vitiligo-like leukoderma seen in patients with systemic sclerosis has a clinical resemblance to idiopathic vitiligo that has begun to repigment as a result of treatment; that is, perifollicular macules of normal pigmentation are seen within areas of depigmentation. The basis of this leukoderma is unknown; there is no evidence of inflammation in areas of involvement, but it can resolve if the underlying connective tissue disease becomes inactive. In contrast to idiopathic vitiligo, melanoma-associated leukoderma often begins on the trunk, and its appearance, if spontaneous, should prompt a search for metastatic disease. It is also seen in patients undergoing immunotherapy for melanoma, including ipilimumab, with cytotoxic T lymphocytes presumably recognizing cell surface antigens common to melanoma cells and melanocytes, and is associated with a greater likelihood of a clinical response.

There are two systemic disorders (neurocristopathies) that may have the cutaneous findings of piebaldism (Table 72-9). They are *Shah-Waardenburg syndrome* and *Waardenburg syndrome*. A possible explanation for both disorders is an abnormal embryonic migration or survival of two neural crest–derived elements, one of them being melanocytes and the other myenteric ganglion cells (leading to Hirschsprung disease in Shah-Waardenburg syndrome) or auditory nerve cells (Waardenburg syndrome). The latter syndrome is characterized by congenital sensorineural hearing loss, dystopia canthorum (lateral displacement of the inner canthi but normal interpupillary distance), heterochromic irises, and a broad nasal root, in addition to the piebaldism. The facial dysmorphism can be explained by the neural crest origin of the connective tissues of the head and neck. Patients with Waardenburg syndrome have been shown to have mutations in four genes, including *PAX-3* and *MITF*, all of which encode DNA-binding proteins, whereas patients with Hirschsprung disease plus white spotting have mutations in one of three genes—endothelin 3, endothelin B receptor, and *SOX-10*.

In *tuberous sclerosis*, the earliest cutaneous sign is macular hypomelanosis, referred to as an ash leaf spot. These lesions are often present at birth and are usually multiple; however, detection may require Wood's lamp examination, especially in fair-skinned individuals. The pigment within them is reduced, but not absent. The average size is 1–3 cm, and the common shapes are polygonal and lance-ovate. Examination of the patient for additional cutaneous signs such as multiple angiofibromas of the face (adenoma sebaceum), ungual and gingival fibromas, fibrous plaques of the forehead, and connective tissue nevi (shagreen patches) is recommended. It is important to remember that an ash leaf spot on the scalp will result in a circumscribed patch of lightly pigmented hair. Internal manifestations include seizures, mental retardation, central nervous system (CNS) and retinal hamartomas, pulmonary lymphangioleiomyomatosis (women), renal angiomyolipomas, and cardiac rhabdomyomas. The latter can be detected in up to 60% of children (<18 years) with tuberous sclerosis by echocardiography.

Nevus depigmentosus is a stable, well-circumscribed hypomelanosis that is present at birth. There is usually a single oval or rectangular lesion, but when there are multiple lesions, the possibility of tuberous sclerosis needs to be considered. In *linear nevoid hypopigmentation*, a term that is replacing hypomelanosis of Ito and segmental or systematized nevus depigmentosus, streaks and swirls of hypopigmentation are observed. Up to a third of patients in a tertiary care setting had associated abnormalities involving the musculoskeletal system (asymmetry), the CNS (seizures and mental retardation), and the eyes (strabismus and hypertelorism). Chromosomal mosaicism has been detected in these patients, lending support to the hypothesis that the cutaneous pattern is the result of the migration of two clones of primordial melanocytes, each with a different pigment potential.

Localized areas of decreased pigmentation are commonly seen as a result of cutaneous inflammation (Table 72-10) and have been observed in the skin overlying active lesions of sarcoidosis (see "Papulonodular Skin Lesions," below) as well as in CTCL. Cutaneous infections also present as disorders of hypopigmentation, and in *tuberculoid leprosy*, there are a few asymmetric patches of hypomelanosis that have associated anesthesia, anhidrosis, and alopecia. Biopsy specimens of the palpable border show dermal granulomas that contain rare, if any, *Mycobacterium leprae* organisms.

HYPERPIGMENTATION

(Table 72-11) Disorders of hyperpigmentation are also divided into two groups—localized and diffuse. The localized forms are due to an epidermal alteration, a proliferation of melanocytes, or an increase in pigment production. Both seborrheic keratoses and acanthosis nigricans belong to the first group. *Seborrheic keratoses* are common lesions, but in one rare clinical setting, they are a sign of systemic disease, and that setting is the sudden appearance of multiple lesions, often with an inflammatory base and in association with acrochordons (skin tags) and acanthosis nigricans. This is termed the *sign of Leser-Trélat* and alerts the clinician to search for an internal malignancy. *Acanthosis nigricans* can also be a reflection of an internal malignancy, most commonly of the gastrointestinal tract, and it appears as velvety hyperpigmentation, primarily in flexural areas. However, in the majority of patients, acanthosis nigricans is associated with obesity and insulin resistance, although it may be a reflection of an endocrinopathy such as acromegaly, Cushing's syndrome, polycystic ovary syndrome, or insulin-resistant diabetes mellitus (type A, type B, and lipodystrophic forms).

A proliferation of melanocytes results in the following pigmented lesions: *lentigo*, *melanocytic nevus*, and *melanoma* (Chap. 105). In an adult, the majority of lentigines are related to sun exposure, which explains their distribution. However, in the Peutz-Jeghers and LEOPARD (*l*entigines; *E*CG abnormalities, primarily conduction defects; *o*cular hypertelorism; *p*ulmonary stenosis and subaortic valvular stenosis; *a*bnormal genitalia [cryptorchidism, hypospadias]; *r*etardation of growth; and *d*eafness [sensorineural]) syndromes, lentigines do serve as a clue to systemic disease. In *LEOPARD syndrome*, hundreds of lentigines develop during childhood and are scattered over the entire surface of the body. The lentigines in patients with *Peutz-Jeghers syndrome* are located primarily around the nose and mouth, on the hands and feet, and within the oral cavity. While the pigmented macules on the face may fade with age, the oral lesions persist. However, similar intraoral lesions are also seen in Addison's disease, in Laugier-Hunziker syndrome (no internal manifestations), and as a normal finding in darkly pigmented individuals. Patients with this autosomal dominant syndrome (due to mutations in a novel serine threonine kinase gene) have multiple benign polyps of the gastrointestinal tract, testicular or ovarian tumors, and an increased risk of developing gastrointestinal (primarily colon) and pancreatic cancers.

In the *Carney complex,* numerous lentigines are also seen, but they are in association with cardiac myxomas. This autosomal dominant disorder is also known as the *LAMB* (*l*entigines, *a*trial myxomas, *m*ucocutaneous myxomas, and *b*lue nevi) *syndrome* or *NAME* (*n*evi, *a*trial myxoma, *m*yxoid neurofibroma, and *e*phelides [freckles]) *syndrome*. These patients can also have evidence of endocrine overactivity in the form of Cushing's syndrome (pigmented nodular adrenocortical disease) and acromegaly.

The third type of localized hyperpigmentation is due to a local increase in pigment production, and it includes *ephelides* and *café au lait macules* (CALMs). While a single CALM can be seen in up to 10% of the normal population, the presence of multiple or large-sized CALMs raises the possibility of an associated genodermatosis, e.g., neurofibromatosis (NF) or McCune-Albright syndrome. *CALMs* are flat, uniformly brown in color (usually two shades darker than uninvolved skin), and can vary in size from 0.5–12 cm. Approximately 80–90% of adult patients with *type I NF* will have six or more CALMs measuring ≥1.5 cm in diameter. Additional findings are discussed in the section on neurofibromas (see "Papulonodular Skin Lesions," below). In comparison with NF, the CALMs in patients with *McCune-Albright syndrome* (polyostotic fibrous dysplasia with precocious puberty in females due to mosaicism for an activating mutation in a G protein [$G_s\alpha$] gene) are usually larger, are more irregular in outline, and tend to respect the midline.

In incontinentia pigmenti, dyskeratosis congenita, and bleomycin pigmentation, the areas of localized hyperpigmentation form a pattern—swirled in the first, reticulated in the second, and flagellate in the third. In *dyskeratosis congenita*, atrophic reticulated