Table 25-2 Representative Variant Forms of Melanocytic Nevi

Nevus Variant	Diagnostic Architectural Features	Cytologic Features	Clinical Significance
Congenital nevus	Deep dermal and sometimes subcutaneous growth around adnexa, neurovascular bundles, and blood vessel walls	Identical to ordinary acquired nevi	Present at birth; large variants have increased melanoma risk
Blue nevus	Non-nested dermal infiltration, often with associated fibrosis	Highly dendritic, heavily pigmented nevus cells	Black-blue nodule; often confused with melanoma clinically
Spindle and epithelioid cell nevus (Spitz nevus)	Fascicular growth	Large, plump cells with pink-blue cytoplasm; fusiform cells	Common in children; red-pink nodule; often confused with hemangioma clinically
Halo nevus	Lymphocytic infiltration surrounding nevus cells	Identical to ordinary acquired nevi	Host immune response against nevus cells and surrounding normal melanocytes
Dysplastic nevus	Coalescent intraepidermal nests	Cytologic atypia	Potential marker or precursor of melanoma

combination thereof. The *café au lait* spots seen in neurofibromatosis (Chapter 27) are similar to freckles histologically, but differ in that they are larger, arise independently of sun exposure, and contain aggregated melanosomes (macromelanosomes), which can be seen within the cytoplasm of melanocytes in electron micrographs.

MORPHOLOGY

Freckles are generally small (1 to several mm in diameter), tan-red or light brown macules that appear after sun exposure. Once present, freckles fade and darken in a cyclic fashion during winter and summer, respectively. This is not because of changes in the number of melanocytes, but in the degree of pigmentation. Hyperpigmentation of freckles results from increased amounts of melanin pigment within basal keratinocytes. Associated melanocytes may be slightly enlarged but are normal in density.

Lentigo

The term lentigo (plural, lentigines) refers to a common benign localized hyperplasia of melanocytes occurring at all ages, but often initiated in infancy and childhood. There is no sex or racial predilection, and the cause and pathogenesis are unknown.

MORPHOLOGY

Lentigines may involve mucous membranes as well as the skin and consist of small (5 to 10 mm across), oval, tan-brown macules or patches. Unlike freckles, lentigines do not darken when exposed to sunlight. The essential histologic feature is **linear (nonnested) melanocytic hyperplasia** restricted to the cell layer immediately above the basement membrane that produces a hyperpigmented basal cell layer. So characteristic is this pattern that the term *lentiginous* is used to describe similar cellular proliferations within the basal cell layer in melanocytic tumors, such as in lentiginous nevi and in certain melanomas (termed *acral lentiginous melanomas*). Elongation and thinning of the rete ridges are also commonly seen in a lentigo.

Melanocytic Nevus (Pigmented Nevus, Mole)

Melanocytic nevi (known colloquially as moles) are common benign neoplasms caused in most cases by acquired activating mutations in components of the Ras signaling pathway. Most of us have at least a few "moles" and probably regard them as mundane and uninteresting. However, in truth moles (or melanocytic nevi) are diverse, dynamic, and biologically fascinating neoplasms. There are numerous subtypes of melanocytic nevi that are distinguished based on their clinical and histologic features; Table 25-2 provides a summary of salient features of some commonly encountered forms. Acquired melanocytic nevi are the most common type and are found in virtually all individuals.

Pathogenesis. Proof that nevi are neoplasms comes from studies showing that many have acquired mutations that lead to constitutive activation of NRAS or the serine/threonine kinase BRAF, which lies immediately downstream of RAS (described in Chapter 7 and later under Melanoma). Given that RAS signals have potent transforming activity and are thought to have key roles in many full-blown cancers, it is reasonable to ask why nevi only rarely give rise to melanomas. One answer appears to lie in the phenomenon referred to as oncogene-induced senescence. Expression of either activated RAS or BRAF in normal human melanocytes causes only a limited period of proliferation that is followed by a permanent growth arrest mediated by the accumulation of p16/INK4a, a potent inhibitor of several cyclin-dependent kinases, including CDK4 and CDK6 (Chapter 7). This protective response is disrupted in melanoma and some precursor lesions that give rise to melanoma.

MORPHOLOGY

Common acquired melanocytic nevi are tan to brown, uniformly pigmented, small (usually less than 6 mm across), relatively flat macules or elevated papules with well-defined, rounded borders (Figs. 25-2*A* and 25-3*A*). They may become more prominent during pregnancy, indicating a degree of hormone sensitivity. Melanocytic nevi are thought to progress through a series of morphologic changes over time. The earliest lesions are believed to be **junctional nevi**, which consist of aggregates or nests of round cells that grow along the dermoepidermal junction (Fig. 25-2*B*). Nuclei of nevus cells are uniform and rounded in contour, contain inconspicuous nucleoli, and show little or no mitotic activity. Eventually, most junctional nevi grow into the underlying dermis as nests or cords of cells to form **compound nevi** (Fig. 25-3*B*). In older lesions the epidermal nests may be lost entirely to form pure **intradermal nevi.**