ming the study period. The subjects with BA x-rays received more GH injections and had more frequent visits documented in the NCGS database than did the cohort with no BA measurements. This would suggest that NCGS investigators find it of value to obtain BA measurements in most subjects. Although the slightly improved height SDS and height age outcomes during treatment of the subjects with BA readings might be attributed to their older age and pubertal status, there still remains the suggestion that somehow radiographs are used by the NCGS investigators to maximize GH therapy. Because final height data were not yet available, it is possible that by assessing skeletal maturation at frequent intervals, GH treatment might be extended longer, other agents (such as sex steroids or luteinizing releasing hormone analogues) might be added more often and in a more efficacious manner, or, because of more frequent visits, subjects might be more compliant with treatment regimens, all which would ultimately improve the outcome of the cohort followed with BA radiographs.

The conclusion of this study, that it is important to follow BA x-rays for the pediatric endocrinologist, is supported by the survey of GH treatment practices that was conducted by Wyatt et al6 in 1993 and reported in 1995. Of the 251 pediatric endocrinologists surveyed, BA determinations were used by 60% of them to determine who should start GH treatment, and BA delay was ranked 5 of 14 on the scale of auxologic and laboratory criteria used to initiate GH. These findings were similar to the percentages of those who ranked obtaining a BA determination as an important criterion to discontinue GH. Again, 61% of those surveyed stated that BA was important, and they ranked it 5 of 14 in criteria used to stop GH therapy.

There is no doubt that assessment of skeletal maturation is at the foundation of research performed evaluating GH treatment.7–9 Although BA radiographs are used to distinguish benefit from harm during studies of GH efficacy in novel clinical situations and in innovative therapeutic regimens, what role BA radiographs play during routine clinical practice has been questioned. These data from the NCGS support the notion that not only do pediatric endocrinologists find it of value to obtain BA determinations at enrollment, but that they also find it beneficial to assess serially skeletal development. BA assessment should be considered an important component of the follow-up of patients treated with GH.

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The Physiology of Pigmented Nevi

Jay Kincannon, MD, and Christine Boutzale, BS

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 quantitatively. *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.

**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 $< 1.5 \text{ cm}$ in diameter, medium-size nevi range from 1.5 to 19.9 cm in diameter, and giant nevi are $\geq 20 \text{ cm}$ 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 blond, light brown, or red hair.\(^7,8\)

Children are more likely to have nevi if their mother has numerous nevi or if they have a family history of melanoma.\(^8\) AMN show a fairly consistent progression of growth. Initially, the cells typically proliferate at the dermal–epidermal junction. With time, they begin also to involve the upper dermis. This compound stage eventually will lose its junctional component, leaving only an interdermal nevus in the final stage.

Clinically, these nevi are round, brown, or black, flat, or slightly raised. The skin creases are preserved. A striated pattern in the skin may be noted, which reflects the histologic picture of melanocytes involving the rete ridges. Cytologically, the cells are fairly bland.

Clinically, compound nevi also are similar to junctional nevi in that they are of uniform color and often are described as macules. They can also present as verrucal papules. Histologically, compound nevi consist of nests of melanocytes as well, but are located in the dermis and are either spindled or neurally differentiated. Also consistent with junctional nevi is the appearance of the epidermis, with slightly increased numbers of enlarged melanocytes between nests of nevomelanocytes. In nevi that are completely benign, the junctional component usually extends to approximately the same depth as the dermal component.

Infradermal nevi, as the name implies, are located in the dermis and have no junctional component. Clinically, they appear the least pigmented of the three classes because the deeper into the dermis the melanocytes are clustered, the less pigment is seen at the surface of the skin. These cells are smaller than their more superficial counterparts, have less intracellular pigment, and display rare mitotic figures. If any pleomorphism is observed, the clinician should initiate additional investigation because this could indicate developing melanoma.

Congenital melanocytic nevi (CMN) are present in 1% to 2% of newborns at birth. The clinical appearance of CMN can be varied, but typically appear as a sharply demarcated plaque with or without coarse hairs. They are light or dark brown and are solitary in 95% of cases (except with giant CMN, in which satellite nevi exist). The cells in this nevus type often are clustered at the dermal–epidermal junction. These cells go deeper into the dermis than do acquired nevi, and therefore tend to have more neural differentiation. The cells of congenital nevi also are more likely to invade blood vessels, nerves, and erector pili muscles. Clinically, they can be $< 1.5 \text{ cm}$ 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 meningial 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. Three types have been described. They are the cellular blue nevus, the common blue nevus, and the combined blue nevus-nevomelanocytic nevus.

The common blue nevus is smaller, less raised, and less locally aggressive than is the cellular variety. Approximately half of the common blue nevi are solitary and located on the dorsal aspects of the hands and feet. The cellular nevus more often are found on the sacrum or buttock and can be associated with benign lymph node metastasis. The compound blue nevi are often first thought to be melanomas because of their often irregular, elevated surface. Blue nevi are most commonly acquired, albeit at an early age. As with other melanocytites situated deep within the dermis, the cells of the blue nevus resemble Schwann cells.

**FACTORS AFFECTING GROWTH OF NEVI**

It has been suggested that physiologic conditions, such as pregnancy, puberty, or systemic corticosteroids,\(^10\) and human growth hormone therapy\(^11\) 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
adulthood, a new or changing mole, numerous nevi, light skin color, a family history of melanoma, dysplastic nevus syndrome, giant congenital nevus, severe childhood sunburns, and immunosuppression.15

An important characteristic of melanoma is its overall asymmetry in contrast to the typical symmetry of benign lesions. Also, the size of the lesion is important to note. The larger a pigmented lesion is over 5 or 6 mm across, the more likely it is to display atypia in its cells. Both the length and width of lesions should be measured. Melanoma usually has a more irregular, notched, or scalloped border. Raised lesions and lesions with increased surface markings as viewed by tangential lighting are at increased risk for malignant transformation.

CONCLUSION

Many factors influence the clinical appearance of AMN, including sun exposure, pregnancy, puberty, and immunosuppression. Growth hormone has been implicated as a possible factor contributing to changes seen in AMN; however, there are no current data suggesting that growth hormone is at all involved in malignant transformation of these nevi into melanoma. At present, the most effective means of prevention and early detection of melanoma include routine skin examination, sun avoidance during peak hours, and use of sunscreen.

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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. Pediatrics 1999;104:1045–1049; acquired melanocytic nevi, growth hormone, melanoma, Noonan syndrome, Turner syndrome.

ABBREVIATIONS. GH, growth hormone; AMN, acquired melanocytic nevi; GHD, growth hormone deficiency; NCGS, National Cooperative Growth Study; SCI, skin color index.

Growth hormone (GH) therapy has been reported to have a reversible stimulatory effect on the size of acquired melanocytic nevi (AMN) in children with isolated GH deficiency (GHD) and with Turner syndrome.1 Recent reviews of safety issues in the use of GH have reflected the concern that it may influence mole growth.2,3 However, increased AMN count rather than size is a known risk factor for melanoma.4 Furthermore, acromegaly, a condition of chronic GH excess, is not associated with an increased risk of skin cancer.5–13 It is believed generally that the number of AMN is greater in Turner syndrome,14 but there does not appear to be an increased risk of melanoma in this condition either. It is not known whether GH ther-
The Physiology of Pigmented Nevi
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Jay Kincannon and Christine Boutzale
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