represents yet another mechanism of unleashing RAS signaling.

- *Mutations that activate telomerase.* Reactivation of telomerase, the enzyme activity that preserves telomeres and protects cells from senescence, has long been known to be important in cancer (Chapter 7), but how this occurs has been mysterious. Recently, sequencing of sporadic melanomas identified mutations in the promoter of *TERT*, the gene that encodes the catalytic subunit of telomerase, in roughly 70% of tumors, making *TERT* the most commonly mutated gene yet identified in this cancer. As might be anticipated, the mutations increase *TERT* expression, suggesting that they act as an antidote to senescence. The *TERT* promoter mutations create new binding sites for Ets family transcription factors, which are known to be up-regulated by BRAF signaling, providing a mechanistic link between these two oncogenic events. These findings strongly suggest that mutations that turn on telomerase have a key role in the development of most melanomas.

MORPHOLOGY

Unlike benign nevi, melanomas show striking **variations in color**, appearing in shades of black, brown, red, dark blue, and gray (Fig. 25-8*A*). On occasion, zones of white or flesh-colored hypopigmentation also appear, sometimes due to focal regression of the tumor. **The borders of melanomas are irregular and often notched**, unlike the smooth, round, and uniform borders of melanocytic nevi.

Central to understanding the progression of melanoma is the concept of radial and vertical growth phases. **Radial growth** describes the horizontal spread of melanoma within the epidermis and superficial dermis (Fig. 25-8*B*). During this initial stage

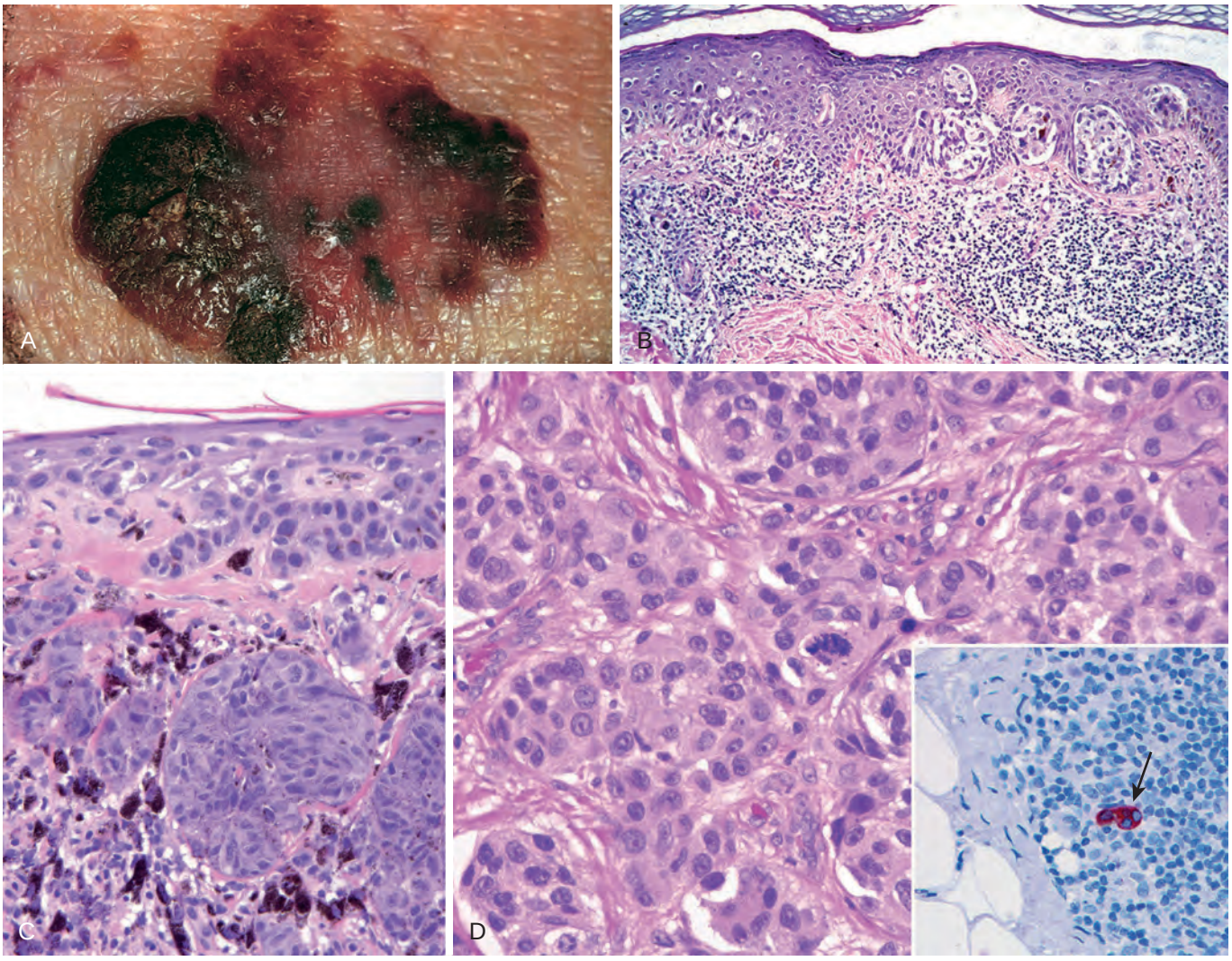

Figure 25-8 Melanoma. **A,** Typical lesions are irregular in contour and pigmentation. Macular areas correlate with the radial growth phase, while raised areas correspond to nodular aggregates of malignant cells in vertical growth phase. **B,** Radial growth phase, showing irregular nested and single-cell growth of melanoma cells within the epidermis and an underlying inflammatory response within the dermis. **C,** Vertical growth phase, demonstrating nodular aggregates of infiltrating cells. **D,** High-power view of melanoma cells. The *inset* shows a sentinel lymph node with a tiny cluster of melanoma cells *(arrow)* staining for the melanocytic marker HMB-45. Even small numbers of malignant cells in a draining lymph node may confer a worse prognosis.