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Editor

Nevogenesis

Mechanisms and Clinical Implications of Nevus Development

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Preface

The theories of how nevi develop including hypotheses regarding mechanisms of inception, growth, and ultimate senescence have received surprisingly little attention since Paul Gerson Unna originally proposed the "Abtropfung" theory of nevogenesis over 100 years ago. For almost a century this theory of nevogenesis was accepted as truth and remained uncontested. Over the past few decades some researchers, based on newly acquired observations from histopathology and embryogenesis, have questioned the validity of the "abtropfung" theory in favor of the "hochsteigerung" theory. In essence the "hochsteigerung" theory is the reverse of the "abtropfung" theory with the former stating that nevus cells migrate from the dermis to the epidermis and the latter stating that nevus cells migrate from the epidermis to the dermis. However, new insights grained from the epidemiology of nevi, cross-sectional and longitudinal study of nevi, dermoscopy and confocal microscopy investigation of nevi, as well as the cellular and molecular study of nevi bring into question the aforementioned theories. The focus of this book is to help elucidate what is currently known about nevogenesis, help stimulate thought in this field by bringing into question some of the established nevogenesis theories while at the same time providing possible alternative pathways explaining the life cycle of nevi, and encourage further research in the field of nevogenesis. Since nevi are associated with an increased risk of melanoma, understanding nevogenesis may help to unravel some of the mysteries of melanomagenesis.

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Nevogenesis: Changing Theories

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Mark E. Burnett, Alon Scope,
and Ashfaq A. Marghoob

Introduction

The life cycle of most individual melanocytic nevi is shorter than the lifetime of the individual harboring them [1–3]. We are born with few or no nevi and enter old age with few or no nevi, while nevi development occurs between these two time periods (Fig. 1.1) [2–8]. This conception of nevogenesis appears relatively straightforward from a cross-sectional perspective, when only total nevus counts are considered.

However, longitudinal follow-up of individual nevi has elucidated important details about the inception and growth, as well as the disappearance of nevi. The development of new nevi is a common event in youth; in fact, 75 % of children between ages 11 and 14 (5th to 8th grade) develop new nevi [9]. Moreover, approximately 30 % of adults over the age of 20 and 16 % of individuals over the age of 45 develop new nevi over a follow-up period of 49 months (unpublished data). Because cross-sectional studies have shown that nevus counts decrease with older age, nevus involution was thought to occur late in life. Yet, longitudinal dermoscopic follow-up of individual nevi shows that, in fact, 28 % of children between the ages of 11 and 14 also have nevi that disappear [9]. Thus, younger age groups exhibit higher rates of new nevi forming than nevi regressing, resulting in a net increase in nevus counts [9]. The opposite appears to be the case in adult life with more nevi regressing than new nevi forming, resulting in a net decrease of total nevus counts. As a corollary, events in the life cycle of a single melanocytic nevus, namely, inception and growth, followed by senescence and, finally, involution, may occur at any age [10–13].

How do nevi form and develop? Until recently, two competing theories have held sway over thought regarding inception and development of an individual nevus. *Abtropfung* [14], or downward migration, has been the predominant textbook teaching regarding nevogenesis for decades but was challenged more recently by a competing theory of upward migration, known as *Hochsteigerung* [15]. These theories imply that variation in the morphologic appearance of nevi may represent different stages in the life cycle of a nevus. However, again, longitudinal in vivo observation studies using dermoscopy [16] and reflectance confocal

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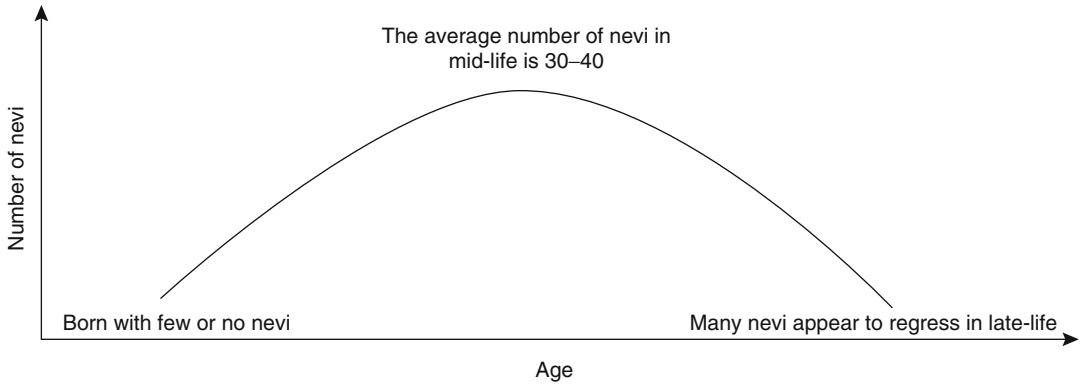

Fig. 1.1 Total nevus counts take place along an arc-like trajectory over the course of one's lifetime. Usually individuals are born with no nevi, develop multiple nevi by midlife, and then lose their nevi in old age. However, the inception, growth, and involution of individual nevi can occur at any age. In other words, a child can develop a new nevus that grows and involutes within a few years. This process can also occur in adults

microscopy [17] suggest that nevi may, in fact, be developing along distinct pathways. As such, an alternate stem-cell-based theory has been postulated [12, 18] that precursor stem cells incur mutations and/or are subject to local influences which ultimately result in the development of different nevus subtypes. In addition, emerging evidence has suggested that different types of nevi may convey different risks of melanoma development [19].

Thus, understanding how nevi arise, what determines their growth, what leads to their growth arrest or senescence, and their eventual involution, will help shed light on the genesis of melanoma. To this end, the purpose of this review is to summarize pivotal studies which have prompted a reevaluation of widely held theories of nevogenesis. Specifically, we will explain the prevailing theories of *Abtropfung* [14] and *Hochsteigerung* [15], then present data from recent studies that challenge these paradigms. Finally, we will integrate these insights into contemporary hypotheses of the life cycle of nevi.

Challenge to Traditional Theories of Nevogenesis

Abtropfung and Hochsteigerung Theories of Unidirectional Melanocyte Migration

Two opposing nevogenesis theories have prevailed for decades. These theories attempt to describe the natural evolution of nevi as a process of unidirectional melanocytic migration. The first theory, put forth in 1893 by Paul Gerson Unna, is referred to as *Abtropfung*, literally "dropping off" [14]. According to Unna's theory, proliferation of melanocytes in nevi develops from within the epidermis and migrates downward into the dermis over time (Fig. 1.2). This implies that the developmental stages in the life history of nevi begin with the formation of junctional proliferations which move progressively down through the dermoepidermal junction (DEJ), becoming compound nevi that include both junctional and dermal components; these nevi later complete the migration into the dermis, losing their junctional component, thereby forming dermal nevi. Early cross-sectional studies [20] provided support for this theory by reporting a predominance of dermal nevi among older individuals. Once the nevus was dermal, it could remain as such indefinitely, develop Schwannian features (i.e., become a so-called neurotized nevus), or disappear by involuting. Current textbook [21–23] dogma reinforces this position, teaching that nevus cell maturation takes place along a trajectory of downward migration, starting in the epidermis and culminating in the dermis.

Almost a century later, in 1984, Stewart F. Cramer postulated a second competing theory referred to as *Hochsteigerung*, literally "upward climbing" [15]. Based on an expanding body of embryogenetic knowledge demonstrating the

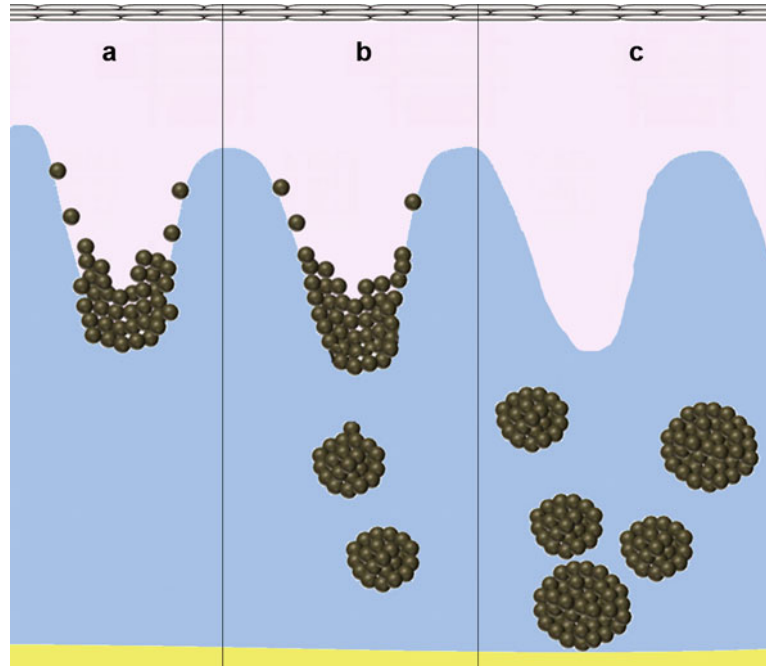

Fig. 1.2 In 1893, Paul G. Unna proposed the concept of *Abtropfung*, according to which melanocytic nevus cells first develop and proliferate in the epidermis and subsequently drop off to the dermis over time (adapted from: Unna [14]). This process would lead to formation of junctional nevi with a dermoscopic reticular pattern (**a**), followed by compound (**b**), and finally dermal nevi with a dermoscopic globular pattern (**c**)

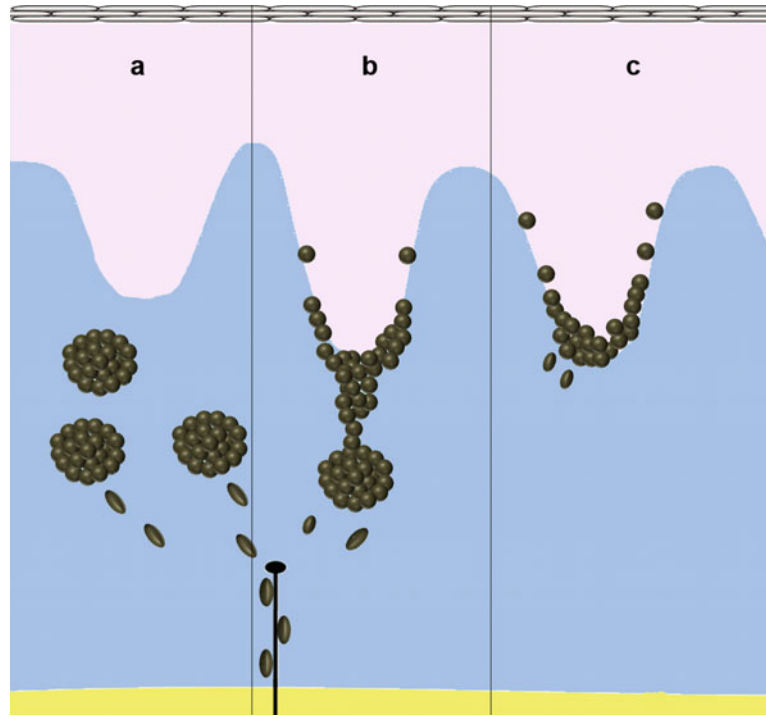

Fig. 1.3 In 1984, Stewart F. Cramer put forth the theory of *Hochsteigerung*, which posited that inception and growth of nevi resulted from an upward migration of nevus cells along individual nerve fibers ascending through the dermis. This process would lead to the formation of dermal nevi with a dermoscopic globular pattern (**a**), followed by compound (**b**), and finally junctional nevi with a reticular dermoscopic pattern (**c**) (adapted from: Cramer [15])

origin of melanocytes from the neural crest, Cramer posited that inception and growth of nevi recapitulates embryogenesis, resulting in the upward migration of nevomelanocytes along individual nerve fibers which ascend through the dermis (Fig. 1.3). According to Cramer's theory, it would follow that migration into the dermis, followed by proliferation, results in an intradermal nevus just as ascent into the epidermis would result in a junctional nevus. Migration of some melanocytes into the epidermis, while other melanocytes fail in reaching this destination and

remain in the dermis, would result in a compound nevus. This process is believed to occur both during fetal development and, importantly, in the maintenance of normal skin tissue throughout postnatal life. Therefore, it stands to reason that a progression from one nevus type to another (e.g., from dermal to compound to junctional nevus) should be observable by conducting cross-sectional histopathologic analysis of nevus type by age.

The *Abtropfung* and *Hochsteigerung* theories of nevogenesis are not the only theories proposed for how nevi evolve. A two-compartment theory of nevogenesis, originally hypothesized by Masson in 1951 [24], has recently found traction in embryologic work performed in chick embryos [25]. This theory holds that melanocytes in the epidermis give rise to the junctional and superficial dermal portions of nevi, while Schwann cells are responsible for giving rise to nevic components residing in the deeper, reticular portion of the dermis. Specifically, intraepidermal melanocytic precursors may move downward while intradermal cells may move upward, thereby encompassing melanocyte migration schemes which parallel both *Abtropfung* and *Hochsteigerung*, respectively. The direction of nevomelanocytic precursor cell migration in nevogenesis is not readily discernible, but a recent embryological study has provided further support for the idea that cells in separate compartments contribute differentially to nevus subtypes [25].

Data Challenging the Unidirectional Melanocyte Migration Theories

Evidence from Cross-Sectional Histopathologic Studies

Unna's theory of *Abtropfung* implies that junctional nevi would be the most prevalent nevus pattern among youth. This would be followed by the appearance of compound nevi later in life. Finally, dermal nevi should predominate in later life. In contrast, Cramer's theory of *Hochsteigerung* suggests a predominance of dermal nevi in youth followed by a concurrent decrease in dermal nevi and increase in junctional nevi in later life. Indeed, our understanding to date of the prevalence of nevi type by age group has been largely underpinned by data gathered from cross-sectional studies.

In an attempt to correlate nevus type with age, Worret and Burgdorf published a histopathologic study in which over 3,500 melanocytic nevi from patients of all ages were evaluated [26]. Congenital melanocytic nevi (CMN) were excluded. The researchers found that compound nevi were very common in children and became progressively less common with age, while dermal nevi remained stable in all age groups. Furthermore, junctional nevi were not found in any of the children under the age of 10. Aside from this exception, the incidence of junctional nevi remained relatively stable across all age groups.

Another histopathologic study, conducted by Westhafer et al., also provided important data regarding the prevalence of nevi type by age. The researchers examined biopsy reports from 1,645 melanocytic lesions excised over the course of 1 year at a major medical center [27]. Using these data, they determined the age distributions from a total of 184 junctional nevi. Their findings demonstrate that while junctional nevi occur at all ages, peak incidence occurs between the third and fifth decades of life.

In both histopathologic studies, the findings regarding age as a function of nevus type speaks against the theory of *Abtropfung*, where one might expect a predominance of junctional nevi in youth followed by decreasing incidence of such nevi with increasing age. Rather, the aforementioned studies found the opposite to be true. These observations could, in fact, be more congruent with the *Hochsteigerung* theory or with the stem-cell-based theory that was eluded to earlier.

Evidence from Dermoscopic Studies

The rationale for dermoscopic study of nevogenesis hinges on the relationships between the structures visualized dermatoscopically (in vivo gross pathology) and the underlying histopathologic findings (microscopic pathology). These relationships provide a framework to study and better

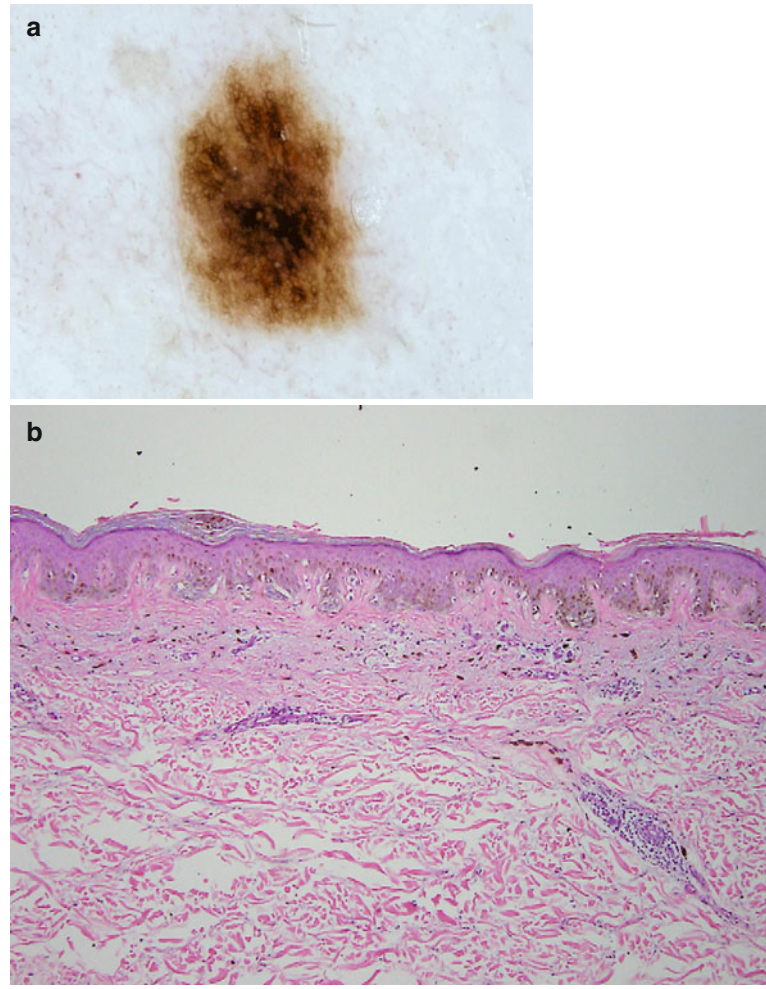

Fig. 1.4 Junctional reticular patterns correlate histologically with melanin in melanocytes and keratinocytes along the rete ridges of the DEJ

understand the in vivo evolution of melanocytes in nevi over time. Examples of these histopathologic correlates are well illustrated by both globular and reticular dermoscopic patterns.

Reticular dermoscopic patterns correlate histopathologically with melanin in melanocytes and keratinocytes along the rete ridges of the DEJ [28–31] (Fig. 1.4). Nevi displaying a reticular pattern represent either junctional or compound nevi [32] (Figs. 1.5 and 1.6). Globules seen under dermoscopy reflect intradermal and, at times, junctional nests of melanocytes representing either intradermal or compound nevi (Figs. 1.7 and 1.8). For example, central globules that are seen dermoscopically in compound nevi are mostly correlated to dermal nests. While globules usually correspond to intradermal melanocytic nests, it is important to acknowledge that some small light brown or tan-colored globules may, in fact, correspond to junctional nests in growing nevi; for instance, the peripheral globules seen dermoscopically in growing dysplastic nevi are typically junctional nests. Additionally, the color of globules seen under dermoscopy is influenced by the amount of melanin present in the melanocytic nests, and also by the anatomic depth of the nests. Thus, the color of globules can provide clues as to the location of the melanocytic nests; for example, blue-gray globules are indicative of melanocytic nests residing in the reticular dermis, the blue-gray color being the reflection of Tyndall light scattering of short-wavelength blue light [33].

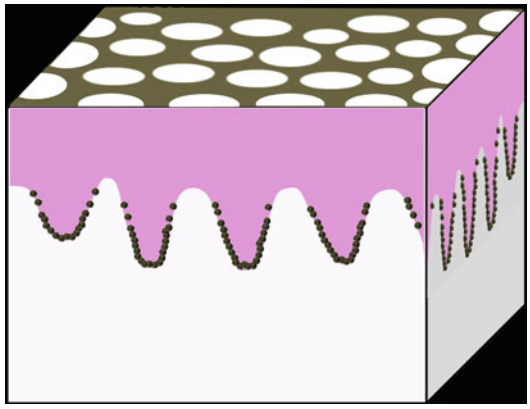

Fig. 1.5 Pigmented network represents melanin in melanocytes and keratinocytes along the dermo-epidermal junction. When viewed dermatoscopically, per unit area, the rete ridges contain more melanin than the suprapapillary plate. Thus, the "egg-crate"-like architecture of the dermoepidermal interface produces the reticular pattern, in which the rete ridges appear as dark lines and the suprapapillary plate as holes

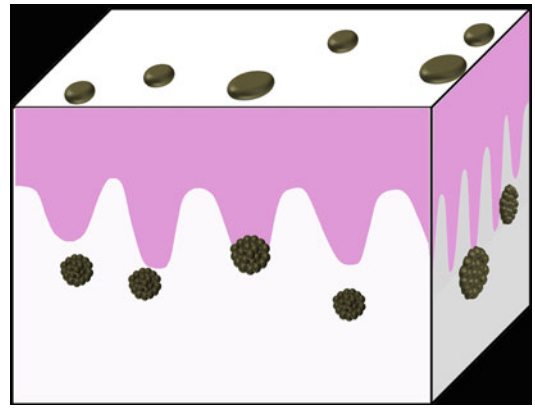

Fig. 1.7 Although globules seen under dermoscopy may reflect pigmented nevomelanocytic nests in the dermis or at the dermoepidermal junction (DEJ), most of the time they correspond to dermal nests and are seen in intradermal or compound nevi

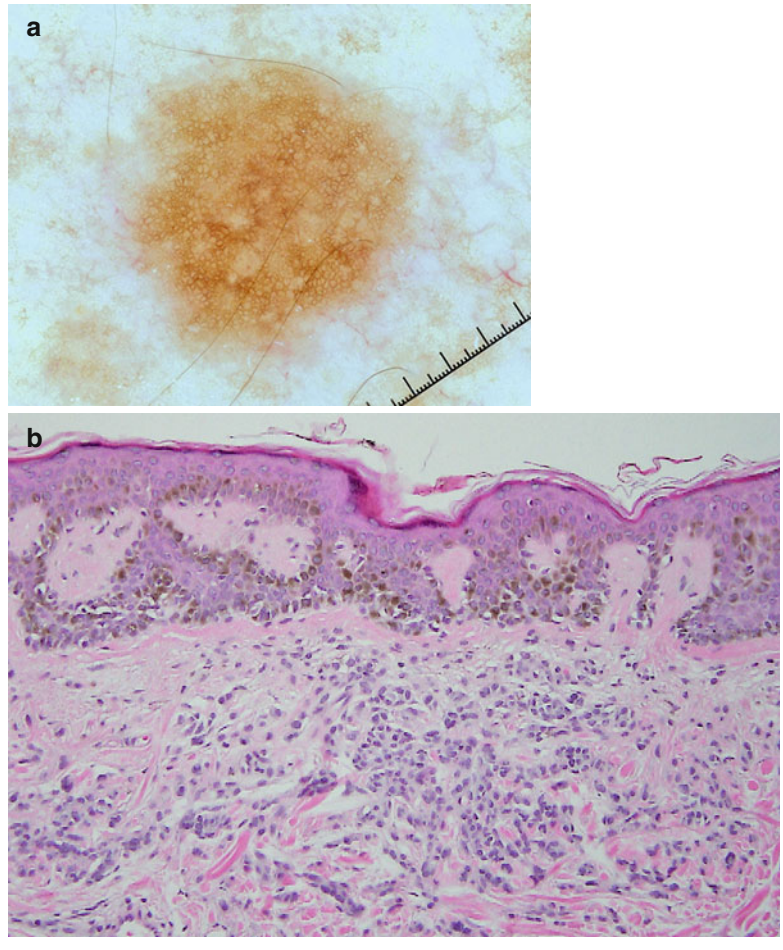

Fig. 1.6 Some reticular nevi are not pure junctional nevi but are actually histologically compound nevi in which the globules are not visible on dermoscopy. Compound nevi correlate histologically with melanin in nevo melanocytes present both at the rete ridges of the DEJ and in the dermis