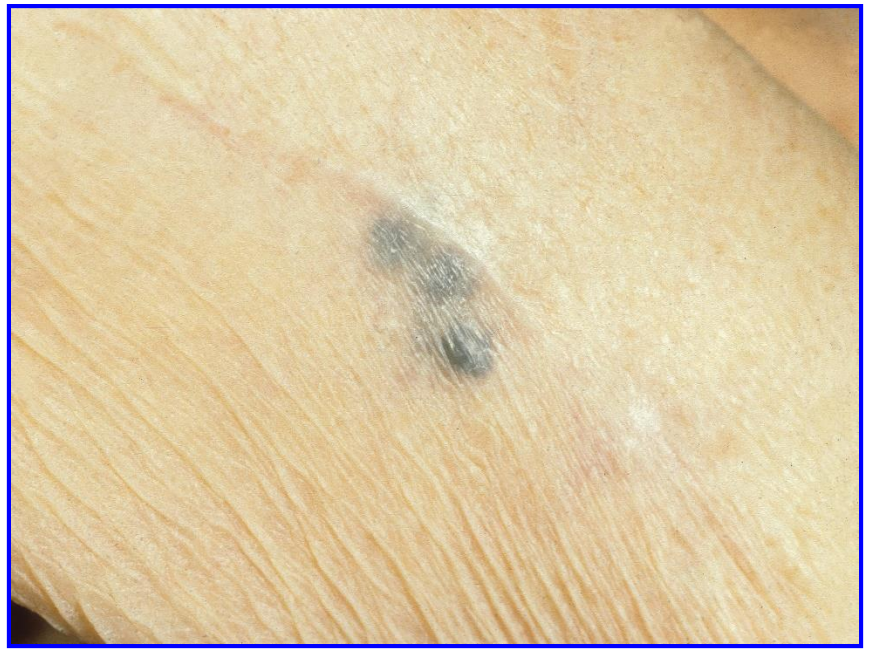
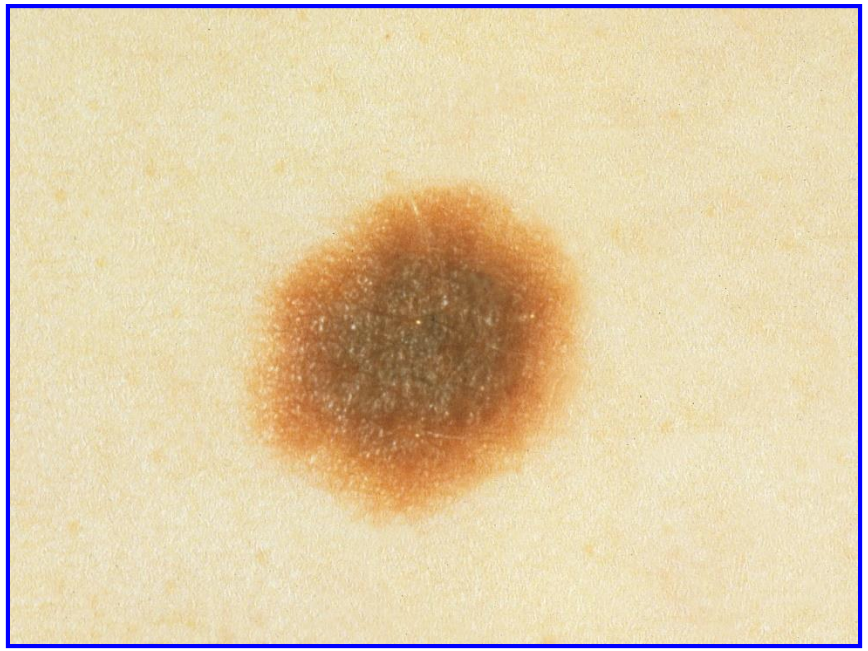
# Spitz's Nevus – Recurrence as Melanoma





W. Weyers

Zentrum für Dermato-pathologie Freiburg

**Spitz's Nevus – Recurrence as Melanoma**

Festsymposium für Prof. Paul, Nürnberg, 23.8.2008

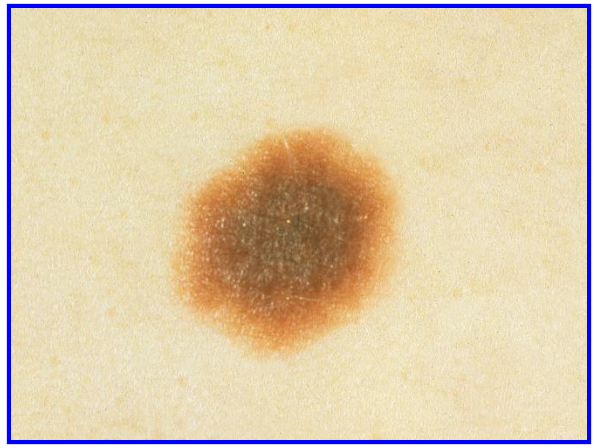
"Spitz's Nevus – Recurrence as Melanoma" is the subject of my presentation, but can a nevus recur as a melanoma? Logic tells us that this is impossible. Nothing can come back as something else.

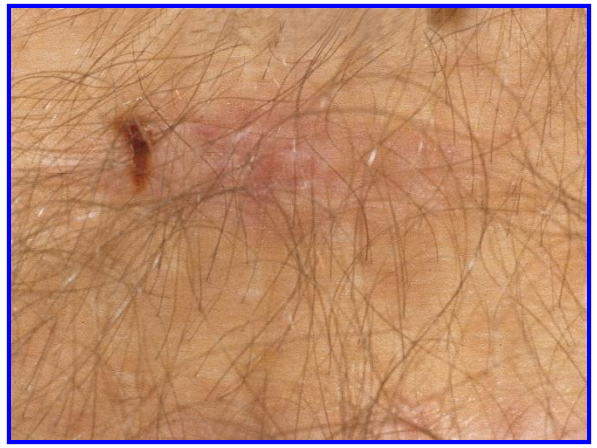
For example, if Eberhard Paul, who years ago came to Nuremberg, decides to travel to Los Angeles to visit his old friend Alistair Cochran, and then returns home, he may have changed to some extent,

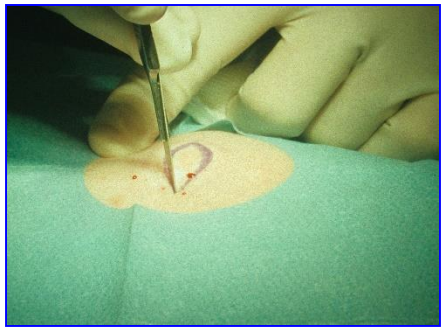
but he is still Eberhard Paul.

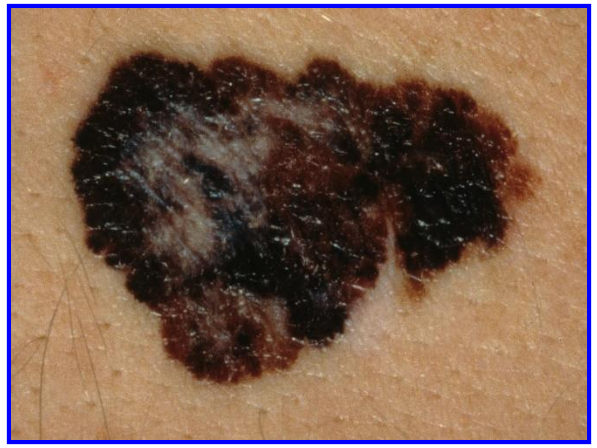
It may happen that somebody else, like Alistair Cockran, travels from Nuremberg to Los Angeles and then comes back again, a little older and wiser perhaps,

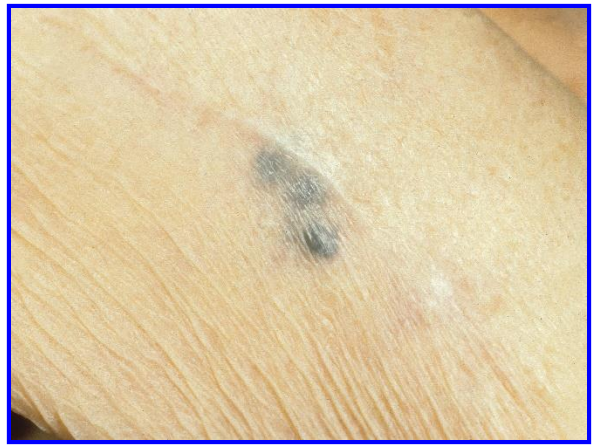
but to suggest that somebody left as Eberhard Paul and came back as Alistair Cockran would be plain crazy.



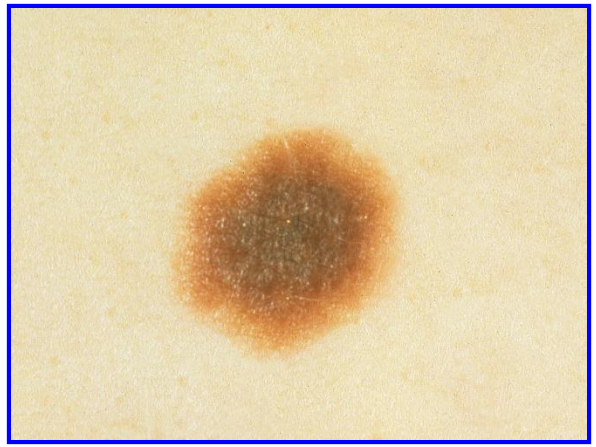


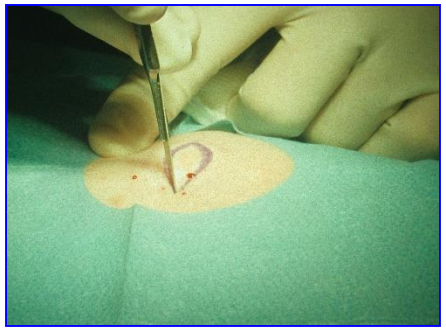


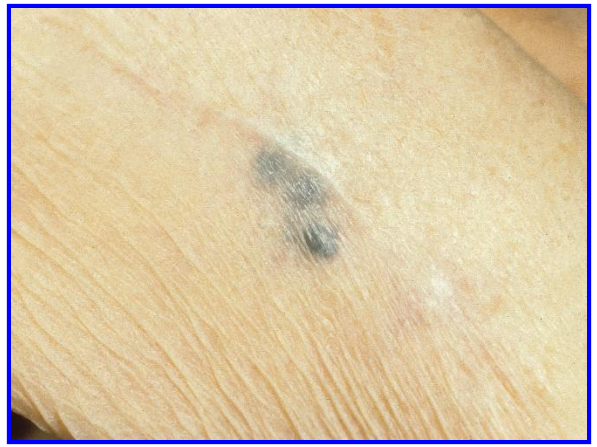




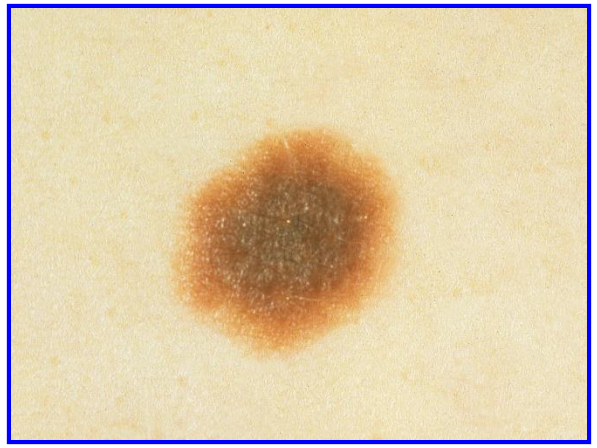
The same applies to melanocytic neoplasms. If a nevus is excised incompletely, it may recur as a nevus. A melanoma may recur as a melanoma – it's quite simple.



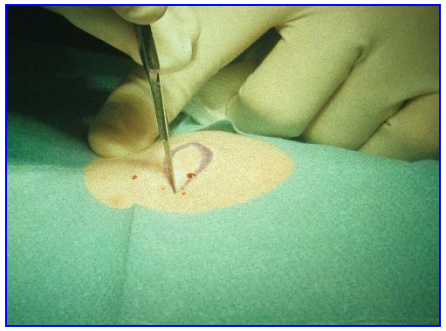




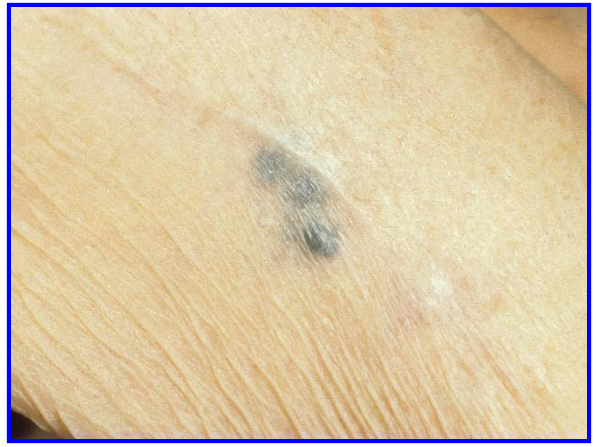
An incompletely excised nevus, however, cannot recur as melanoma. That is inconceivable, and, therefore, the title of my presentation,



# Spitz's Nevus –



# Recurrence as Melanoma



"Spitz's nevus – recurrence as melanoma," seems to make no sense at all. Nevertheless, this is what is happening currently, not biologically, but conceptually. I consider this to be a dangerous development that may come to bear severely on patients, and that's why I chose that subject for my presentation of today.

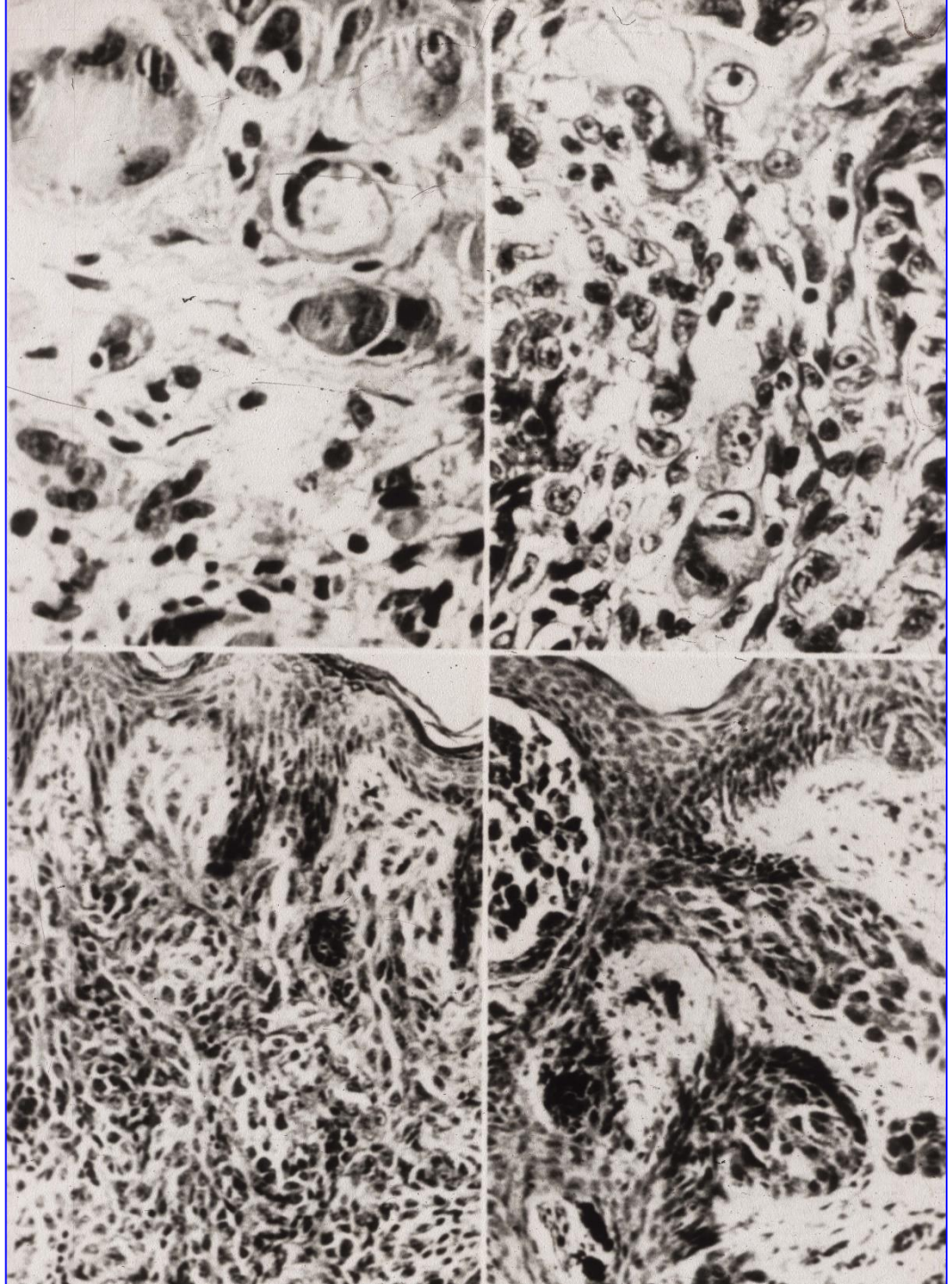
# MELANOMAS OF CHILDHOOD *

SOPHIE SPITZ, M.D.

*(From the Pathology Laboratories of the Memorial Hospital, New York, N.Y.)*

It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor. The disparity in behavior of the melanomas of adults and children, despite the histologic similarity of the lesions occurring in the different age groups, is obviously a matter of fundamental importance and the following questions immediately arise: Does the histologically malignant melanoma of children differ in any structural detail from that of adults? Can the clinical behavior of these lesions be predicted from their histologic structure? What, if any, are the factors known to influence the clinical behavior? Should the melanomas of children be treated any differently from the melanomas of adults?

You may know that Sophie Spitz, when she described those nevi 60 years ago, considered them to be authentic melanomas, namely, melanomas of childhood. She, like other researchers of that time, was puzzled by the finding that those so-called “melanomas of childhood”

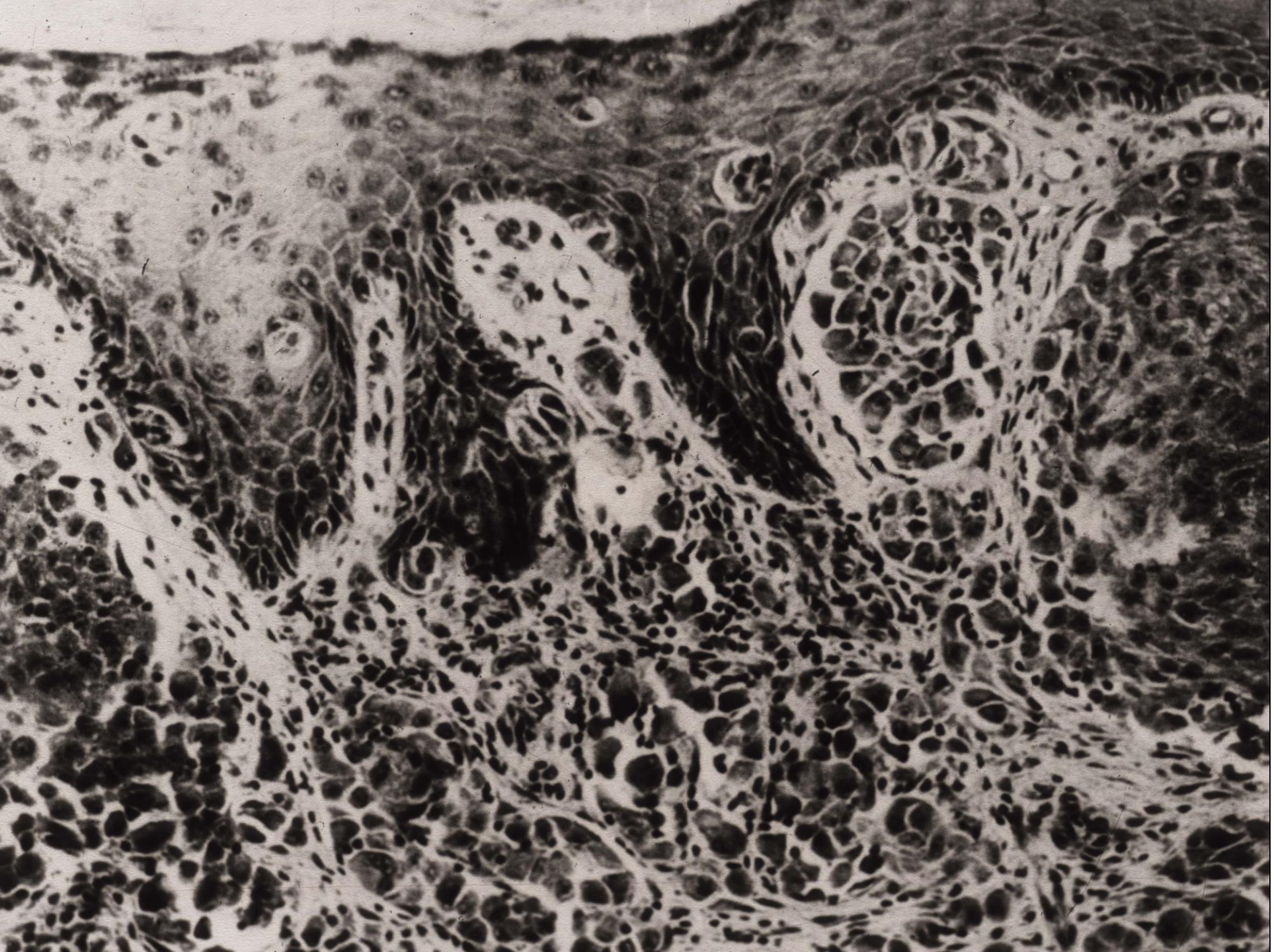


that seemed to fulfill all cytologic criteria for malignancy, being composed of atypical cells with large, pleomorphic nuclei, took a benign course. In her series of 13 patients, all of whom had thick lesions, only one developed metastases and died, but Spitz wrote

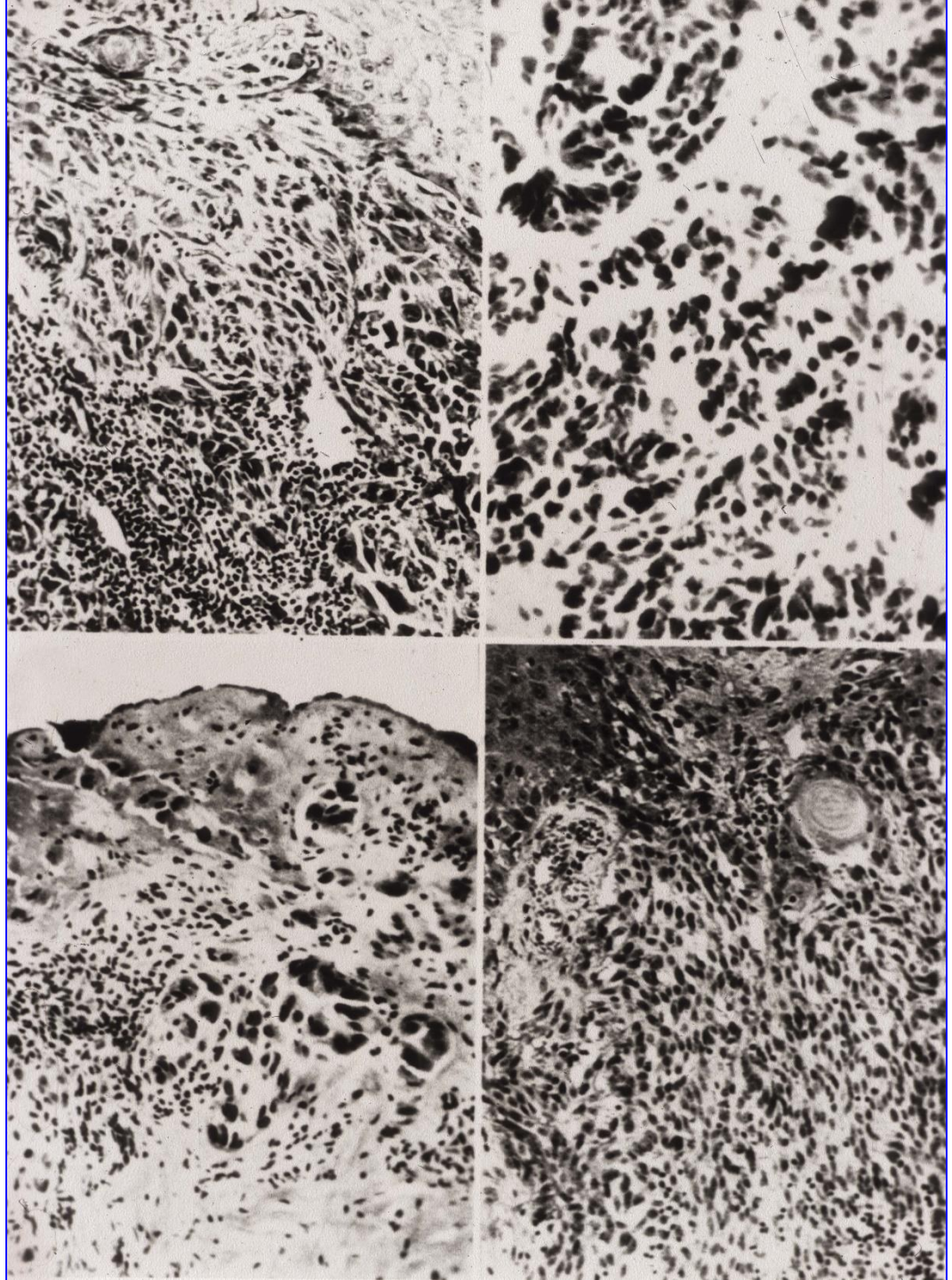
This one fatal case, occurring in a 12-year-old girl, was distinctly different histologically as well as clinically from the group as a whole.

Sophie Spitz, 1948

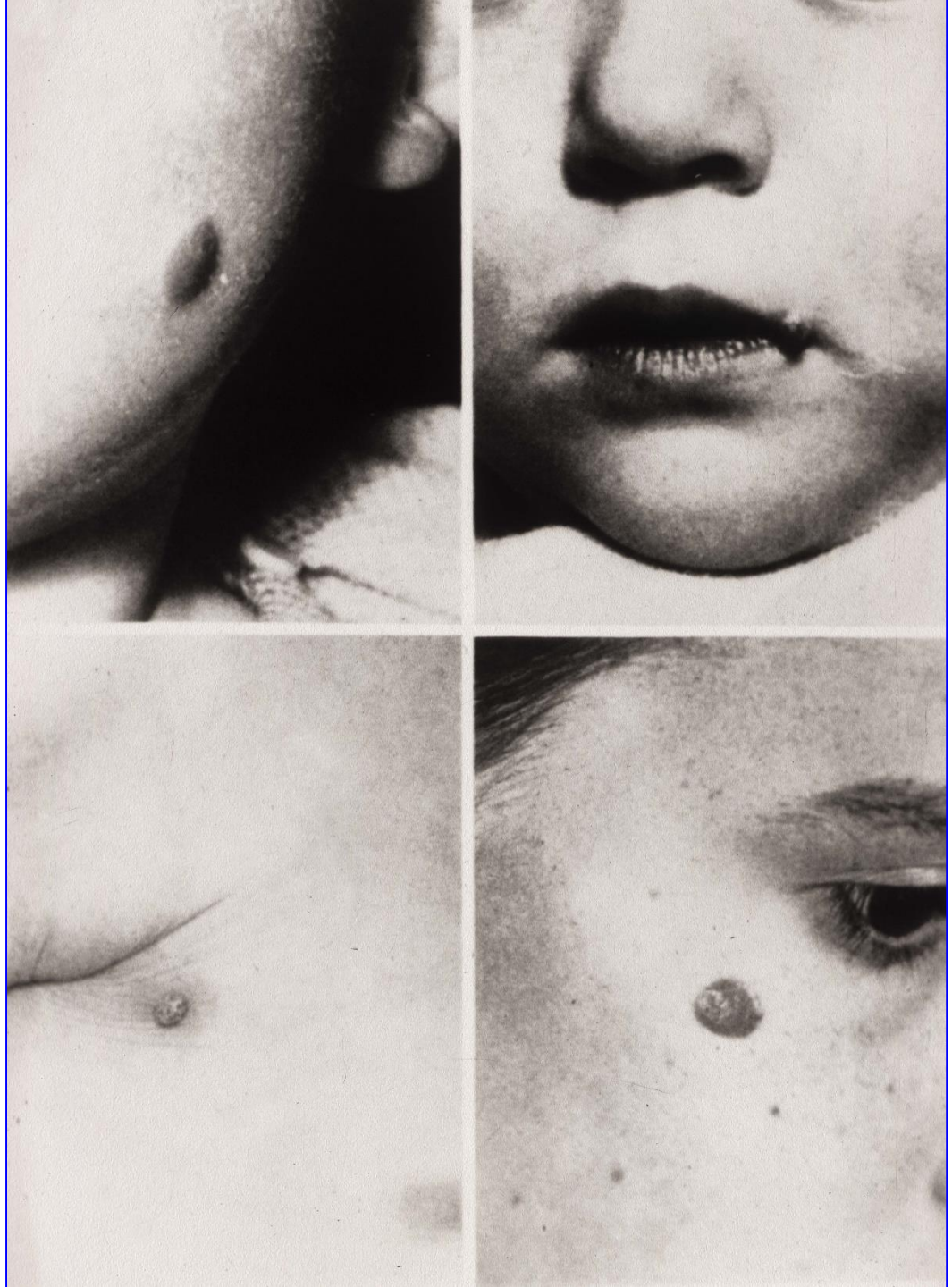
*"this one fatal case, occurring in a 12-year-old girl, was distinctly different histologically as well as clinically from the group as a whole."* In other words, the fatal case was a true melanoma and did not resemble the other twelve tumors, apart from the fact that it also occurred in a child.



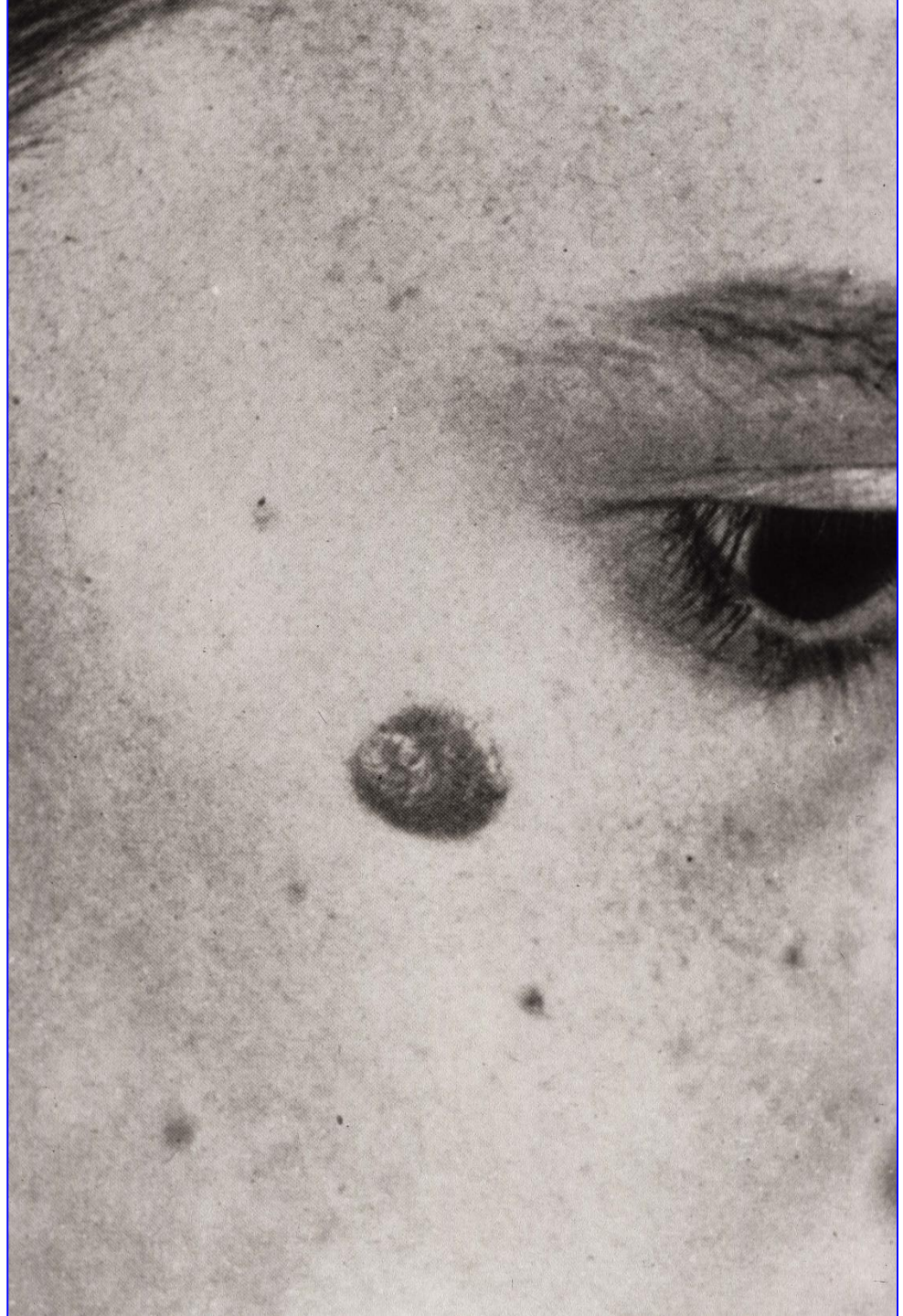
Spitz tried to determine whether the twelve non-fatal lesions had any histopathologic characteristics that allowed them to be distinguished from melanomas of adults, and she noted several such features which are used for diagnosis of Spitz's nevi to this date, including epithelial hyperplasia and hyperkeratosis. However, she failed to take into account the architecture of the lesions.



All photomicrographs were taken at high magnification and do not reveal that the lesions under discussion were symmetrical and sharply circumscribed.



This can be told from the clinical pictures that accompanied her article. As a pathologist not trained in the rudiments of clinical dermatology, Spitz did not take clinical features into account.



Otherwise, she might have concluded that the lesions were truly benign.

# MALIGNANT MELANOMA

## *A Clinicopathological Analysis of the Criteria for Diagnosis and Prognosis*

ARTHUR C. ALLEN, M.D., AND SOPHIE SPITZ, M.D.

WE PREVIOUSLY PRESENTED EVIDENCE that was intended primarily to clarify in a practical, workable manner the criteria for the histological diagnosis of nevi, juvenile melanomas, and malignant melanomas.[2, 3, 4, 19, 20] This was done because it appeared that the recondite histogenetic concepts then in vogue had not measurably supplied the answers to what the pathologist needed to know in order to be able to state confidently that a given lesion, particularly the small one, was or was not malignant. Accordingly, we defined in detail the clinical and histological features of the melanocarcinoma and of each of the several varieties of nevi. From these details there was acuminated a set of facts and principles, which, in essence, stated:

ty.[2, 19, 20] In addition, because it was apparent that several of the lesions were not autochthonous but, rather, represented a stage in the evolution of the junctional nevi, a histogenetic concept embodying this relationship was outlined.[2] In accordance with this concept, the junctional nevi, the intradermal nevi, the juvenile melanomas, and the melanocarcinomas of both skin and mucous membranes are of epithelial rather than of neural origin.

These, then, represented the broad principles of our concepts of the histogenesis and the diagnostic criteria of the nevi and melanocarcinomas, impressions that were derived from a unique opportunity through which we were privileged to examine an enormous concentra-

Sophie Spitz and her husband, Arthur Allen, arrived at that conclusion five years later. In this article in 1953,

## Classification

Before proceeding with the results of this study, it might be of some use briefly to review and to amplify certain of the characteristics of the individual nevi, most of which have been detailed elsewhere.[2, 3, 4, 19, 20] We classify the lesions as follows:[2]

A. Benign*

1. Intradermal nevus (common mole)
2. Junctional nevus
3. Compound nevus
4. Juvenile melanoma
5. Blue (Jadassohn-Tièche) nevus

B. Malignant

1. Melanocarcinoma (from junctional nevus or compound nevus)
   (1) superficial
   (2) deep
2. Malignant blue nevus

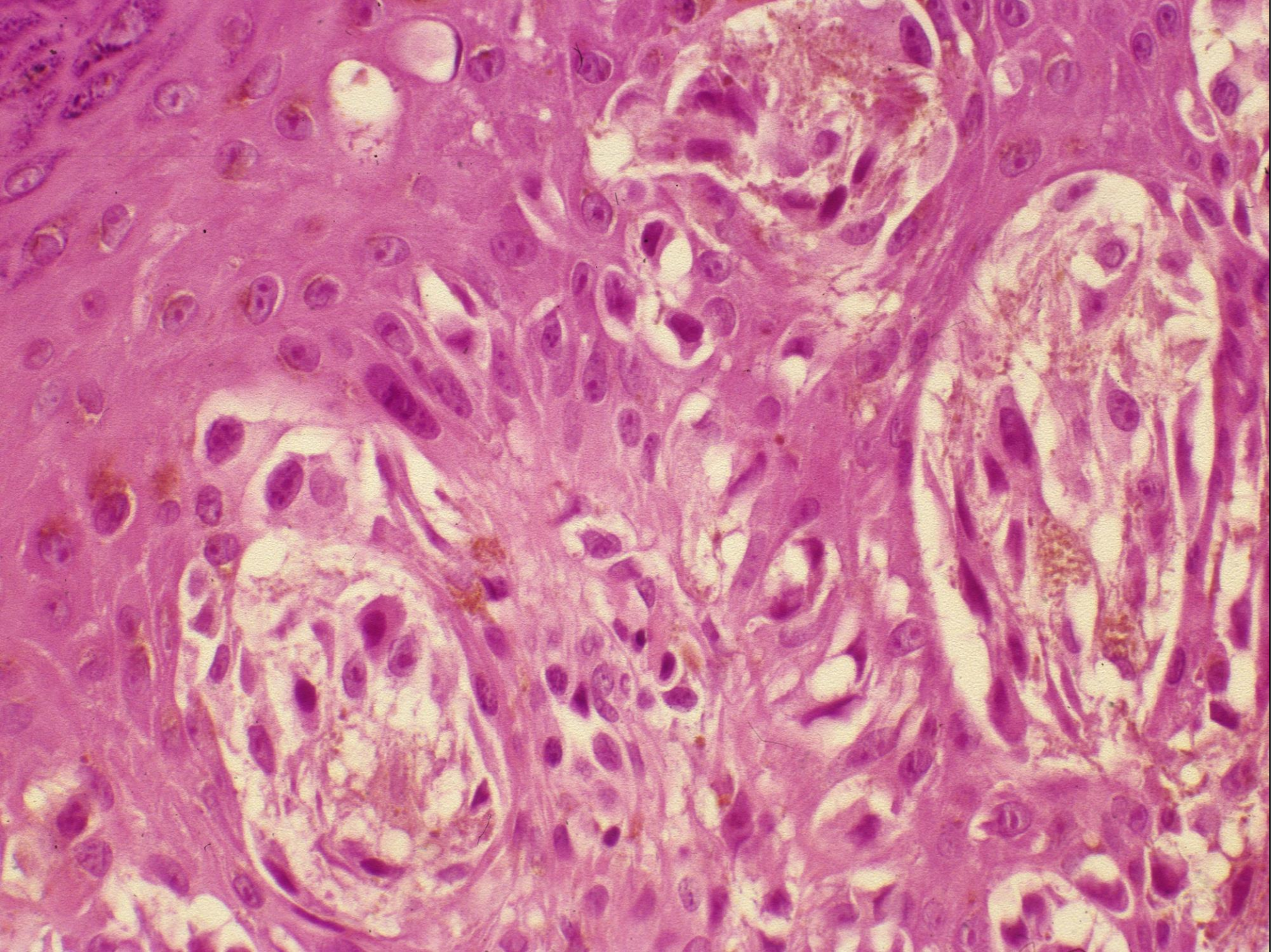
they classified “juvenile melanoma,” among other nevi, as benign. That concept came to be accepted, the name was changed into Spitz’s nevus,

**TABLE 4 DIFFERENTIAL DIAGNOSIS HISTOPATHOLOGIC OF SPITZ'S NEVUS AND MELANOMA***

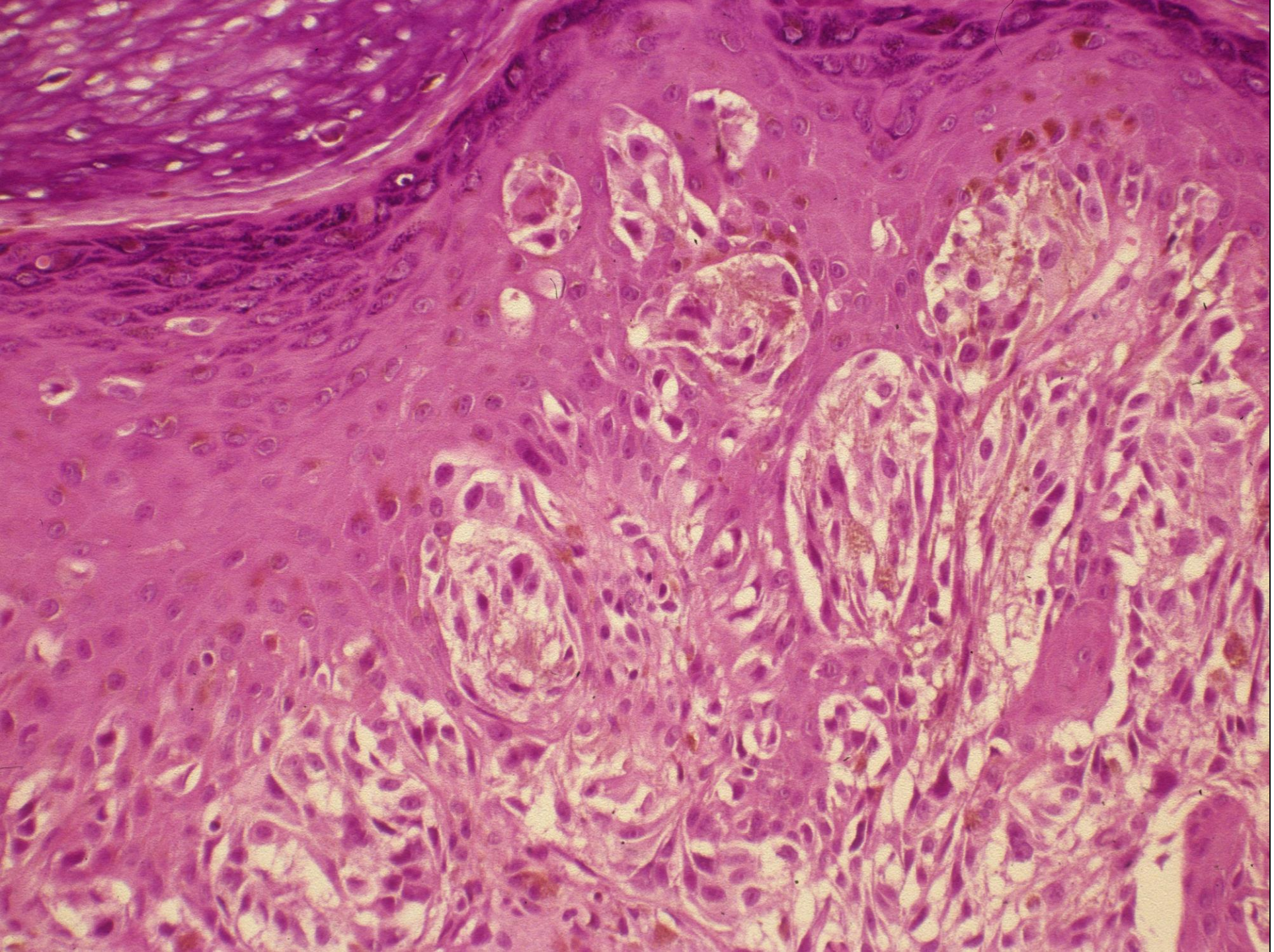
| Spitz's nevus | Melanoma |
|---|---|
| 1. Symmetric | 1. Asymmetric |
| 2. Well circumscribed | 2. Poorly circumscribed |
| 3. Maturation of melanocytes with descent progressive | 3. No maturation of melanocytes with descent progressive |
| 4. Wedge shape of the proliferation of melanocytes sometimes; at other times base rather flat | 4. No wedge shape in fashion symmetrical of the proliferation; base uneven |
| 5. Melanocytes do not form a sheet in the reticular dermis | 5. Melanocytes sometimes form a sheet in the reticular dermis |
| 6. No necrosis *en masse* in aggregations in the dermis | 6. Necrosis en masse in aggregations in the dermis sometimes |
| 7. Nests/fascicles of melanocytes in the epidermis predominate over melanocytes disposed as solitary units | 7. Melanocytes disposed as solitary units predominate over nests/fascicles in some high power fields often |
| 8. Nests/fascicles of melanocytes in the epidermis relatively equidistant from one another | 8. Nests/fascicles of melanocytes in the epidermis not equidistant from one another |
| 9. Nests/fascicles of melanocytes in the epidermis relatively uniform in size and shape | 9. Nests/fascicles of melanocytes in the epidermis vary markedly in size and shape |
| 10. Nests/fascicles of melanocytes in the epidermis and dermis tend to be discrete; no crowding, little confluence, and no formation of aggregations having shape bizarre geometrically | 10. Nests/fascicles of melanocytes in the epidermis and dermis tend to crowding and confluence with formation sometimes of aggregations having shape peculiar geometrically |
| 11. No pagetoid melanocytes in pagetoid pattern in the epidermis | 11. Pagetoid melanocytes sometimes in the dermis and in the epidermis, the latter often in pagetoid pattern |
| 12. Few, if any, melanocytes in the upper half of the lesion with large nuclei and scant cytoplasm | 12. Melanocytes in the upper half of the lesion often have large nuclei and scant cytoplasm |
| 13. No small nuclei of melanocytes in number except for those at the base (a consequence of maturation) | 13. Small nuclei may predominate in melanocytes throughout the neoplasm |
| 14. No predominance of melanocytes with vesicular nuclei and a prominent nucleolus dead center | 14. Melanocytes with vesicular nuclei and a prominent nucleolus dead center may predominate |
| 15. Mononucleate and binucleate melanocytes common | 15. Mononucleate and binucleate melanocytes uncommon |
| 16. Edema may be marked in the upper part of the dermis | 16. No edema in the upper part of the dermis as a rule |
| 17. Lymphocytes often around venules throughout the neoplasm | 17. Lymphocytes usually patchy at the periphery of the neoplasm |
| 18. No signs of regression, i.e., fibrosis and/or melanosis in a thickened papillary dermis | 18. Signs sometimes of regression, i.e., fibrosis and/or melanosis in a thickened papillary dermis |

* There are exceptions to each individual criterion listed here for differentiation of Spitz's nevus from melanoma; taken together, however, the criteria enable distinction between them to be achieved in the majority vast of instances.

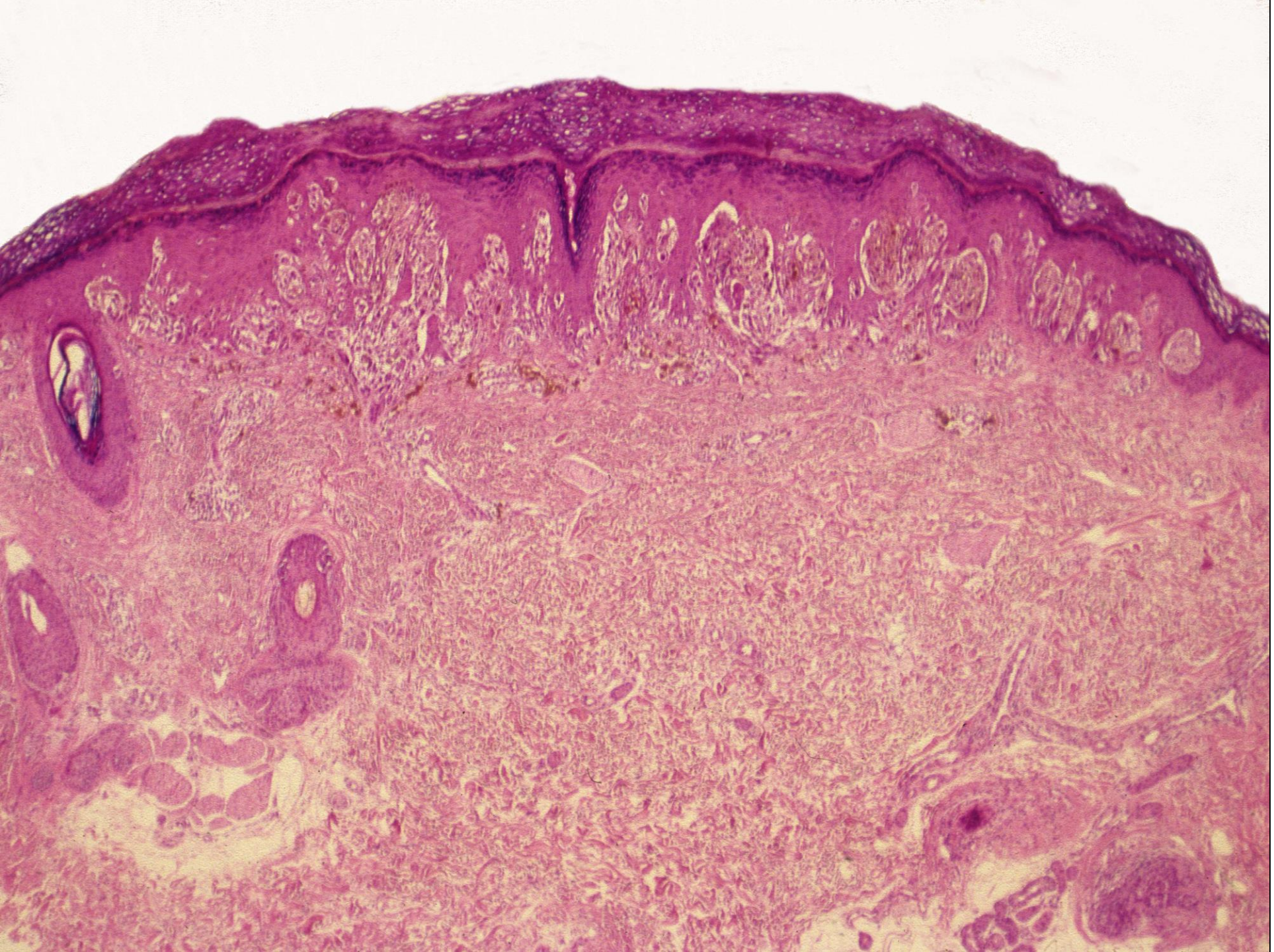
and an extensive list of criteria was established that serve to distinguish Spitz's nevus from melanoma. On the basis of those criteria, diagnosis of a Spitz's nevus is usually fairly easy.



For example, Spitz’s nevi are composed of melanocytes with large, pleomorphic nuclei, some of which are present in the upper reaches of the epidermis, just as in melanoma,



but the nests of melanocytes are sharply circumscribed, often demarcated by clefts from surrounding keratocytes, and arranged perpendicularly to the skin surface. Nests predominate over single melanocytes and are distributed in regular fashion.



Most importantly, Spitz's nevi are symmetrical and sharply circumscribed. If all those criteria are fulfilled, diagnosis of a Spitz's nevus is unequivocal. However, as in all diseases, there are cases that are not so straightforward and in which diagnosis is difficult.
Morphologically, the boundary between Spitz's nevus and melanoma is not always sharp,

# Spitz nevi

Elen M. Casso, MD, Caron M. Grin-Jorgensen, MD, and Jane M. Grant-Kels, MD
*Farmington, Connecticut*

The Spitz nevus has long been defined as a benign melanocytic lesion that shares many histologic features with malignant melanoma. Despite the diagnostic criteria established for these two entities, their histologic similarities continue to make their distinction somewhat difficult. Uncertainties also exist with regard to the natural history of the Spitz nevus; the true pattern of this lesion's biologic behavior remains elusive. As a result, controversies exist with respect to appropriate therapy. To examine these controversies, the epidemiology, clinical features, and histopathology of Spitz nevi, as well as the role of recent molecular and immunohistochemical diagnostic studies, are discussed. However, the primary focus of this article is the natural course, prognosis, and treatment of the Spitz nevus. A review of 716 cases of Spitz nevi, compiled from 13 papers published from 1948 to 1990, is presented. After analyzing this and other available data, we propose that at this time Spitz nevi and malignant melanoma cannot easily be categorized as distinct entities and that perhaps they actually exist along one continuum of disease. Because of this uncertainty and the difficulties in differentiating these two lesions, we recommend that treatment include complete excision of all Spitz nevi followed by reexcision of positive margins if present. (J AM ACAD DERMATOL 1992;27:901-13.)

and this has prompted some authors to suggest that this is also the case, biologically, that *"Spitz nevi and malignant melanoma cannot easily be categorized as distinct entities and that perhaps they actually exist along one continuum of disease."*

The suggestion that there is a continuous evolution of a nevus into a melanoma is not new.

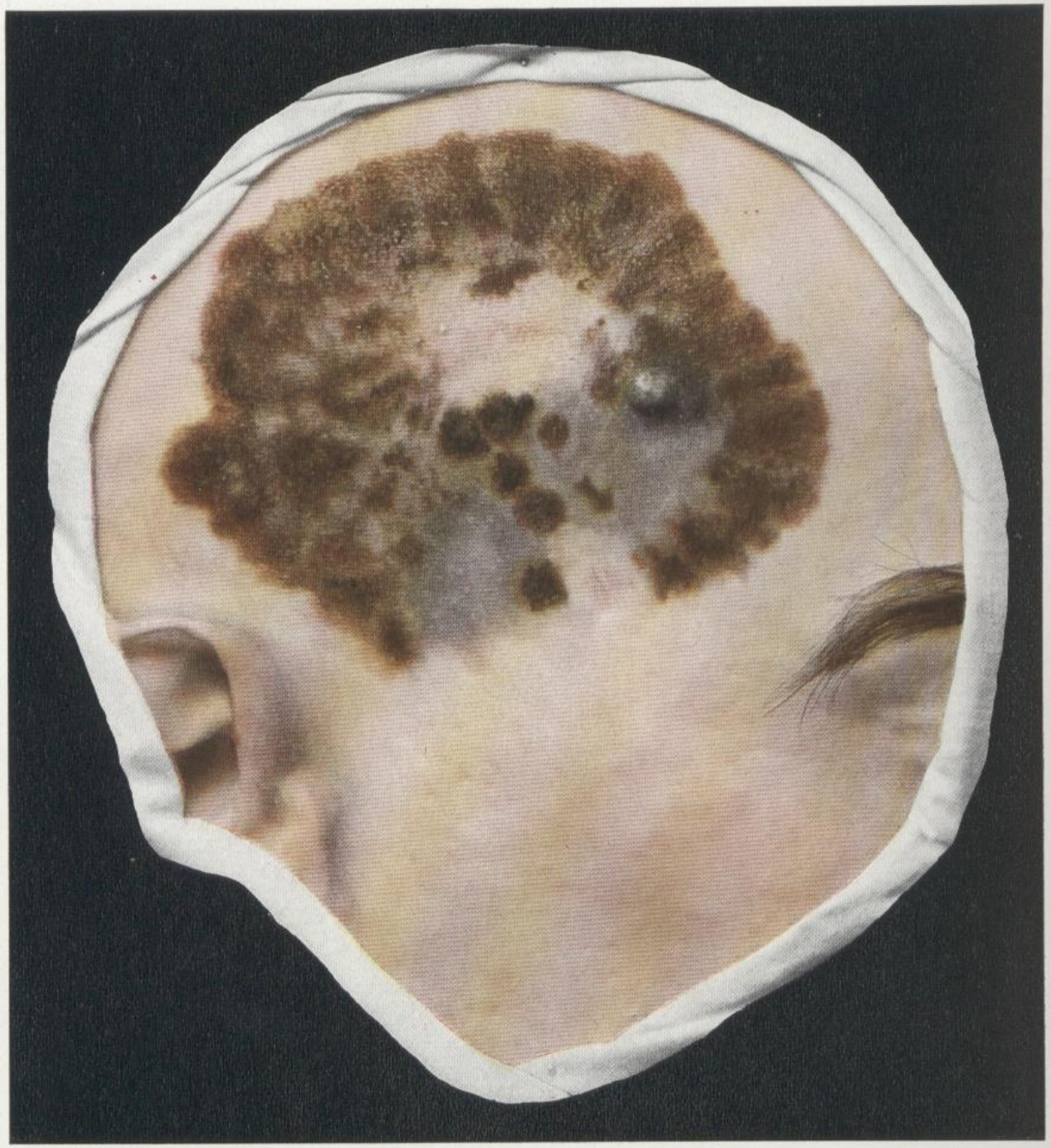
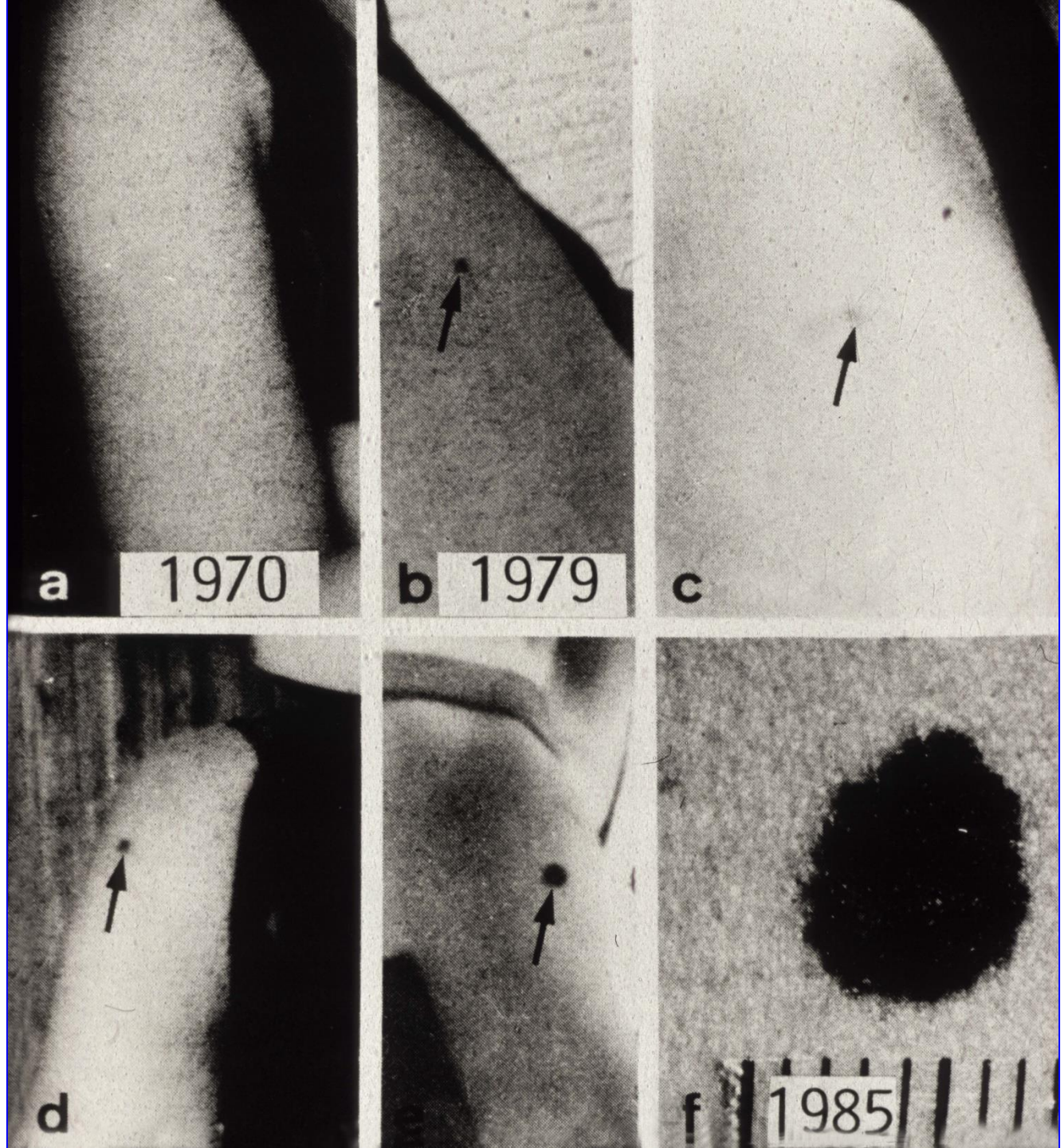
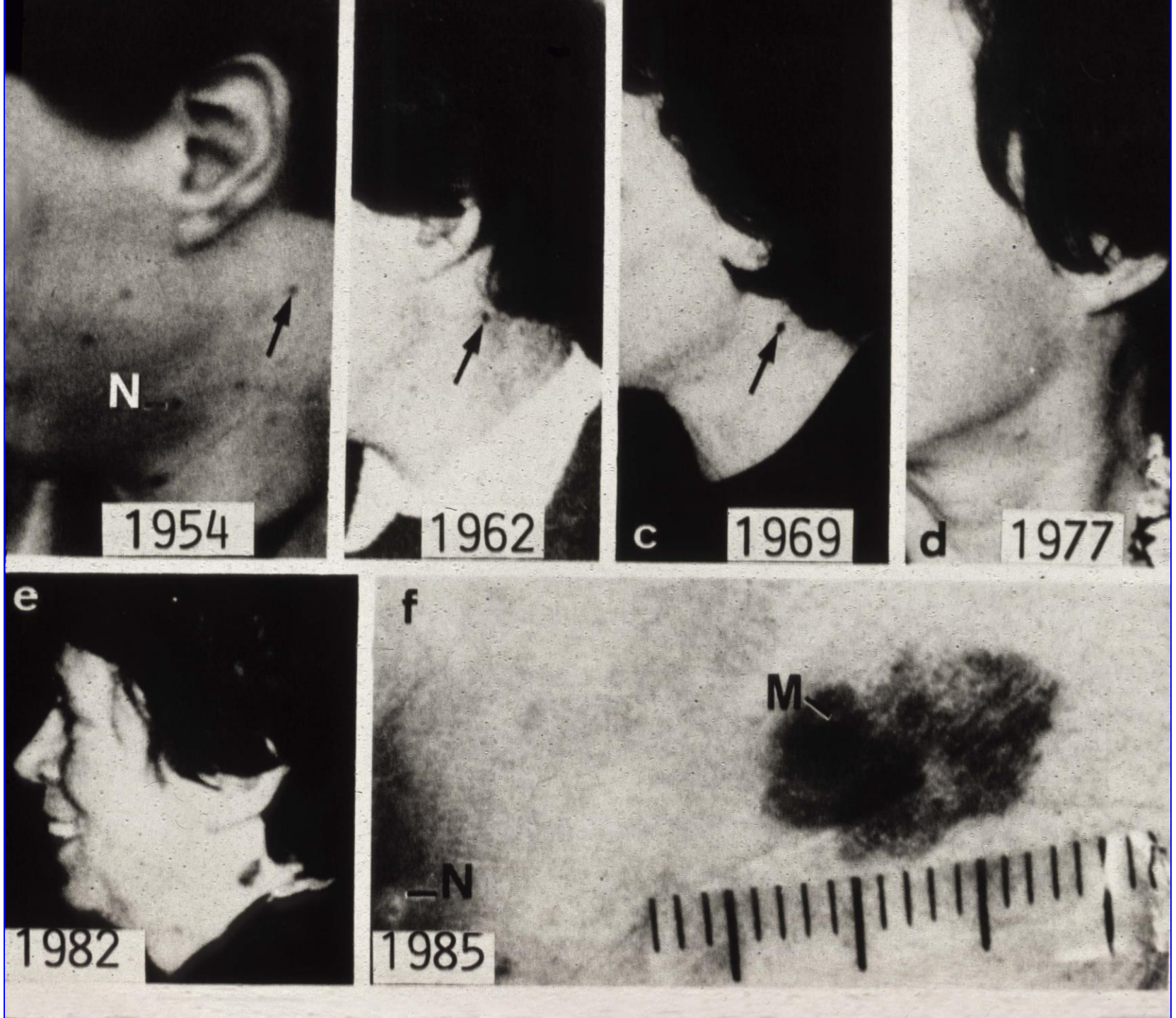


Abb. 47. Ausgedehnte melanotische Präcancerose mit Tumorbildung oder Naevus tardus in maligner Entartung?

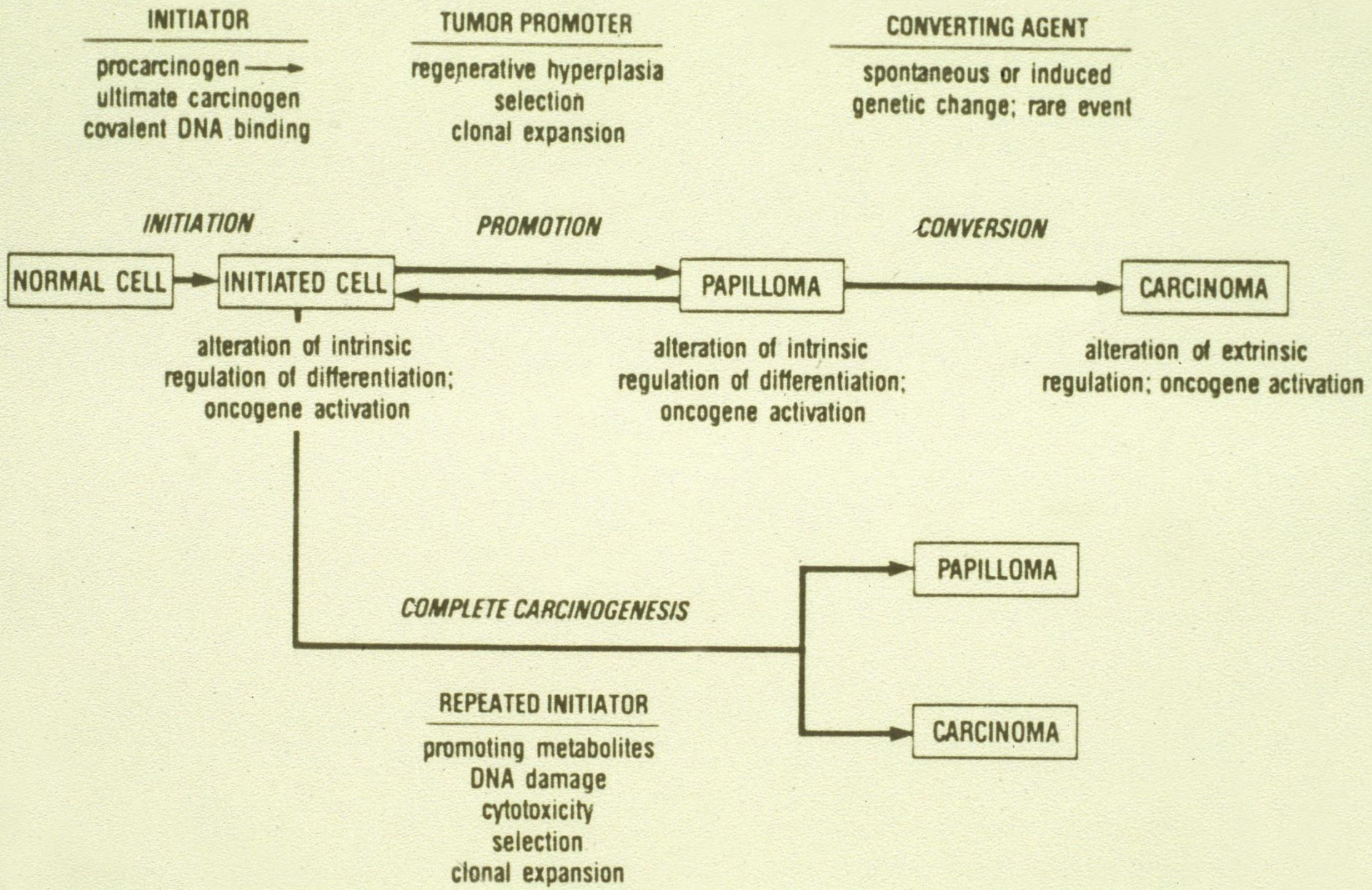
Formerly, all melanomas have been said to result from malignant transformation of a pre-existing nevus. Today, however, we know that most so-called pre-existing nevi are, in actuality, early stages of melanoma.




A melanoma is a melanoma from the outset, and the gradual evolution of it over many years, without any evidence of transformation,

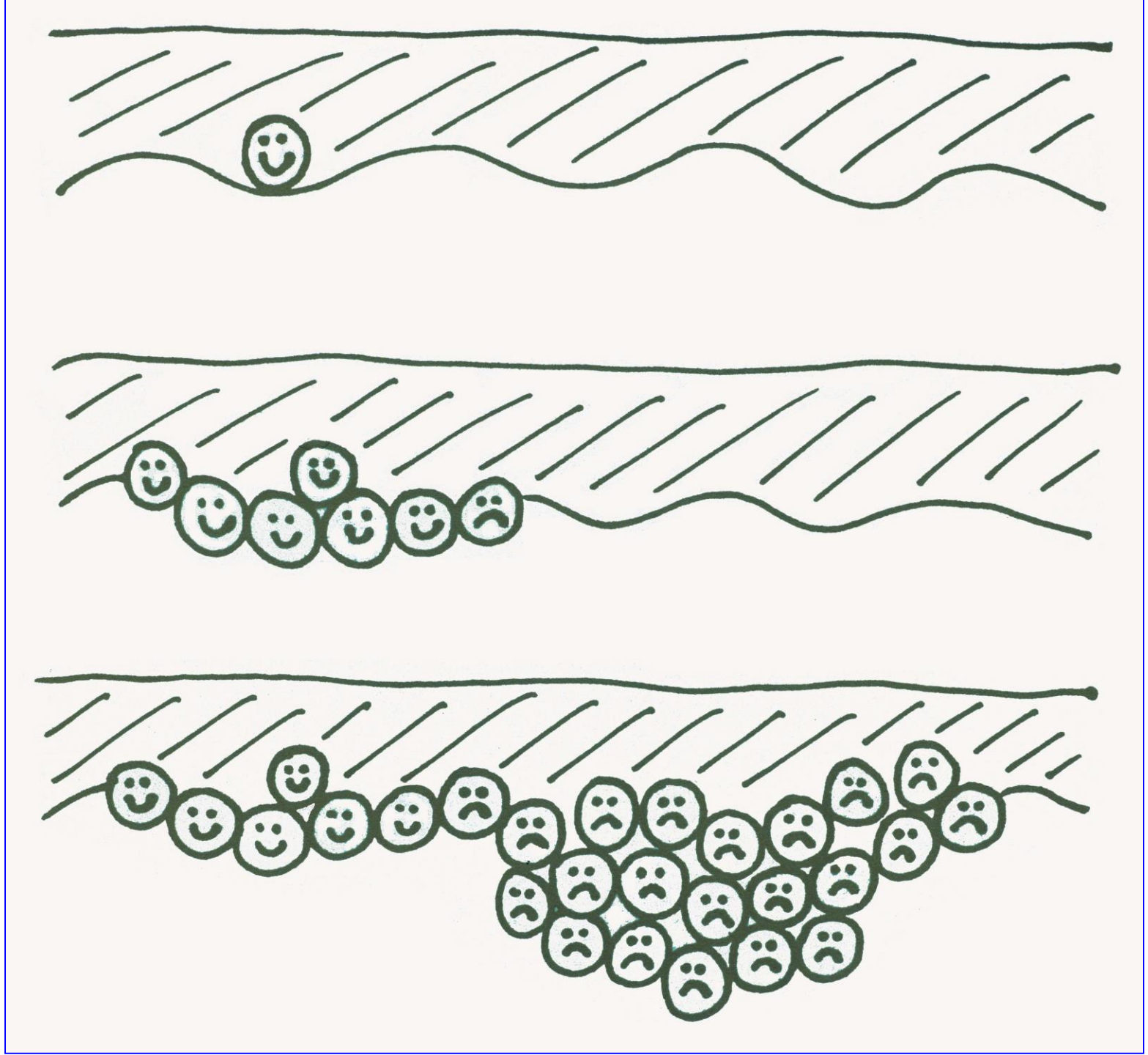



has been demonstrated elegantly by Eberhard Paul in photokatamnestic studies. Nevertheless, the concept of a continuous evolution from nevus to melanoma is still en vogue,

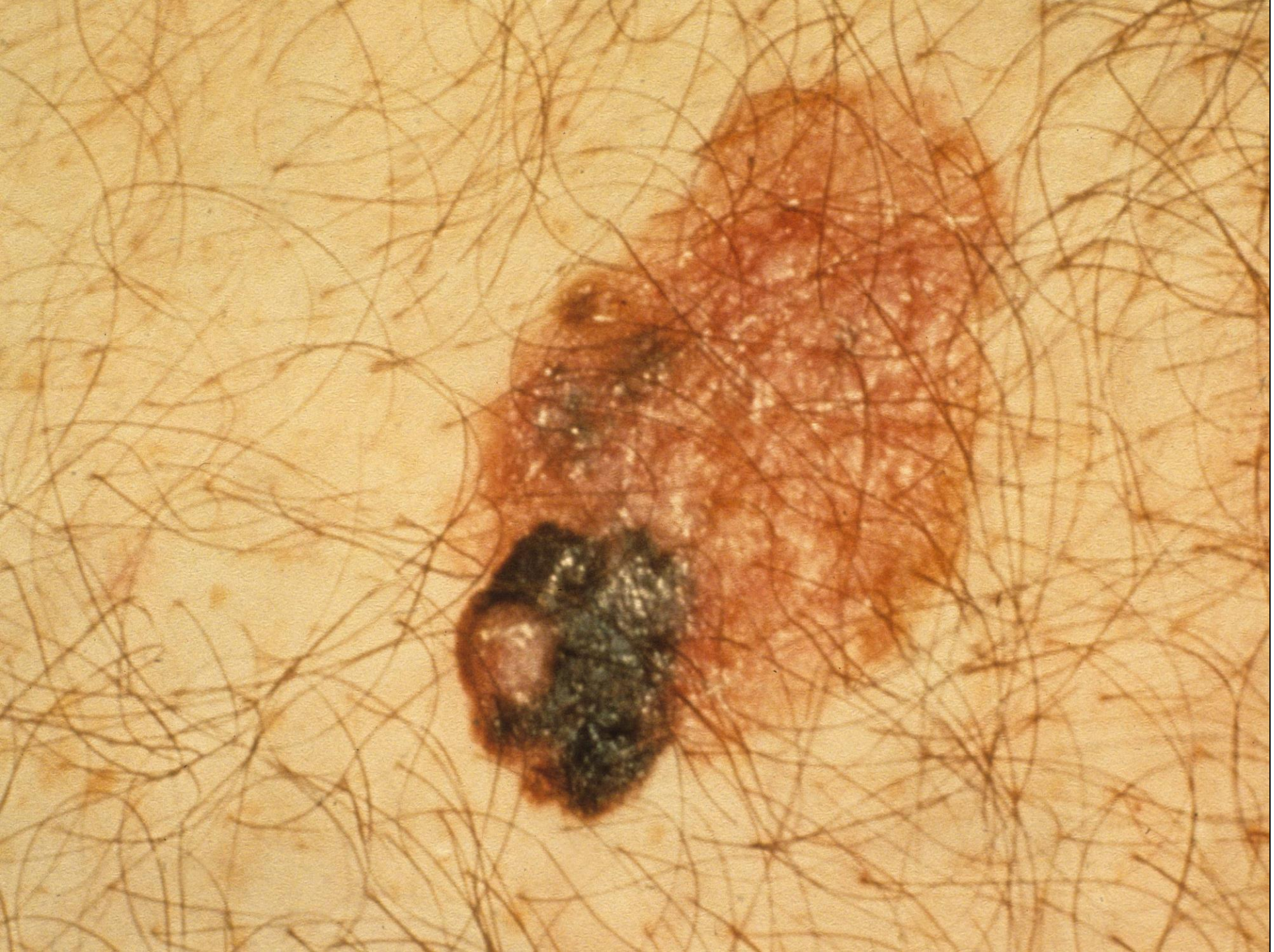



based on the concept of multistep carcinogenesis, according to which initiation by an oncogenic stimulus may lead to a benign neoplasm that, by conversion through other stimuli, may transform into a malignant neoplasm.

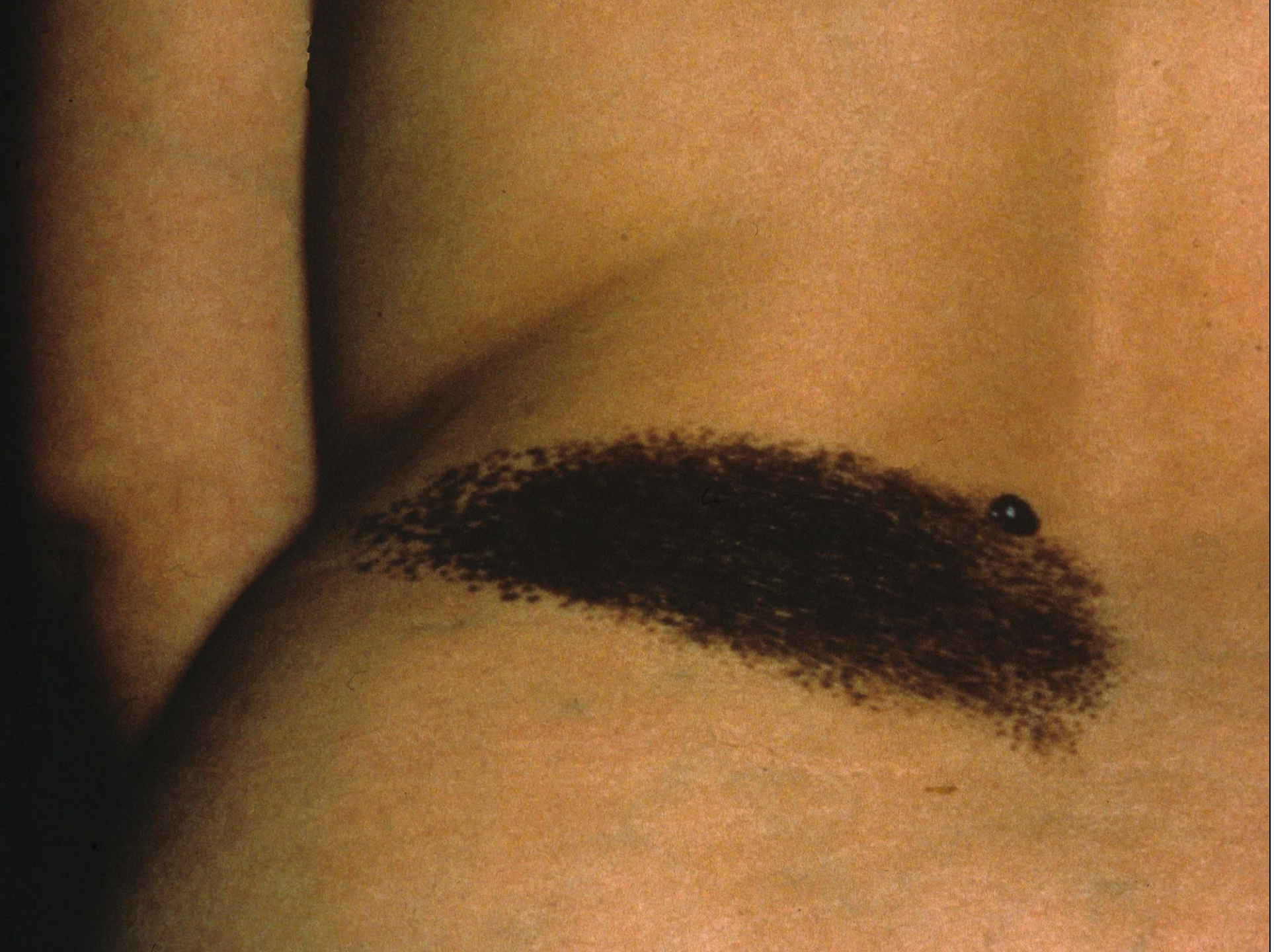
There is no question that many changes are requisite for producing a malignant tumor, but those changes occur at a cellular level, followed by clonal proliferation of the altered cell.



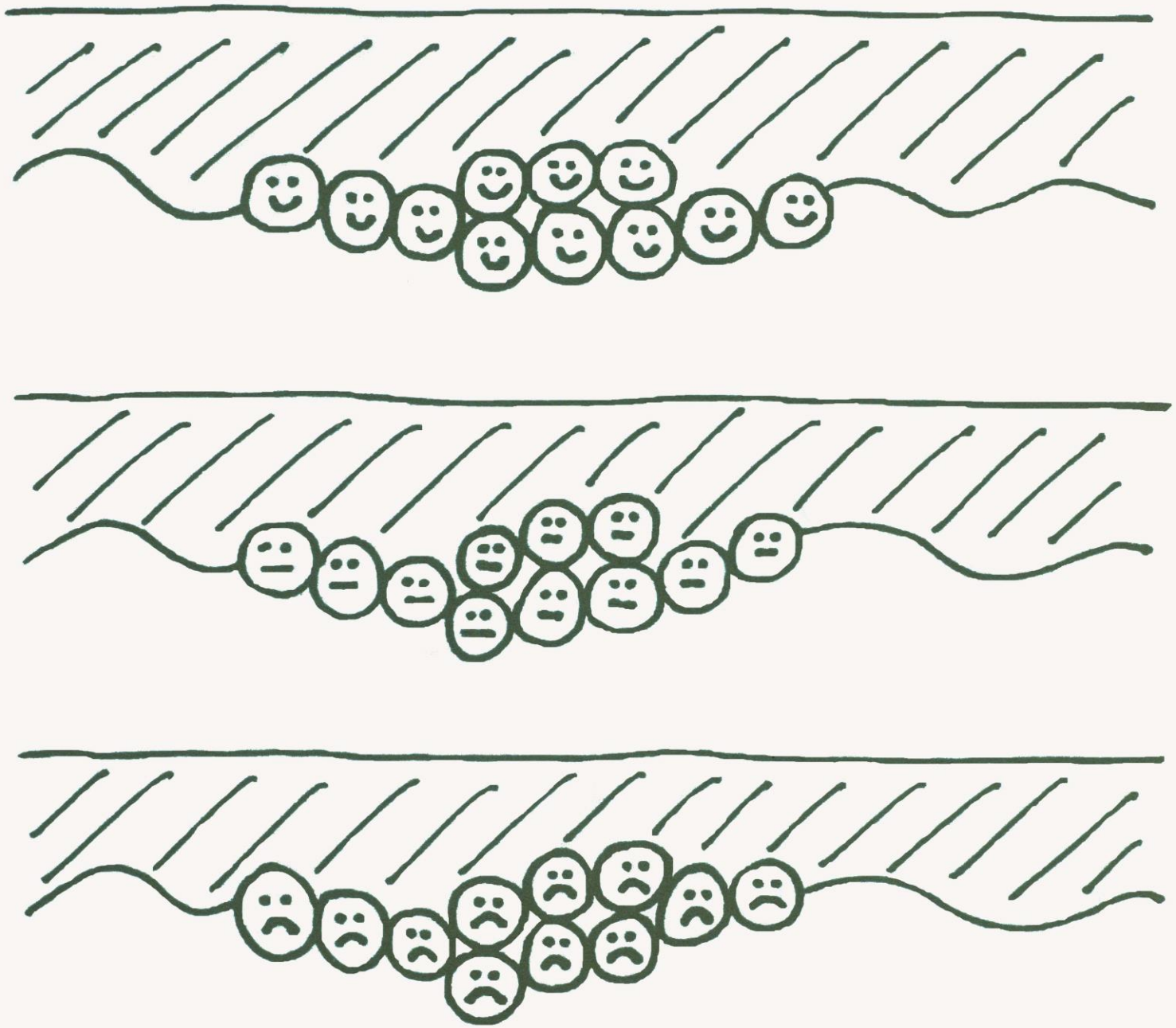
In other words, a benign cell with a broad smile may be induced to proliferate, but is still benign and gives rise to a benign neoplasm. Then one of those benign cells may become malignant and, through clonal proliferation, may give rise to a malignant neoplasm that exists next to the benign one. This chain of events is not uncommon in melanocytic neoplasms.



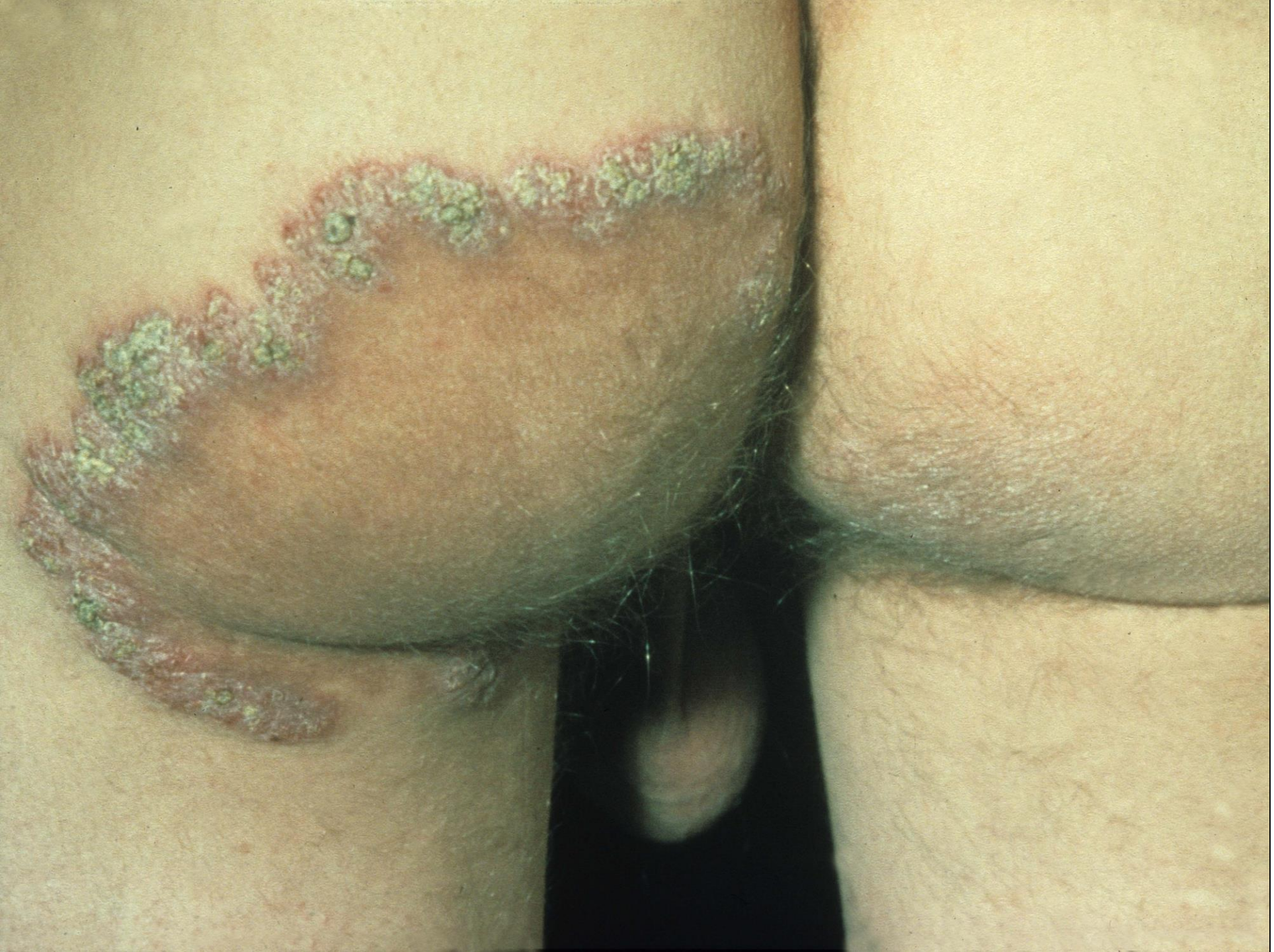
Approximately 20% of melanomas have been estimated to arise on the basis of a pre-existing nevus.



In general, nevi associated with melanomas are Clark's nevi or congenital nevi. The association of a melanoma with a Spitz's nevus is practically unheard of.

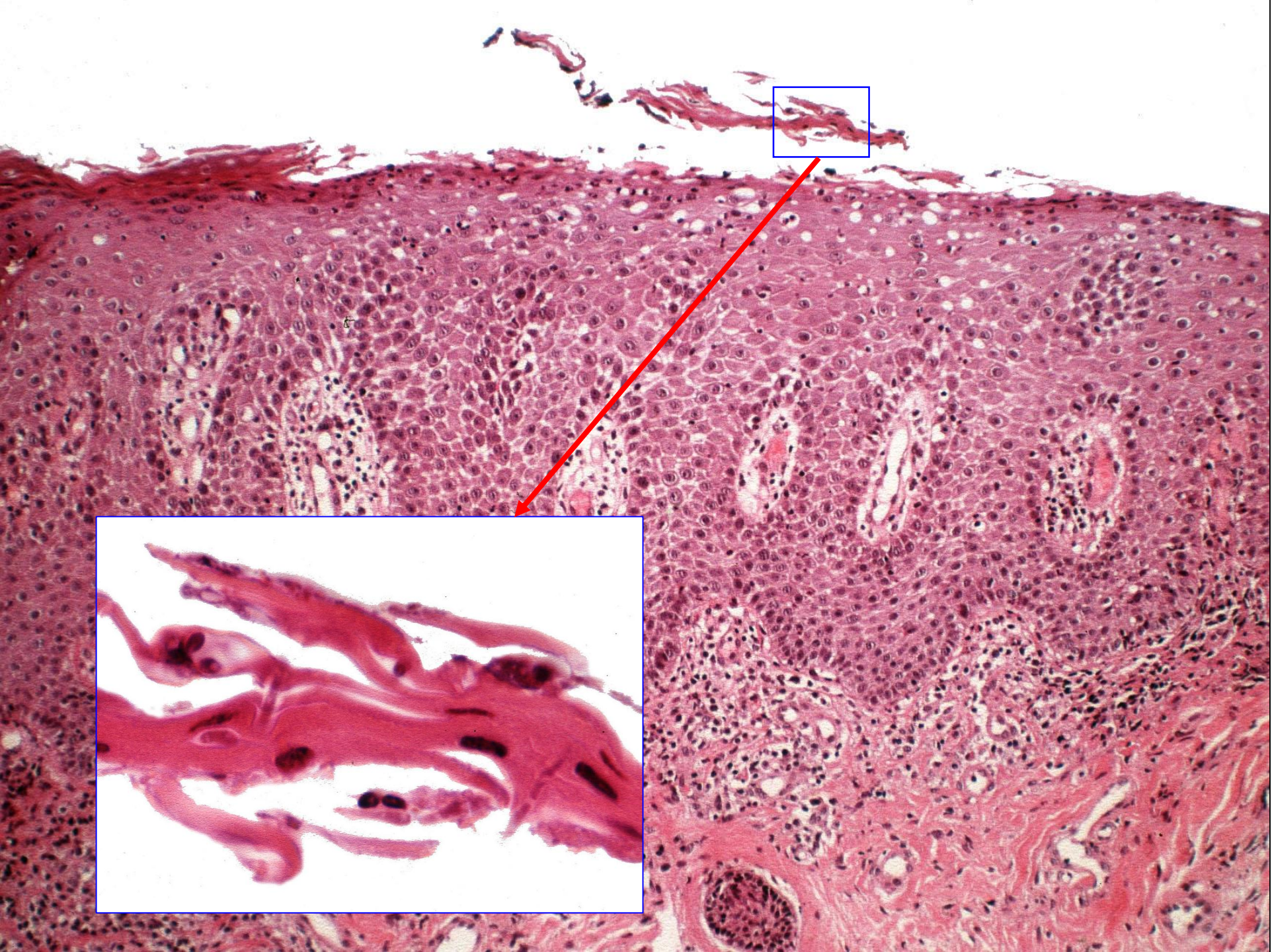


Moreover, the concept of a continuous evolution of a Spitz's nevus or a dysplastic nevus into melanoma, is very different. According to that concept, the entire nevus changes. All cells that are smiling in the beginning first become slightly upset, and end up as fully malignant. The diagnostically challenging cases are attributed to the middle position, but there is no evidence at all that such a transitional stage of a lesion composed entirely of slightly upset cells actually exists. In other words, a melanoma may grow on a nevus,



just as a fungus may grow on human skin, but there is no evidence that the entire nevus transforms into melanoma, just as a human being does not transform into a fungus only because the fungus grows on it.

In other diseases, we have no problem in separating morphology and biology from one another. For example, it is well known that a fungal infection may resemble psoriasis, clinically



and histopathologically, but nobody would suggest that those diseases are related to one another biologically. And yet, this is just what happens in melanocytic neoplasms. In cases in which differential diagnosis becomes difficult, a transition biologic is being postulated, and this tendency threatens to erase all progress made in former years.

The juvenile melanoma is a benign lesion. It is a variant of a compound nevus and has no greater vulnerability to cancerous transformation than any other compound nevus … To say that a completely resected juvenile melanoma has given rise to metastasis is, in effect, to admit that an error in diagnosis has been made and that a malignant melanoma has been mistaken for a juvenile melanoma.

A. C. Allen, Arch Derm 1960; 82: 325

Already in 1960, Arthur Allen came to the following conclusions: *"The juvenile melanoma is a benign lesion. It is a variant of a compound nevus and has no greater vulnerability to cancerous transformation than any other compound nevus … To say that a completely resected juvenile melanoma has given rise to metastasis is, in effect, to admit that an error in diagnosis has been made and that a malignant melanoma has been mistaken for a juvenile melanoma."*

This statement is clear and logical but, by now, it has been challenged, and without any compelling reason.

The American Journal of Surgical Pathology 13(11): 931–939, 1989


# Spindle Cell and Epithelioid Cell Nevi with Atypia and Metastasis (Malignant Spitz Nevus)

Kathleen J. Smith, LTC MC USA, Terry L. Barrett, CDR MC USN,
Henry G. Skelton III, CDR MC USN,
George P. Lupton, COL MC USA, and James H. Graham, M.D.

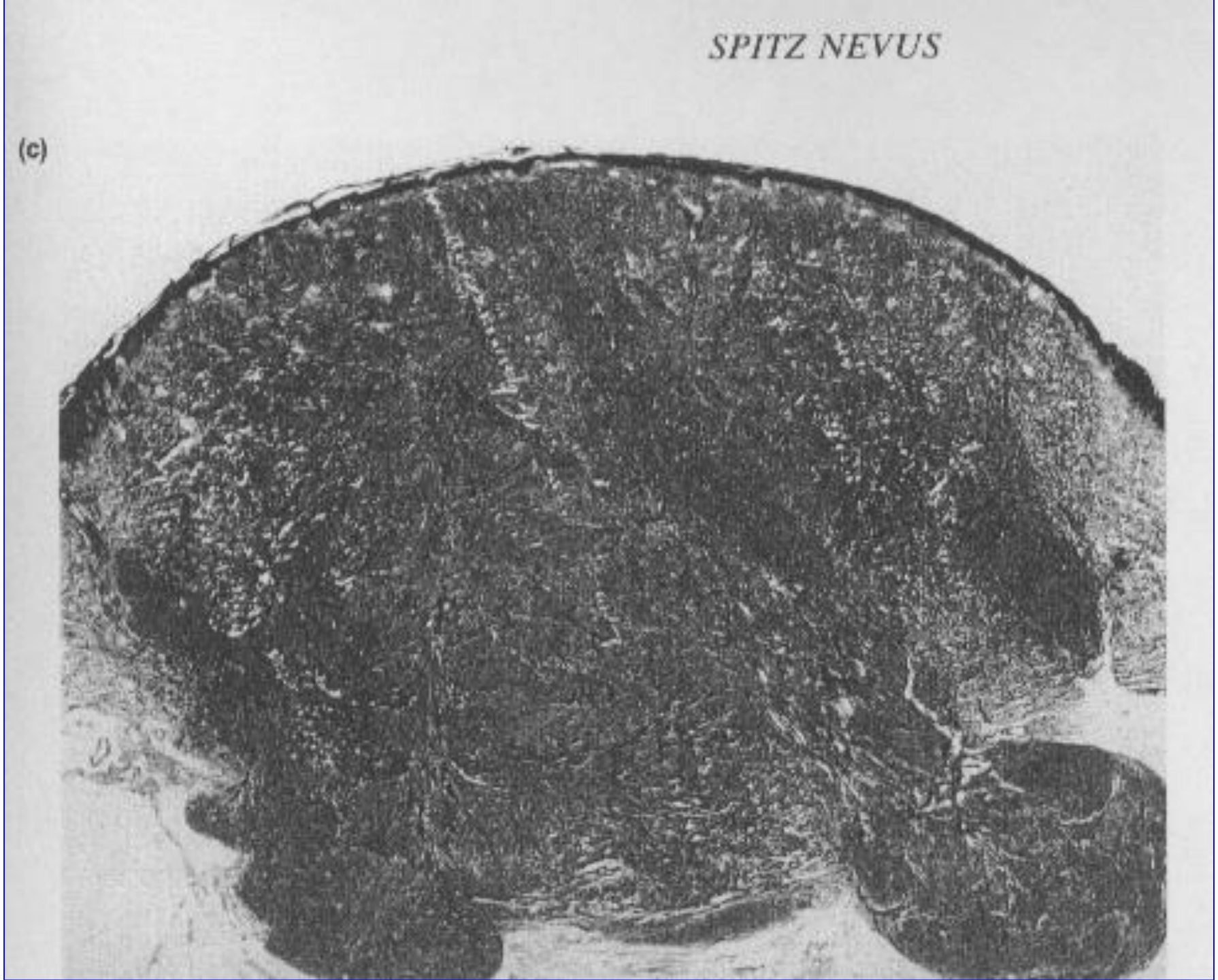
We report on the clinical and pathologic features of 32 lesions diagnosed as malignant spindle cell and epithelioid cell nevus (S&E nevus). Because of the clinical or initial histopathologic diagnosis of malignant melanoma, six patients had lymph node dissection. Three of these patients also had an enlarged lymph node. In all six cases, metastatic spindle or epithelioid cells were found in at least one of the resected lymph nodes. Of the 30 patients with follow-up information, including all six patients with lymph node metastases, all are alive and well. No recurrences or further metastases have been found. On histopathologic reevaluation, all the lesions had features of S&E nevi. Study of these cases suggests that although some lesions with features of S&E nevi may involve local lymph nodes, widespread metastases do not result.
**Key Words:** Spindle cell and epithelioid cell nevus—Nevi with metastasis—Spitz nevus—Skin.

*Am J Surg Pathol 13(11): 931–939, 1989.*

The histologic criteria for the diagnosis of spindle cell and epithelioid cell nevus (S&E nevus) were first described in 1948 by Dr. Sophie Spitz (25). Prior to Dr. Spitz's publication, S&E nevi were considered to be histologically indistinguishable from malignant melanomas (MM) of adults (19); they were called "juvenile melanomas." Because they were (thought) to be highly susceptible to malignant transformation, the treatment of choice was surgical removal prior to puberty (19). However, Pack and Angelem stated in 1939 that these juvenile melanomas seldom metastasize (19) and lethal MM in children are very rare.

In 1954, McWhorter and Woolner reviewed the material at the Mayo Clinic and confirmed the opinion of Spitz that "juvenile melanomas" are clini-

In 1989, Smith and colleagues of the Armed Forces Institute of Pathology in Washington published an article titled "Spindle cell and epithelioid cells nevi with atypia and metastasis (malignant Spitz nevus)." Of 32 patients with lesions diagnosed as Spitz's nevus, six had lymph node metastasis.




On the basis of the photomicrographs shown in the article, the primary lesions were clearly not Spitz's nevi but melanomas, being huge, asymmetrical,

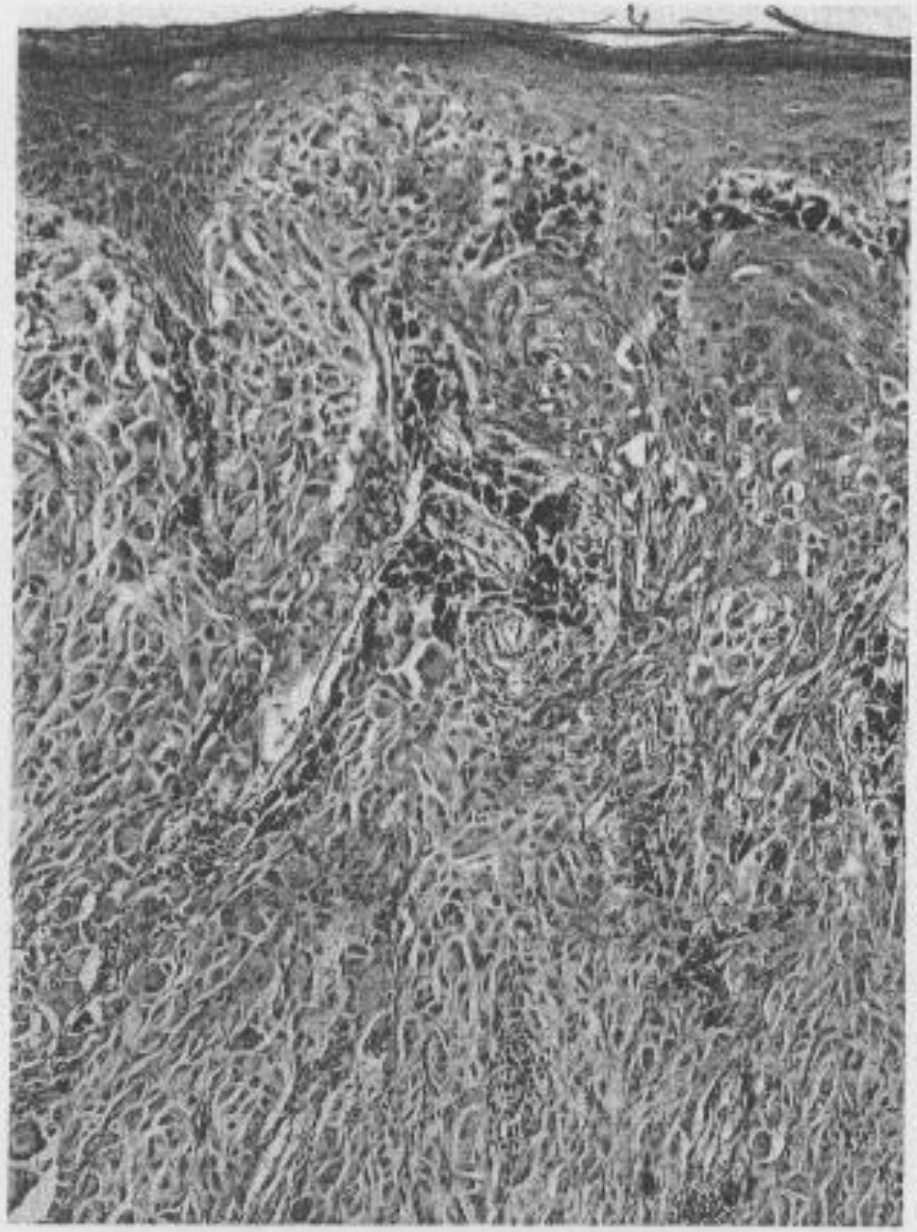


**FIG. 3.** Epidermal acanthosis, as shown in this higher-power view of Fig. 1b, is a frequent finding. Characteristic Touton-type giant cells may also be seen in the nodal metastasis.

and composed of sheets of melanocytes

**FIG. 7.** Mitotic figures may be present deep in the nevus.

with many mitotic figures, including atypical ones. And yet, only because patients did not develop additional metastases in a follow-up period of 2 to 10 years,

The benign clinical course in each of these cases, including those with lymph node metastasis, suggests that these lesions have the ability to metastasize to local lymph nodes but are not capable of widespread metastasis … We would not classify these lesions as malignant melanomas because they have not shown the potential for widespread metastases.

K. J. Smith et al; Am J Surg Pathol 1989; 13: 931

the authors concluded:
*"The benign clinical course in each of these cases, including those with lymph node metastasis, suggests that these lesions have the ability to metastasize to local lymph nodes but are not capable of widespread metastasis … We would not classify these lesions as malignant melanomas because they have not shown the potential for widespread metastases."*

Of course, this was pure speculation, violated all principles of oncology, and ignored the well-known fact

# Ultra-Late Recurrence (15 Years or Longer) of Cutaneous Melanoma

**Hensin Tsao**, M.D., Ph.D.[1]
**A. Benedict Cosimi**, M.D.[2]
**Arthur J. Sober**, M.D.[1]

[1] Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts.

[2] Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts.

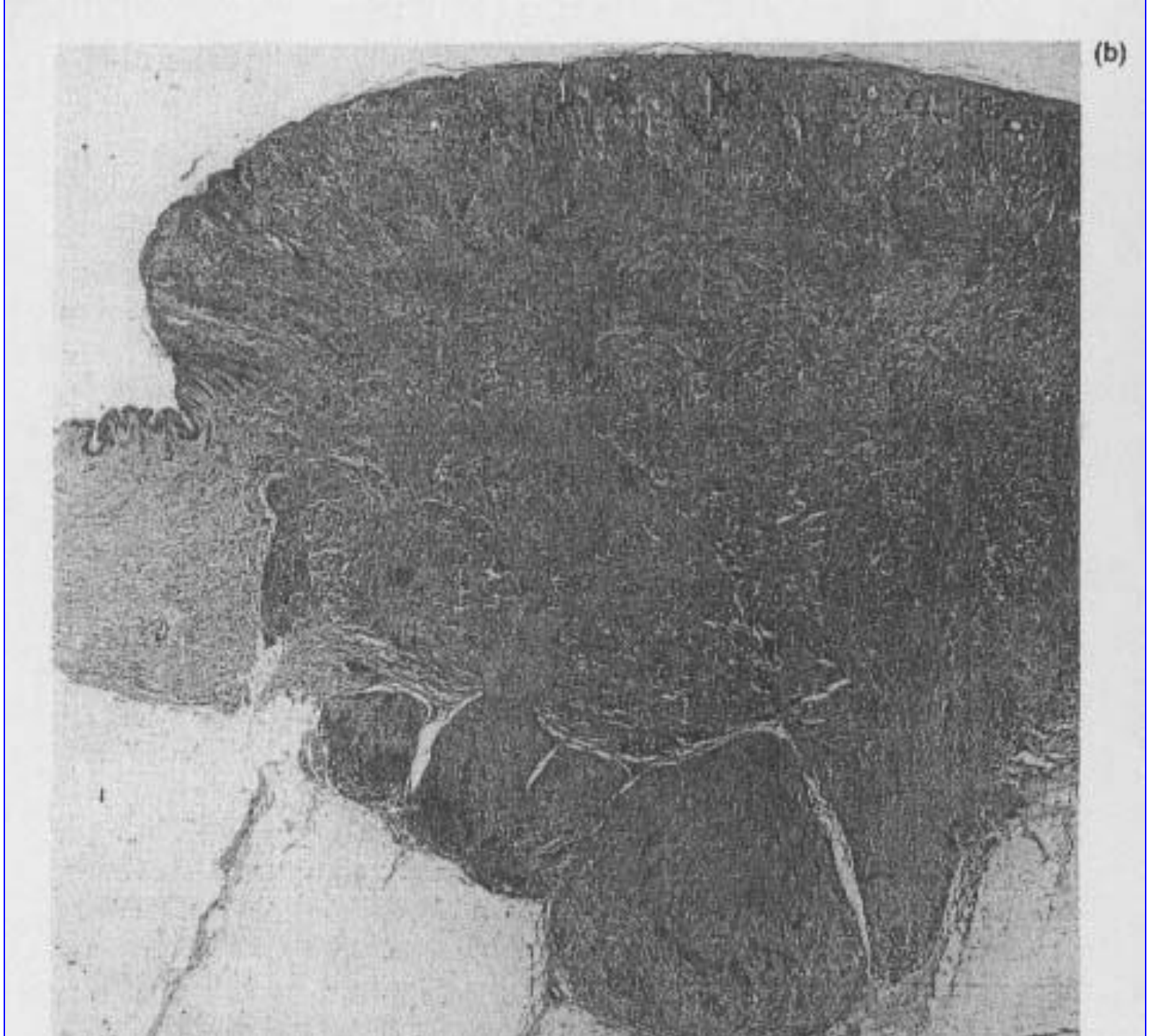
**BACKGROUND.** Melanoma can remain clinically quiescent for decades before regional or distant recurrence appears. This protracted disease free interval challenges the concept of a "cure" for melanoma.

**METHODS.** To understand this prolonged dormancy better, the authors retrospectively studied patients who developed recurrent melanoma 15 years or longer after their initial diagnosis ("ultra-late" recurrence). These cases were identified from 2766 melanoma diagnoses available in the Cancer Registry at the Massachusetts General Hospital (MGH). Histologic features of the primary lesion were also included when possible.

**RESULTS.** Twenty cases were retrieved from the MGH database. There were equal numbers of women and men, although women were younger at the time of initial diagnosis (mean age of women: 29.8 years vs. 43.0 years for men). No patients had more than one primary cutaneous melanoma. The trunk was the most common primary site (35%), although there was no predominant anatomic localization. The average disease free interval was 17.3 years for women, 20.0 years for men, 18.1 years for patients with regional recurrence, and 19.0 years for patients with distant metastases. Distant recurrence was the most common type of recurrence (50% of women and 60% of men). The estimated probability of survival (5 years after recurrence) was 0.8 for regional disease and 0.2 for distant disease. With the available histologic records, it appears that almost all tumors were Clark Level III or IV with thicknesses ranging from 0.8–2.3 mm. In contrast to the published cases, this study did not find that women with lower extremity melanomas were at higher risk for developing ultra-late recurrence.

**CONCLUSIONS.** Ultra-late recurrence of melanoma, although uncommon, can occur in any patient without identifiable risk factors. Because many prognostically favorable melanomas (thin melanomas on extremities) can recur after prolonged disease free intervals, the possibility of delayed recurrence remains and must be kept in mind. ***Cancer* 1997;79:2361–70.** 

that metastases of melanoma often become manifest only after many years.




Nevertheless, the idea of a spitzoid melanocytic neoplasm with diminuished malignant potential was born, and this was just what pathologists needed. Why?

Because differential diagnosis between Spitz's nevus and melanoma continues to pose problems. Criteria for distinction of those entities are sometimes difficult to assess and may be conflicting with one another.

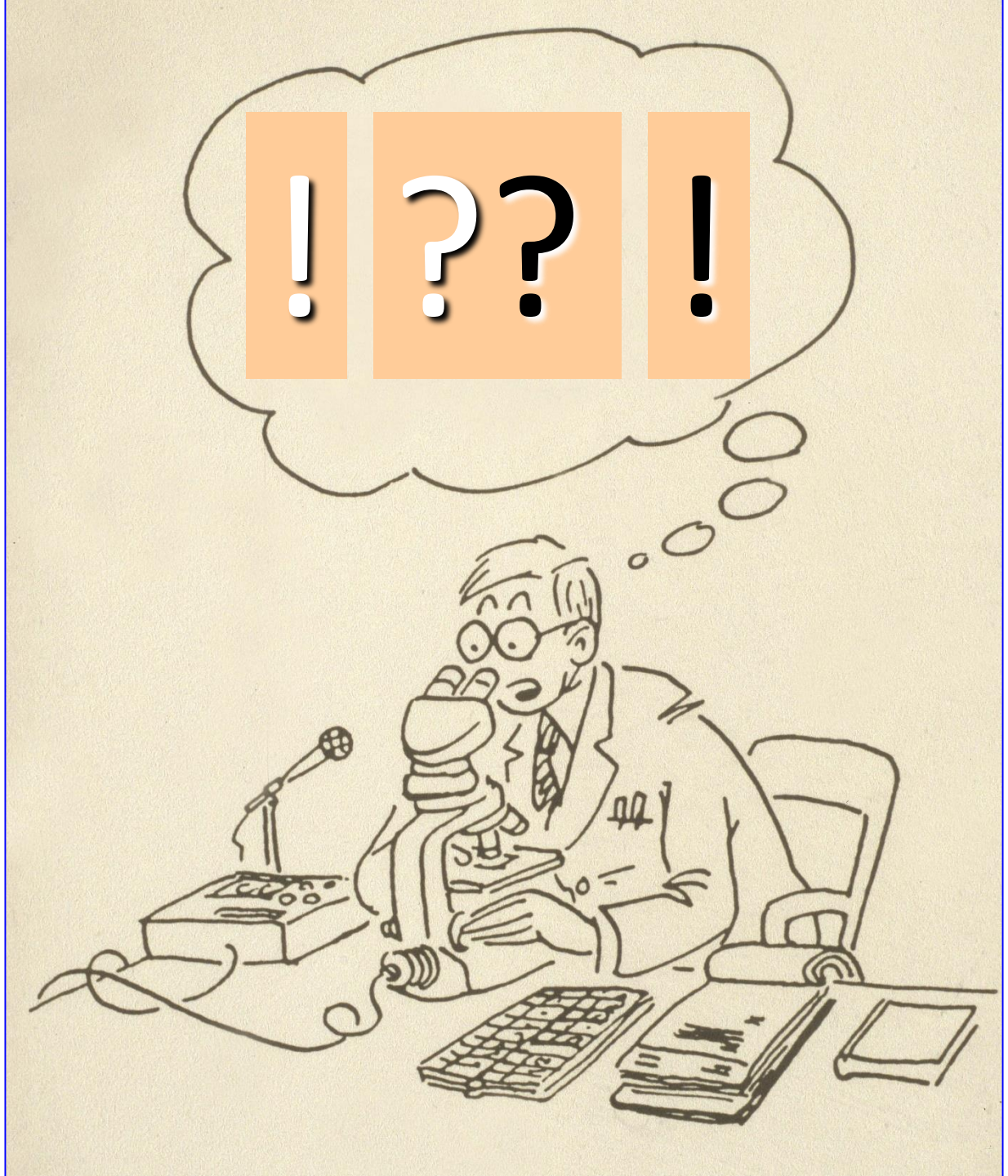
# Atypical Spitz Nevi/Tumors: Lack of Consensus for Diagnosis, Discrimination From Melanoma, and Prediction of Outcome

RAYMOND L. BARNHILL, MD, ZSOLT B. ARGENYI, MD, LYNN FROM, MD, L. FRANK GLASS, MD, JOHN C. MAIZE, MD, MARTIN C. MIHM, JR., MD, MICHAEL S. RABKIN, MD, PHD, SALVE G. RONAN, MD, WAIN L. WHITE, MD, AND MICHAEL PIEPKORN, MD, PHD

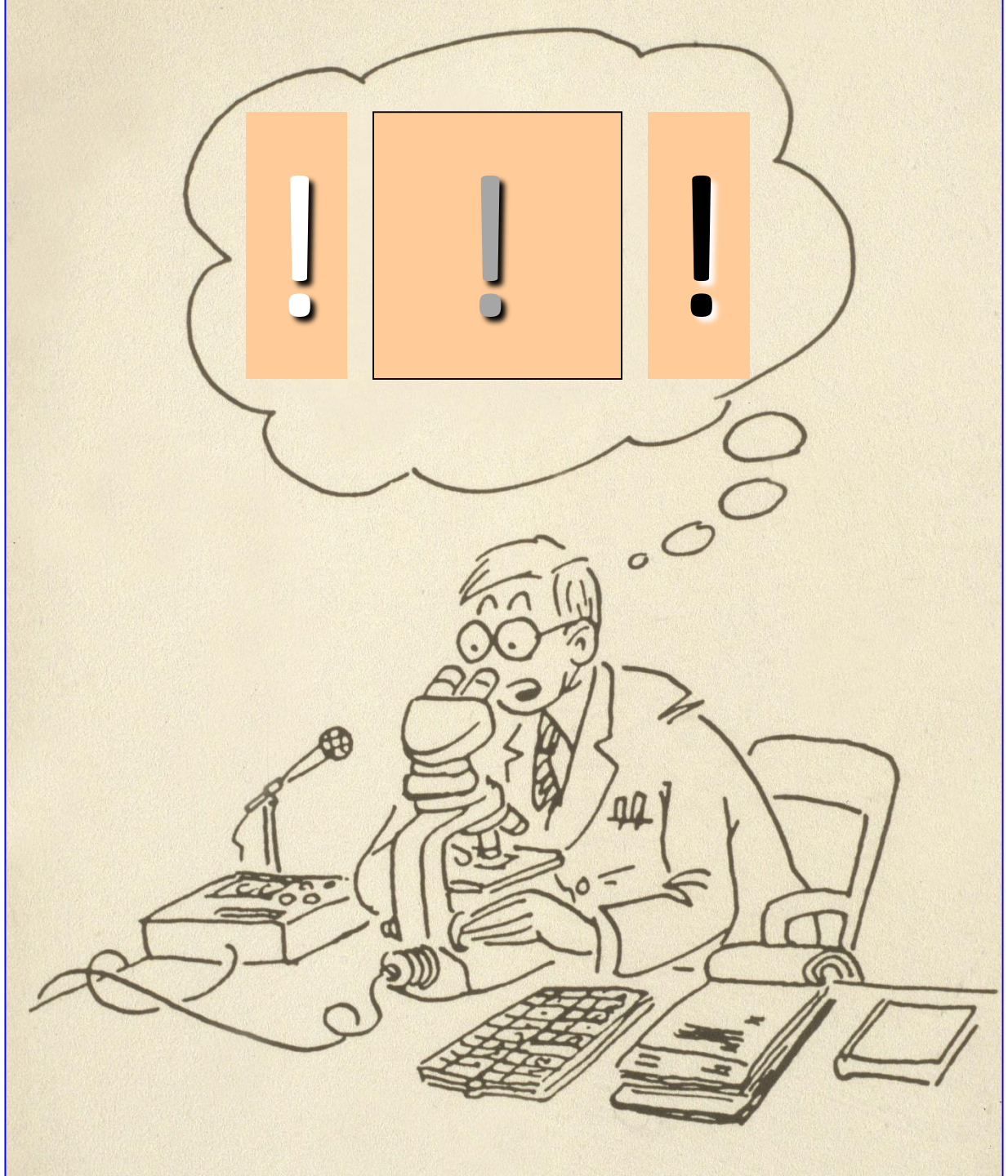
The biological nature of Spitz nevi/tumors and their diagnostic distinction from, or relationship to, melanoma remain unresolved issues. In this report, a series of 30 melanocytic lesions removed from 28 patients, including atypical Spitz nevi/tumors and metastasizing Spitzoid tumors/melanomas, were evaluated by a panel of dermatopathologists to evaluate interobserver diagnostic concordance and to assess the prognostic power of histological criteria. For inclusion in the study, each lesion had to display some criteria for the Spitz nevus, and in addition one of the following was required: (1) definitive clinical outcome such as metastasis or death of disease, or (2) long-term follow-up if the patient remained disease free. Each lesion was reviewed independently and blinded as to the clinical data by 10 pathologists, who categorized them as (1) typical Spitz nevus/tumor, (2) atypical Spitz nevus/tumor, (3) melanoma, (4) tumor with unknown biological potential, or (5) other melanocytic lesion. There was limited discussion of criteria before the review. Evaluation of 17 Spitzoid lesions yielded no clear consensus as to diagnosis; in only one case did six or more pathologists agree on a single category, regardless of clinical outcome. Notably, however, some lesions that proved fatal were categorized by most observers as either Spitz nevi or atypical Spitz tumors. Conversely, seven or more pathologists scored 13 lesions as melanoma. These results illustrate (1) substantial diagnostic difficulties posed by many Spitz tumors, especially those with atypical features, even among experts, and (2) the lack of objective criteria for their distinction from melanoma and for gauging their malignant potential. Nevertheless, our observations do suggest that a biological relationship exists between the Spitz nevus/tumor and melanoma. HUM PATHOL 30:513-520. 

*Key words:* Spitz nevus, Spitz tumors, melanoma, interobserver concordance, prognosis.

Such challenging lesions have been referred to vaguely as “atypical Spitz nevi,” a term that has never been defined. In 1999, Barnhill and co-workers had a series of “atypical Spitz nevi” assessed by a group of so-called “experts,” each of whom evaluated the lesions separately, and he found that there was *“lack of consensus of diagnosis, discrimination from melanoma, and prediction of outcome.”*




In short, there are cases in which even experts do not know whether the lesion is benign or malignant, black or white, something that pathologists do not like to admit.



Therefore, they tend to give the diagnosis of a greyish, slightly malignant lesion. In short, problems in differential diagnosis seize to exist when a lesion that is equivocal diagnostically is claimed to be equivocal biologically. This makes life much easier but, unfortunately, only for the pathologist, and not for the patient.

# Cutaneous Melanoma and Atypical Spitz Tumors in Childhood

*Raymond L. Barnhill, M.D., Thomas J. Flotte, M.D., Mary Fleischli, M.D., and Antonio Perez-Atayde, M.D.*

***Background.*** **Malignant melanoma in childhood is rare. As a result, the biology and natural history of melanoma in this age group is still poorly understood. Although the majority of Spitz nevi are benign regardless of atypical features, a particular problem is the continued confusion of Spitz nevi with atypical features with melanoma and the lack of specific criteria for their distinction. The latter discrimination is perhaps not so difficult when Spitz nevi are minimally atypical; however, the greater the atypia, the more challenging is this discrimination.**

***Methods.*** **All cases of malignant melanoma referred to Children's Hospital (Boston, MA) and to one of the authors were examined during the period of 1959–1995. Criteria for inclusion in the study included: (1) age up to 15 years; (2) availability of microscopic slides; and (3) availability of demographic data.**

***Results.*** **There were 11 males and 12 females, ranging in age from 2 to 15 years (mean age, 9.4 years). Histopathologically, the 23 tumors were categorized into four subgroups: (1) small cell melanoma (5); (2) adult-like melanoma (6); (3) Spitz-like melanoma (3), and (4) atypical Spitz tumors (9). The small cell melanomas were notable for localization to the scalp, significant thickness, and fatal outcome. The adult-like melanomas resembled typical tumors occurring in adults. The one fatal Spitz-like melanoma was located on the neck of a 14-year-old male. Two tumors in this group metastasized to regional lymph nodes, but were not associated with further aggressive disease on follow-up despite treatment with surgical excision only. The atypical Spitz tumors were characterized by significant thickness and abnormal features including prominent cellularity and mitotic activity.**

***Conclusions.*** **Anatomic site and cell type may be important prognostic factors in addition to tumor thickness for childhood melanoma, but these tumors require further study. In addition, the biologic potential of atypical Spitz tumors has not been characterized sufficiently.** ***Cancer*** **1995;76:1833–45.**

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Received April 7, 1995; revision received June 30, 1995; accepted July 21, 1995.

**Key words: malignant melanoma, childhood, Spitz nevus, skin, melanocytic nevus.**

Malignant melanoma in childhood is rare.[1–24] As a result, the biology and natural history of melanoma in this age group is still poorly understood, and this is related to a number of factors:

1. Because of its rarity, only a limited number of cases have been reported.
2. Of particular importance, almost all of these reports are not population-based and thus are characterized by significant referral bias.
3. The tumors in many series have not been subjected to careful histopathologic study and microstaging.
4. There is continued confusion of Spitz nevi and melanoma and, in general, a lack of objective criteria for their distinction.[15,16,20,23 25,26]
5. Because of the latter problem, some reports have included only melanomas associated with metastasis. The tendency to include only metastasizing melanomas in such reports clearly has resulted in a skewed population of childhood melanomas. Yet metastasis and/or death may be the only objective criteria for diagnosing true childhood melanoma.
6. Many reports have not had sufficiently long follow-up to determine the natural history of childhood melanoma.

Given the latter problems associated with the characterization of childhood melanoma, we report herein our experience at Children's Hospital (Boston, MA) with the histopathologic description of 23 childhood melanomas and atypical Spitz tumors.

## Materials and Methods

All cases of cutaneous malignant melanoma were retrieved from the surgical pathology files of the Depart-

But this is not all. The term “atypical Spitz tumor” is used increasingly not only for lesions that are equivocal but also for clear-cut melanomas that already have metastasized. In this article in “Cancer” in 1995,

Examination of the two metastasizing Spitz tumors and nine atypical Spitz lesions in this series revealed … features of Spitz nevus in addition to atypical features, including large size; significant depth; cellularity; cellular atypia; dermal deep, and, occasionally atypical mitoses. Many of the last mentioned features have specifically been cited as indicative of melanoma.

R.L. Barnhill et al.; Cancer 1995; 76: 1833

Barnhill wrote: *"Examination of the two metastasizing Spitz tumors and nine atypical Spitz lesions in this series revealed … features of Spitz nevus in addition to atypical features, including large size; significant depth; cellularity; cellular atypia; dermal deep, and, occasionally atypical mitoses. Many of the last mentioned features have specifically been cited as indicative of melanoma."* This is no wonder because those features are well established criteria for recognition of melanoma.

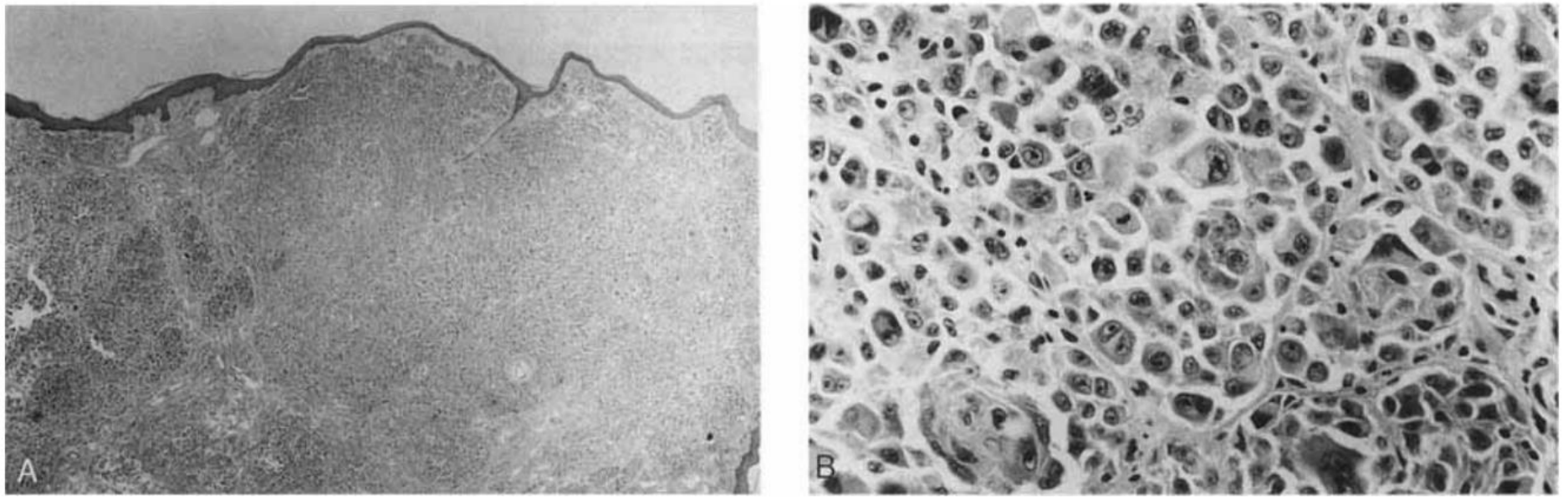


Figure 7. Metastasizing Spitz tumor diagnosed as malignant melanoma. (a) There is a large cellular nodule occupying most of the field. The cellular population extends into the deep reticular dermis (H & E, original magnification ×40). (b) High magnification of (a) shows a confluent and discohesive population of large epithelioid cells in the dermis. Many of the cells have abundant, ground-glass cytoplasms with angulated cellular contours. The cells contain large nuclei that are frankly bizarre in some instances. Multinucleate giant cells are also present (H & E, original magnification ×400).

And this is a lesion: a clear-cut melanoma – broad, deep, with sheets of atypical cells. Every novice in dermatopathology can make the diagnosis of melanoma here, but Barnhill refers to the lesion as *“atypical Spitz tumor.”* He even retreats the original correct diagnosis of malignant melanoma and claims that this is a *“metastasizing Spitz tumor diagnosed as melanoma.“*

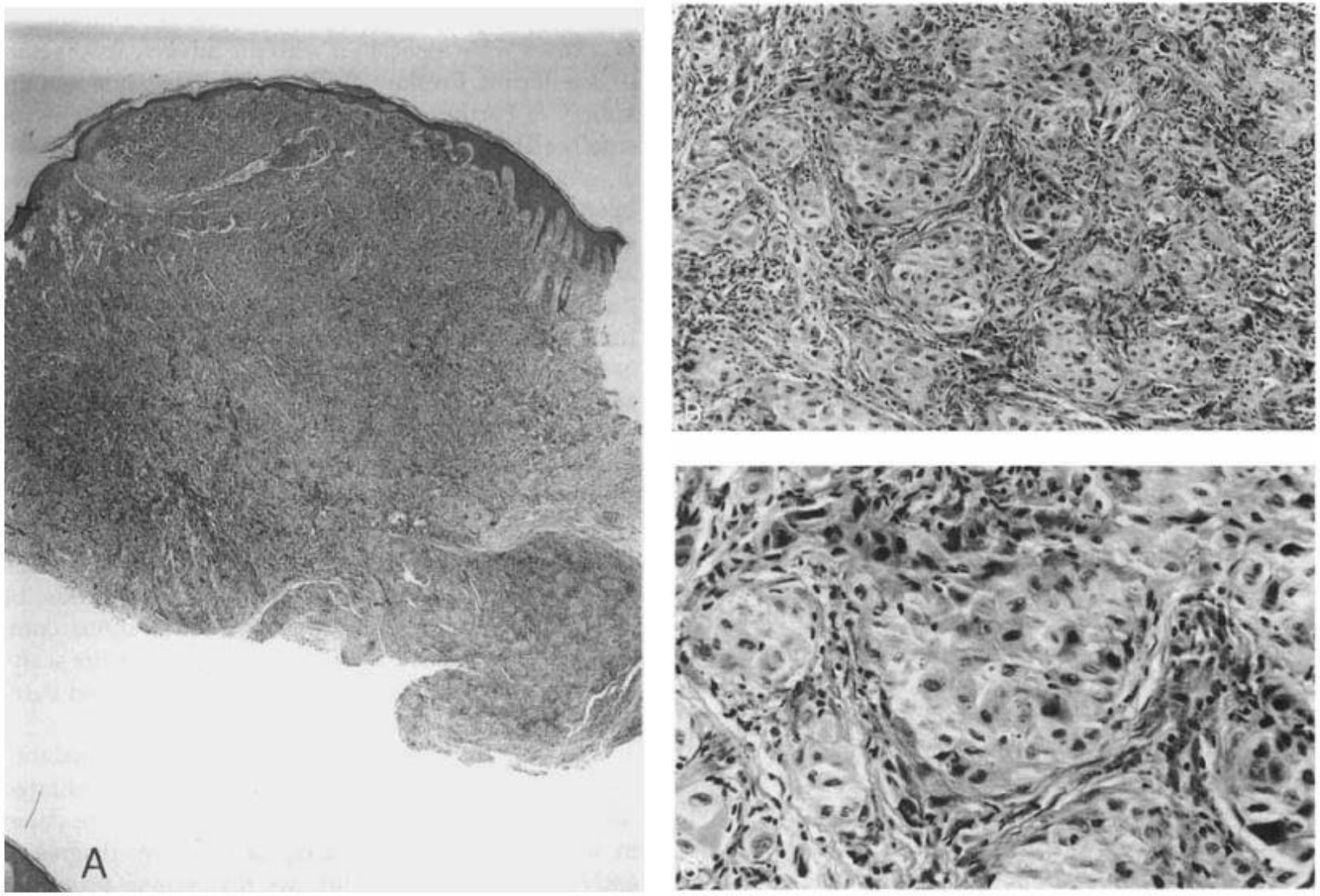


Figure 8. Atypical Spitz tumor. (a) This specimen exhibits an asymmetric, deeply infiltrating proliferation (H & E, original magnification ×40). (b) This field shows small cellular aggregates composed of epithelioid cells in the deepest portion of the tumor. The aggregates are separated by fibrous tissue (H & E, original magnification ×200). (c) High power magnification of (b) shows epithelioid cells with abundant cytoplasm. The cells also exhibit considerable nuclear pleomorphism and occasional hyperchromatism (H & E, original magnification ×400).

Nobody knows because, in order to assess prognosis of a particular neoplasm, it must first be defined. Nobody has defined "spitzoid melanoma" which precludes any valid statistical analysis. The seemingly better prognosis of so-called "atypical Spitz tumors" may simply be caused by inclusion, in statistical analyses, of patients with wholly benign nevi so that the mortality of the group as a whole is not so high.

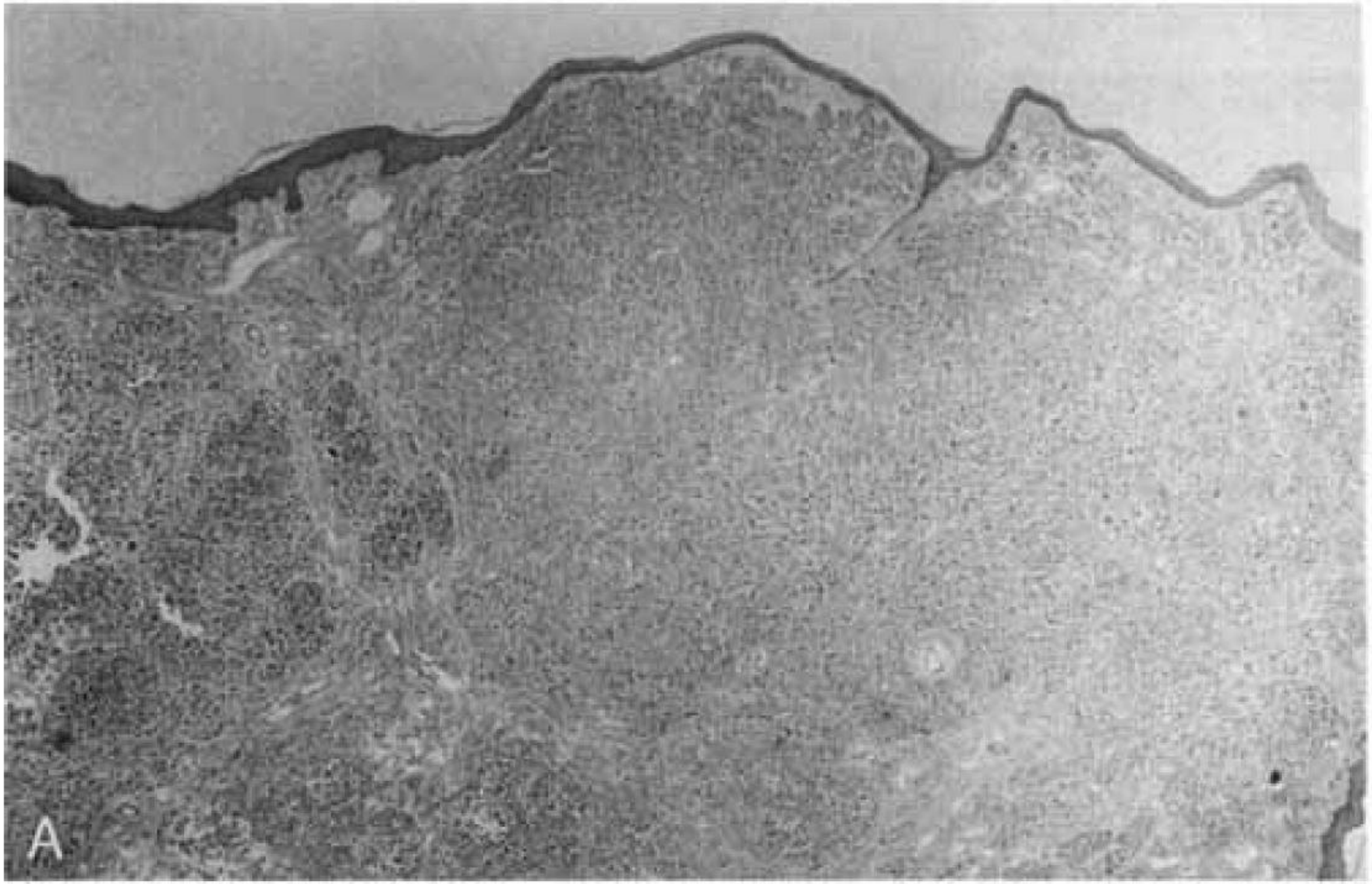


Figure 7. Metastasizing Spitz tumor diagnosed as malignant melanoma.

I have no doubt that, in a lesion such as this one that has already metastasized, prognosis is grim. Maybe the patient will survive for some years because of young age and a good immune response, but, in all likelihood, he is going to die of melanoma.

*Histopathology* 2001, 38, 448–453

# Spitzoid malignant melanoma in teenagers: an entity with no better prognosis than that of other forms of melanoma

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Fabrizi G & Massi G
(2001) *Histopathology* 38, 448–453

**Spitzoid malignant melanoma in teenagers: an entity with no better prognosis than that of other forms of melanoma**

*Aims*: A rare form of melanoma in teenagers closely simulates Spitz naevus and is claimed to have a good prognosis. The aim of this study is to identify the clues for a confident diagnosis of this entity and to confirm the peculiarly good prognosis.
*Methods and results*: Two cases of melanoma with Spitzoid features were compared with Spitz naevus and it was found that the major distinctive criteria are: mitoses and single cell necrosis in the deepest part of the lesion, cellular and particularly nuclear and nucleolar pleomorphism, and growth pattern in solid sheets of cells. More subtle clues were the asymmetric distribution of pigment and the thinning of the epidermis with parakeratosis and exudate in the cornified layer. Both of the lesions reached the mid-dermis. There was a fatal outcome in both patients after generalized metastatic spread. The metastatic disease in one of the cases appeared 15 years after the excision of the primary lesion.
*Conclusions*: Spitzoid melanoma in teenagers can be distinguished from Spitz naevus if strict criteria are followed. Spitzoid melanoma does not show a better prognosis than other types of melanoma if the follow-up is prolonged enough.

Keywords: differential diagnosis, melanoma, Spitz naevus, teenagers

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The notion that "atypical Spitz's nevi" are capable of lymph node but not of widespread metastases has been disproven already. For example, in 2001 Fabrizi and Massi reported on deaths of two teenage patients and concluded that *"Spitzoid malignant melanoma in teenagers"* is *"an entity with no better prognosis than that of other forms of melanoma."*

Melanoma of childhood

Spitz ’s nevus

Melanoma

However, the question of whether or not there is a spitzoid type of melanoma with a relatively favorable prognosis is not so important. The important issue is that Spitz’s nevus, which originally was misperceived as melanoma and came to be recognized as a benign lesion, recurs, like a bumerang, as melanoma.

Much of the current controversy regarding the nature of Spitz lesions resides in the designation, ‘nevus’. Spitz lesion is not a nevus; it is a true neoplasm with potential for progressive local growth … Spitz characterizes these lesions as ‘juvenile melanoma’; perhaps if we return to such a designation, order could be restored to the category.

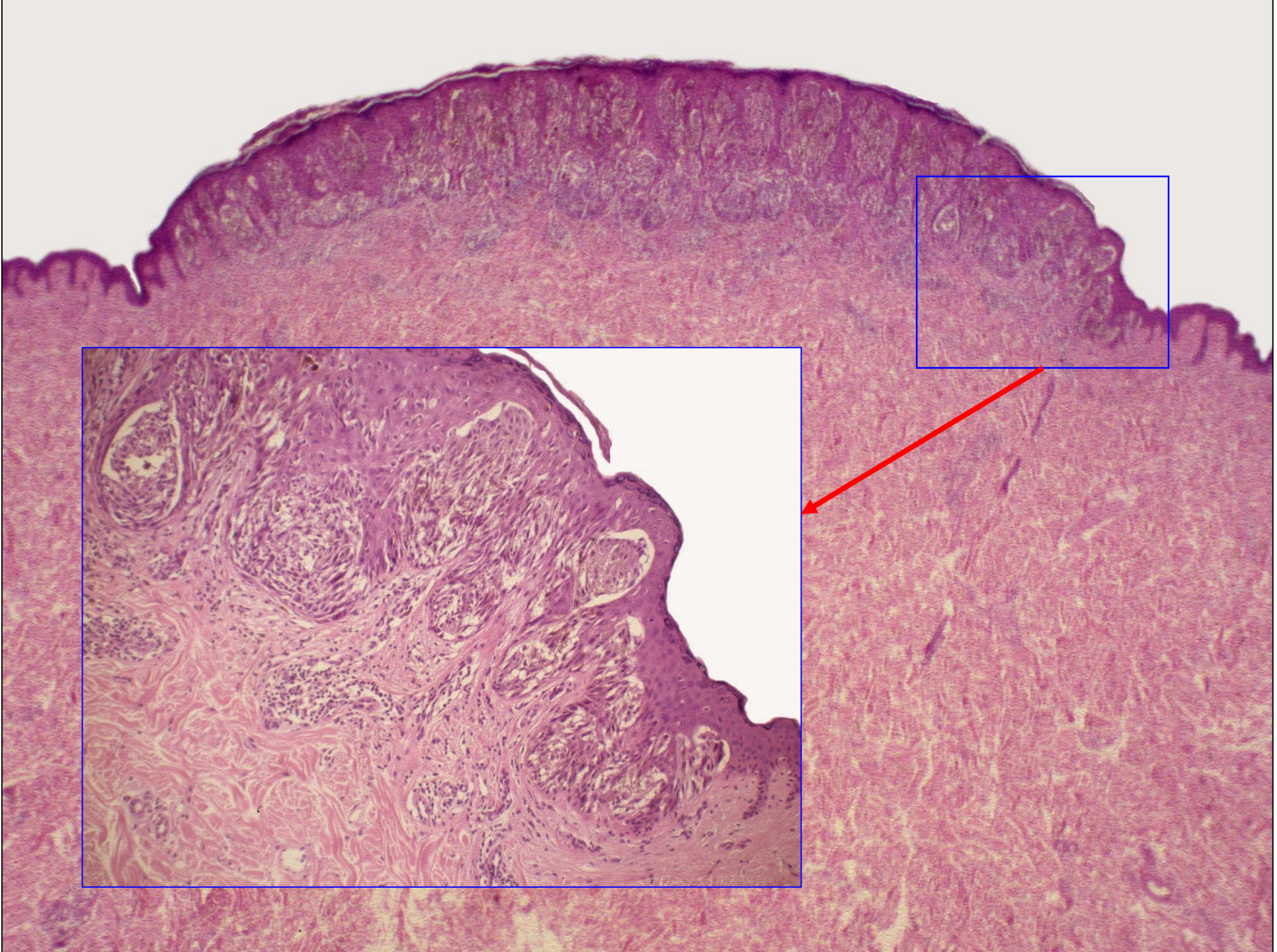
Richard J. Reed, 2004

In 2004, Richard Reed stated that *“much of the current controversy regarding the nature of Spitz lesions resides in the designation, ‘nevus’. Spitz lesion is not a nevus; it is a true neoplasm with potential for progressive local growth … Spitz characterizes these lesions as ‘juvenile melanoma’; perhaps if we return to such a designation, order could be restored to the category.”*

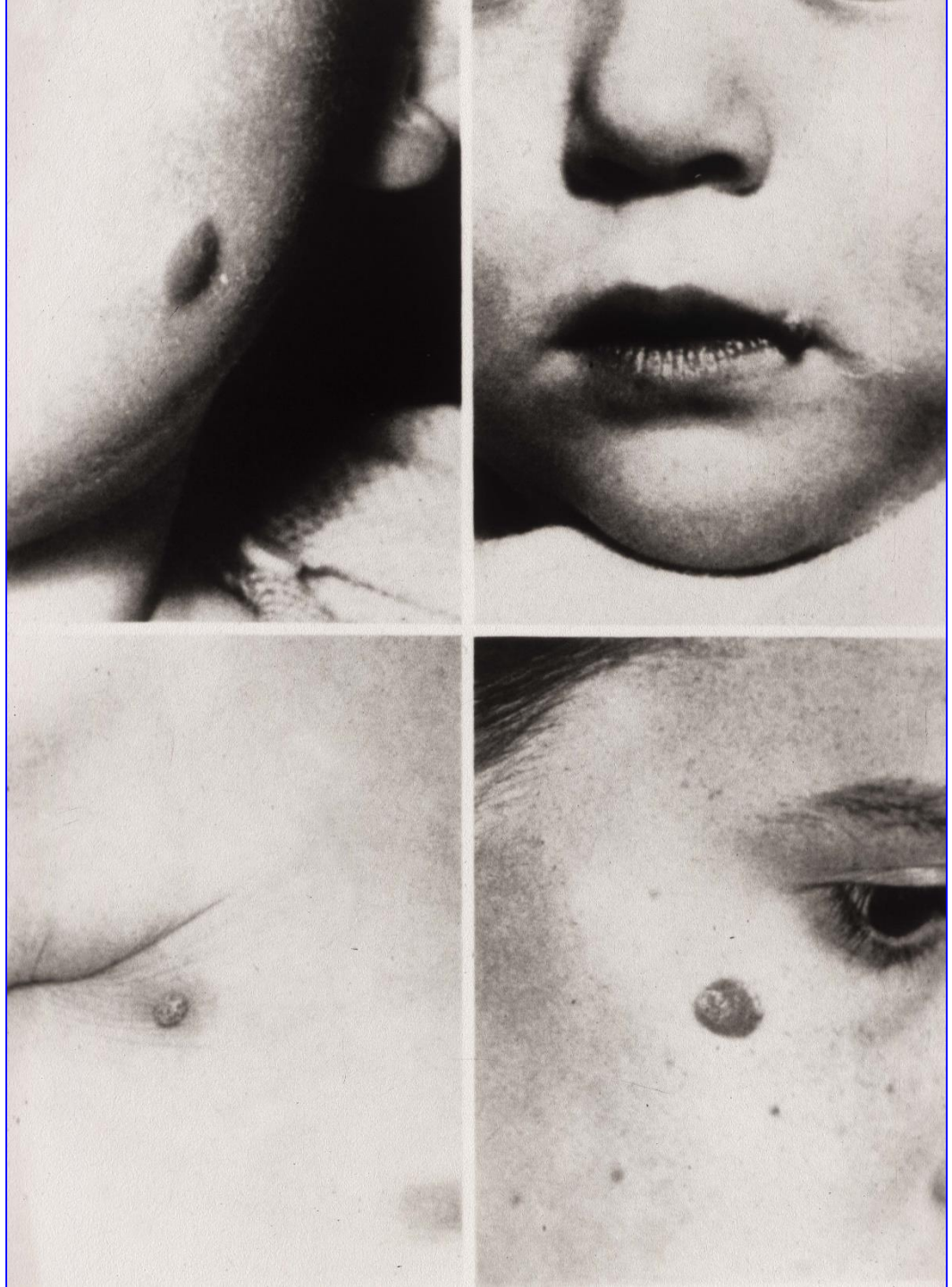
# Spitzoid tumors … represent a group of low-grade malignant melanocytic tumors, different from “common” melanomas.

Lorenzo Cerroni, Am J Dermatopathol 2005; 27: 366

In 2005, Lorenzo Cerroni of Graz claimed that “*spitzoid tumors … represent a group of low-grade malignant melanocytic tumors, different from ‘common’ melanomas.”* The problem with those statements is that they no longer pertain only to spitzoid lesions in which diagnosis is difficult, but to all Spitz’s nevi, including those that are clearly benign.



In the vast majority of Spitz's nevi, histopathologic diagnosis is easy because all criteria that have been established in the course of many years are fulfilled. Sometimes, even clinical diagnosis is easy and dependable –



just think of the clinical pictures in Spitz’s original article.

# Spindle and Epithelioid Cell Nevus (Spitz Nevus)

## Natural History Following Biopsy

Valda N. Kaye, MD, Louis P. Dehner, MD

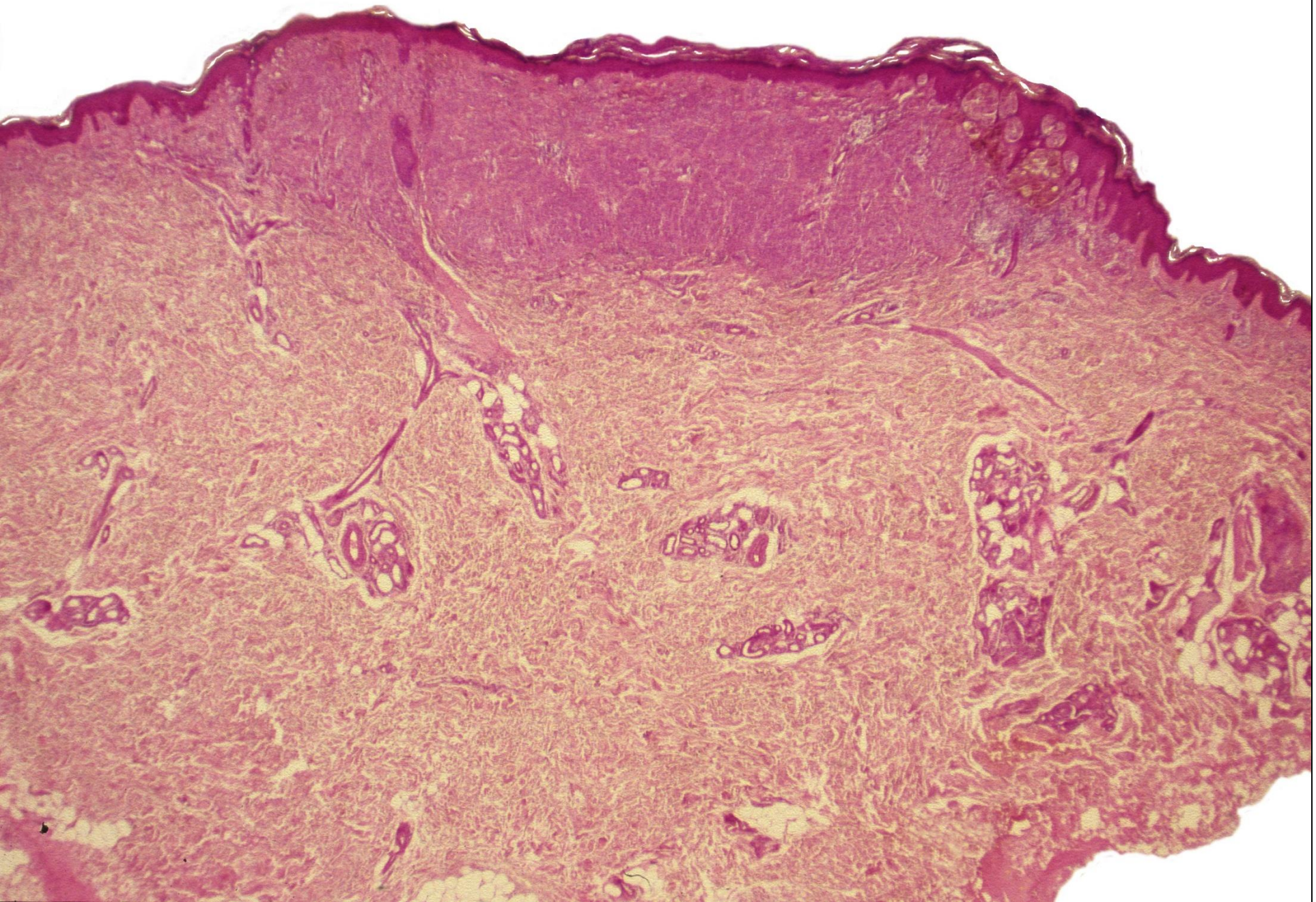
• A clinical follow-up study of 49 cases of spindle and epithelioid cell nevus is presented to address the question about the potential for local recurrence. Only 19 (39%) of the 49 lesions were initially excised en toto, and the remainder (30 cases) had positive margins; six of the latter spindle and epithelioid cell nevi were reexcised, and no evidence of a residual nevus was found in five of the six cases. There were no recurrences in the 49 patients during an average follow-up period of 5.0 years (range, 1 to 10 years). The rarity of recurrent spindle and epithelioid cell nevus would justify a conservative approach to management, with clinical follow-up alone recommended after a subtotal excision, when the pathologic diagnosis is unequivocal.

(*Arch Dermatol.* 1990;126:1581-1583)

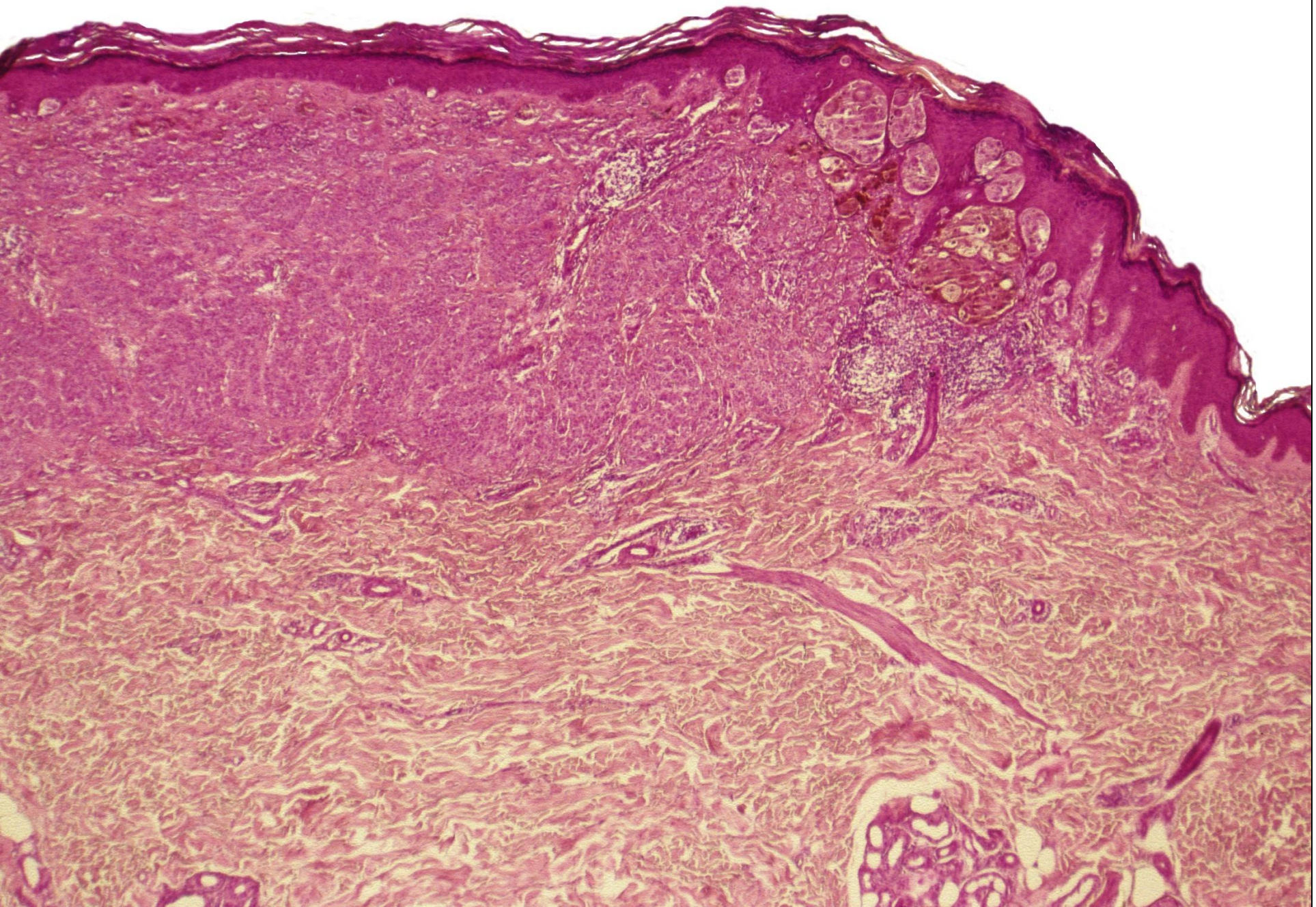
subtle; only the presence of giant cells in the former lesion was considered as a reliably differentiating feature.[2] Spitz was impressed with the lack of correlation between the depth of invasion and prognosis, since deep juvenile melanomas neither recurred nor metastasized, in contrast to relatively superficial malignant melanomas, which did metastasize.

When a diagnosis of malignant melanoma is established on the basis of a biopsy or an excision, a reexcision of the site is the usual practice, with some discussion about the appropriate centrifugal distance from the center of the original lesion.[3] However, the appropriate management of an SEN, especially when it has been "shaved" or otherwise incompletely excised, is less well established. Rhodes[3] simply advises

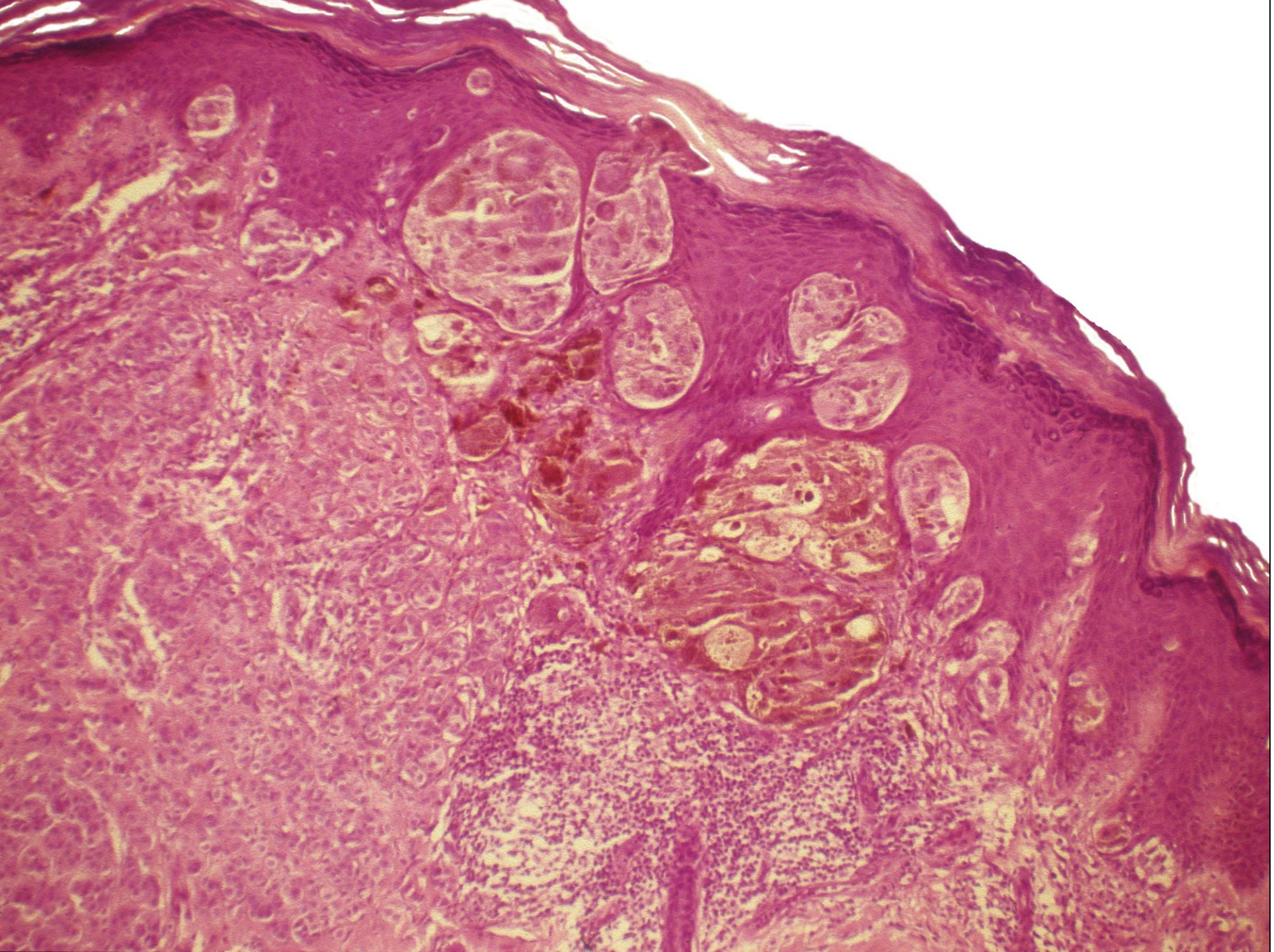
Moreover, the lesions are known to behave like every other nevus. Even following an incisional biopsy, Spitz's nevi hardly ever recur. We know, therefore, they are benign.



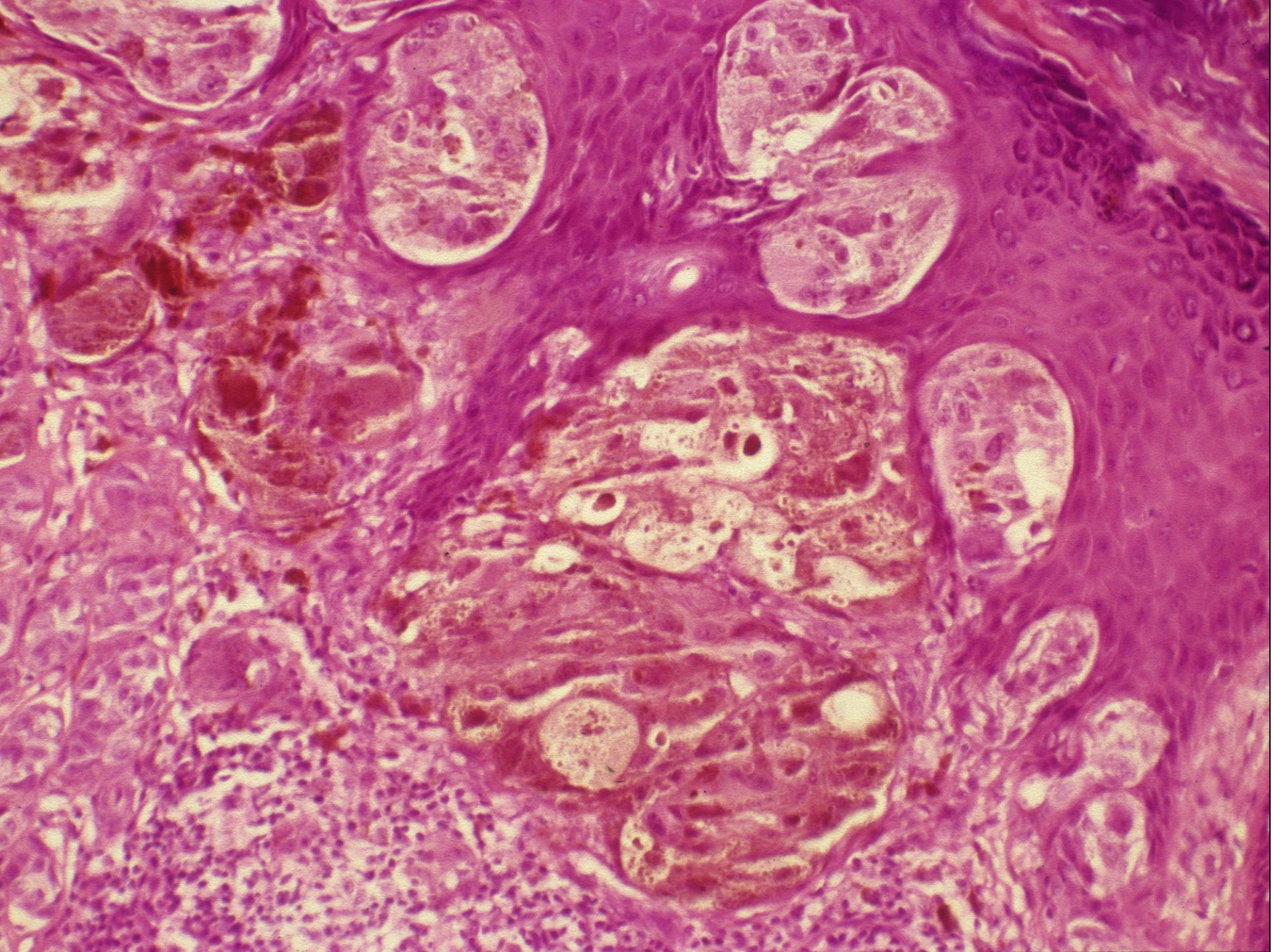
It is true that problems in differential diagnosis are not rare, but without a clear conceptual distinction between benign and malignant, there is no impetus to resolve those problems. Take this lesion, for example. It is well circumscribed and composed of large epitheliod melanocytes.



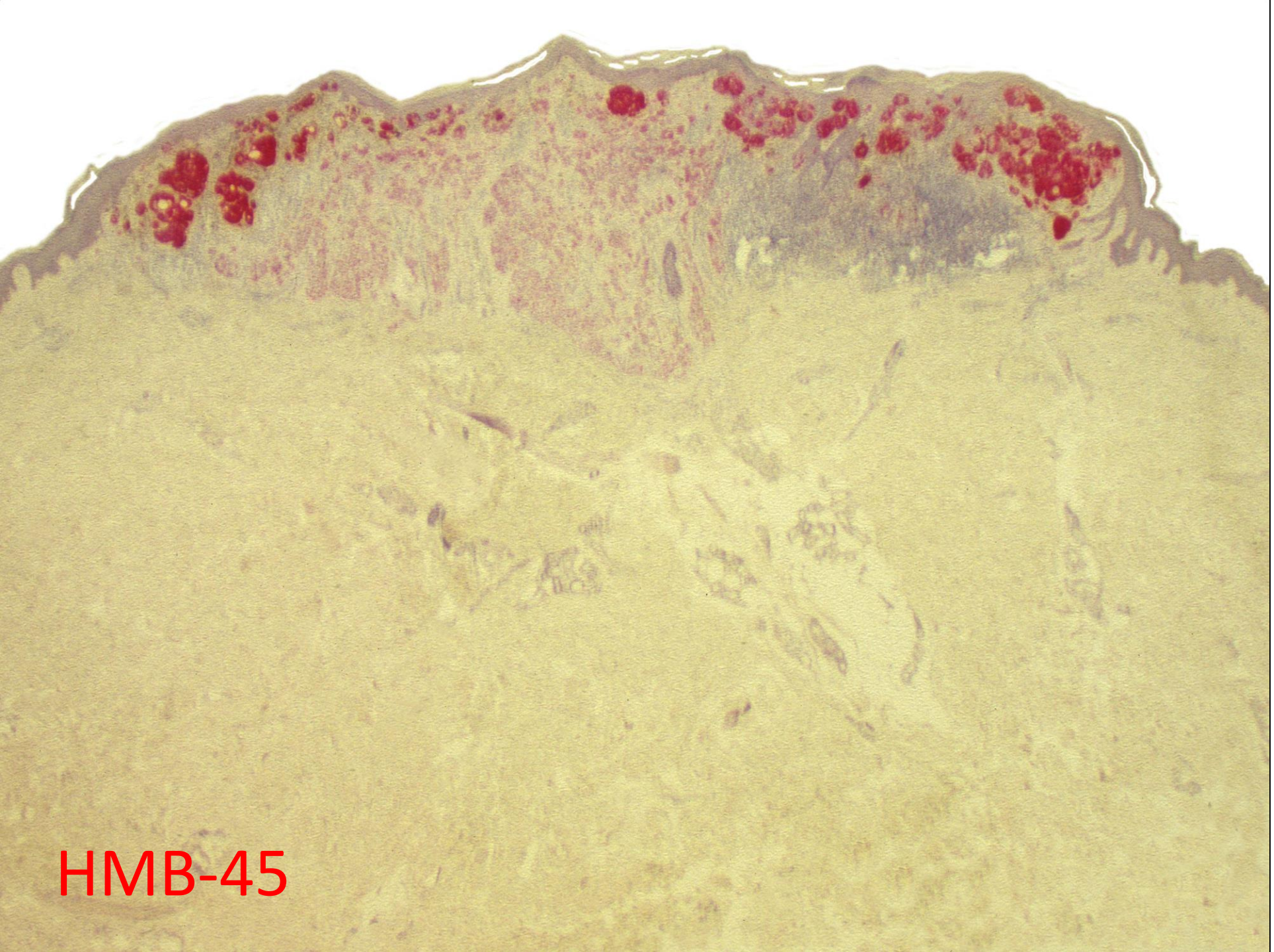
Only few of them are present in the upper reaches of the epidermis. Moreover, there is maturation of melanocytes with progressive descent in the dermis, epithelial hyperplasia, and compact orthokertaoses – all features consistent with a Spitz's nevus.



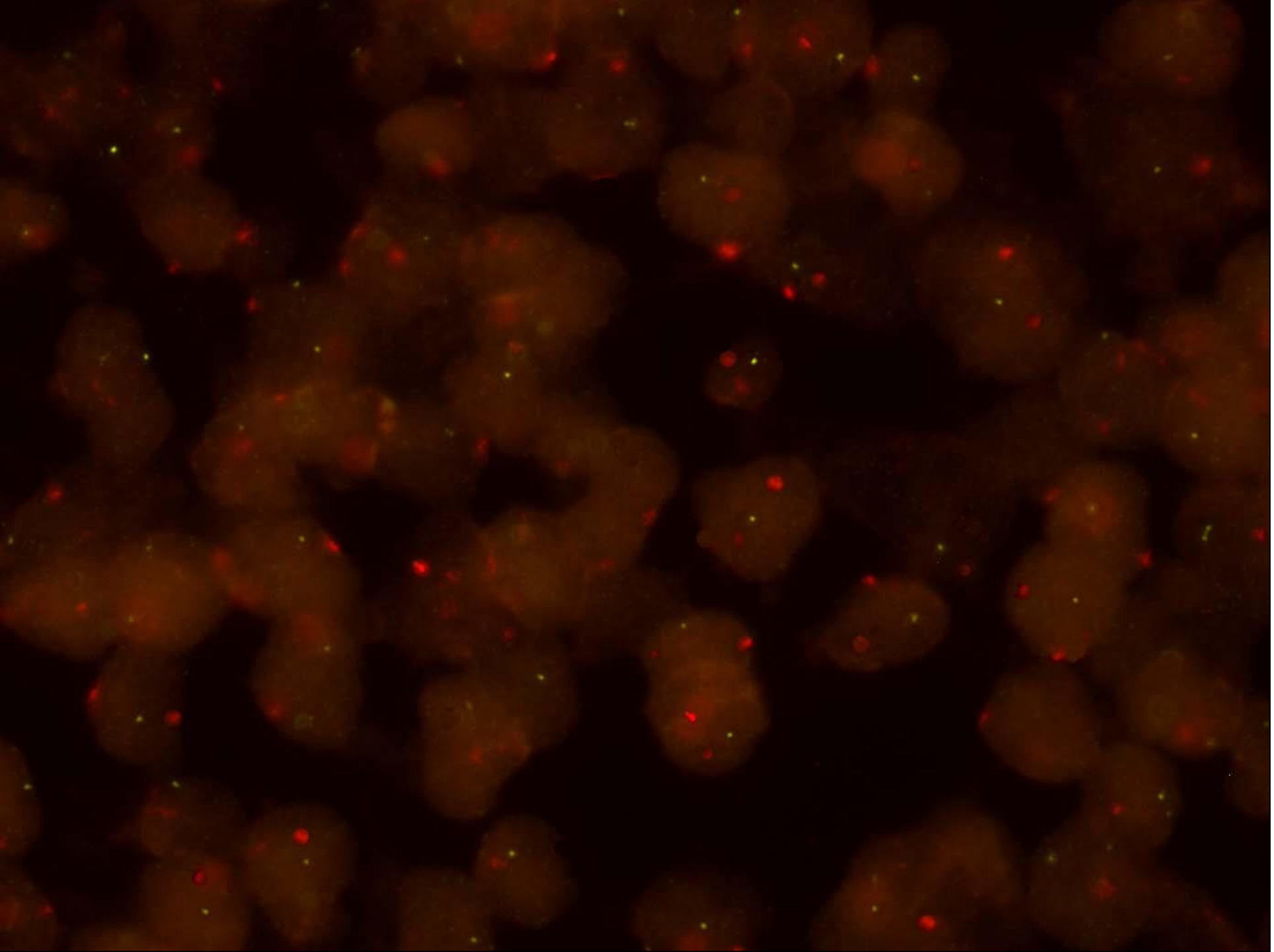
However, a circumscribed population of melanocytes with large, deeply pigmented cytoplasm is located at one edge of the neoplasm but not the other. Hence, the lesion is asymmetrical. But does this make it a melanoma?



If one thinks of this lesion as an “atypical Spitz’s nevus” with borderline malignant potential, the problem is resolved, or rather, left to the clinician and patient. If one tries to determine what it really is, one has to study it further, for example, by cutting additional sections,




by doing immunohistochemistry, which suddenly reveals those unusual cells also at the other edge,



or by performing molecular studies. In contrast to Spitz’s nevi, melanomas are usually associated with a variety of genomic abberations that may be detected by techniques such as FISH,

J Cutan Pathol 2004: 31: 266–270
Blackwell Munksgaard. Printed in Denmark



Journal of
Cutaneous Pathology

# The T1796A mutation of the *BRAF* gene is absent in Spitz nevi

**Background:** BRAF, a serine/threonine kinase, is a component of the retrovirus-associated sequence (RAS)–RAF–extracellular-regulated protein kinase (ERK)–MAP kinase signal transduction pathway mediating signals from RAS to ERK.
The T1796A single point mutation in exon 15 of the *BRAF* gene has recently been reported in a high percentage of malignant melanomas and benign melanocytic lesions such as congenital nevi, compound nevi, intradermal nevi and dysplastic nevi. The T1796A mutation has been shown to promote cell proliferation.
**Methods:** We screened 21 Spitz nevi and six spitzoid malignant melanomas for the presence of the T1796A *BRAF* mutation.
**Results:** The T1796A *BRAF* mutation could not be detected in any of the 21 Spitz nevi but was present in two of the six spitzoid malignant melanomas.
**Conclusions:** Our results, in conjunction with data from a previous investigation, suggest that the melanocytic proliferation of Spitz nevi might be induced by components of the RAS–RAF–ERK–MAP kinase pathway different from *BRAF*, possibly combined with other genetic aberrations. The lack of the T1796A *BRAF* mutation might be of practical importance in distinguishing Spitz nevi from other melanocytic lesions simulating Spitz nevi as a part of a future complex diagnostic assay.

Palmedo G, Hantschke M, Rütten A, Mentzel T, Hügel H, Flaig MJ, Yazdi AS, Sander CA, Kutzner H. The T1796A mutation of the *BRAF* gene is absent in Spitz nevi.
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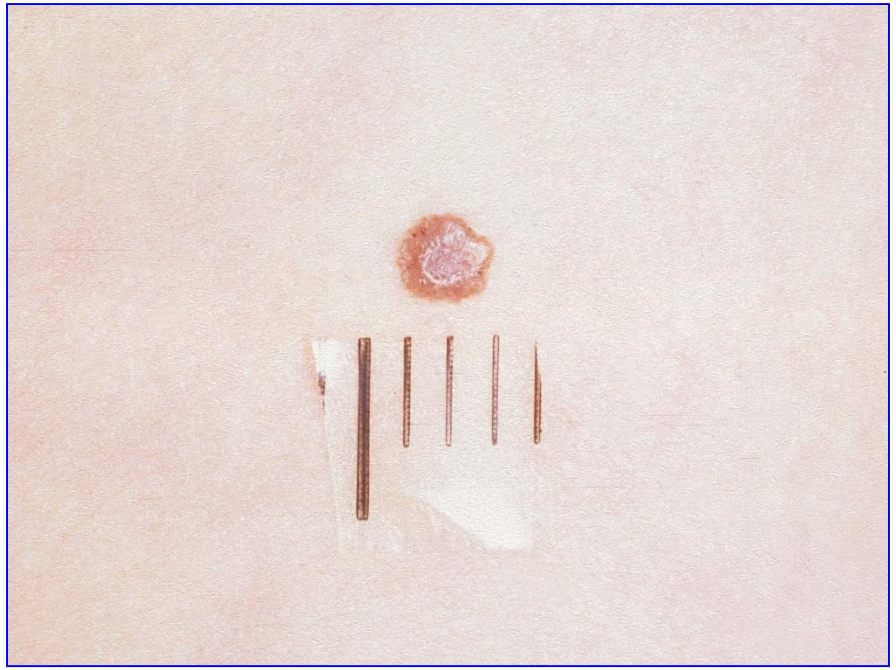
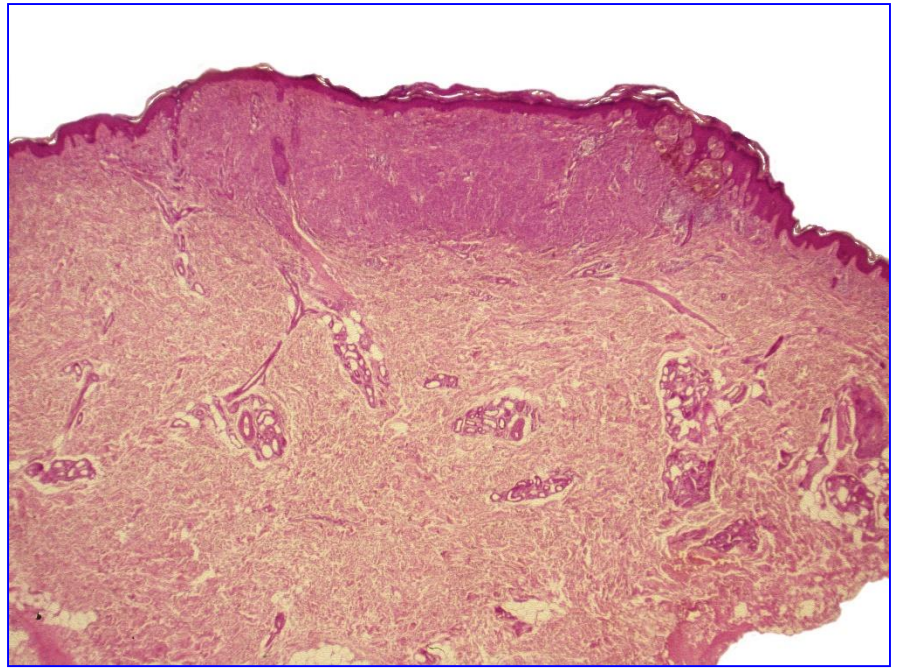
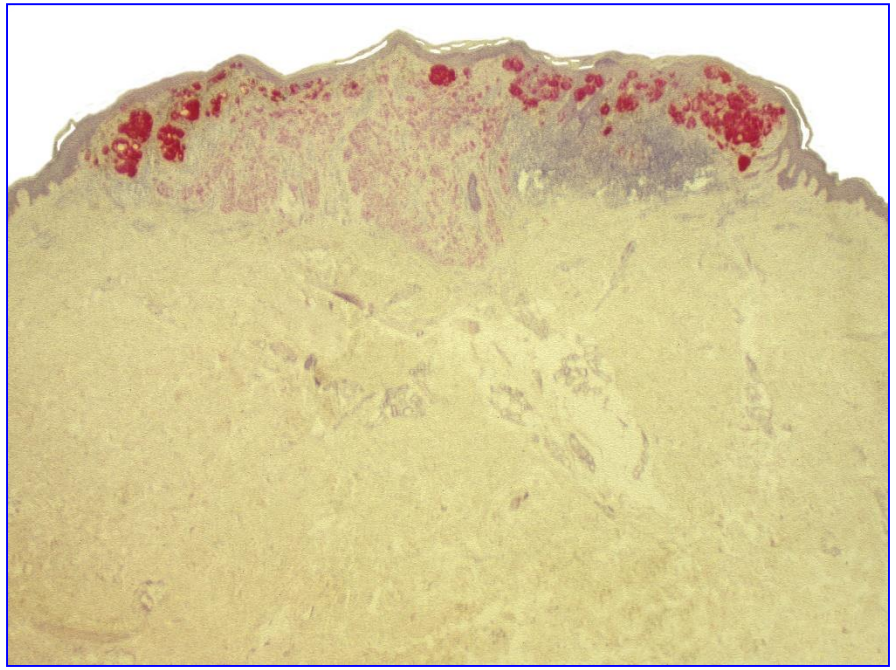
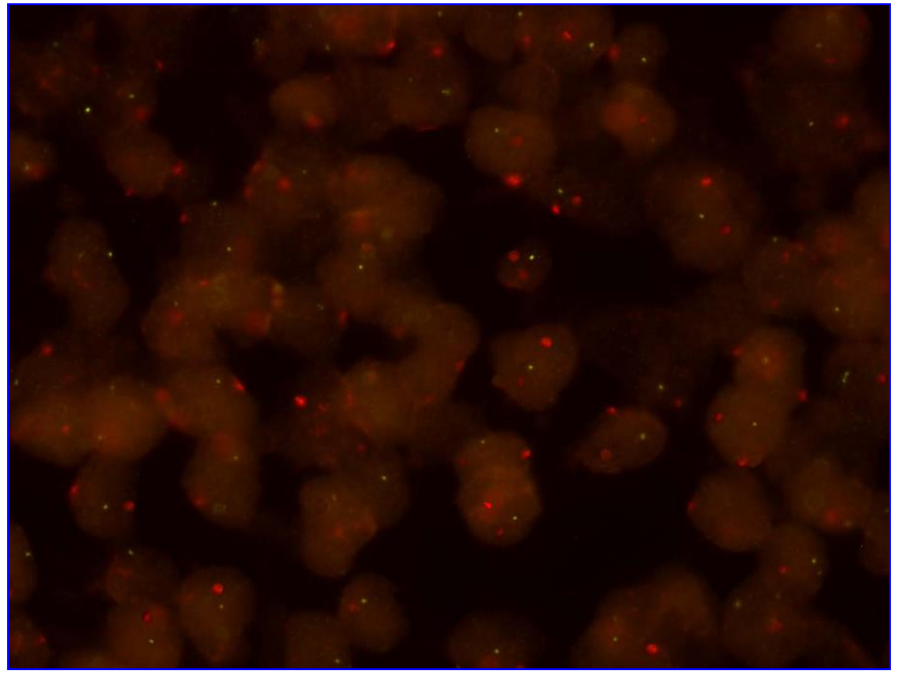
and even a simple PCR may be helpful because a mutation in the BRAF gene, common in melanomas, is rare in Spitz's nevi.

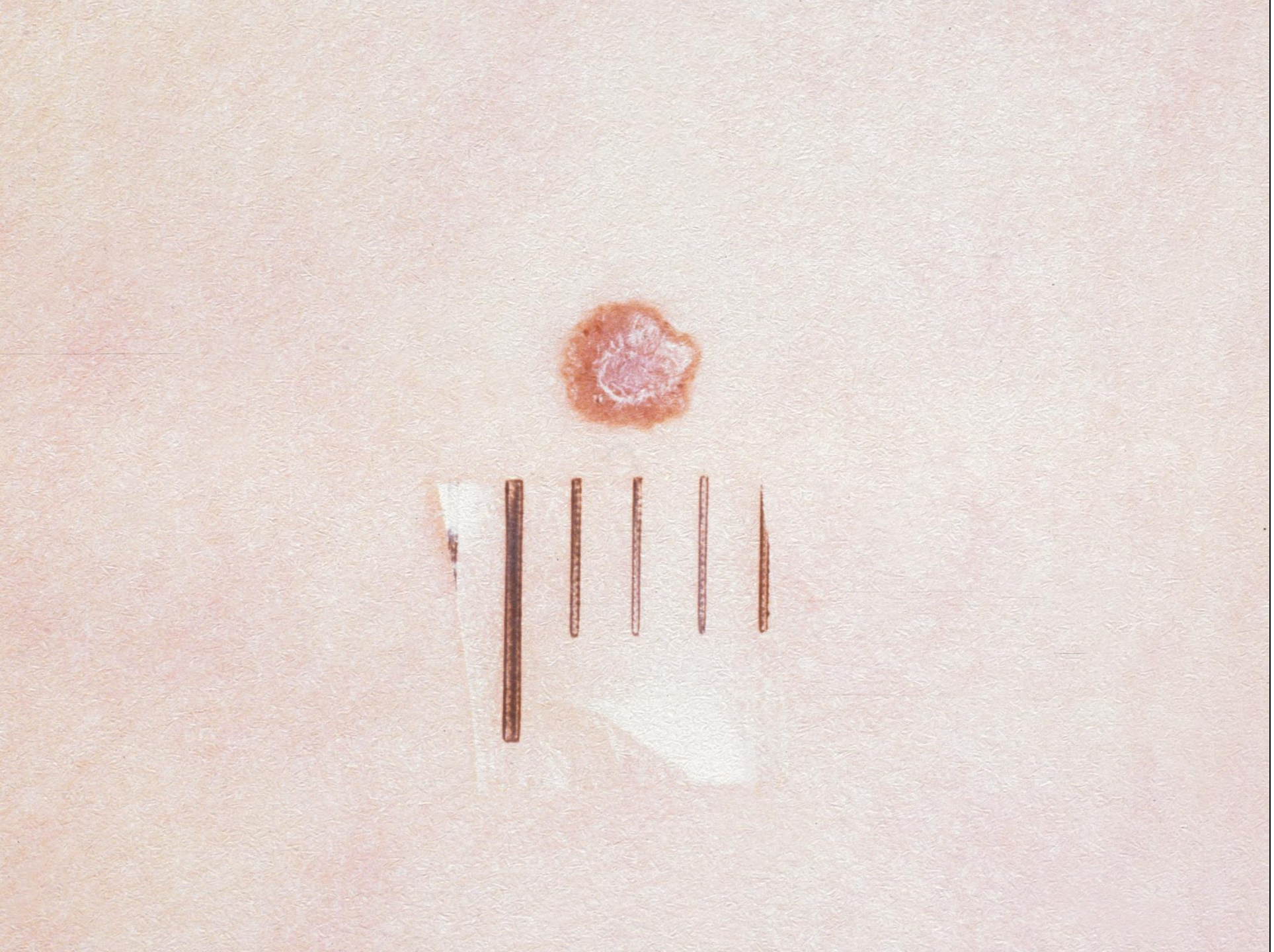








In sum, Spitz's nevus may be difficult to diagnose histopathologically, and in that instance, immunohistochemical and molecular studies, and even a clinical picture, may be helpful. In the vast majority of cases, however, the diagnosis of Spitz's nevus is easy, and it confirms that one is dealing with a wholly benign lesion.



To tell the 10 year-old boy harboring this nevus, or his parents, that this is a *“melanocytic tumor of low malignant potential”* is absolutely irresponsible, and, in that regard, a firm stand is necessary in order to prevent Spitz’s nevus from recurring, conceptually, as melanoma.