made almost 200 years ago, but a potential precursor of melanoma was not identified until 1978 when Clark and colleagues described the lesions that are now referred to as *dysplastic nevi*. Several lines of evidence support the concept that some dysplastic nevi are precursors of melanoma. One of the most compelling pieces of evidence involves studies of families affected by *dysplastic nevus syndrome*, an autosomal dominant disorder in which a tendency to develop multiple dysplastic nevi and melanoma are co-inherited. The probability that a person with dysplastic nevus syndrome will develop melanoma is over 50% by age 60, and at-risk individuals sometimes develop several melanomas at multiple sites. Even more directly, apparent transformation of dysplastic nevi to melanoma has been documented histologically.

Although dysplastic nevi can give rise to melanoma, the vast majority of such lesions are clinically stable and never progress. Conversely, not all melanomas in individuals with dysplastic nevus syndrome arise from dysplastic nevi, suggesting that these lesions may be best viewed as indicators of increased melanoma risk. Indeed, melanoma may arise in individuals completely lacking in dysplastic nevi. Dysplastic nevi may also occur as isolated lesions in otherwise normal individuals, in which case the risk of malignant transformation is very low.

Pathogenesis. Clark and associates have proposed stages in the development of dysplastic nevi and their eventual progression to melanoma (Fig. 25-5), presumably through stepwise acquisition of mutations or epigenetic changes. Indeed, like conventional nevi, dysplastic nevi also frequently have acquired activating mutations in the *NRAS* and *BRAF* genes. What then distinguishes dysplastic nevi from typical melanocytic nevi? An important clue comes from individuals with dysplastic nevus syndrome. Such individuals often have inherited loss of function mutations in *CDKN2A*. As discussed further under melanoma, *CDKN2A* encodes several proteins including p16/INK4a (described in more detail under melanoma), which you will recall is a negative regulator of cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase 6. Other affected families have mutations in *CDK4* that make the CDK4 protein resistant to inhibition by p16/INK4a. Thus, it appears that RAS or BRAF activation and increased CDK4 activity contributes to the development of dysplastic nevi. However, not all patients with germline mutations in *CDKN2A* or *CDK4* have dysplastic nevi, and not all familial dysplastic nevi are associated with mutations in these genes. As a result it is suspected that additional genes influence whether dysplastic nevi occur in a particular individual; the identities of these modifier genes, as well as the other genes that are responsible for the syndrome, are being sought. One possible suspect is germline mutations that increase the expression of *TERT*, the gene that encodes the catalytic subunit of telomerase (described later under Melanoma).

MORPHOLOGY

Dysplastic nevi are **larger than most acquired nevi (often greater than 5 mm across) and may number in the**

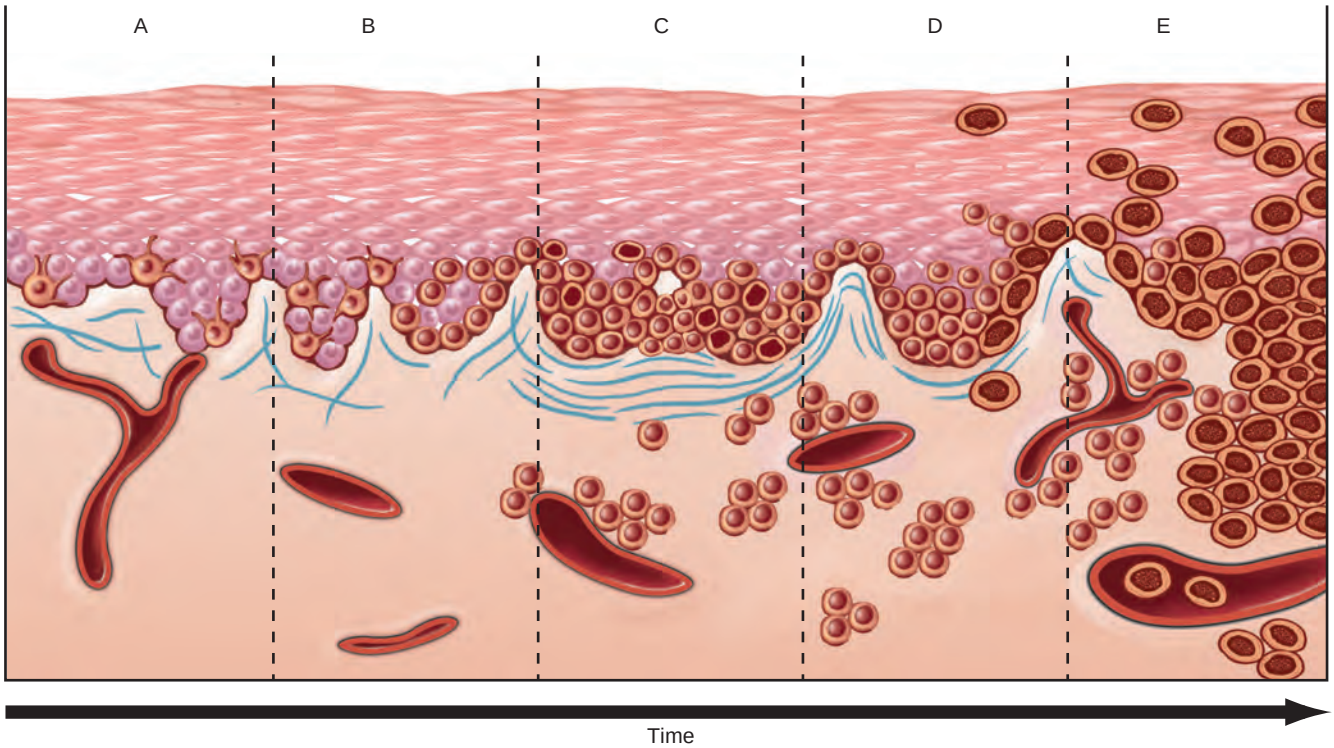

Figure 25-5 Potential steps of tumor progression in dysplastic nevi. **A,** Lentiginous melanocytic hyperplasia. **B,** Lentiginous junctional nevus. **C,** Lentiginous compound nevus with abnormal architectural and cytologic features (dysplastic nevus). **D,** Early melanoma, or melanoma in radial growth phase (large dark cells in epidermis). **E,** Advanced melanoma (vertical growth phase) with malignant spread into the dermis and vessels. The risk of malignant transformation of any single dysplastic nevus is small, but appears to be higher than that of typical nevi.