ABSTRACT. Melanocytes are pigment-producing cells derived from the neural crest. These specialized exocrine cells produce melanin, which is packaged and dispersed to neighboring keratinocytes in organelles called melanosomes. Within the melanocyte, tyrosine is converted to dopa, and then dopaquinone via the bifunctional enzyme tyrosinase. Dopaquinone is oxidized further to form the pigment melanin. Each epidermal melanocyte secretes melanosomes to approximately 36 adjacent keratinocytes, forming an epidermal melanin unit. Genetically programmed constitutive skin color is determined by the amount of cutaneous melanin pigmentation.

The common mole or acquired melanocytic nevus (AMN) is a collection of nevomelanocytes grouped into nests located in the epidermis (junctional nevus), dermis (dermal nevus), or both (compound nevus). It is hypothesized that nevomelanocytes are derived from either epi-
dermal melanoblasts or dermal Schwann cells. AMN first appear at ~1 year of age, peaking in number during the second or third decades of life, and disappearing by the seventh to ninth decades. AMN may appear suddenly or become more prominent in response to sun exposure, cortisone and corticotropin, blistering diseases, chemotherapy, immunosuppression, and other factors that are not well-defined. Reports of AMN increasing in size and darkening in color during puberty and pregnancy have been reported but not quantitated systematically. *Pediatrics* 1999;104:1042–1045; melanocytes, keratinocytes, acquired melanocytic nevi.

**ABBREVIATIONS.** AMN, acquired melanocytic nevus; CMN, congenital melanocytic nevus.

The incidence of malignant melanoma is increasing within the population. Risk factors for the development of cutaneous melanoma include: 1) a new or changing mole; 2) adulthood (15 years or older); 3) family history of melanoma; 4) dysplastic nevus syndrome; 5) large congenital nevus (>20 cm); 6) several nevi; 7) white race; 8) severe childhood sunburns; and 9) immunosuppression.

**BIOLOGY OF MELANOCYTES**

Melanin, the skin pigment that is the primary determinant of skin color, is produced by melanocytes, which make up ~15% of the basal layer of sun-exposed skin and 6% of unexposed skin. In its primary role of absorbing ultraviolet light, melanin is deposited in keratinocytes of the interfollicular epidermis, thus protecting the genome of the dividing basal keratinocytes and melanocytes. The melanosomes are located supranuclearly in the melanocytes before being distributed throughout the cell to provide maximal protection from damaging ultraviolet light. Melanin also has been shown to be a free oxygen–radical scavenger, protecting the metabolically active keratinocyte from any free radicals that are generated.

Embryologically, melanocytes are cells that emigrate from the lateral ridges of the neural plate as the ridges join to form the neural tube. Using HMB-45, a monoclonal antibody, melanoblasts have been identified in fetal skin at ~7 weeks of gestation.1 At 15 to 16 weeks of gestation, melanin synthesis begins, followed shortly by melanosome transfer at ~20 weeks.2 The cells then migrate to the basal layer of the dermal–epidermal junction.

One melanocyte provides pigment to approximately 36 keratinocytes, forming what is known as an epidermal melanin unit. The pigment is formed, packaged into vesicles, and transferred to keratinocytes via dendrites. The outcome of pigment transfer from melanocytes to keratinocytes differs among races. In black skin, melanosomes are dispersed individually, whereas in white skin, the melanosomes are in clusters with a surrounding membrane.3 This pattern of distribution affects the absorption and reflection of light, accounting for the major difference in skin color among the races.

Melanin production begins as one process that ends with two distinct options for completing the pathway. What is known as a premelanosome is formed in the smooth endoplasmic reticulum, whereas the rough endoplasmic reticulum is producing the copper-containing oxidase known as tyrosinase. Final maturation occurs in the Golgi apparatus as tyrosinase is transported by coated vesicles to the premelanosome. There it catalyzes the conversion of tyrosine to dopa and then dopaquinone, which is oxidized further to form the pigment melanin.

Eumelanin is a black–brown pigment, whereas pheomelanins are pigments that contribute primarily to hair color. The biochemical pathway for the production of pheomelanin varies somewhat to yield a more yellow–red color.

**BIOLOGY OF PIGMENTED NEVI**

Melanotic nevi, or moles, are quite common. Usually brown, they vary in shape and size, and can be found anywhere on the skin. A pigmented nevus is a benign proliferation of cells with melanocytic differentiation. These cells can be formed from either pre-existing melanocytes or cells called nevomelanocytes. The origin of the nevomelanocyte is the nevomelanoblast. Embryologically, nevomelanoblasts are melanocytes within the neural crest.1 The cells migrate to the epidermis and dermis, where they differentiate into nevomelanocytes. One hypothesis is that the nevomelanoblasts in the upper dermis and epidermis are derived from epidermal melanocytes, whereas those in the lower dermis are from Schwann cells of nerves. For a melanocyte to express a normal morphology, it must be located in the basement membrane zone. Recent studies show that when melanocytes migrate to other locations, they lose dendrite expression, decrease production of melanin and enzymes such as tyrosinase, and morphologically begin to resemble Schwann cells.4 These cells become round instead of dendritic, and store rather than transfer the melanin they produce. Melanocytic nevi and nevomelanocytic nevi are of importance because histologically, they can resemble melanomas, or malignant proliferation of cells with melanocytic lineage. It is important to distinguish both with certainty for the purpose of appropriate treatment.

**CLASSIFICATION OF NEVI**

The common mole or AMN consists of nests of melanocytes, as opposed to normal melanocytes placed singly along the basement membrane. These nests are divided for classification purposes into three groups by location. Those along the dermal–epidermal junction are called junctional nevi. Those in the dermal–epidermal junction and the dermis are compound nevi. Those only in the papillary and reticular dermis are intradermal nevi. Nevi increase in frequency with age until middle age, when they reach a plateau in frequency and begin to migrate lower in the dermis and involute spontaneously.

Nevi also are classified by the age at which they occur. Congenital nevi are present within the first 6 months of life. Acquired nevi arise later in life. This distinction is significant because congenital nevi are
apparently more likely to become malignant than their acquired counterparts.5

A third classification of nevi, particularly with regard to congenital nevi, is based on the size of the lesion. Small nevi are <1.5 cm in diameter, medium-size nevi range from 1.5 to 19.9 cm in diameter, and giant nevi are ≥20 cm in diameter.6

Histologically, nevi are classified generally as having atypical cells, as in dysplastic nevi, or normal cytology, as in the common nevus.

Any additional features associated with the nevus, such as other prevalent cell types or tissue types, also are used to further distinguish among types of nevi. One example is the halo nevus. Clinically, halo nevi are described as a pigmented macule with surrounding depigmentation. Histologically, they have a lymphocytic infiltrate.

Clearly, many variants of nevi exist, but this discussion centers primarily on the clinical morphology of the various types of AMN. There are five types of AMN based on gross appearance. They can be flat, slightly elevated, papillomatous, dome-shaped, or pedunculated, and are associated more commonly with phenotypes such as blue or green eye color and tor pili muscles. Clinically, they can be <1.5 cm for the smallest type. Alternatively, a giant congenital nevus can cover the scalp, a limb, or the entire back. Giant nevi have an increased risk of melanoma and have been associated with meningeal melanocytosis.9

Another variant of the melanocytic nevus is the blue nevus. Distinguished by its typical bluish–black or blue–gray color, it consists of cells deep in the dermis. This nevus owes its unique color to the abundance of melanin transmitting from the deep location offset by the color of the normal surrounding skin.

FACTORS AFFECTING GROWTH OF NEVI

It has been suggested that physiologic conditions, such as pregnancy, puberty, or systemic corticosteroids,10 and human growth hormone therapy11 produce changes in nevi. However, it is not clear exactly how much change can be attributed to these conditions. Sun exposure and blistering disease also can cause nevi to become increasingly pigmented. Sun can induce the junctional component to proliferate. If one of these factors is suspected to account for pigment change in a particular nevus, all nevi should be affected. If only one nevus has changed, a biopsy should be performed to check for malignant transformation. Recent change of any parameter of a nevus, such as color, shape, or size, should be evaluated, as should any new onset of pain, pruritus, ulceration, or bleeding. A biopsy of the lesion is the recommended measure at this time for diagnostic and possible therapeutic purposes.

MELANOMA

Melanoma is of increasing concern, as its frequency within the population is increasing. Skin examinations are important, especially for patients with risk factors. Some common risk factors are
Melanocytic Nevi in Children Treated With Growth Hormone

David Wyatt, MD

ABSTRACT. There is concern that growth hormone (GH) therapy may influence the growth of melanocytic nevi. In a review of the experience of the National Cooperative Growth Study, we found no excess of skin cancer in children who were treated with GH. We also reviewed our experience in 90 children with GH deficiency and 24 with Turner syndrome. We found no difference in the nevi count between control subjects and children with GH deficiency, even after many years of GH therapy. Nor was there any relation between the duration of therapy and the nevi count. Children with Turner syndrome had more nevi, but there was no relation to the duration of GH therapy. These findings and the absence of a greater frequency of skin cancer in acromegaly are reassuring. It is unlikely that GH therapy has a significant influence on nevi count or the risk of skin cancer.

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From the Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin.

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Address correspondence to Dr Wyatt, Department of Pediatrics, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226.

E-mail: dtwyatt@mcw.edu

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