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EXCISION OF MELANOMA IN HISTORICAL PERSPECTIVE: TRIUMPH OF IRRATIONALITY FOR NEARLY A CENTURY

Many concepts of diseases and of treatment of them can be understood only if placed in historical perspective. Surgical treatment of melanoma is an apt example. Concepts about that malignant neoplasm embraced fervently at the turn of the century formed the basis for guidelines of surgical treatment that were developed and soon found worldwide acceptance. Meanwhile, although concepts about biologic behavior of melanoma have changed, precepts concerning treatment of it have not. The idea that prognosis of melanomas can be enhanced by doing wider excisions for thicker neoplasms is still maintained by most authors; virtually every textbook of surgery and dermatology advises wider margins for thicker melanomas. None of them, however, attempt to provide a logical explanation for this dictum.

ORIGIN OF THE CONCEPT OF "WIDE AND DEEP EXCISION"

The dogma of "wide and deep excision" became established in the last decade of the 19th century. Before that, prognosis of melanoma was thought to be so grave that many authors refrained entirely from any form of therapy. Moriz Kaposi, for instance, stated in 1872 that melanomas began *"with the development of roundish nodules of the size of a grain, pea, or bean... They remain disseminated for a while, then several of them became confluent and form an irregular, bumpy, larger nodule... Already early in the course, the lymphatic nodules are firmly indurated ..., and the process leads to death in a surprisingly short period of time."*[1]

Because of a concept like that of Kaposi, melanomas were recognized only in a far advanced stage, and patients often died soon after excision of them. This phenomenon affected Kaposi's approach to therapy as reflected in these lines written by him: *"According to general experience, the extirpation even of the very first nodules cannot halt the subsequent course. For this reason, the operation is carried out only very rarely, and the first symptom of pigmented cancer is regarded as an ominous sign of a rapidly fatal course."*[1]

At the turn of the century, melanoma was thought to be the most malignant of all neoplasms in humans. Therapeutic intervention not only was deemed to be useless, but even to be harmful because of its putative potential to enhance likelihood of metastasis. In the ever so slowly growing literature about melanoma, however, more and more patients with survival for long periods were recorded. This recognition resulted in change in concept of therapy. Already in 1857, William Norris had suggested excision *"of all the disease with abundance of the surrounding substance."*[2] In 1892, Herbert Snow advocated wide excision and dissection of the draining lymph nodes,[3] and, in 1903, Frederic Eve recommended *"free excision or amputation in accordance with the position and extent of the disease."*[4]

All of this set the stage for a statement of great importance in treatment of melanoma. It appeared in an article, in 1907, by the British surgeon William Sampson Handley. Handley who commented about *"strong microscopic evidence that the process of dissemination in malignant melanoma is primarily one of centrifugal lymphatic permeation... The crucial point to settle as*

determining the prospects of surgical interference in malignant melanoma is this: At what period is lymphatic dissemination supplemented by blood dissemination? ... Fortunately it would appear that as a general rule blood invasion does not take place at an early stage."[5]

On the basis of this new view of the disease, Handley advised that surgical excision of melanomas be enlarged in order to remove potential aggregations of neoplastic cells in adjacent lymphatic vessels: *"The incision, situated as a rule about an inch from the edge of the tumour, should be just deep enough to expose the subcutaneous fat."*[5] Between the dermis and subcutis, Handley advised that the excision should be extended further at the periphery and in depth to include fascial lymphatic vessels.

Handley had already achieved prominence through studies on dissemination of breast cancer. His experience with melanoma, however, was extremely limited. His statements in the Lancet were based on a careful microscopic study of lymph node metastases in but one patient who had died from metastases of melanoma. Handley himself admitted in his article that *"No opportunity of investigating the spread of permeation round a primary focus of melanotic growth has fallen to me."*[5] His recommendations about treatment of cutaneous melanoma, therefore, were offered without his ever having studied a single example of it!

Virtually every statement about treatment of melanoma issued in the ensuing seven decades was based on the recommendations of William Sampson Handley, although his fellow surgeons exaggerated the numbers proposed by him greatly. It was not long before "an inch" (2.54 cm) became 5 cm. The phrase "wide and deep excision" soon became the most important slogan in treatment of melanoma, although generally accepted guidelines in regard to the margins of excision were yet to be agreed on. In 1952, Pack *et al.* asked: *"What is meant by the term 'wide local excision'? It cannot be definitely stated how wide a margin of normal skin around the melanoma is necessary to be adequate and safe. But the term is used to distinguish it from the usual local excision of a benign skin lesion with only a few millimeters of normal skin margin."*[6] Two years later, Weder and Watson added: *"In any excision worthy of the name, skin grafting or some other plastic procedure* [for melanoma] *is necessary to close the defect."*[7]

In those years, the recommendations exceeded by far the one inch margin of excision that had been advocated by Handley. Sylven, in 1950, insisted that *"primary melanomas should be treated as a surgical emergency and the widest possible block excision should be performed ... In suitable cases classified as stage I, no surgeon should desist from early amputation of fingers, toes, or the external ear."*[8] In 1951, Gage and Dawson stated: *"For malignant melanomas as radical a procedure as the patient's condition will permit is indicated. There should be no hesitancy in performing forequarter or hindquarter amputations on patients with malignant melanoma located on or in the extremities."*[9] Petersen, in 1962, proposed eccentric excision of melanomas with extension of surgical margins in the direction of anticipated flow of lymph. For wholly intraepithelial melanomas, a margin of 1 cm was considered by him to be sufficient; for thin invasive melanomas, he suggested margins of 6 cm to the distal side and 7 cm to the proximal side of the neoplasm. For treatment of nodules of melanoma, Peterson recommended *"eccentric excision as above, but extended to 6, 8, and 15 cm ... Even the most extensive excisions compare favourably in results, both in appearance and function, with those following extensive burns and traffic accidents where large areas of skin have been lost"* (Fig. 1).[10] By the 1960s, a margin of 5 cm for advanced melanomas prevailed and for three decades thereafter became the credo of melanoma therapy.[11,12] In 1981, Davis paraphrased that credo in these words: *"Better a big scar than a small tombstone."*[13]

Two arguments were advanced as reasons for wide and deep excision of melanomas; to wit, they prevent persistence of any part of the primary neoplasm and development of satellite metastases, *i.e.*, of clinically invisible metastases in the immediate vicinity, *i.e.*, within 5 cm, of the primary neoplasm. The entire concept was based on the incorrect assumption that persistence at the local site of primary melanomas and development of satellite metastases of melanoma were common. Furthermore, it was believed that a satellite metastasis could be the source of further lymphogenic and hematogenic spread. The ultimate objective of wide and deep excisions was prevention of further metastases.

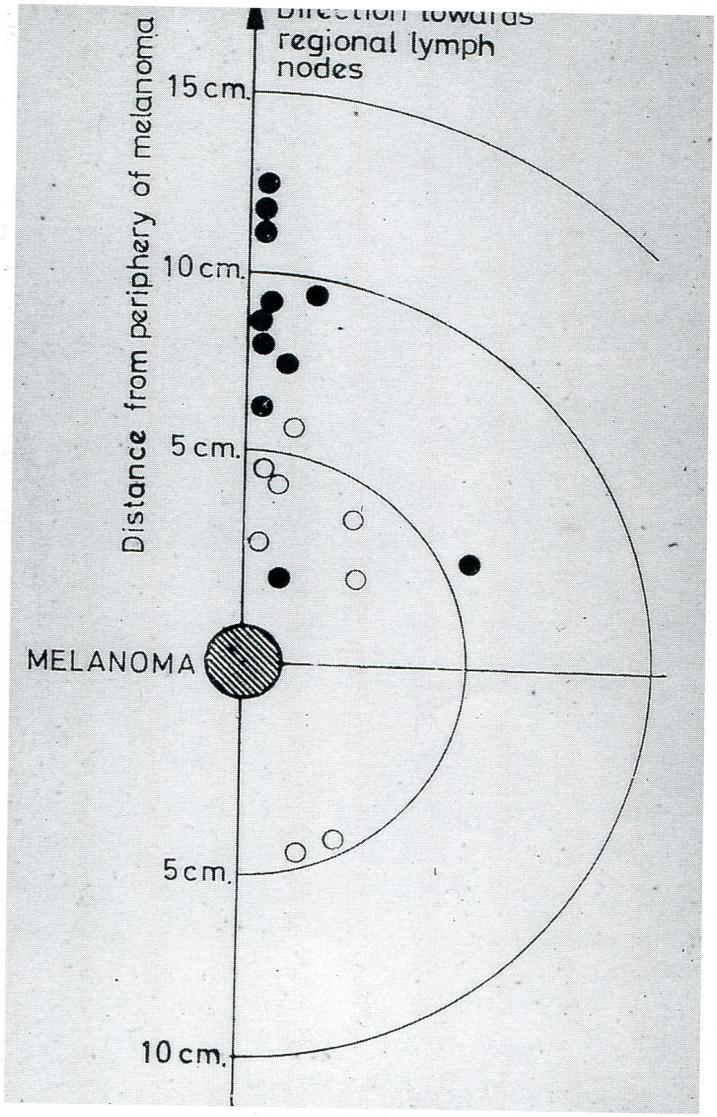

FIG. 1 *Figure from the article by Petersen et al. (Br J Plast Surg, 1962): most metastases were situated outside a 5 cm radius around the primary melanoma. For that reason, Petersen urged margins of excision of up to 15 cm.*

PURPORTED OBJECTIVE OF WIDE AND DEEP EXCISION : REMOVAL OF OCCULT SATELLITE METASTASES

An attempt to remove occult satellite metastases was the rationale for Petersen's concept of therapy of melanoma. On the basis of an analysis of 39 patients with metastases to skin, Petersen developed his theory of "chain formation." By this he referred to cutaneous metastases lying *"on a line between the site of the primary and the regional lymph nodes... The fact that the eruption of the nodules generally starts distally and works proximally allows us to suggest that not only chain formation, but a chain reaction may be taking place, the later nodules being second-degree or third-degree metastases... It must be concluded that the very first lymphatic skin deposit to make its appearance must be treated in as radical and speedy a manner as the primary... "*[10] In Petersen's view, metastases of this kind were removed best prior to the appearance of them clinically.

Petersen's recommendations in regard to therapy were logical extensions from his concept of the biologic behavior of melanoma. Today, that concept is known to be wrong. As a rule, cutaneous metastases are not lined up in a "chain," but distributed randomly because dissemination often is through the blood stream. Even if a "chain" is formed, hardly ever is there any evidence of a "chain reaction," *i.e.*, metastases progressively further away from the primary neoplasm usually do not appear later than those in the immediate vicinity of it (Fig. 2). Furthermore, it has become evident that strict separation between lymphatic and hematogenous metastases of melanoma is not consonant with actual behavior of that malignant neoplasm. The lymphatic and blood vascular systems are known to have numerous connections, thereby allowing disseminating neoplastic cells to pass rapidly

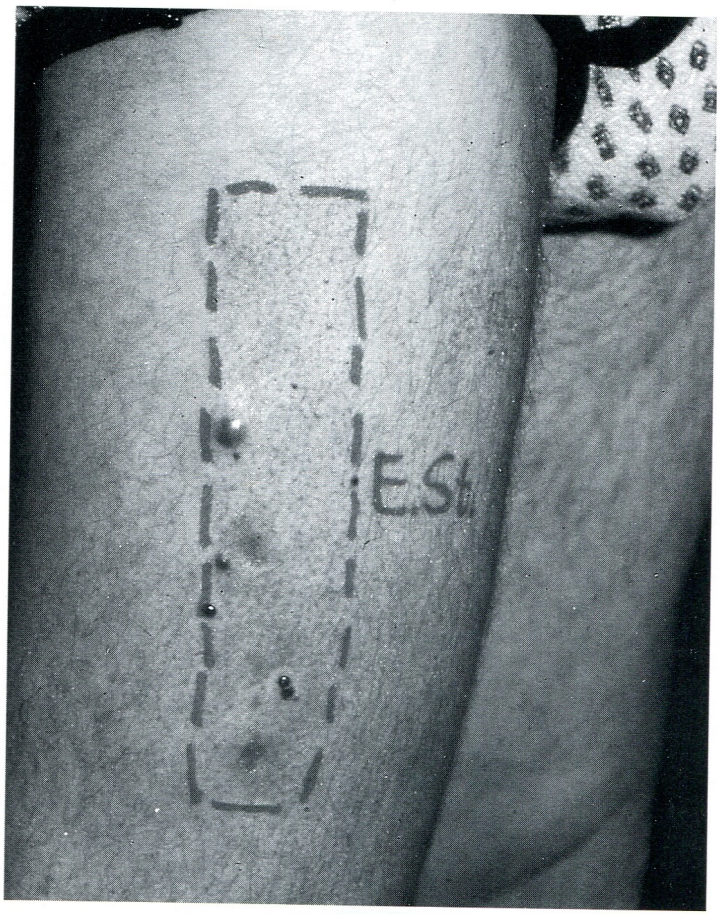

FIG. 2 *Cutaneous metastases of a melanoma on the right thigh: The metastases are lined up in a "chain," but the metastases that are larger and appeared earlier are situated further from the primary neoplasm. There is no evidence here to support Petersen's idea of "chain reaction."*

from one of those systems to the other.[14,15] The very appearance of satellite metastases, therefore, implies that dissemination of neoplastic cells is not confined to a zone within 5 cm of the primary neoplasm, but has occurred far beyond that zone.[16,17,18] Accordingly, prognosis is grim: In a study of 428 patients with satellite metastases, death occurred in about one third of patients in a period of between two and five years following diagnosis of the primary neoplasm.[19] The five-year disease-free survival rate is less than 40%[20] and the 10 year survival in one series (personal communication, Alfred W. Kopf, M.D.) was nil.

In times past, prognosis of persons with satellite metastases was thought, erroneously, to be relatively favorable vis-a-vis those with distant metastases. This misperception was caused by failure to distinguish clearly between persistence of primary melanoma at a local site after incomplete excision of it and of satellite metastases—entirely different phenomena that were referred to by the same name, *i.e.*, "local recurrence," and lumped together in statistical analyses. For this reason, prognosis of persistent primary melanomas was considered to be worse than it actually was and that of satellite metastases to be better than it really was. Whether cutaneous metastases occur within an arbitrary radius of 5 cm around a primary melanoma ("satellite metastases") or outside of it ("in-transit metastases") is known today to be irrelevant to survival.[21]

In short, satellite metastases are a sign of distant metastases. Therefore, prophylactic removal of clinically inapparent satellite metastases cannot be expected to be curative, and it is not. Wide excision, no matter how wide, cannot prevent development of metastases, a fact proved also by the not uncommon occurrence of metastases at the periphery of a skin graft applied to the site of excision of the primary melanoma (Fig. 3).

Last, prophylactic removal of clinically inapparent satellite metastases is complicated by the fact that precise location of such metastases cannot be foretold. This problem was already evident in the study of Petersen: in most cases, the first metastases were situated outside a 5 cm radius of the primary neoplasm (Fig. 1).[10] For this reason Petersen concluded that excisions of melanomas had to be extended even further than 5 cm. Taking into account all the information available currently, the opposite conclusion is compelling: Wide excisions with the aim of removing occult satellite metastases are irrational and should not be undertaken.

FIG. 3 *Metastases of melanoma within a skin graft: Even extensive excisions do not prevent development of metastases near the site of a primary melanoma when metastases had occurred before the surgical procedure designed to remove the primary melanoma.*

PURPORTED OBJECTIVE OF "WIDE AND DEEP EXCISION": PREVENTION OF PERSISTENCE AT THE LOCAL SITE OF PRIMARY MELANOMAS

In former times, all melanomas were thought to derive from malignant transformation of a melanocytic nevus. This concept, advanced by both Virchow and Unna, prevailed until the end of the 1960s. Clinically, a flat zone of melanoma was interpreted incorrectly as representing a pre-existing melanocytic nevus. Accordingly, histopathologists interpreted as melanoma only the intradermal, *i.e.*, "invasive," part of the neoplasm. The intra-epithelial part of melanomas that in most specimens extends beyond the dermal component of the melanoma was interpreted wrongly as a remnant of a nevus. This mentality reached full flower in 1953 when Allen and Spitz stated that "*... every melanocarcinoma of the skin or mucous membranes arises from a junctional or compound nevus ... fortunately, only a small percentage of junctional nevi undergoes cancerous transformation. However, in those restive junctional nevi, in which anaplastic and certain qualitative changes have occurred ..., the odds are enormous that this ALTERED*

junctional nevus, if allowed to remain, in time would evolve into a melanocarcinoma. The active or precancerous junctional nevus has one or more of the following features: (1) the general features of nuclear anaplasia such as hyperchromatism, increase in nuclear and nucleolar size, irregular nuclear vacuolization, and mitotic figures; (2) subepithelial inflammatory reaction consisting preponderantly of lymphocytes; and (3) cytoplasmic vacuolization and fine melanin pigmentation reaching to the uppermost layers, that is, to the stratum granulosum and stratum corneum..."[23]

Curiously, decades before, all of the changes described by Allen and Spitz had been noted by Darier, Dubreuilh, and Miescher to be histopathologic signs of melanoma.[24] Unaware of that, Allen and Spitz concluded: "*The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must... depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION.*"[23] The dogma that melanomas resulted from transformation of melanocytic nevi was so deeply ingrained that Allen and Spitz could not infer that the intra-epithelial proliferation of abnormal melanocytes seen by them represented melanoma at the site where it begins, namely, in the epidermis. Instead, they conjured a theory of activation of melanocytes, a notion they expressed thus: "*It is as if in the presence of a melanocarcinoma in one part of the body, some circulating humoral influence is exerted on moles elsewhere... it is our impression that in patients with cutaneous melanocarcinomas there is a tendency to activate junctional nevi. Possibly that tendency receives more concentrated expression in the epidermis in the vicinity of the primary tumor.*"[23]

The hypothesis of activation of melanocytes had direct consequences for therapy of melanoma. In 1962, Petersen wrote that "*melanocytes are linked together by... processes to form a continuous system in the skin ... This is of importance when one comes to consider the margin of excision of a lesion, for the malignant potential of a malignant lentigo will often have been communicated to cells outside the zone of visible pigmentation... The linking together of epidermal melanocytes by their dendritic processes provides the means by which these potentials may be passed from one cell to the next.*"[10] By invoking the imaginary concept of "activation of melanocytes," Petersen was able to explain to his satisfaction not only regrowth of primary neoplasms after seemingly complete excision of them, but also development of satellite metastases: threat of an invisible and irresistibly expanding "malignant potential" justified extensive surgical excisions.

The concept that melanocytes of melanoma were capable of activating normal melanocytes in the immediate vicinity of it was embraced by many authors who introduced the notion to the literature under terms like "contamination theory"[25] or "field effect."[11] In 1970, Wong reported on the presence of individual atypical melanocytes 5 cm beyond the ostensible border of melanomas.[26] Although Wong himself pointed out the non-specificity of such atypical melanocytes, his findings were regarded as evidences in favor of the "contamination theory."

Until today, the possibility of activation of normal melanocytes by humoral substances released from a primary melanoma is given credence in some quarters. After decades of clinical and laboratory studies, however, no evidence has ever been offered to justify the existence of such substances. When more than one melanoma occurs in a single person, which is uncommon, hardly ever are the two neoplasms situated near one another. Analyses of distribution and atypia of melanocytes in specimens of re-excised melanomas failed to provide evidence of a field effect.[27] Still adhering to the concept of "active junctional nevus," Cochran, in 1969, averred that atypical melanocytes were not distributed evenly in the vicinity of a melanoma, but unevenly, being more dense and widespread on one side of it.[11] This observation is not explained best by a concept of normal melanocytes activated by humoral factors released by the primary melanoma, but rather by asymmetry of a melanoma consequent to its having grown at different rates in different directions.

In the last decades, numerous studies have indicated that margins of excision of melanoma do not influence length of survival.[16–18, 28–37] Likewise, the frequency of satellite metastasesis is not decreased when margins of excision are reduced. As long ago as 1966, Olsen stated that there were no differences in the number of "local recurrences" between two groups of patients, one of whom had been treated by excisions with a margin of 5 cm, the other by exci-

sions with a margin of less than 1 cm. In melanomas 1 mm or less in thickness, "local recurrences" after narrow excisions hardly ever are seen.[17,31,32,36,38] In a prospective study of 612 patients with melanomas up to 2 mm in thickness, Veronesi and Cascinelli noted only four "local recurrences" following excision with a 1 cm margin.[36] In melanomas measuring more than 2 mm in thickness, "local recurrences" are seen more frequently and are slightly more common after narrow, than after wide, excisions. This difference, however, is attributable to increased likelihood of satellite metastases which, in most studies, have not been distinguished from persistence of primary neoplasms at the local site.[33,39] This interpretation is supported further by lack of influence of margins of excision on length of survival.

In sum, the "contamination theory," for many years the most important argument in favor of wide and deep excisions, is not supportable. Computer-based analyses of the architecture of malignant neoplasms indicate that expansion of melanomas is a continuous phenomenon consequent to proliferation and migration of neoplastic cells.[40]

CURRENT TREATMENT OF MELANOMA

Today, the limits of a melanoma can be determined morphologically with a high degree of accuracy based on repeatable findings as assessed through a conventional light microscope. Nevertheless, melanomas continue to be treated by excisions wider and deeper than are necessary. There has been an adjustment in the extent of margins of excision, but it has not been based on logic.

The impulse to reduce margins of excision was provided by assessment of prognosis of melanomas. In the 1960's, Mehnert and Heard, and then Clark, had emphasized the importance of depth of melanomas in regard to prognosis.[41,43] Breslow, in 1970, noted a close correlation between the thickness of a melanoma and the prognosis of it.[43] Today, "tumor thickness" is considered to be the single most important factor for gauging prognosis of melanoma. Based on the finding that patients with melanomas whose thickness was less than 0.76 mm had an excellent prognosis, Breslow urged that elective lymph node dissections for such neoplasms be abandoned [43] and, a few years later, he called for margins of excision being reduced.[30]

Breslow's studies on prognosis of melanomas helped to prevent countless patients around the globe from being subjected to unnecessary and excessive surgical procedures. Nevertheless, his recommendations on margins of excision were based on two mistakes in logic that brought discussion of surgical treatment of melanomas to a standoff. For one, Breslow adjusted margins of excision according to prognosis of melanomas, *i.e.*, probability of metastases based on thickness. On the contrary, margins of excisions must be adjusted to the probability of persistence of melanoma at the local site. For another, Breslow used the vertical extent of a melanoma as the decisive criterion for extent of excision horizontally; instead, the horizontal extent of excision should depend on the horizontal, not on the vertical, diameter of a neoplasm.

Failure to distinguish between persistence of a primary melanoma at the local site and satellite metastases seemed to give credence to Breslow's observations: correlation between "tumor thickness" and "local recurrence" were substantiated by numerous studies. As a consequence, surgical treatment of melanomas still is dominated by rigid systems that link "tumor thickness" to margins of excision. Based on statistical examinations and biological considerations, both of which lack validity, surgeons are advised by histopathologists to remove, for example, a 1 cm margin of normal skin around a melanoma less than 1 mm thick, 2 cm for one that measures less than 2 mm in thickness, and 3 cm for melanomas thicker than 2 mm.[44,45] This 1-2-3 rule is easy to remember, but difficult to comprehend because it is illogical.

In order to satisfy claims for adequate margins of excision of melanomas, tens of thousands of scars of melanomas already removed completely are re-excised every year and subjected to histopathologic examination which, of course, reveals nothing but fibrosing granulation tissue or a scar.[27,46] The procedure does nothing to improve prognosis of melanoma. Excision of a melanoma should be deep enough to remove the deepest part of the neoplasm, and wide enough to include the most peripheral extent of it. Anything more than that is unnecessary, potentially harmful psychologically because patients may be disfigured by it, and expensive.[47] If a melanoma that measures 1 cm in diameter is excised with a margin of only 1 cm, a skin defect of 3 cm is produced which,

if closed primarily, leaves a scar that is about 14 cm long.[48] Wider margins usually necessitate a plastic procedure in order to close the skin defect. Considering current knowledge about melanoma, this treatment can no longer be condoned.

NARROW, CONTROLLED EXCISION FOR MELANOMAS

Should treatment of melanoma be different from that of other malignant neoplasms? In regard to basal-cell and squamous-cell carcinomas, for example, the objective of surgery is complete removal of neoplastic cells. Achievement of that aim is controlled by histopathologic examination of the margins of the specimen. Already in 1983, Ackerman and Scheiner proposed that the very same procedure be applied to melanomas: "*... The surgeon should excise what he or she judges clinically to be the entire neoplasm and only little more than that. The specimen should then be submitted for histologic assessment of all its margins; if no neoplastic melanocytes are found in the margins, no further surgery is warranted, because there is nothing more of the primary neoplasm to excise.*"[39] Ackerman and Scheiner were the first to stress how illogical it was for surgeons to excise normal tissue in breadth for malignant neoplasms of any kind by virtue of their depth. The authors contended that once a melanoma had been removed completely, no matter how narrow the margins, there was nothing more that a surgeon could or should do. If no metastases had occurred prior to the surgical procedure, the patient was cured; if metastases had occurred already, the patient was doomed no matter how many centimeters were extirpated in breadth and depth.

Of course, assessment histopathologically of surgical margins is not without limitations. It may be exceedingly difficult at times to distinguish neoplastic cells at the periphery of a melanoma from "normal" melanocytes in surrounding skin. That is true especially for sun-damaged skin whose epidermis often houses an increased number of melanocytes with large nuclei. As a rule, large melanocytes on skin injured severely by sunlight are monomorphous, stained uniformly, and positioned equidistant from one another. Sometimes, however, a clear-cut distinction between "normal" and neoplastic melanocytes may not be possible.[49,50] These difficulties in cytologic interpretation, however, are not unique for melanomas, but are also encountered in other malignant neoplasms, *e.g.*, extramammary Paget's disease, angiosarcoma, and dermatofibrosarcoma protuberans. Despite that fact, no calls are heard for inflexible wide margins of excision for those malignant neoplasms. Instead, surgeons excise what they consider to be the entire lesion, and perform a re-excision with wider margins only if a histopathologist, on examination of sections, indicates that neoplastic cells extended to, or very near, margins.

In contrast to those malignant neoplasms, a melanoma that persists at a local site is easily detectable because of production of melanin. When a melanoma

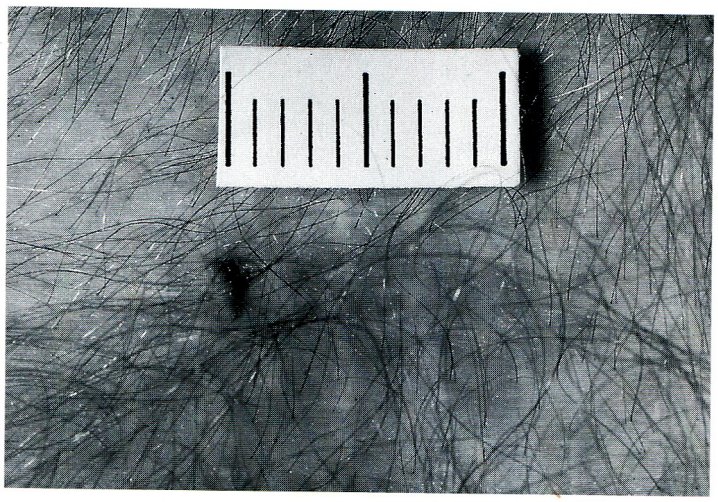

FIG. 4 *Persistence of an incompletely excised melanoma: The persistent neoplasm could be recognized easily and treated readily because pigmentation was obvious. Histopathologically, neoplastic melanocytes were seen to be confined to surface and adnexal epithelium.*

FIG. 5 *Relatively sharply demarcated melanoma: Within the epidermis, the number of solitary melanocytes is increased for only a few rete ridges beyond the last nest. The surrounding epidermis is normal. Despite the thickness of this melanoma, re-excision is not warranted because the neoplasm has been removed completely.*

persists at a local site because of incomplete excision, it usually appears at first as a flat pigmented lesion, *i.e.*, melanoma *in situ* (Fig. 4). A clinician, *e.g.*, a surgeon, having followed a patient closely after ostensible removal of a primary melanoma, needs only excise the persistent pigmented macule in its entirety. If a histopathologist verifies that removal has been complete, the patient can be assured that the neoplasm will not again persist at the local site. Careful follow-up by the managing physician is still mandatory.

Fortunately, persistence of melanoma at a local site is extremely rare, even with narrow margins of excision, because the extent of most melanomas is clearly definable by microscopy (Fig. 5). Of 906 melanomas examined in regard to circumscription, we found almost one third of them to be well circumscribed, 106 by nests (11.7%) and 149 by an increased number of solitary melanocytes which did not extend beyond the last nest for more than five rete ridges (16.4%). A decision whether or not the lesions had been removed completely was possible in the vast majority of cases.[51]

Discussion about excision of melanomas should no longer dwell on how superficial or deep and narrow or wide an excision should be; margins of excision should be adjusted to the actual extent of the individual neoplasm,[46, 52, 53] a decision that is both logical and beneficial to patients.

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