

The dysplastic nevus: From historical perspective to management in the modern era

Part I. Historical, histologic, and clinical aspects

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Date of release: July 2012

Expiration date: July 2015

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doi:10.1016/j.jaad.2012.02.047

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Since its description in the 1970s, the dysplastic nevus has been a source of confusion, and whether it represents a precursor to melanoma remains a controversial subject. Although a Consensus Conference in 1992 recommended that the term “dysplastic nevus” no longer be used, the histologic diagnosis continues to present a therapeutic quandary for dermatologists and other physicians, and there remains significant variation in clinical management. In part I of this continuing medical education review, we will discuss the historical origins of the term, the evidence for its distinct histologic basis, and its clinical significance. (J Am Acad Dermatol 2012;67:1.e1-16.)

Key words: common nevus; dysplasia; dysplastic nevus; melanoma; nevus.

THE BASIS OF THE CONTROVERSY

Key points

- The term “dysplastic nevus” is confusing and may have unintended meanings
- In our opinion, the terms “dysplastic nevus” and “atypical nevus” should not be interchangeable

Since the advent of the term in the late 1970s, “dysplastic nevi” (DN) have been a source of both confusion and controversy. The heart of the matter is whether (and to what extent) DN represent premalignant lesions that will progress to melanoma.¹ There are those who view DN as a discreet entity of clinical significance,²⁻⁴ while others dismiss the concept entirely.⁵ DN were originally described in melanoma-prone families, with the implication that such lesions had a higher risk of transformation to melanoma than “nondysplastic” nevi.⁶⁻⁸ This presumption has been promulgated over the years by multiple factors. First, the routine practice of grading nevus cytologic atypia as mild, moderate, or severe (see below) implies directed progression of DN towards melanoma. Similarly, the common reference to DN as “pre-malignant” (or “pre-melanoma”) lesions suggests they are analogous to actinic keratoses or colon polyps which do evolve (albeit at very low rates) to carcinoma. Finally, dermatologists often refer to nondysplastic nevi as “benign” or “normal”

CAPSULE SUMMARY

- The dysplastic nevus was first described in the 1970s in families with a high prevalence of nevi and melanoma.
- The term has been problematic, given the uncertainty over whether dysplastic nevus represents a premalignant (melanoma precursor) lesion.
- Dysplastic nevus is a distinct histologic entity that may or may not be associated with clinical atypia.
- The presence of dysplastic nevus is a cutaneous marker for increased melanoma risk.
- Whether the rate of dysplastic nevus transformation to melanoma is greater than that of “nondysplastic” or common nevi depends on clinical context and is debatable.

(rather than common or banal), which may carry the unintended implication that DN by contrast are not benign (ie, they may be malignant). To further muddy the waters, the terms “atypical nevus” and “DN” have been used interchangeably in the literature, which is inappropriate on two grounds. First, one represents a clinical finding (atypical nevus) while the other is a histologic description (DN); and second, the terms are not synonymous, because lesions lacking clinical atypia may reveal dysplasia and some DN may not exhibit clinical atypia (see below). Given these considerations, this review will collectively refer to all nondysplastic nevi as “common nevi” (CN) and give the most attention to studies based on histologically defined lesions (ie, confirmed DN).

Lack of consensus

Key points

- There is no consensus on terminology among dermatologists or dermatopathologists
- The term “dysplastic nevus” should not be abandoned

A Consensus Conference at the National Institutes of Health (NIH) defined, among other things, the histologic basis of “early” melanoma and DN.^{9,10} The panel recommended that the term “DN” be

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Dr Grossman is supported by the Department of Dermatology and the Huntsman Cancer Foundation.

Conflicts of interest: None declared.

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0190-9622/\$36.00

Abbreviations used:

CN:	common nevus
DN:	dysplastic nevus
DNS:	dysplastic nevus syndrome
FAMMM:	familial atypical multiple-mole melanoma

abandoned and a new nomenclature be adopted: “nevus with architectural disorder, accompanied by a statement describing the presence and degree of melanocyte atypia” (ie, mild, moderate, or severe). No guidelines for clinical management of these lesions were issued. Over the years, a number of editorials appeared in the literature to weigh in on the controversy.¹¹⁻¹⁵

In 2005, Shapiro et al¹⁶ surveyed all 856 active members of the American Society of Dermatopathology and 1100 (13%) active members of the American Academy of Dermatology and reported that the term “DN” continued to be favored (39% and 62%, respectively) by respondents of these groups. By comparison, the Consensus Conference—recommended terminology was the second most popular verbiage (25% and 15%, respectively).

Some dermatopathologists have promoted using the term “Clark nevus” instead of DN.⁵ Rather, we believe that the term “DN,” despite its problems, should not be abandoned—it has become entrenched in our dermatologic language and practice. We argue that it represents a distinct histologic entity, and that a critical consideration of all of the historical, clinical, and molecular aspects of this lesion type (parts I and II of this continuing medical education article) will lead to a better understanding of its biologic significance and more rational management by practitioners.

HISTORICAL AND CLINICAL ASPECTS

Origin of the concept

Key points

- The field can be traced back to three seminal papers published in the late 1970s
- Atypical nevi in melanoma-prone families were described, and given different “syndrome” names

Cawley¹⁷ is credited with the first description of familial melanoma based on cases of cutaneous melanoma in a father and two of his three children. There were subsequent reports of melanoma-prone families in the 1960s and early 1970s.^{18,19} However, the concept of the DN and its association with melanoma came from clinical observations of nevi in several melanoma-prone families in the late 1970s and early 1980s. First, the dermatopathologist

Wallace H. Clark and colleagues at the University of Pennsylvania described distinctive nevi in 37 patients from six melanoma families with “B-K mole syndrome” (B and K were the first letters of the names of two “unusually helpful” patients).⁶ Second, Henry T. Lynch at Creighton University and colleagues reported a similar nevus phenotype in a melanoma-prone family.²⁰ These phenotypic “syndromes” were referred to respectively as B-K mole syndrome and familial atypical multiple-mole melanoma (FAMMM) syndrome. Third, David Elder and colleagues at the University of Pennsylvania coined the term “dysplastic nevus syndrome” (DNS), with familial and sporadic variants.²¹ Within a span of three years, three different names had been given to describe nevus phenotypes in melanoma-prone families. These three “syndromes” as described in these papers will be discussed in further detail because they represent the genesis of the concept of the DN and the origins of the controversy surrounding these lesions, and introduced the issues of nomenclature that have persisted from 1978 to the present.

In Clark et al’s original report,⁶ the authors compiled six melanoma-prone families totaling 69 members in three or four generations, 25 of whom had cutaneous melanoma. Of these 25 patients, 17 were clinically examined, and it was deemed that 15 of them had B-K mole syndrome. These patients were clinically defined as having <10 to >100 nevi, exhibiting variability of size (from 5-15 mm in diameter), border, and color. Histologically, the nevi were defined as atypical melanocytic hyperplasias, with mesenchymal changes in the papillary dermis and a lymphocytic infiltrate. It was stated that the term “atypical melanocytic hyperplasia is synonymous with melanocytic dysplasia,” defined as “individual melanocytes or small clusters of melanocytes that have some structural features of malignant melanocytes, but whose potential for development into obvious melanoma is obscure. The situation is precisely analogous to cervical dysplasia and senile keratoses: foci of squamous cells that have some structural features of malignancy, but may remain indolent, regress completely, or progress to obvious carcinoma.”

In Lynch et al’s report,²⁰ a single cancer and melanoma-prone family with five generations was described. Four individuals developed melanoma, and three of these had atypical and numerous (>200) nevi. They proposed that “observation of melanoma in association with a distinguishing cutaneous phenotype characterized by multiple large moles, irregular in shape, colored reddish-brown to

pink, with evidence of pigmentary leakage, and with an apparent autosomal dominant mode of inheritance, may constitute a new familial syndrome.” Referring to Clark’s paper, which was published several months earlier, they added: “We believe that our more descriptive term ‘familial atypical multiple mole melanoma’ syndrome...is a much more meaningful term than ‘B-K mole’ syndrome. We believe that our term will provide physicians with a better basis for recognition and comprehension of the genetic significance of this newly described syndrome.”

The paper by Edler et al,²¹ as noted above, introduced the term “DNS” and postulated the existence of sporadic and familial variants. The authors reported on 79 patients with primary cutaneous melanoma but no family history of melanoma. Total body photographs that had been taken of these patients were reviewed retrospectively, and the patients were segregated into groups. Group I (5 patients) had no other identifiable nevi or pigmented lesions, while group IIA (8 patients) had a few small lesions on the buttocks that were <3 mm in diameter, and group IIB (7 patients) had from two to five larger buttock lesions (0.5-1.5 cm). These patients also had lesions elsewhere, and the photographs suggested that many of them were suspicious, so that additional biopsy specimens of the lesions were obtained in all but one patient. It was estimated that these patients each had on average 26 nevi. Of the 13 additional biopsy specimens, one revealed a second primary melanoma, three were unremarkable melanocytic nevi, and nine revealed “microscopic atypia similar to that described in the familial B-K mole syndrome.” Group III was the largest, composed of 59 patients that were deemed to have “normal” nevus patterns. No additional biopsy specimens of these lesions were obtained. Elder et al²¹ also expanded upon the histologic features of DN, including “nuclear pleomorphism and hyperchromatism, with a lymphocytic inflammatory response and associated fibroplasia.” Two types of dysplasia were described: epithelioid cell dysplasia and lentiginous melanocytic dysplasia. Epithelioid cell dysplasia consisted of epithelioid cells with dusty pigment, prominent nucleoli, lateral fusion and pleomorphism of nests, and nevus cells having small hyperchromatic nuclei located in the papillary dermis. Lentiginous melanocytic dysplasia was described as having prominent cytoplasmic retraction artifact, irregular (nonnested) basal melanocytic growth that was junctional without a dermal component. It was also reported in this paper that DN are precursors to melanoma, based on the dysplasia noted microscopically.

These three papers formed the backbone of the myriad studies that followed concerning DN, their role in the histogenesis of melanoma, and the controversy over their diagnosis and management.

Relationship to familial melanoma

Key points

- Numerous studies have documented the relationship of atypical nevi to familial melanoma
- There have been multiple attempts to define atypical/dysplastic nevi-related syndromes

These early studies of melanoma kindreds suggested a close relationship with these clinically atypical and histologically DN. It was noted early on, however, that this nevus phenotype was not required for melanoma development in these kindreds, given that Clark et al⁶ described two family members who developed melanoma without having clinically atypical or DN. An autosomal dominant mode of inheritance of the nevus phenotype has been described in melanoma-prone families.²² It has been reported that up to 30% to 40% of these families harbor a mutation in the *CDKN2A* locus, which encodes the p16 and ARF tumor suppressor proteins.²³ Rare mutations have also been described in several families in the protooncogene *CDK4*.²⁴ Bishop et al²⁵ examined five families with known p16 mutations and characterized them phenotypically. They reported that p16 mutation carriers were more likely to have ≥ 2 clinically atypical nevi (odds ratio [OR], 3.1), the presence of nevi on the buttocks (OR, 4.4) or dorsal surfaces of the feet (OR, 4.2), and to have a total nevus number of >100 (OR, 3.4). In this study, the histologic features of these nevi in patients with “atypical mole syndrome” were not examined or discussed.

A case control study²⁶ in the United Kingdom using these same criteria to define atypical mole syndrome found that 40 of 266 (15%) patients with melanoma fulfilled these nevus criteria compared to only seven of 305 (2%) controls. Of 32 families of these melanoma patients that were screened, 15 (47%) had members with the atypical mole syndrome phenotype, although only one individual in the group had a history of melanoma. As in many such studies, the histology of these nevi was not examined.

In perhaps the largest study to follow melanoma-prone families longitudinally, Tucker et al²⁷ noted that the majority of clinically atypical nevi in 33 families remained stable or regressed over a 25-year period. Although some melanomas were seen to arise in these nevi, melanoma also arose de novo and in clinically typical nevi. It is possible that melanoma-prone

families or those with known genetic mutations (such as in p16) have a greater risk of developing melanoma from nevi, although this is not the case in the majority of patients with sporadic atypical nevi (discussed below).

The current definition of DNS remains confusing, especially with regard to the histologic entity DN, and various names (atypical mole syndrome, FAMMM syndrome, and B-K mole syndrome) continue to be used in some quarters. According to the 1992 NIH Consensus statement⁹ alluded to above, a diagnosis of the FAMMM syndrome or DNS requires (1) melanoma in one or more first- or second-degree relatives, (2) the presence of a large number of nevi (>50) with many having atypical clinical features, and (3) nevi that have distinct histologic features. The Dutch Working Group²⁸ proposed that DNS could be diagnosed in patients having a personal history of melanoma and one or more clinically atypical nevi. A British group²⁵ has proposed criteria that include (1) ≥ 100 nevi >2 mm (50 nevi if <20 years of age or >50 years of age), (2) two or more clinically atypical nevi (nevus >5 mm, irregular edge and pigmentation), (3) one or more nevi on the buttocks, and (4) ≥ 2 nevi on the dorsal surfaces of the feet.²⁵ It should be noted that the recommendations from the NIH Consensus conference⁹ are the only criteria among these early classifications of DNS that include histology as a defining feature of this syndrome, while other criteria do not incorporate histologic dysplasia in defining DNS. These criteria are summarized in Table I.

Clinical features of dysplastic nevi

Key points

- **Dysplastic nevi exhibit clinical features generally not associated with common nevi**
- **Many studies are problematic because of a lack of histologic correlation**

As noted above, Clark et al⁶ reported that nevi in these families exhibited distinct characteristics based on size, border, and pigmentation. Many studies that followed serve to refine the clinical description of the atypical nevus^{29,30}; however, a shortcoming of most studies is the lack of histologic correlation or confirmation (as noted above and discussed below).

These nevi are usually isolated, but rarely may be agminated.³¹ The clinical characteristics used by Tucker et al³² clinically defined the atypical nevus as being ≥ 5 mm in size and having flatness (being entirely flat or having a flat component). In addition, two of three characteristics were also necessary: (1) variable pigmentation, (2) irregular and asymmetric outline, and (3) having indistinct borders (Fig 1).

Table I. Proposed definitions for dysplastic nevus syndrome

National Institutes of Health Consensus criteria ⁹	
Occurrence of melanoma in	≥ 1 first- or second-degree relatives
Large number of nevi (often >50), some of which are	clinically atypical
Nevi with certain distinct histologic features	
Dutch working group criteria ²⁸	
Sporadic dysplastic nevus syndrome	
Melanoma and	≥ 1 severely clinically atypical nevi
Familial dysplastic nevus syndrome	
Two close relatives with melanoma (with or without	atypical nevi)
	≥ 1 relative with atypical nevi
Revised (British group) dysplastic nevus syndrome score ²⁵	
>100 nevi of size >2 mm (≥ 50 if <20 or >50 years of age)—	1 point
>2 atypical nevi—	1 point
>1 nevus on buttocks—	1 point
>2 nevi on the dorsal surfaces of the feet—	1 point
If total score is >2, the patient has dysplastic nevus	syndrome

These were the criteria used in what is the largest case control study studying melanoma risk and nevi discussed above. The Dutch Working Group²⁸ has used the following criteria for atypical nevi: (1) ≥ 5 mm in diameter, (2) vague border, (3) asymmetric shape, (4) irregular pigmentation, and (5) red hue. Obviously, the most clinically relevant criteria would be those features most highly associated with melanoma risk. As mentioned above, Bishop et al²⁵ provided some data regarding nevus phenotype and melanoma risk.

While dermatoscopic criteria have also been developed by a number of groups^{33,34} for the evaluation of melanocytic nevi, several studies were specifically designed to examine clinically atypical nevi. In a large study, Hofmann-Wellenhof et al³⁵ classified atypical nevi into six dermatoscopic types that were subclassified by pigmentation pattern. They reported that most patients had nevi with a predominant (ie, signature) dermatoscopic feature, and further noted that eccentric peripheral hyperpigmentation was a rare (7.5%) finding in atypical nevi and recommended that such nevi be closely monitored or perhaps biopsy specimens be obtained to rule out melanoma. Annessi et al³⁶ studied 198 atypical macular melanocytic lesions that were histologically diagnosed as either DN or thin melanoma and reported that diagnostic accuracy varied by method of analysis, with the correct diagnosis rendered in 82.3%, 79.3%, and 71.2% of lesions using qualitative pattern analysis, the ABCD rule, and the

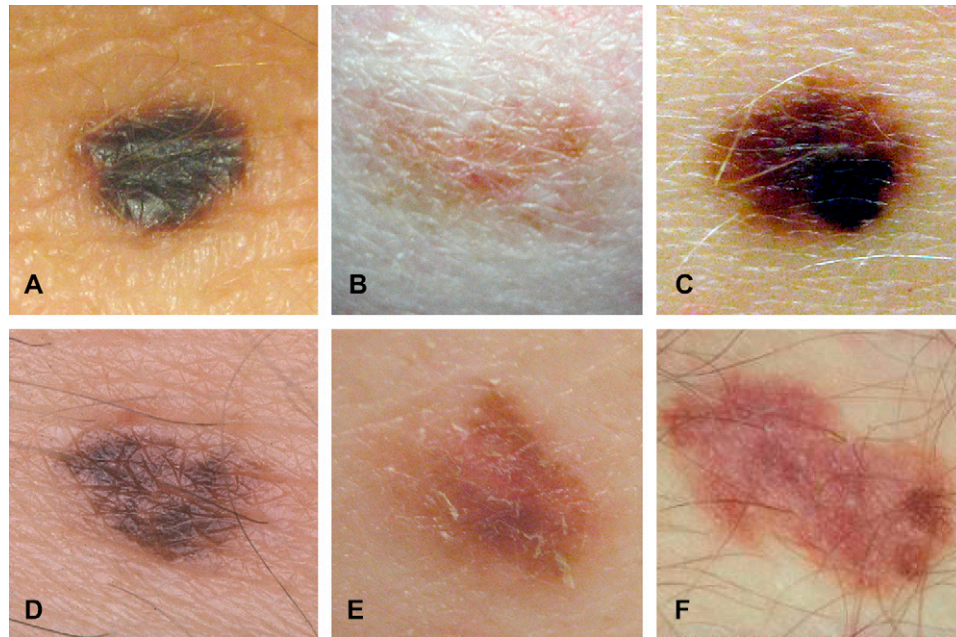


Fig 1. Clinical features of atypical nevi. Indistinct borders are evident in lesions (A), (B), and (C). Variable pigmentation is seen in these lesions and in the lesions seen in (D), (E), and (F). Irregular borders are present in many of these lesions.

7-point checklist methods, respectively. The diagnostic accuracy for melanoma for the three methods was 70.8%, 67.8%, and 57.7%, respectively. The presence of light brown structureless areas was highly associated with a diagnosis of melanoma (OR, 27.9). Often under dermatoscopy, DN show a homogeneous pattern centrally with reticulated network³⁷ or dots^{38,39} peripherally, with these heterogeneous regions thought to represent an active growth state. Finally, confocal microscopy has been used to study DN, which exhibit characteristics intermediate between CN and melanoma with respect to size and diameter of the dermal papillae and irregularity in cell size.⁴⁰

HISTOLOGIC FEATURES

Basic histopathology

Key points

- **Dysplastic nevi exhibit distinct histologic features that are well described**
- **Melanocyte cytology and distribution, along with dermal characteristics, distinguish dysplastic nevi from common nevi**

Although some melanocytic neoplasms may be difficult if not impossible to classify under conventional light microscopy, there is abundant literature describing the histologic nature of DN. In their original description of DN, Clark et al⁶ enumerated four main features: (1) atypical melanocytic hyperplasia, (2) melanocytes with cytologic features characteristic

of malignant melanocytes, (3) mesenchymal changes in the papillary dermis (eosinophilic fibroplasia), and (4) lymphocytic infiltrate (Fig 2). While these criteria remain the basis for defining DN, at least four groups subsequently published additional criteria to help pathologists and dermatopathologists identify and categorize DN. These include groups representing the University of Pennsylvania⁴¹ (Table II), the World Health Organization⁴² (Table III), the European Organization for Research and Treatment of Cancer⁴³ (Table IV), and Duke University⁴⁴ (Table V). In addition, Pozo et al,⁴⁵ recognizing the pitfalls of categorizing atypia in a nevus, proposed an algorithm to segregate low- from high-grade dysplasia, which was accomplished with a diagnostic accuracy of 99.5% in their study.

The World Health Organization enumerated major and minor criteria for the histologic diagnosis of DN.⁴² The major criteria are: (1) basilar proliferation of atypical melanocytes which must extend at least three rete ridges or “pegs” beyond the dermal component and (2) organization of this proliferation in a lentiginous or epithelioid-cell pattern (Fig 2). The minor criteria include: (1) the presence of lamellar fibrosis or concentric eosinophilic fibrosis, (2) neo-vascularization, (3) an inflammatory response, and (4) the fusion of rete ridges. Using these criteria, a diagnosis of DN requires both major criteria and at least two minor criteria. Using 20 different histologic features, the mean overall concordance of diagnosis reported for 1400 histologic specimens was 92%. The

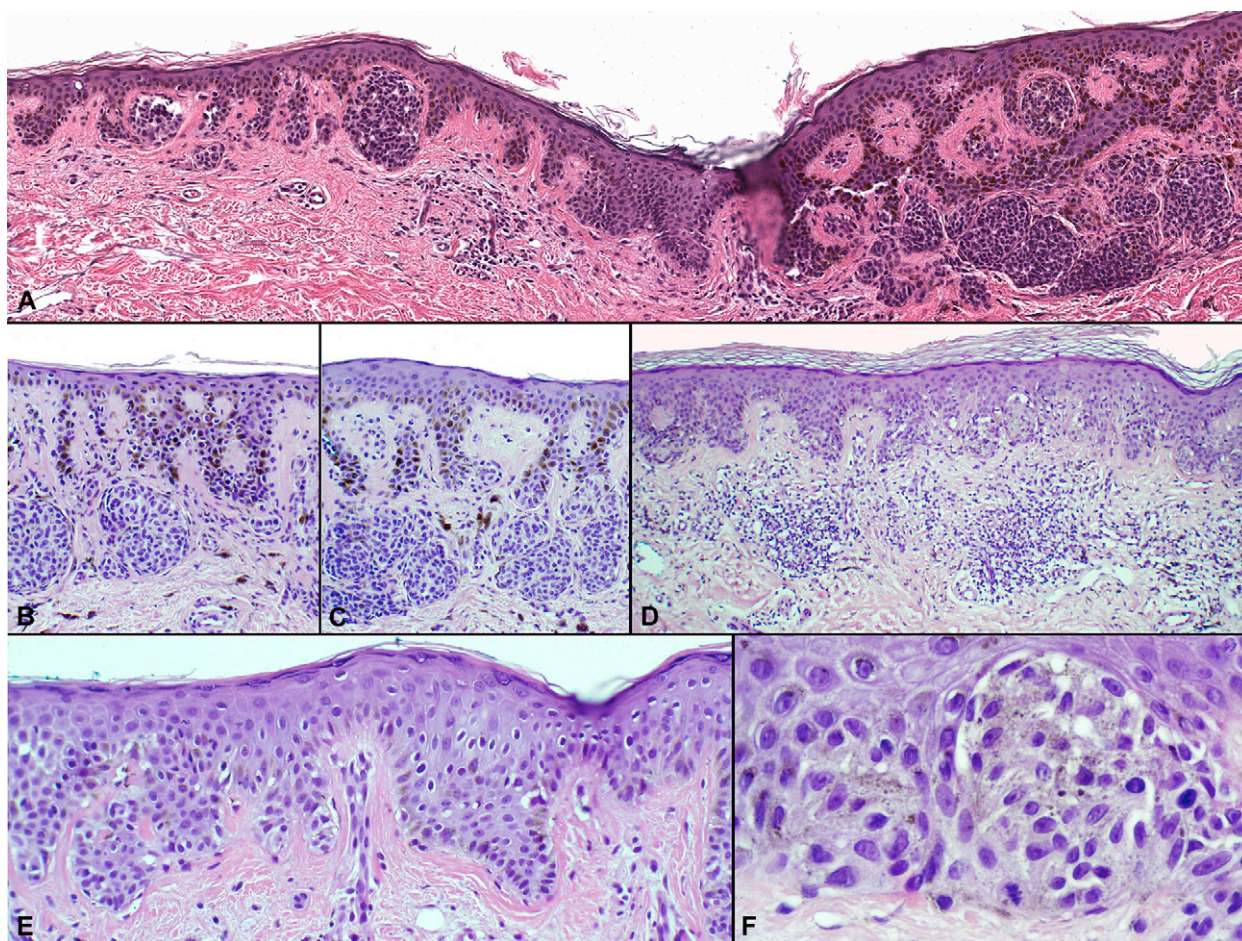


Fig 2. Histologic features of dysplastic nevi. **A**, Architectural disorder, including lateral asymmetry and “shouldering.” **B**, Lentiginous melanocytic hyperplasia with bridging of rete ridges and **(C)** cellular atypia. **D**, Patchy lymphocytic host response. **E**, Prominent eosinophilic fibroplasia. **F**, Variable and “random” cytologic atypia and mitotic junctional activity. (Original magnification: **A**, $\times 40$; **B**, **C**, and **E**, $\times 200$; **D**, $\times 100$; **F**, $\times 600$.)

histologic specimens included CN, DN, and radial growth phase melanomas, with 10 dermatopathologists participating.

These features may not be uniformly observed throughout individual nevus specimens. Barr et al⁴⁶ examined 298 DN and found that 36% displayed heterogeneity with respect to atypical features. It has been reported that DN have deranged melanogenesis as indicated by reactivity with monoclonal antibody HMSA-2.⁴⁷ HMSA reactivity is a feature of melanocytes in DN and melanomas, but not CN.⁴⁸ Another distinction between CN and DN may be observed by immunohistochemical staining for type IV collagen. Lebe et al⁴⁹ reported the lack of staining in most CN, while 21 of 33 DN showed a continuous pattern of type IV collagen surrounding junctional nests in a concentric fashion while a discontinuous immunostaining pattern was observed in remaining cases.

On the other hand, there are those who believe that DN have never been fully characterized and do not

constitute a specific entity. The most prolific proponent of this view was A. Bernard Ackerman. Dr Ackerman criticized the usage and inconsistency of the term “dysplasia” in pathology, and argued that features of the clinically atypical nevus and the histologic DN are essentially the same criteria that are used to distinguish a banal nevus from melanoma.^{5,12} Ackerman maintained that all benign nevi could be classified as one of four types: (1) Unna nevus, with polypoid morphology and thickened papillary dermis; (2) Meisher nevus, dome-shaped with nevus cells arranged in a wedge configuration; (3) Spitz nevus, characterized by a benign silhouette of epithelioid or spindled cells having large nuclei with abundant cytoplasm; and (4) Clark (or dysplastic) nevus.

The problem with dysplasia

Key points

- Use of the term “dysplasia” connotes a cytologic change towards neoplasia

Table II. Histologic criteria proposed by Clark et al⁴¹

Architecture	Nests bridge rete
	Nests at the side of rete
	Single cells between nests, nests predominating
	Lentiginous elongation of rete
	Anastomosis of rete
Host response	Little or no pagetoid spread
	Patchy lymphocytic infiltrate
	Eosinophilic fibroplasia
	Lamellar fibroplasia
	Prominent vessels
Cytology	Variable slight to moderate atypia
	Few (if any) mitoses
	Occasional macronuclei
	Scattered epithelioid nevus cells
	Scattered cells with finely granular melanin

• **Dysplastic nevi may not be akin to epithelial dysplasias in other tissues**

One criticism, leveled by Ackerman and others, is use of the term “dysplasia” in describing the histologic characteristics of DN. Elder et al² noted that “the term is not without ambiguity, but...firmly entrenched and widely understood by physicians of most specialties.” While the term “dysplasia” is entrenched, we feel it is poorly understood by most clinicians and not rigorously defined or applied by most pathologists. Dysplasia is translated from the Greek *dys*- (bad or malfunction) and *-plasia* (growth, development, or change), connoting a change in cytology towards neoplasia or malignancy. The original descriptions of DN, and in particular their histologic features, suggested that these lesions may indeed be akin to epithelial dysplasia noted in actinic keratoses, colon polyps, and cervical intraepithelial dysplasia, which are all known to be potential precursor lesions of carcinoma. Evidence that DN are true precursor lesions of melanoma is not convincing from the published literature, as discussed below. A new consensus must be approached so that medical students, residents, dermatologists, and those in other specialties taking care of patients with clinically atypical nevi have a clearer message regarding the potential (or lack thereof) for melanoma arising in these nevi.

The NIH Consensus Conference^{9,10} and subsequent commentaries¹²⁻¹⁴ have endorsed changes in the nomenclature, recommending the phrase “nevus with architectural disorder.” Ackerman and others have advocated the term “Clark nevus” both in honor of its initial descriptor and to reinforce the

Table III. World Health Organization criteria for the diagnosis of dysplastic nevi⁴²

Major criteria*	Basilar proliferation of atypical melanocytes, extending at least three rete ridges beyond dermal component
	Organization of proliferation in lentiginous or epithelioid cell pattern
Minor criteria*	Lamellar or concentric eosinophilic fibrosis
	Neovascularization
	Inflammatory response
	Fusion of rete ridges

*The diagnosis of dysplastic nevi requires fulfillment of both major criteria and 2 minor criteria.

Table IV. European Organisation for Research and Treatment of Cancer Cooperative Group criteria⁴³

Common nevus	<2 features noted below for dysplastic nevi
Dysplastic nevus	≥ 3 of the following features: marked junctional proliferation, irregular nevus nests, large nuclei, and lymphohistiocytic infiltrate
Melanoma in situ	Pagetoid growth Continuous junctional proliferation

notion that it is a nevus variant. However, both these terms have had little support in the dermatology and dermatopathology communities, as evidenced by multiple surveys conducted.^{16,50,51} As noted above, dermatopathologists and dermatologists favor the term “DN” to the NIH-recommended nevus with architectural disorder.¹⁶ However those with dual training in dermatology and dermatopathology prefer the phrase nevus with architectural disorder.

Interpathologist correlations

Key points

- **Most studies show good intraobserver reproducibility but poor interobserver correlation**
- **There are many overlapping histologic features of common nevi and dysplastic nevi**
- **The main difficulty with dysplastic nevi relates to stratification of melanocytic dysplasia**

Many studies have been undertaken to characterize the intra- and interobserver reproducibility of diagnosing DN and the grading of dysplasia present in nevi. There are obviously major difficulties inherent in performing such studies, namely variation in

Table V. Duke University grading system for dysplastic nevi⁴⁴

Architectural disorder	Junctional component nested at both edges Overall symmetry >5% of nests cohesive Suprabasal spread (prominent or at edge) >50% confluence of proliferation Single-cell proliferation absent or focal (mild, 0-1 criteria; moderate, 2-3 criteria; severe, 4-6 criteria)
Cytologic atypia	Nuclei round or oval and euchromatic Nuclei larger than those of basal keratinocytes Nucleoli prominent Cell diameter twice that of basal keratinocytes (mild, 0-1 criteria; moderate, 2 criteria; severe, 3-4 criteria)

both the histologic criteria and the observers themselves. Some of these studies will be specifically discussed below, although most appear to show good intraobserver reproducibility but poor interobserver correlation.

It is clear that there are many overlapping histologic features of CN and DN. In a study restricted to clinically typical acquired melanocytic nevi, Klein et al⁵² examined 58 nevi and found at least one histologic feature of DN present in 88% of lesions. In addition, it was noted that two or more histologic features of DN were present in 69% of specimens and three histologic features were found in 29%. Several studies address interobserver agreement in distinguishing DN from CN or melanoma. Duncan et al⁵³ showed an overall concordance of 77% (κ values 0.55-0.84) in a study involving five dermatopathologists. Similarly, Piepkorn et al⁵⁴ found that while intraobserver reproducibility was substantial, interobserver concordance was only fair among six pathologists reviewing 149 melanocytic lesions, despite differences in criteria. Moreover, the World Health Organization melanoma program found a 92% mean overall concordance in distinguishing CN, DN, and radial growth phase melanomas based on their criteria.⁴² By contrast, there is typically less concordance seen in grading nevi (ie, classifying mild, moderate, or severe atypia). The previously cited study indicated that experience of the dermatopathologist may be important, because more experienced dermatopathologists had a grading concordance ranging from 35% to 58% (κ values 0.38-0.47), while less experienced dermatopathologists had a concordance between 16% and 65%

(κ values 0.05-0.24).⁵³ The main difficulty with DN does not necessarily seem to be its histologic diagnosis per se, but rather the stratification of melanocytic dysplasia. One study found, however, that given a set of rigid criteria (with a 1-5 scoring system), these discrepancies improved but were not entirely eliminated, as a panel of five dermatopathologists and two melanoma specialists were within one grade of the mean on 88% of the cases, and in only 3% of the cases did they differ by two or more grades.⁵⁵

Another difficulty in the histologic evaluation of these nevi is the apparent heterogeneity with respect to atypical features within individual nevi,⁴⁶ as noted above. Such heterogeneity within lesions is not only problematic for scoring degrees of dysplasia in a nevus, but also may lead to missing a diagnosis of melanoma arising within the nevus in some cases. Of course, the main clinical concern is distinguishing severe dysplasia from melanoma. Studies have shown that there is difficulty in distinguishing "severe cytologic dysplasia" in the junctional component of melanocytic proliferations from melanoma in situ and superficial dermal invasion. For example, Cook et al⁵⁶ found that 17% of previously diagnosed melanomas were reclassified as benign lesions with atypia, whereas 2% of lesions previously diagnosed as benign were reclassified as melanoma upon further review by a panel of eight pathologists. It is important to mention that most studies were performed with "expert dermatopathologists," and as such may not generalize to those with general anatomic pathology training or dermatologists who read their own slides. In one study, 17.6% of pathologists offered a false positive diagnosis of melanoma in situ for lesions diagnosed as DN by a panel of expert pathologists.⁵⁷ It is likely that the disparity in the diagnosis of benign versus malignant melanocytic neoplasms that occurs in the real world is likely to be underestimated in the literature.

Correlation of nevus dysplasia and melanoma risk

Key point

- Development of dysplastic nevi is associated with increased melanoma risk

Most previous studies attempting to correlate nevus and melanoma risk were based on patients' clinical phenotype (ie, clinically atypical nevi) rather than histologic examination of their nevi. Very few studies have attempted to correlate the presence of DN, as defined histologically, with melanoma risk. Arumi-Uria et al⁵⁸ retrospectively reviewed 6275 cases of "nevus with architectural disorder" that were then

grouped based on presence of mild (40%), moderate (26%), and severe (5%) cytologic atypia. A history of melanoma diagnosis in these patients with nevi showing mild, moderate, and severe atypia was 5.7%, 8.1%, and 19.7%, respectively. The authors concluded that melanoma risk is higher for persons with DN having higher grades of histologic atypia.

Another study assessed the degree of nevus atypia in three groups: patients with a history of melanoma, those with DN and a positive family history of melanoma, and unrelated spouses without a family history of melanoma. Nevi were evaluated using guidelines from the NIH Consensus Conference guidelines,^{9,10} and a trend in more severe dysplasia increasing from the low risk groups to those with a history of melanoma was noted.⁵⁹ Although studies are few in number, it appears that patients who develop more severe cytologically atypical nevi may have a higher likelihood of developing subsequent melanoma.

Is clinical atypia synonymous with histologic dysplasia?

Key points

- **We regard “atypical nevus” as a clinical term, while “dysplastic nevus” is a histologic term**
- **While atypical clinical features may correlate with histologic dysplasia, this is not always the case**

In the original descriptions of DNS, it was posited that diagnosis of atypical nevus based on clinical features and that of DN based on histologic grounds were synonymous. While this assumption was supported in some earlier studies,⁶⁰⁻⁶² others have shown that this is not necessarily the case. In melanoma patients in which the most clinically atypical lesion was removed, Grob et al⁶³ found that correlation of histologic dysplasia with clinical atypia increased with the number of atypical features. On the other hand, Klein et al⁵² prospectively analyzed 58 clinically benign lesions (<5 mm in diameter, symmetric, uniformly pigmented, with distinct margins and no erythema) and found that 88% had at least one histologic feature of DN, while 69% had two features and 29% had three features.

Another study by Meyer et al.⁶⁴ was performed with family members in multiple melanoma kindreds, in which 100 pigmented lesions were clinically photographed and evaluated histologically. The overall concordance between clinical and histologic atypia was fair, as the presence of macularity and color variegation correlated somewhat with higher grades of histological atypia. Similarly, Annessi et al⁶⁵ found very poor correlation between nevi that were clinically atypical and histologically

dysplastic. In this study, 940 acquired nevi were clinically assessed by five dermatologists, and then blindly examined histologically by a single experienced dermatopathologist. Poor correlation between clinical atypia and histologic dysplasia was evidenced by a κ value of 0.17 (sensitivity 58.4%, specificity 66.6%). In particular, many nevi that were 3 to 5 mm in size and not thought to be clinically atypical were found to exhibit histologic dysplasia.

These studies support the notion that a clinically atypical nevus does not equate to a nevus with histologic dysplasia and vice versa. This again brings into question the clinical usefulness of a histologic diagnosis of DN. What the clinician would mainly like to know is whether the pathologist thinks there is some probability that a given lesion represents melanoma or is not sampled adequately to exclude that possibility.

EPIDEMIOLOGY AND NATURAL HISTORY

How common are dysplastic nevi?

Key points

- **The prevalence of dysplastic nevi is unclear, because most studies did not include histologic confirmation**
- **Dysplastic nevi may be less common than common nevi in the general population, but more common than common nevi in “high-risk” patients**

The prevalence of DN in the general population is unknown, because most epidemiologic studies have been based on clinical examination without histologic confirmation of dysplasia. A study by Steijlen et al⁶⁶ based on autopsy cases estimated the prevalence of DN to be 10%, while Piepkorn et al⁶⁷ estimated their prevalence in Caucasians to be as high as 50%. Lee et al⁶⁸ reported that among 874 new dermatology patients, 2.4% had biopsy specimens that revealed DN (compared to 5.8% revealing CN) on the first visit, suggesting that DN are less common than CN. One study found the number of DN in individuals correlates with total number of melanocytic lesions,⁶⁷ independent of personal or family history of melanoma.⁶⁹ However, a Swedish case control study found rates of histologically diagnosed DN of 40% in patients with history of melanoma versus 8% in controls.⁷⁰ DN tend to be more prevalent in younger adults, although this may partly reflect the disappearance of nevi over time and a tendency towards larger numbers of nevi among more recent birth cohorts.⁷¹ They usually appear in childhood, become readily apparent by puberty, and continue to appear throughout adulthood.⁷¹ Given the importance of genetic determinants in nevus

formation and phenotype (discussed in part II of this review), it seems likely that individual patients will be predisposed to forming CN or DN. Therefore, while DN may be less common than CN in the general population, they may be more prevalent than CN in “high-risk” patients who have a history of melanoma and/or clinically atypical nevi.

Eruptive dysplastic nevi

Key points

- **Many conditions associated with eruptive common nevi have also been associated with rapid development of dysplastic nevi**
- **Eruptive dysplastic nevi may occur after exposure to chemotherapy, melanotropic peptides, or HIV infection**

Various factors have been associated with eruptive CN, such as blistering diseases and immunosuppression secondary to cancer, chemotherapy, or HIV infection. Many of these conditions have also been associated with rapid development of DN. For example, increased numbers of DN have been documented in organ transplant patients within 5 years of onset of immunosuppression.⁷² Induction of multiple atypical melanocytic lesions has frequently been reported in children with malignant hematologic diseases and chemotherapy-induced immunosuppression. Most cases described are of patients with acute lymphoblastic leukemia who developed DN after the completion of chemotherapy.^{73,74} Similar cases have been described in adults, most commonly occurring while receiving 5-fluorouracil for metastatic solid tumors,^{75,76} but also may occur after exposure to 5-fluorouracil⁷⁷ or before chemotherapy exposure in patients with chronic myelogenous leukemia.⁷⁸

There have also been recent reports of patients developing DN after the administration of melanotropic peptides for the purpose of tanning. Cardones and Grichnik⁷⁹ described a 40-year-old man who developed multiple new DN after the self-administration of α melanocyte-stimulating hormone. Similarly, Langan et al⁸⁰ reported two patients presenting with new and rapidly changing DN after the subcutaneous injection of melanotan I and II.

Finally, eruptive DN have been described in patients with HIV. Duvic et al⁸¹ reported seven patients presenting with new nevi revealing histologic dysplasia, which arose as they became symptomatic from HIV infection.

Role of ultraviolet light exposure

Key point

- **Ultraviolet light exposure may promote development of dysplastic nevi**

A role for UV radiation in the development of nevi is somewhat controversial, with some studies showing no relationship between patterns of sun exposure and numbers of nevi in patients⁸² and others reporting significantly increased numbers of nevi on intermittently and chronically sun-exposed areas⁸³ and in children living in sunnier climates.⁸⁴ Most studies purporting to examine the role of UV in promoting the development of DN (compared to CN), however, are difficult to interpret because identification of DN was based on clinical examination alone.⁸³⁻⁸⁶ Stierner et al⁸⁷ found that patients with DNS had larger differences in nevus counts between sun-exposed and sun-protected areas than control subjects, suggesting heightened sensitivity to the “nevogenic” effects of UV light. This finding is consistent with studies showing that nevi in patients undergoing UV B light phototherapy develop more irregular macroscopic and dermoscopic features over time,⁸⁸ but histologic correlates have not been described.

Although sunscreen use can decrease total nevus numbers,⁸⁹ whether this also holds for DN specifically is not known. One study found cells from DN (compared to cells from CN) have increased sensitivity to UV B light-induced DNA damage.⁹⁰

Marker of melanoma risk

Key point

- **Presence of dysplastic nevi are associated with increased melanoma risk in individuals**

There is substantial evidence that patients with DN are at increased risk for developing melanoma. This association was first appreciated in melanoma kindreds, because members of these families appeared to have increased numbers of DN,⁹¹ although some family members with melanoma did not have DN.⁹² Subsequent studies found that the presence of DN did not necessarily correlate with p16 mutations in individuals in these high-risk families.^{93,94} In addition to familial factors, DN increase melanoma risk when associated with increased absolute numbers of nevi.⁹⁵

A number of studies have reported an increased risk of sporadic (nonfamilial) melanoma, ranging from 4- to 15-fold, in patients with DN.^{70,95-98} Interestingly, one study examining new cases of first primary nonfamilial melanoma comprising 61 patients with superficial spreading and 19 patients with nodular subtypes found that DN occur nearly four times more frequently among patients with a previous diagnosis of superficial spreading melanoma relative to nodular melanoma.⁹⁹ Finally, several studies have also implicated DN as an independent

risk factor for developing multiple primary melanomas.^{92,100}

Therefore, while the presence of DN are associated with increased melanoma risk in individuals, the finding of CN-derived melanomas in such patients raises the question of whether in fact individual DN lesions are more likely than CN to progress to melanoma (discussed below).

Dysplastic nevi progression to melanoma

Key points

- **There are no ideal models for studying nevus transformation to melanoma in real time**
- **Most dysplastic nevi do not progress to melanoma**
- **Studies of nevus-derived melanomas reveal similar incidence of melanomas arising in dysplastic nevi and common nevi**
- **Assessing the rate of individual dysplastic nevi versus common nevi transforming to melanoma depends on the relative prevalence of these nevus types**

Although it is clear that DN represent a marker of melanoma risk, there is little direct evidence that individual DN lesions progress to melanoma at any higher rate than CN. Indeed, the heart of the controversy lies in the question of whether DN represents a premalignant lesion. This question of natural history, however, is problematic, because it is not possible to identify a lesion as DN without a biopsy specimen, and the process of obtaining a specimen precludes long-term monitoring of the lesion. Moreover, there is no established animal model for DN in which lesions develop in situ and can be monitored long-term for transformation to melanoma. There is no ideal model for studying nevus transformation to melanoma in real time.

Meyer et al¹⁰¹ transplanted histologically confirmed DN to athymic (nude) mice and found that while more than 90% of the xenografts survived transplantation, most developed an inflammatory response and 30% regressed over a 16-week observation period. Approximately 20% of nevi developed junctional intraepidermal melanocytic hyperplasia in a lentiginous pattern, with cytologic hypertrophy, dendritic morphology, and hypermelanization, but none of the transplanted lesions transformed to melanoma, either spontaneously or after UV irradiation.¹⁰¹ More recent mouse models based on transgenic melanocyte expression of various oncogenes including NRas,¹⁰² mutant CDK4,¹⁰² mutant BRAF,^{103,104} and KRas,¹⁰⁵ or after the repeated topical application of dimethylbenzanthracene,¹⁰⁶ all develop “nevus-like” cutaneous lesions. In some

cases, these lesions may progress to invasive melanoma¹⁰²⁻¹⁰⁵; however, they appear to arise in the dermis without an epidermal or junctional component¹⁰²⁻¹⁰⁵ or consist predominantly of perifollicular melanocytes,¹⁰⁶ and therefore do not represent good histologic correlates of DN.

Clark's early description of DN was in the context of evolution to melanoma, but he acknowledged that most individual DN lesions never progress to melanoma.¹⁰⁷ As noted above, subsequent studies by Tucker et al²⁷ confirmed that most DN in melanoma kindreds regressed or were stable, and only rarely developed into melanoma. Numerous studies, on the other hand, of familial and sporadic melanomas have shown that DN can serve as precursors to melanoma, based on the histologic finding of DN in association with melanoma.^{95,108,109} Assuming that the minimal number of nevi transforming to melanoma per year is roughly equivalent to the number of melanomas diagnosed each year with associated nevic components, Tsao et al¹¹⁰ estimated the lifetime risk of individual nevi (including DN) transforming to melanoma is extremely low, on the order of one in 10,000. Based on the literature, it appears that 20% to 30% of melanomas appear to arise from nevi.¹¹¹⁻¹¹³ Two studies similarly found that approximately 20% of melanomas had a histologically associated DN,^{114,115} while another found DN remnants in association with only 7% (34/512) of melanoma cases.¹¹⁶

The question of whether a DN is more commonly found than CN in association with melanoma has been addressed in multiple studies. Although Black et al¹¹⁷ reported higher rates of DN (32%) versus CN (10%) underlying 500 cases of invasive melanoma, more recent studies have not shown a predominance of DN-derived melanoma. Of 1,126 nevus-derived melanomas reviewed by Sagebiel et al,¹¹⁵ 79% were associated with CN and 21% with DN. In another study of 147 melanomas arising from nevi, Skender-Kalnenas et al¹¹⁸ found that 56% were DN and 44% were CN. Bevona et al¹¹⁹ reported that of 1,606 nevus-associated melanomas, 43% arose from DN and 57% from CN. In a review of melanomas diagnosed in an academic group practice over 10 years, Goodson et al¹²⁰ reported that 66 melanomas arose from CN versus 45 from DN. Similarly, in several studies of patients with nevi monitored by photography, nevus-derived melanomas appear to arise from DN and CN in roughly equivalent proportions.^{29,121-123}

There is potential error in interpreting nevus origin from histologic specimens. The possibility of a collision event (melanoma and nevus arising in adjacent sites) could yield an overestimate of

nevus-derived melanomas, or this proportion could be underestimated because of cases where melanoma destroys the nevus precursor and there is no histologic remnant of nevus. More importantly, the question of whether the rate of melanoma transformation is greater for individual DN versus CN hinges on the relative prevalence of these nevus types. For example, equivalent numbers of DN- and CN-derived melanomas in a patient population in which CN are predominant would suggest that DN have higher rates of transformation to melanoma than CN. On the other hand, similar data in a patient population in which DN predominate would lead to the opposite conclusion. As described above, numerous studies have attempted to assess the prevalence of DN in various patient groups, but many were confounded by the lack of histologic confirmation. Nevertheless, it would seem that the relative likelihood of nevus transformation to melanoma depends upon the clinical context, as noted above.

In conclusion, over the past 30 years, clinicians have struggled with the diagnosis of DN. The terminology has contributed to confusion over understanding how they differ from CN, and predicting their biologic behavior. Many of the early clinical studies were flawed because clinically atypical nevi were often assumed to be DN without histologic confirmation. While the terminology is still debated, there appears to be sufficient evidence to substantiate DN as a histologic entity distinct from CN, although the two cannot be reliably distinguished on clinical examination. There is no evidence that individual DN will inevitably progress through sequentially higher grades of dysplasia, although some of the past terminology and interpretations of the literature have suggested this may be a viable pathway of melanoma development. There is substantial clinical evidence indicating that melanoma most commonly develops *de novo* (ie, from isolated melanocytes rather than from nevi). Less commonly, melanoma arises from preexisting nevi, which may be either CN or DN. Despite the problems inherent in its terminology, the DN has become entrenched in our dermatologic language and practice. It represents a distinct histologic entity, whose biologic significance appears to be more as a marker of melanoma risk rather than a precursor to melanoma. These considerations will be further addressed in part II, which reviews molecular aspects and clinical management of DN.

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