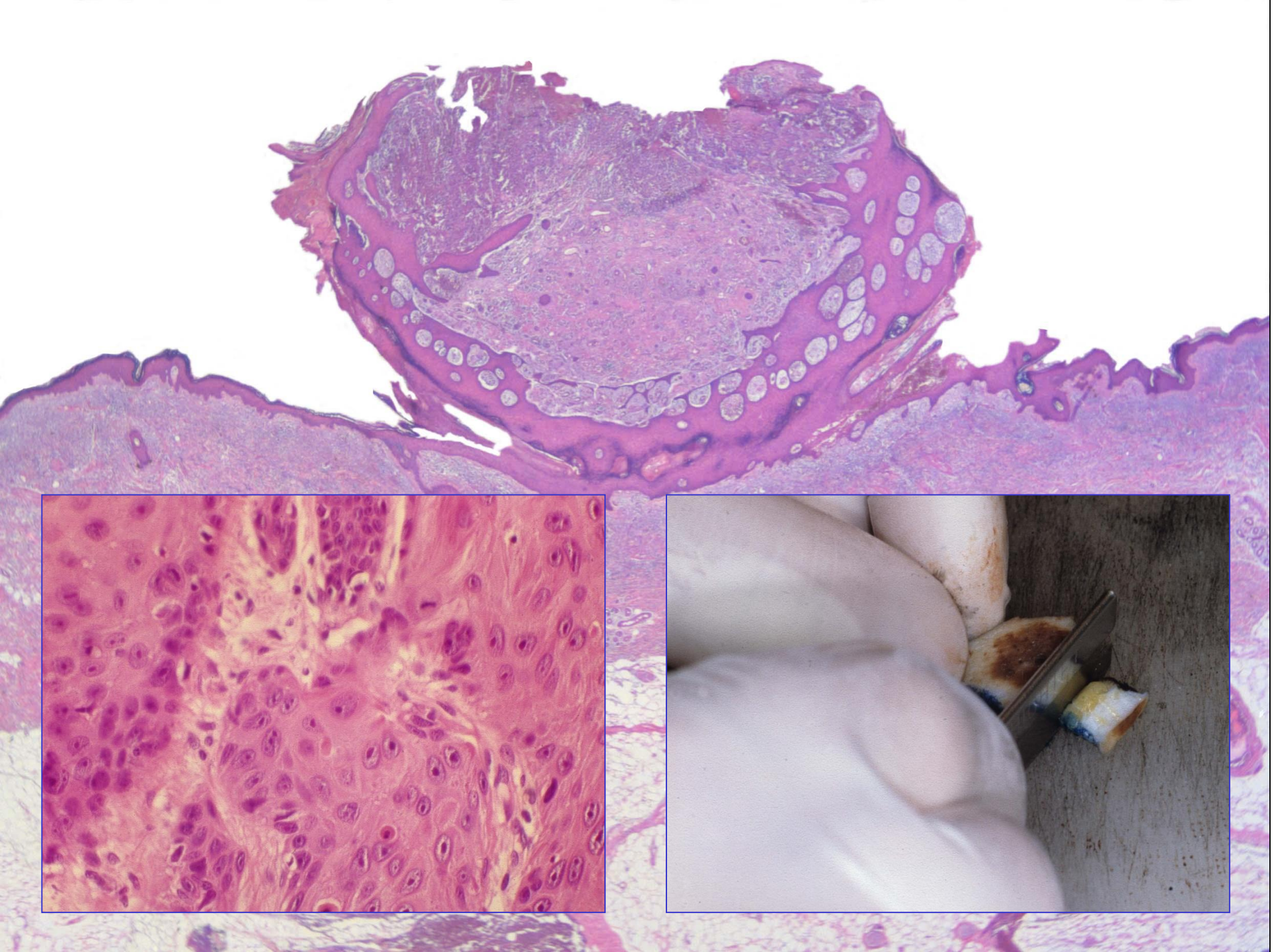
and histopathologically, if loss of neoplastic cells is associated with fibrosis, a dense infiltrate of inflammatory cells, prominent blood vessels and numerous melanophages.



The changes, however, can also be extremely subtle, as in this advanced melanoma in which only few neoplastic cells are left in the exophytic nodule, whereas the periphery shows only subtle fibrosis and some melanophages as clues to the former existence of melanoma. Hence, if no melanocytes can be detected, this does not imply that they have never been there.



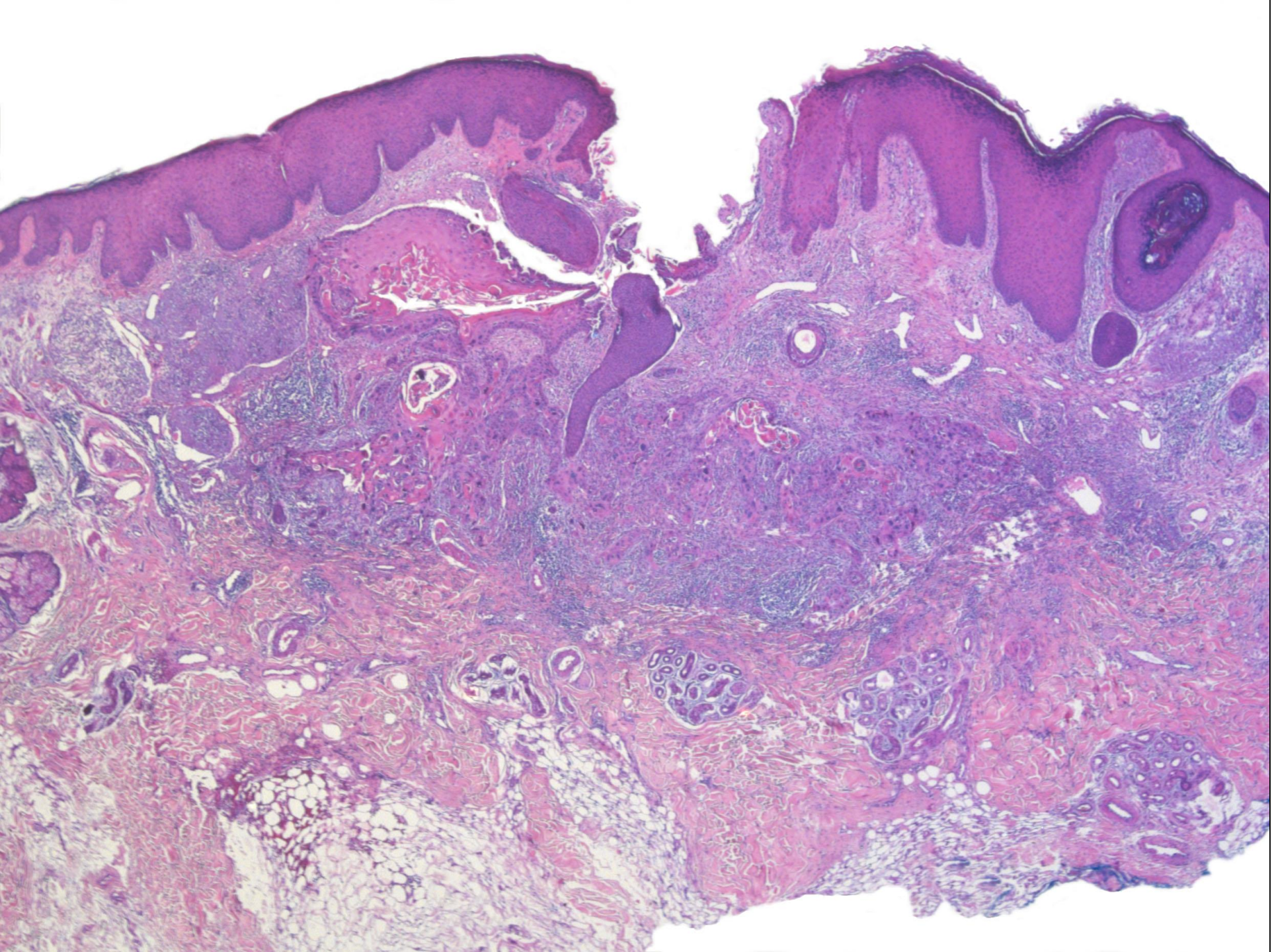
One should also keep in mind that only a small fraction of the specimen is examined histopathologically, no matter how many step sections one cuts, and if one does not find dermal tumor cells in the sections at hand, it does not exclude their presence in other sections.



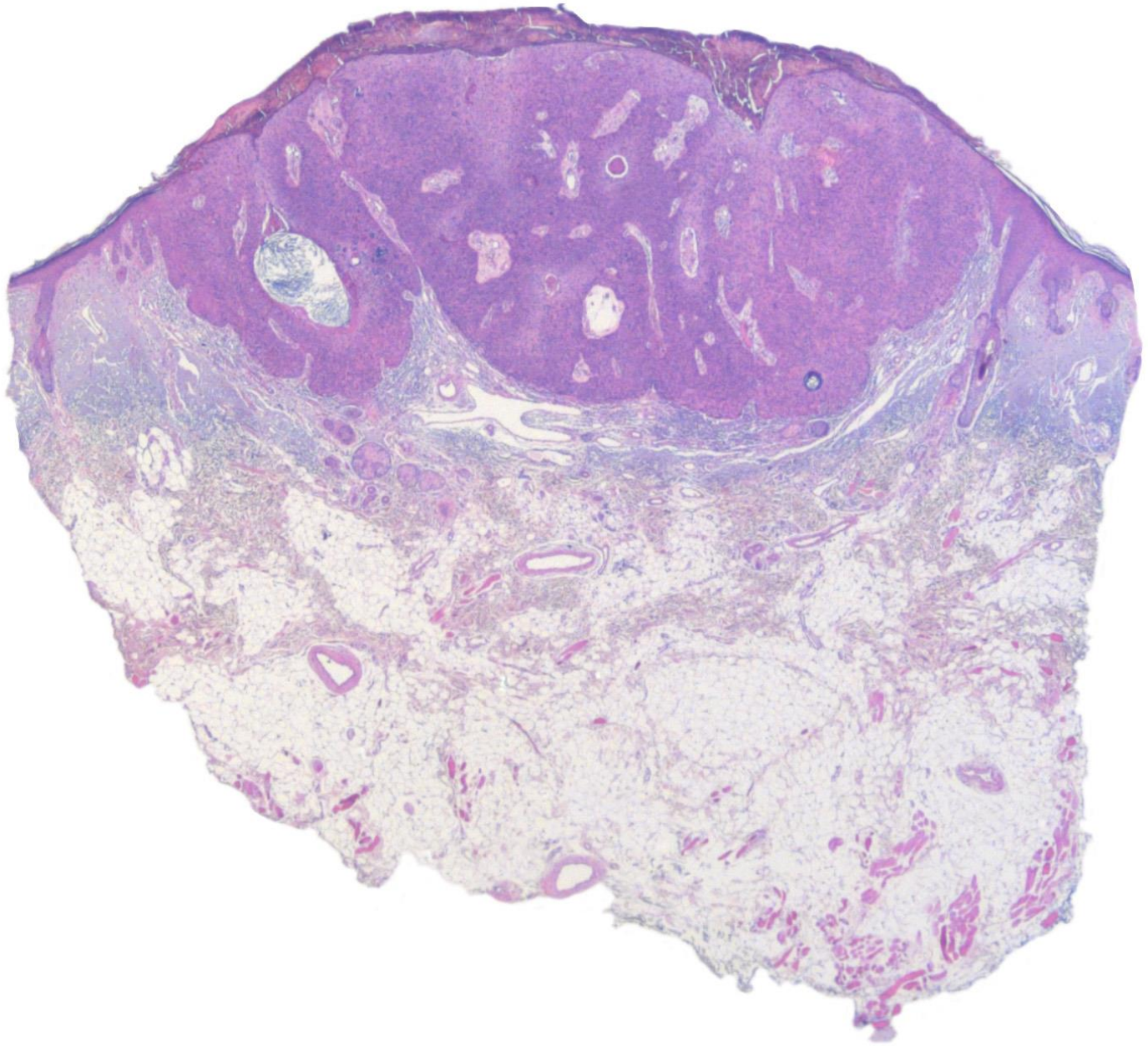
In short, on the one hand, invasion can be simulated by epithelial structures being cut at a tangent,

and on the other hand, secret invasion can never be ruled out. For those reasons alone, invasion should not be used as a conceptual watershed of malignancy.

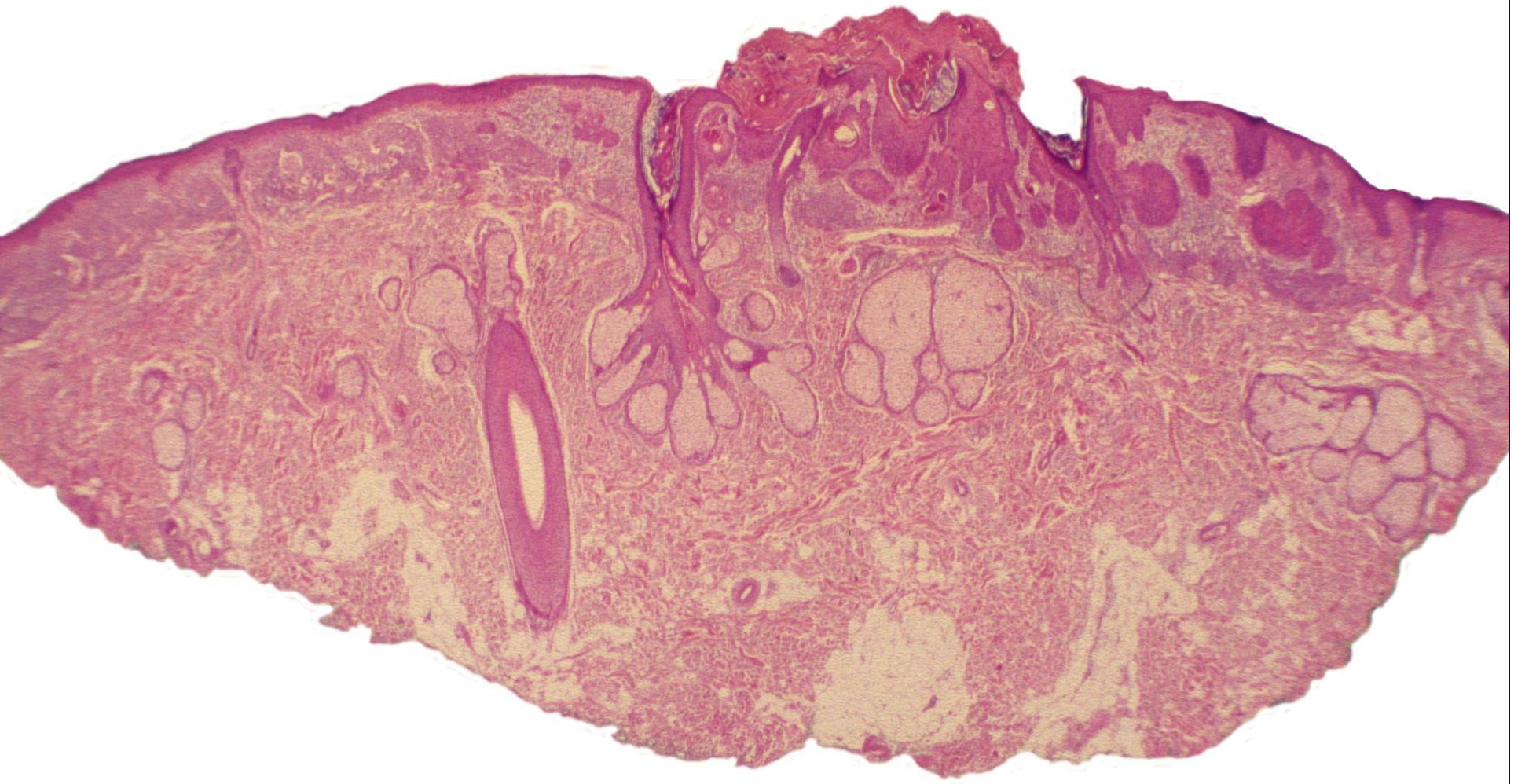
Yet another reason is its paltry biologic significance. Of course, thickness of a lesion and presence of cells in the dermis are correlated with one another, but it has never been shown that invasion per se has any impact on prognosis.



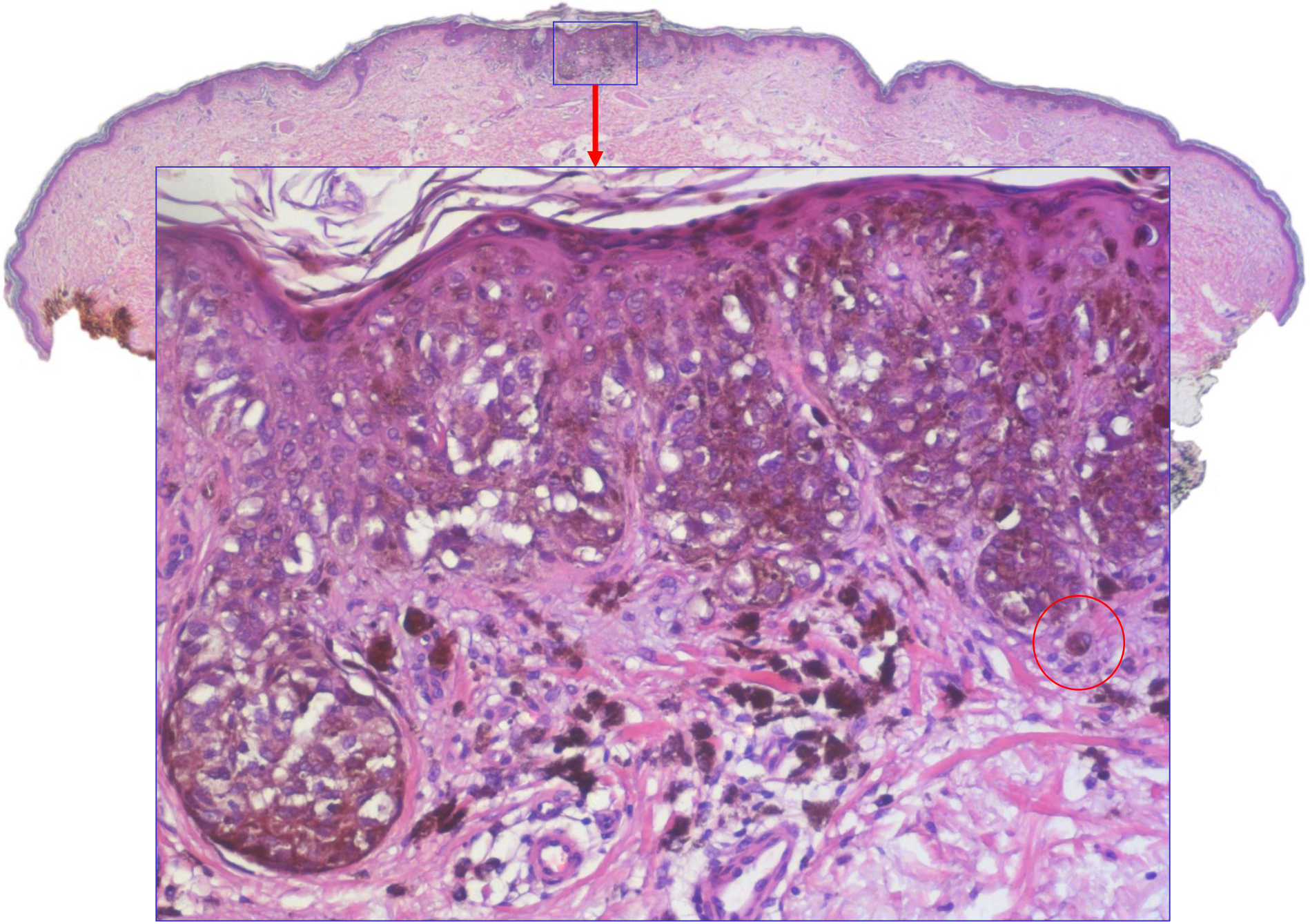
Yet another reason is its paltry biologic significance. Of course, thickness of an epithelial lesion and presence of detached cells in the dermis are correlated with one another, but it has never been shown that invasion per se has any impact on prognosis.



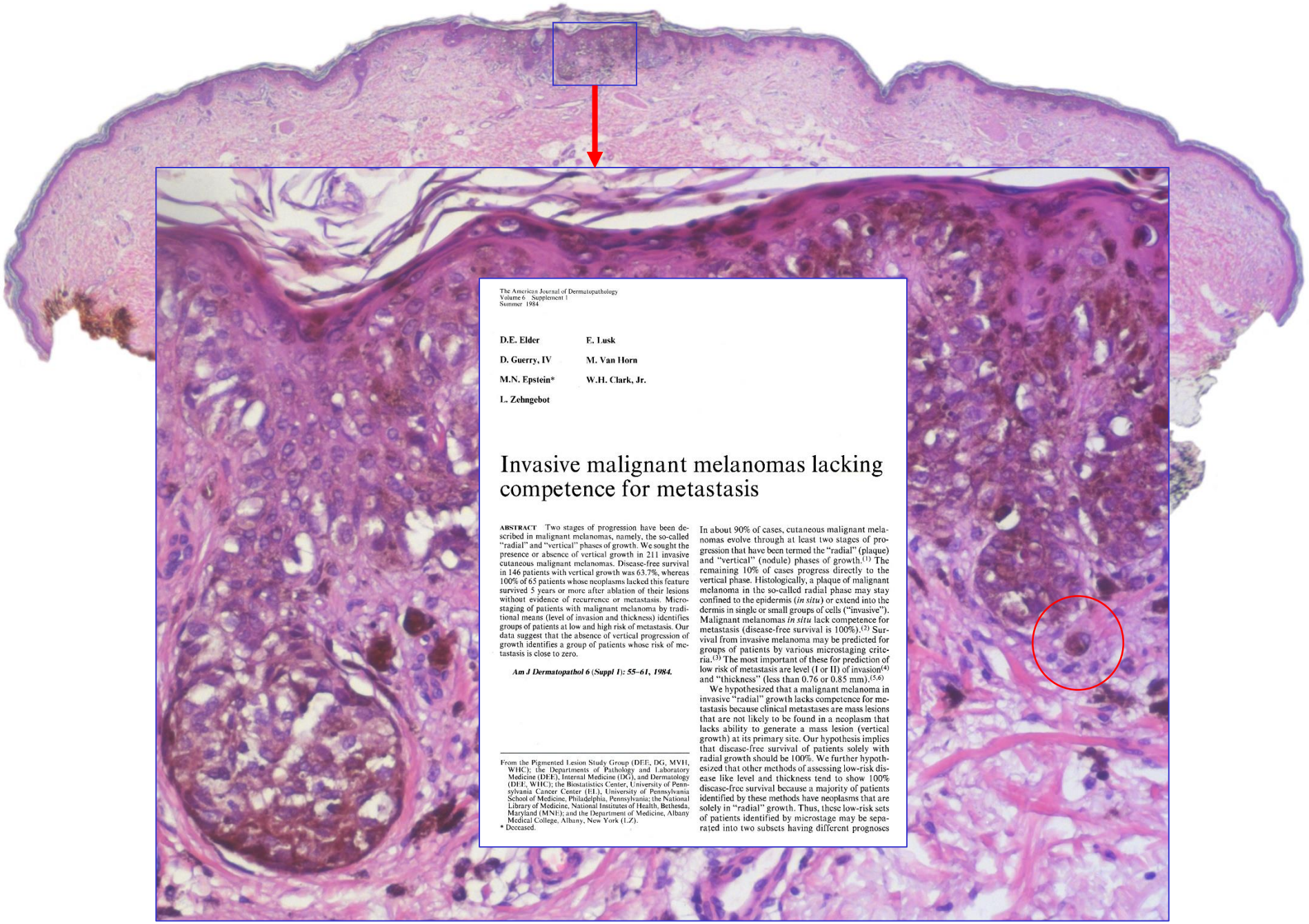
Prognosis of a relatively thick squamous-cell carcinoma without evidence of invasion may be worse



than that of a thin carcinoma in which invasion seems to have occurred. In a lesion such as this one, the question whether or not invasion has begun is utterly irrelevant. If this thin squamous-cell carcinoma is excised completely, the patient is cured.



The same is true for early melanoma. Whether or not a few cells can be detected in the dermis has no impact on prognosis,



The American Journal of Dermatopathology
Volume 6 Supplement 1
Summer 1984

D.E. Elder
D. Guerry, IV
M.N. Epstein*
L. Zehngebot
E. Lusk
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.

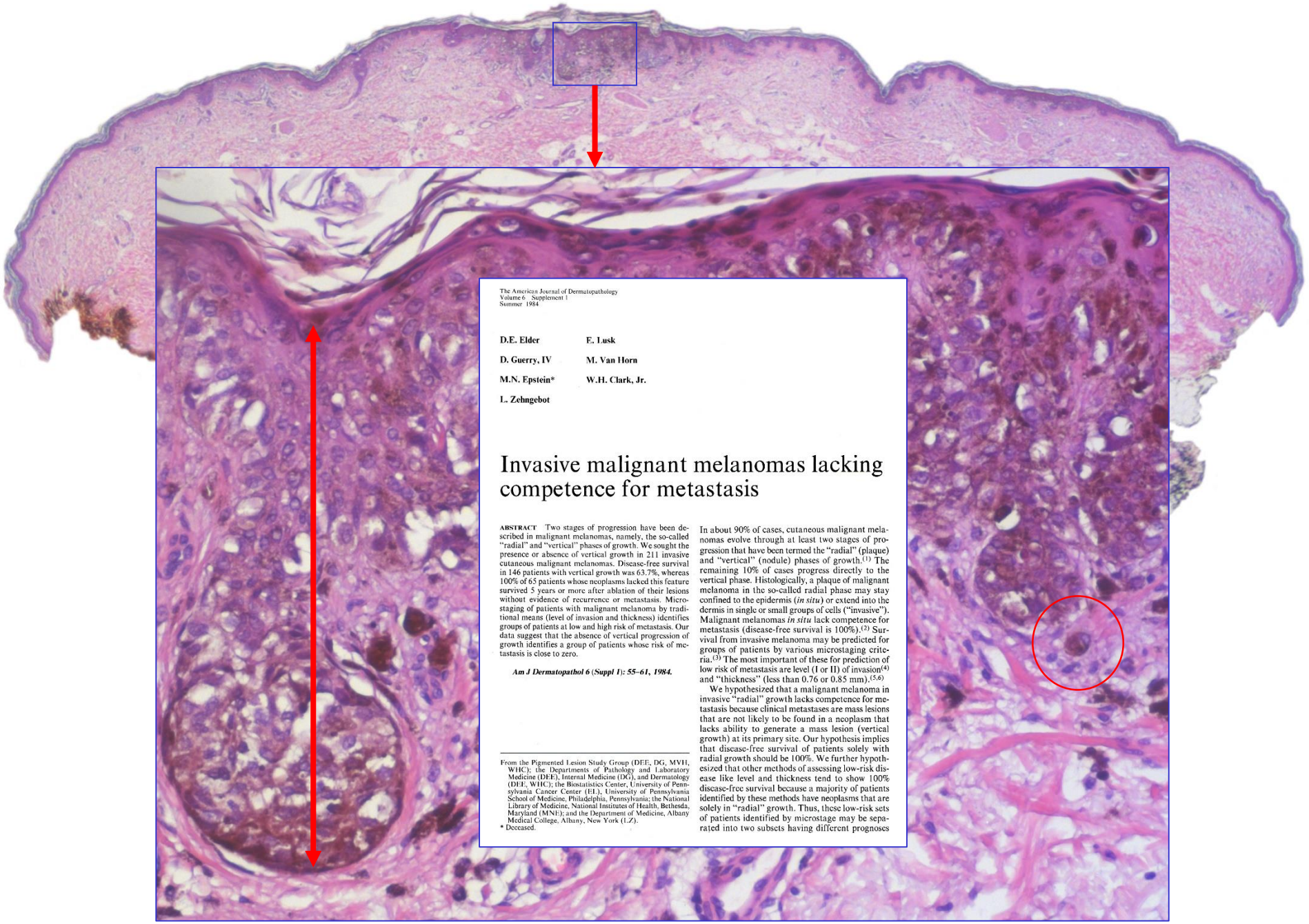
In about 90% of cases, cutaneous malignant melanomas evolve through at least two stages of progression that have been termed the "radial" (plaque) and "vertical" (nodule) phases of growth.[1] The remaining 10% of cases progress directly to the vertical phase. Histologically, a plaque of malignant melanoma in the so-called radial phase may stay confined to the epidermis (*in situ*) or extend into the dermis in single or small groups of cells ("invasive"). 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] and "thickness" (less than 0.76 or 0.85 mm).[5,6]

We hypothesized that a malignant melanoma in invasive "radial" growth lacks competence for metastasis because clinical metastases are mass lesions that are not likely to be found in a neoplasm that lacks ability to generate a mass lesion (vertical growth) at its primary site. Our hypothesis implies that disease-free survival of patients solely with radial growth should be 100%. We further hypothesized that other methods of assessing low-risk disease like level and thickness tend to show 100% disease-free survival because a majority of patients identified by these methods have neoplasms that are solely in "radial" growth. Thus, these low-risk sets of patients identified by microstage may be separated into two subsets having different prognoses

From the Pigmented Lesion Study Group (DEE, DG, MVH, WHC); the Departments of Pathology and Laboratory Medicine (DEE), Internal Medicine (DG), and Dermatology (DEE, WHC); the Biostatistics Center, University of Pennsylvania Cancer Center (EL), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; the National Library of Medicine, National Institutes of Health, Bethesda, Maryland (MNE); and the Department of Medicine, Albany Medical College, Albany, New York (LZ).
* Deceased.

and it has even been claimed that there are *"invasive malignant melanomas lacking competence for metastases."* This is not completely true; any melanoma may metastasize, including those that seem to be in situ, but the risk is negligible, and so is the biologic significance of invasion.

If a gauge for prognosis is needed, it would be preferable, in my view,



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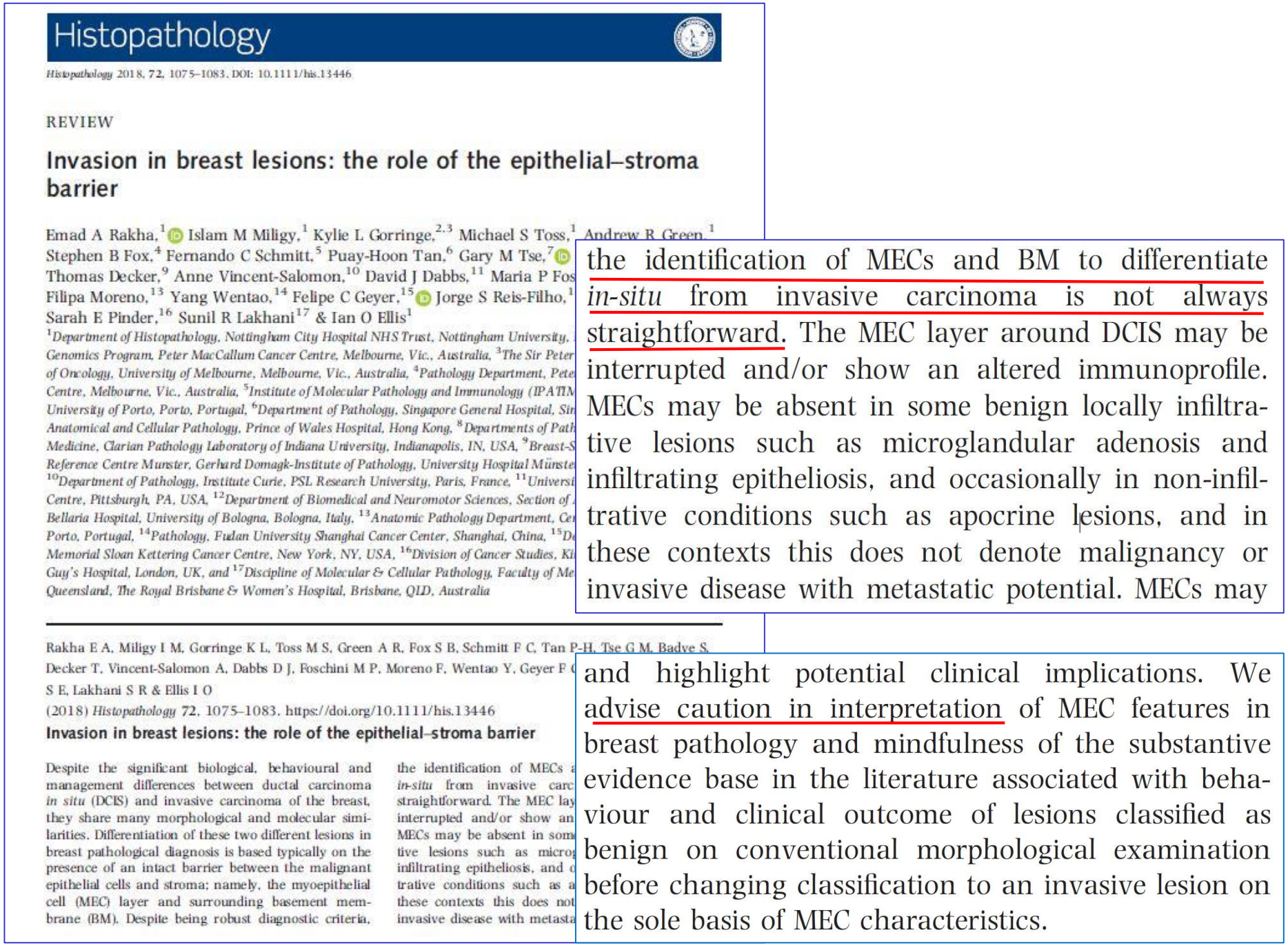
to measure the thickness or volume of a lesion and to waive the criterion of invasiveness. Despite its widespread use in pathology, the latter is flawed, and not only in regard to lesions of the skin.



Histopathology

Histopathology 2018, 72, 1075–1083. DOI: 10.1111/his.13446

REVIEW

Invasion in breast lesions: the role of the epithelial–stroma barrier

Emad A Rakha,[1] Islam M Miligy,[1] Kylie L Gorringe,[2,3] Michael S Toss,[1] Andrew R Green,[1] Stephen B Fox,[4] Fernando C Schmitt,[5] Puay-Hoon Tan,[6] Gary M Tse,[7] Thomas Decker,[9] Anne Vincent-Salomon,[10] David J Dabbs,[11] Maria P Fos… Filipa Moreno,[13] Yang Wentao,[14] Felipe C Geyer,[15] Jorge S Reis-Filho,[1] Sarah E Pinder,[16] Sunil R Lakhani[17] & Ian O Ellis[1]

[1]*Department of Histopathology, Nottingham City Hospital NHS Trust, Nottingham University,* … *Genomics Program, Peter MacCallum Cancer Centre, Melbourne, Vic., Australia,* [3]*The Sir Peter* … *of Oncology, University of Melbourne, Melbourne, Vic., Australia,* [4]*Pathology Department, Pete* … *Centre, Melbourne, Vic., Australia,* [5]*Institute of Molecular Pathology and Immunology (IPATIM* … *University of Porto, Porto, Portugal,* [6]*Department of Pathology, Singapore General Hospital, Sin* … *Anatomical and Cellular Pathology, Prince of Wales Hospital, Hong Kong,* [8]*Departments of Path* … *Medicine, Clarian Pathology Laboratory of Indiana University, Indianapolis, IN, USA,* [9]*Breast-S* … *Reference Centre Munster, Gerhard Domagk-Institute of Pathology, University Hospital Münste* … [10]*Department of Pathology, Institute Curie, PSL Research University, Paris, France,* [11]*Universi* … *Centre, Pittsburgh, PA, USA,* [12]*Department of Biomedical and Neuromotor Sciences, Section of* … *Bellaria Hospital, University of Bologna, Bologna, Italy,* [13]*Anatomic Pathology Department, Ce* … *Porto, Portugal,* [14]*Pathology, Fudan University Shanghai Cancer Center, Shanghai, China,* [15]*De* … *Memorial Sloan Kettering Cancer Centre, New York, NY, USA,* [16]*Division of Cancer Studies, Ki* … *Guy's Hospital, London, UK, and* [17]*Discipline of Molecular & Cellular Pathology, Faculty of Me* … *Queensland, The Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia*

Rakha E A, Miligy I M, Gorringe K L, Toss M S, Green A R, Fox S B, Schmitt F C, Tan P-H, Tse G M, Badve S, Decker T, Vincent-Salomon A, Dabbs D J, Foschini M P, Moreno F, Wentao Y, Geyer F … S E, Lakhani S R & Ellis I O

(2018) *Histopathology* 72, 1075–1083. https://doi.org/10.1111/his.13446

Invasion in breast lesions: the role of the epithelial–stroma barrier

Despite the significant biological, behavioural and management differences between ductal carcinoma *in situ* (DCIS) and invasive carcinoma of the breast, they share many morphological and molecular similarities. Differentiation of these two different lesions in breast pathological diagnosis is based typically on the presence of an intact barrier between the malignant epithelial cells and stroma; namely, the myoepithelial cell (MEC) layer and surrounding basement membrane (BM). Despite being robust diagnostic criteria, the identification of MECs … *in-situ* from invasive carc… straightforward. The MEC lay… interrupted and/or show an… MECs may be absent in som… tive lesions such as microg… infiltrating epitheliosis, and … trative conditions such as a… these contexts this does not… invasive disease with metasta…

the identification of MECs and BM to differentiate *in-situ* from invasive carcinoma is not always straightforward. The MEC layer around DCIS may be interrupted and/or show an altered immunoprofile. MECs may be absent in some benign locally infiltrative lesions such as microglandular adenosis and infiltrating epitheliosis, and occasionally in non-infiltrative conditions such as apocrine lesions, and in these contexts this does not denote malignancy or invasive disease with metastatic potential. MECs may

and highlight potential clinical implications. We advise caution in interpretation of MEC features in breast pathology and mindfulness of the substantive evidence base in the literature associated with behaviour and clinical outcome of lesions classified as benign on conventional morphological examination before changing classification to an invasive lesion on the sole basis of MEC characteristics.

For example, authors of a recent study concerning "invasion in breast lesions" pointed out that *"the identification of myoepithelial cells and basement membrane to differentiate in situ from invasive carcinoma is not always straightforward"* and advised *"caution in interpretation"* of those findings.

Breast Cancer Research and Treatment (2018) 169:9–23
https://doi.org/10.1007/s10549-017-4644-3

REVIEW

Is invasion a necessary step for metastases in breast cancer?

Steven A. Narod[1,2,3] · Victoria Sopik[1,3]

Received: 18 November 2017 / Accepted: 23 December 2017 / Published online: 20 January 2018

Abstract

Purpose To review the empirical evidence to support the conventional (sequential) model of breast cancer progression, which is based on the paradigm that cancer passes through several stages, including an in situ stage prior to an invasive stage, and thereafter (in some cases) disseminates to the lymph nodes and distant organs.

Methods We review the cancer literature of the last 50 years which relates to the prevention of invasive breast cancer (through radiotherapy or surgery) and reductions in the mortality for breast cancer.

Results For both invasive cancers and DCIS, the literature indicates that prevention of in-breast invasive recurrences does not prevent death from breast cancer. Moreover, the presence of residual cancer cells in the breast after breast-conserving surgery does not compromise the cure rate.

Conclusion We propose an alternate (parallel) model of breast cancer wherein there is a small pool of cancer stem cells which have metastatic potential from their inception and which disseminate synchronously through several routes—to the breast stroma, to the lymph nodes and to distant organs. Cancer cells which disseminate to the breast give rise to cells which make up the bulk of the tumour mass but these are not the source of the distant metastases.

Keywords Breast cancer · DCIS · Invasion · Metastasis · Death

In another study, the question was asked whether invasion is *"a necessary step for metastases in breast cancer."* The answer was "no," at least as far as detectable invasion is concerned.

The Fallacy of the Concept of Invasion

- Keratocytes and melanocytes are situated physiologically in the epithelium
- Neoplams of keratocytes and melanocytes begin in the epithelium
- Neoplasms of keratocytes and melanocytes can be recognized while still confined to the epithelium
- Invasion at an early stage is difficult to recognize
- Invasion at an early stage has no impact on prognosis

In sum, the concept of invasion as a prerequisite for malignancy is fallacious because keratocytes and melanocytes are situated physiologically in the epithelium, neoplasms of keratocytes and melanocytes begin in the epithelium; and, in general those neoplasms can be recognized reliably while still confined to the epithelium, whereas invasion at an early stage is difficult to recognize and has no impact on prognosis.

Why, then, is this fallacious concept still en vogue?

OPEN ACCESS

Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

Joann G Elmore,[1] Raymond L Barnhill,[2] David E Elder,[3] Gary M Longton,[4] Margaret S Pepe,[4] Lisa M Reisch,[1] Patricia A Carney,[5] Linda J Titus,[6] Heidi D Nelson,[7,8] Tracy Onega,[9,10] Anna N A Tosteson,[11] Martin A Weinstock,[12,13] Stevan R Knezevich,[14] Michael W Piepkorn[15,16]

For numbered affiliations see end of article.

Correspondence to: J G Elmore jelmore@uw.edu

Additional material is published online only. To view please visit the journal online.

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Accepted: 25 May 2017

ABSTRACT

OBJECTIVE

To quantify the accuracy and reproducibility of pathologists' diagnoses of melanocytic skin lesions.

DESIGN

Observer accuracy and reproducibility study.

SETTING

10 US states.

PARTICIPANTS

Skin biopsy cases (n=240), grouped into sets of 36 or 48. Pathologists from 10 US states were randomized to independently interpret the same set on two occasions (phases 1 and 2), at least eight months apart.

MAIN OUTCOME MEASURES

Pathologists' interpretations were condensed into five classes: I (eg, nevus or mild atypia); II (eg, moderate atypia); III (eg, severe atypia or melanoma in situ); IV (eg, pathologic stage T1a (pT1a) early invasive melanoma); and V (eg, ≥pT1b invasive melanoma). Reproducibility was assessed by intraobserver and interobserver concordance rates, and accuracy by concordance with three reference diagnoses.

RESULTS

In phase 1, 187 pathologists completed 8976 independent case interpretations resulting in an average of 10 (SD 4) different diagnostic terms applied to each case. Among pathologists interpreting the same cases in both phases, when pathologists diagnosed a case as class I or class V during phase 1, they gave the same diagnosis in phase 2 for the majority of cases (class I 76.7%; class V 82.6%). However, the intraobserver reproducibility was lower for cases interpreted as class II (35.2%), class III (59.5%), and class IV (63.2%). Average interobserver concordance rates were lower, but with similar trends. Accuracy using a consensus diagnosis of experienced pathologists as reference varied by class: I, 92% (95% confidence interval 90% to 94%); II, 25% (22% to 28%); III, 40% (37% to 44%); IV, 43% (39% to 46%); and V, 72% (69% to 75%). It is estimated that at a population level, 82.8% (81.0% to 84.5%) of melanocytic skin biopsy diagnoses would have their diagnosis verified if reviewed by a consensus reference panel of experienced pathologists, with 8.0% (6.2% to 9.9%) of cases overinterpreted by the initial pathologist and 9.2% (8.8% to 9.6%) underinterpreted.

CONCLUSION

Diagnoses spanning moderately dysplastic nevi to early stage invasive melanoma were neither reproducible nor accurate in this large study of pathologists in the USA. Efforts to improve clinical practice should include using a standardized

WHAT IS ALREADY KNOWN ON THIS TOPIC

Millions of skin biopsy samples are obtained each year

A pathologist's visual interpretation is the cornerstone for diagnosing melanocytic lesions, including melanoma, yet previous studies have suggested variability among pathologists in their diagnoses

WHAT THIS STUDY ADDS

Diagnoses within the disease spectrum from moderately dysplastic nevi to early stage invasive melanoma are neither reproducible nor accurate

These limitations in histological diagnosis emphasize the need for supplemental reporting paradigms to convey observer derived opinions about diagnostic uncertainty, perceived risk for disease progression, and suggested management

Use of a standardized classification format employing unambiguous language and acknowledging uncertainty in pathology reports might reduce the potential for miscommunication and management errors

Human PATHOLOGY

VOLUME 27 November 1996 NUMBER 11

Editorial

Discordance Among Expert Pathologists in Diagnosis of Melanocytic Neoplasms

Any illusions clinicians may have cherished about repeatability of diagnosis of melanocytic neoplasms by histopathologists reputed to be expert must be shattered by the results of a "Workshop without Walls" sponsored by the National Institutes of Health (NIH) in 1991 and now published in *Human Pathology*.[1] The pathologists who participated in this workshop were A. Bernard Ackerman, Wallace H. Clark, Jr, Harry L. Evans, Mark Allen Everett, Evan R. Farmer, Robert G. Freeman, James H. Graham, Martin C. Mihm, Jr, Richard W. Sagebiel, and Mark R. Wick. The conclusions of

No single pathologist had a disproportionate number of discordant designations." In fact, one expert thought that 21 neoplasms were malignant and 16 were benign, whereas another considered 10 to be malignant, 26 benign, and one indeterminate.

From this data it is obvious that histopathologists purported to be expert at diagnosis of melanocytic neoplasms did not agree with one another most of the time in regard to 37 examples chosen on the basis of their being "classic." How much more disastrous would the results have been had the examples been chosen on the

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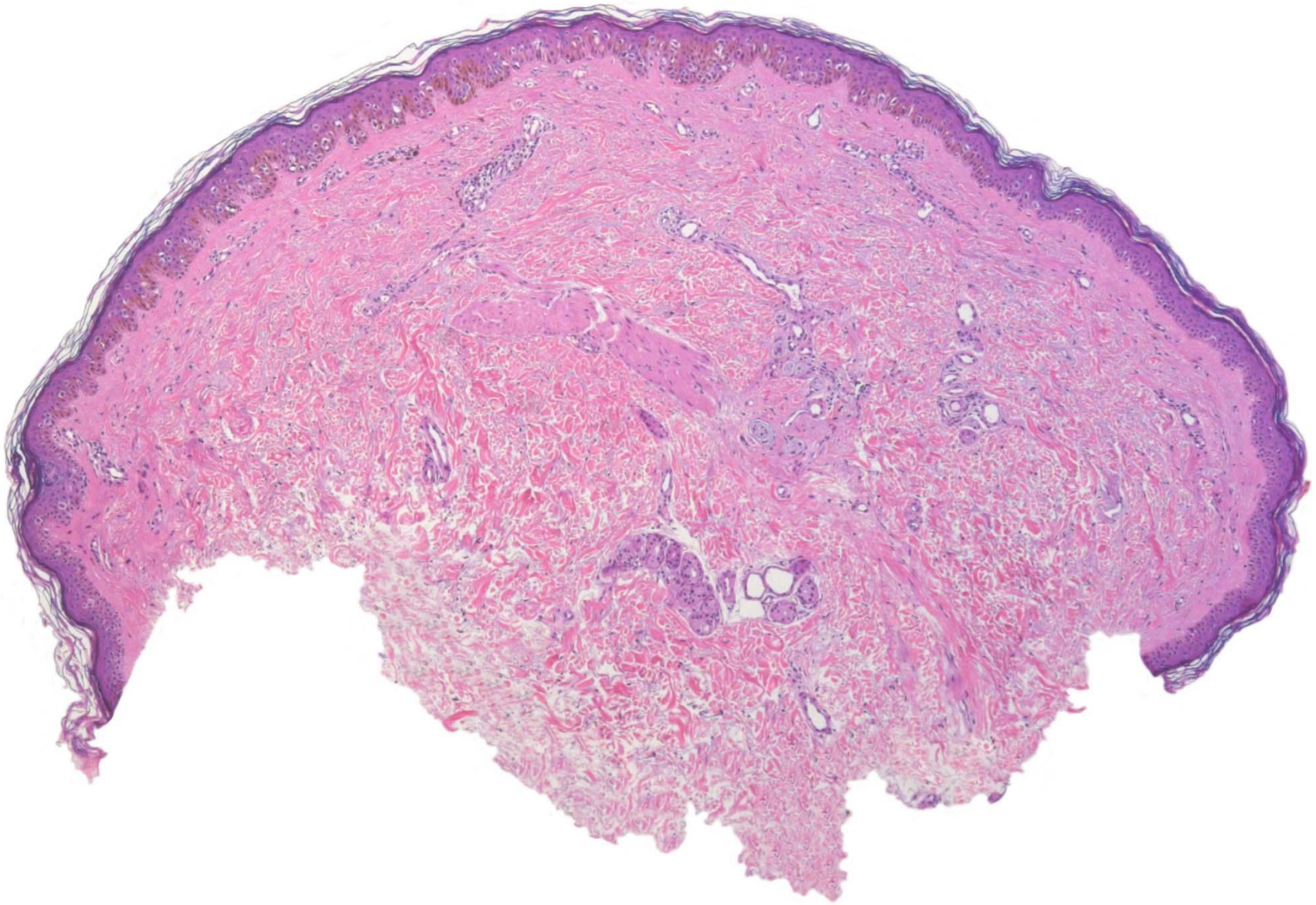
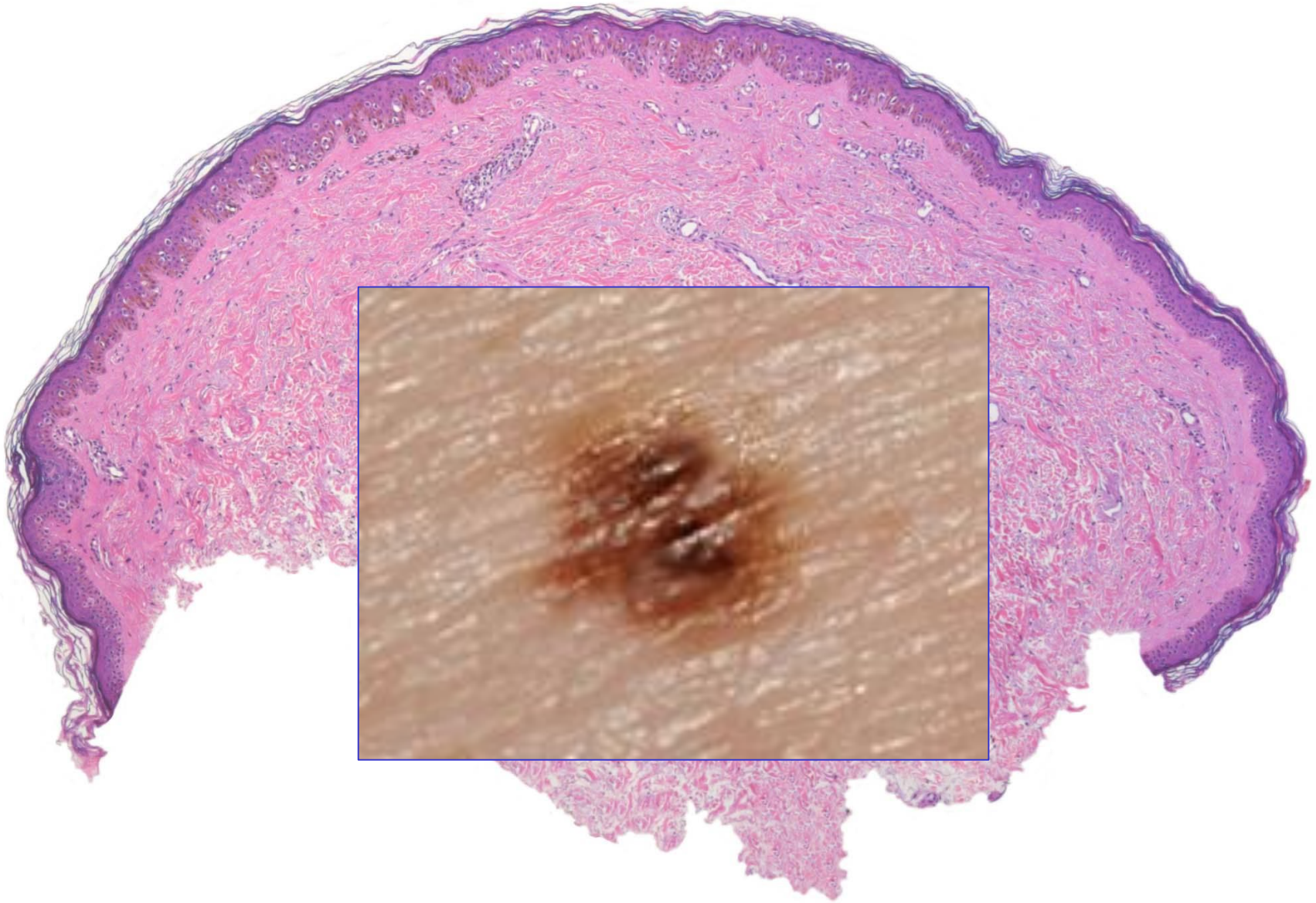
Use of a standardized classification format employing unambiguous language and acknowledging uncertainty in pathology reports might reduce the potential for miscommunication and management errors

The chief reason is discordance even among expert pathologists in the diagnosis of lesions at an early stage. For melanoma, this has been demonstrated abundantly, and a recent study among general pathologists from 10 US states came to the conclusion that *"diagnoses within the disease spectrum from moderately dysplastic nevi to early stage invasive melanoma are neither reproducible nor accurate."*

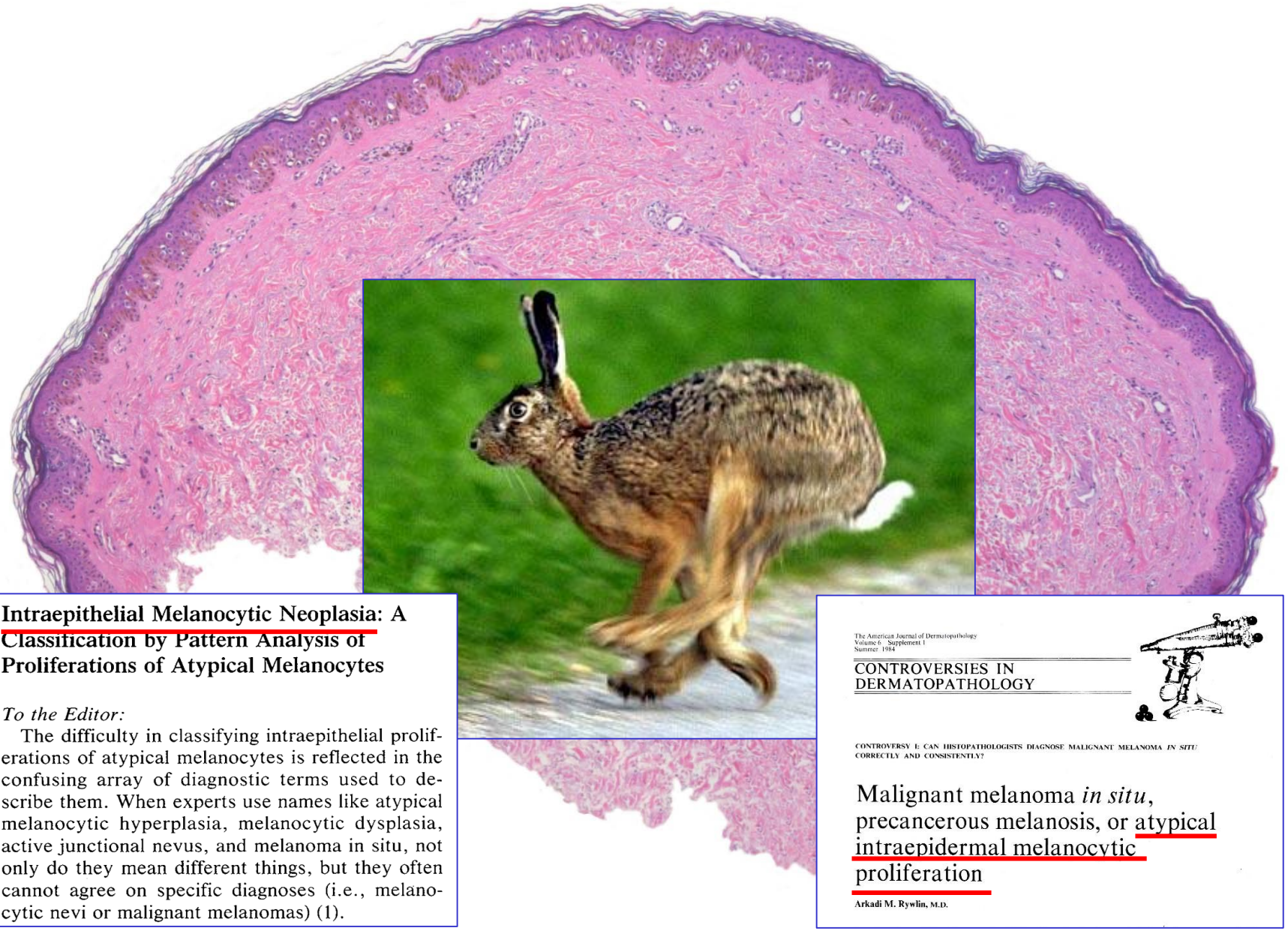


It is well known that histopathologic diagnosis at that stage is a challenging task and often cannot be made with certainty. If one stands up to that challenge, a definite diagnosis may still be possible by gaining additional information,



such as a clinical history or a clinical picture.

Instead, pathologists behave like rabbits: they run away from danger



Intraepithelial Melanocytic Neoplasia: A Classification by Pattern Analysis of Proliferations of Atypical Melanocytes

To the Editor:

The difficulty in classifying intraepithelial proliferations of atypical melanocytes is reflected in the confusing array of diagnostic terms used to describe them. When experts use names like atypical melanocytic hyperplasia, melanocytic dysplasia, active junctional nevus, and melanoma in situ, not only do they mean different things, but they often cannot agree on specific diagnoses (i.e., melanocytic nevi or malignant melanomas) (1).

The American Journal of Dermatopathology
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Summer 1984

CONTROVERSIES IN DERMATOPATHOLOGY

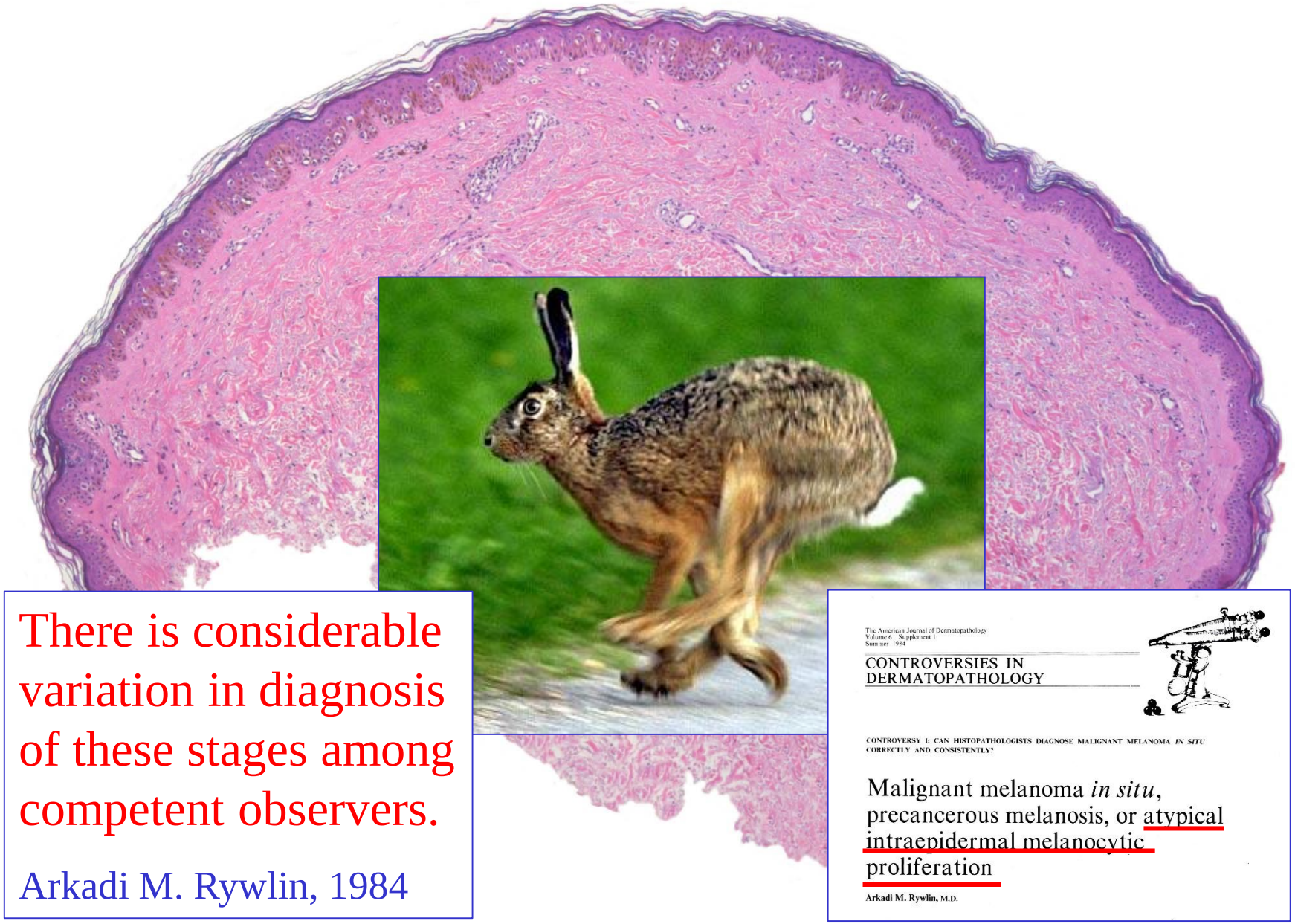
CONTROVERSY I: CAN HISTOPATHOLOGISTS DIAGNOSE MALIGNANT MELANOMA *IN SITU* CORRECTLY AND CONSISTENTLY?

Malignant melanoma *in situ*, precancerous melanosis, or atypical intraepidermal melanocytic proliferation

Arkadi M. Rywlin, M.D.

by resorting to non-specific designations, such as “intraepithelial melanocytic neoplasia” or “atypical intraepidermal melanocytic proliferation.”

In a controversy about the terminology of early melanoma, Rywlin praised the latter term by arguing



There is considerable variation in diagnosis of these stages among competent observers.

Arkadi M. Rywlin, 1984

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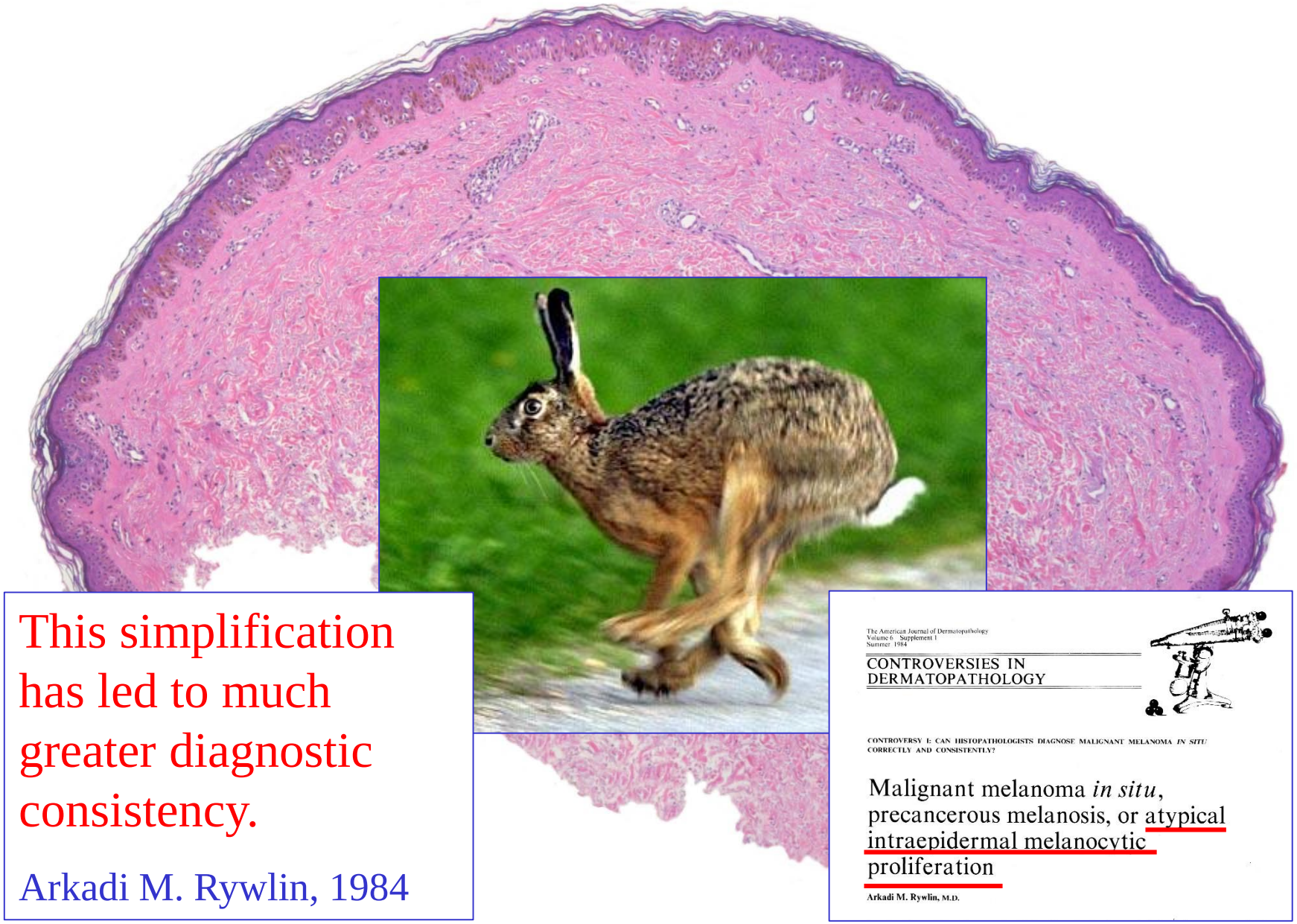
that *"there is considerable variation in diagnosis of these stages among competent observers"* and that



This simplification has led to much greater diagnostic consistency.

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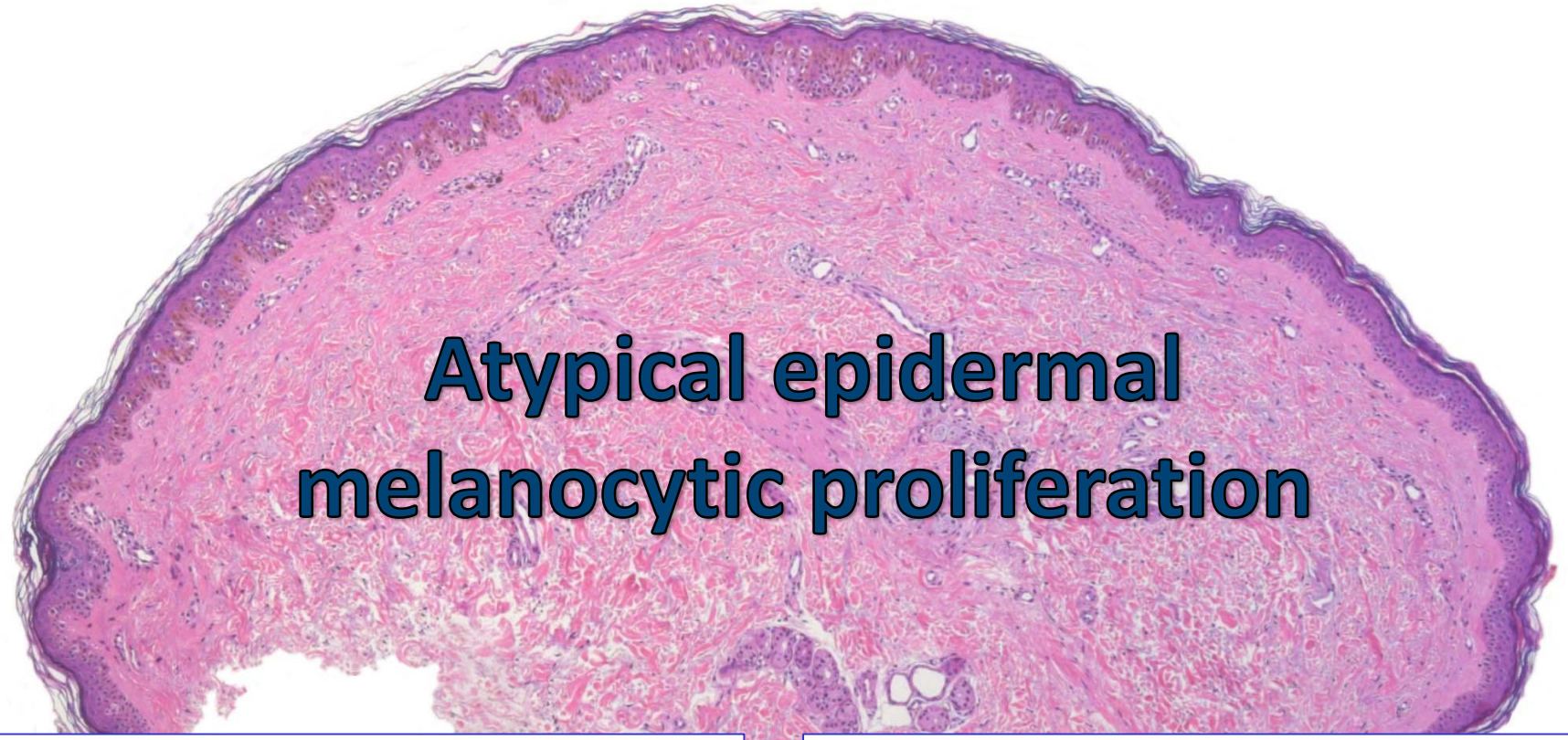
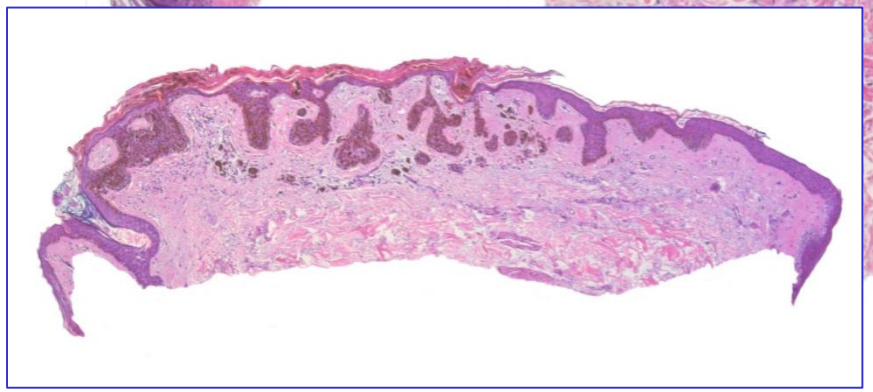
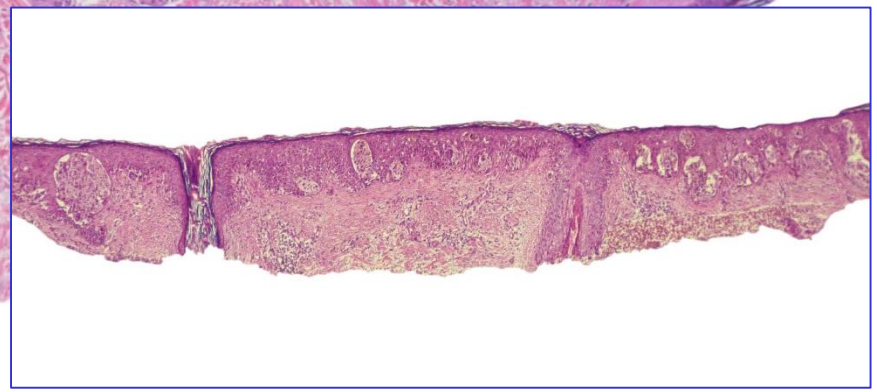
Arkadi M. Rywlin, M.D.

"this simplification has led to much greater diagnostic consistency."





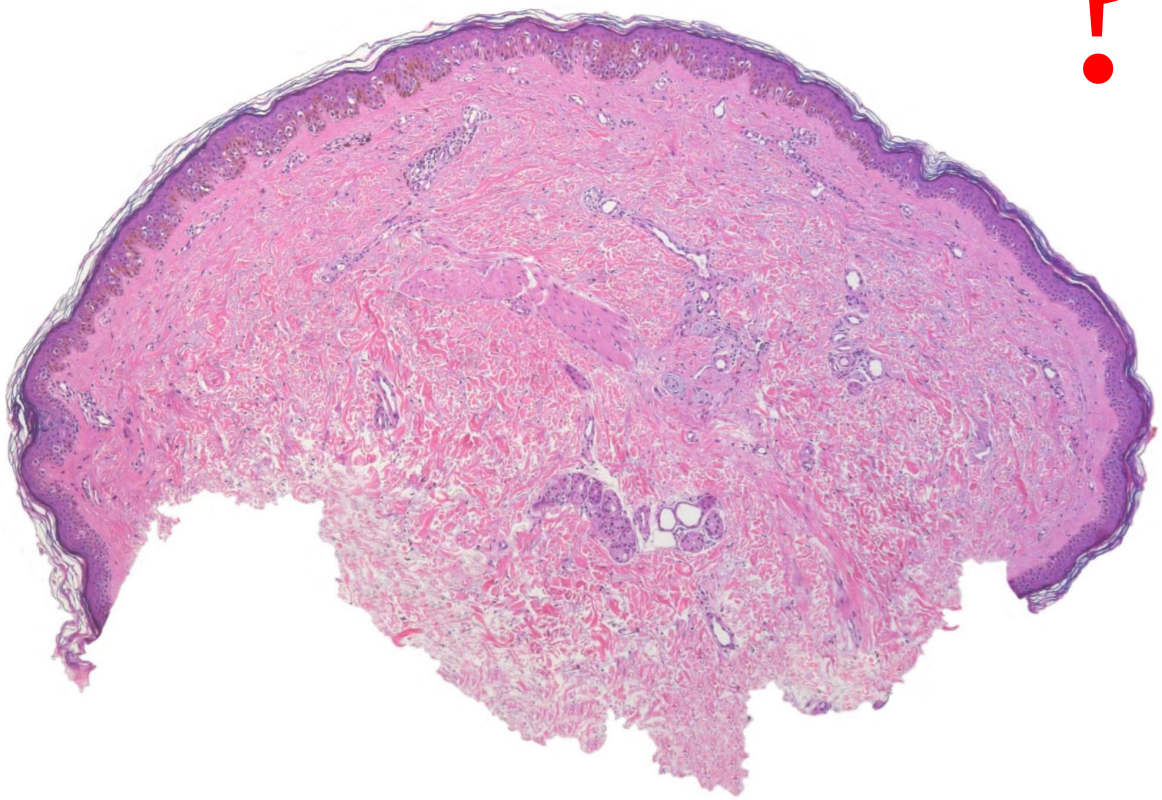


And it is true: by non-committal terms such as “atypical intraepidermal melanocytic proliferation,” diagnostic consistency among pathologists can be improved. However, terms that lump together benign and malignant lesions are no diagnoses.

Pathology report

One could just as well submit a blank page as a pathology report; if all pathologists agreed to do that, there would be even less discordance. But it is the raison d'être of histopathology to give a diagnosis.

Pathology report



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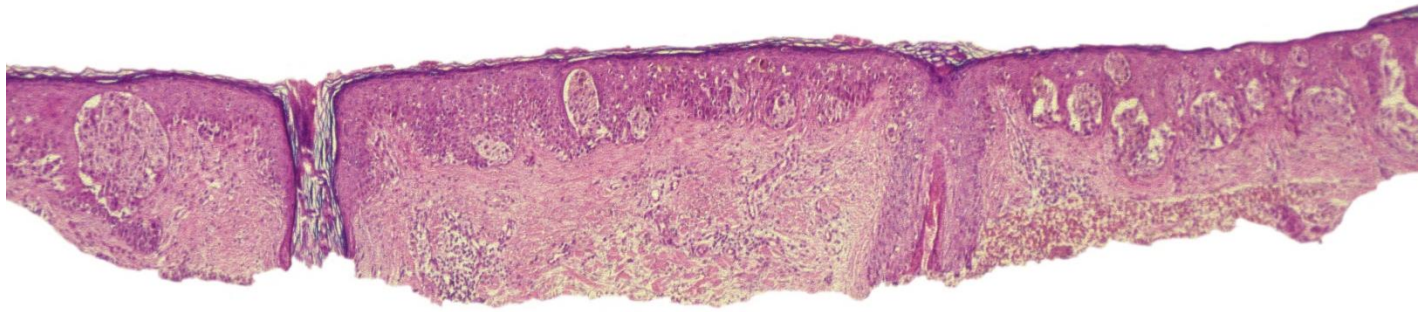
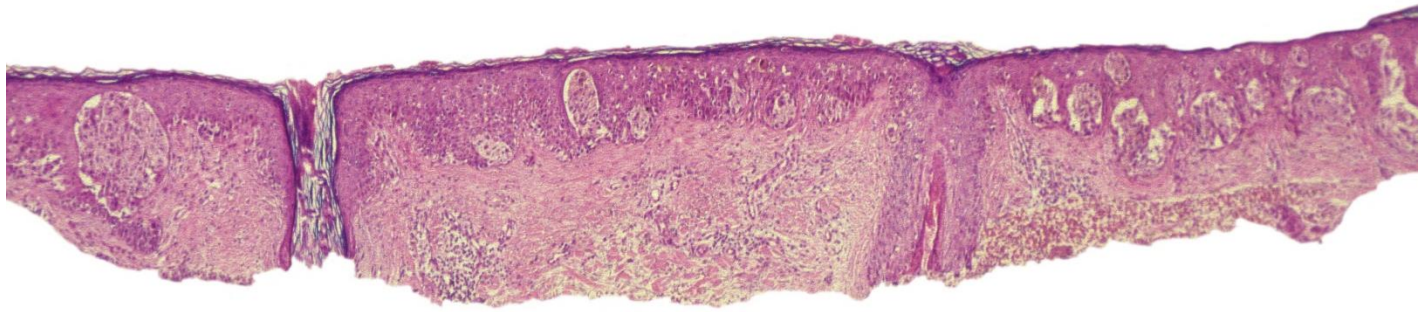
In cases that are difficult to interpret, doubts should be spelled out.

Pathology report



Many cases, however, are easy to interpret, regardless of whether or not there are signs of invasion. This wholly intraepithelial lesion is a melanoma, only 0.2 mm in thickness but melanoma nonetheless, and it irresponsible not to inform the patient, in unequivocal terms,

Pathology report



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Melanoma

that this lesion is malignant.