

Review Article

The Nail Bed, Part I. The Normal Nail Bed Matrix, Stem Cells, Distal Motion and Anatomy

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Submitted: 25 November 2013

Accepted: 28 December 2013

Published: 31 December 2013

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Abstract

The nail bed (NB) has its own matrix that originates from distinctive stem cells. The nail bed matrix stem cells (NBMSC) lie immediately distal to the nail plate (NP) matrix cells and are covered by the keratogenous zone of the most distal NPM (LUNULA). The undivided NBMS cells move distally along the NB basement membrane toward the hyponychium; differentiating and keratinizing at various locations, acting as transit amplifying cells and forming a thin layer of NB corneocytes that contact the overlying onychocytes of the NP, homologous to the inner hair root sheath. At the contact point, the NB corneocytes express CarcinoEmbryonic Antigen (CEA), a glycoprotein-modulating adherence which is also found in hair follicles and tumors. Only when both the NP and the NB are normal do they synchronously move distally. The normal NB keratinizes, expressing keratin K-5 and K-17 without keratohyaline granules. However, during trauma or disease states, it reverts to keratinization with orthokeratosis and expresses K-10, as seen in developmental times. Psoriasis is the only exception. Nail Bed epidermis can express hyperplasia and giant cells in some diseases. A characteristic of the NB is its epidermal/dermal units (E/D units), starting at the NBM and ending at the hyponychium. They are longitudinal and parallel dermal plates overlaid by NB epidermis. The width of a lesion is determined by the number of E/D units involved.

ABBREVIATIONS

CEA: Carcino Embryonic Antigen; E/D: Epidermal/Dermal Unit; HYP: Hyponychium; KZ: Keratogenous Zone; LNF: Lateral Nail Fold; LUN: Lunula; NB: Nail Bed; PNF: Proximal Nail Fold; NBM: Nail Bed Matrix; NP: Nail Plate; NPM: Nail Plate Matrix

INTRODUCTION

Nail investigators have never really believed that there is a nail bed matrix (NBM), separate from the nail plate matrix (NPM). Perhaps this unawareness is because its discovery was described in 1980 and published in a book (1) rather than a peer review journal, which could have made it more easily accessible through search engines. Clinicians have assumed that, the distal movement of the nail bed was generated by the distal movement (growing) of the nail plate (NP) and not by the NB's own matrix cells. The NBM cells have been identified in humans, monkeys and rat. The reason for this updated review is to describe: 1- the independent NB stem cells and matrix, 2- the NB's epidermis/dermis unit, 3- the NB epidermal movement, 4- the NB lack of contribution to the NP, 5- the NB homology to the hair root sheath, 6- the NB's keratinization/differentiation behavior in health versus disease and 7- the close relationship of the NP onychocytes and the NB corneocytes.

Components of the normal human nail unit

Figure 1 is a diagrammatic drawing of the nail unit components and visually illustrates the location of the nail bed matrix (NBM) and its position beneath the distal

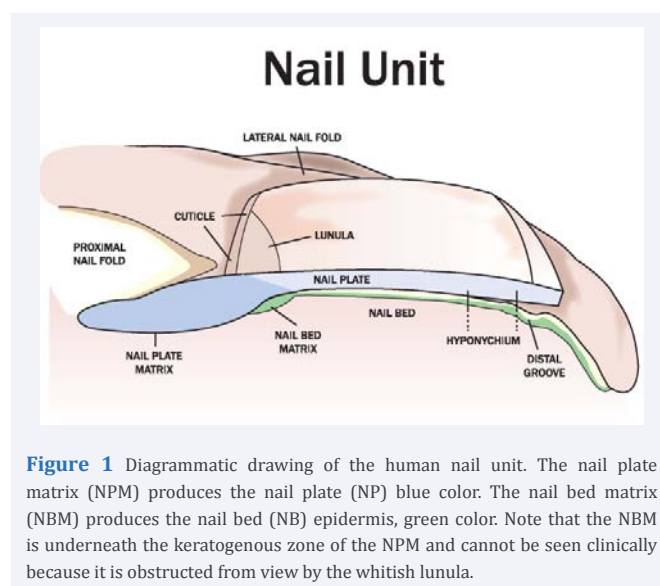


Figure 1 Diagrammatic drawing of the human nail unit. The nail plate matrix (NPM) produces the nail plate (NP) blue color. The nail bed matrix (NBM) produces the nail bed (NB) epidermis, green color. Note that the NBM is underneath the keratogenous zone of the NPM and cannot be seen clinically because it is obstructed from view by the whitish lunula.

keratogenous zone of the NPM (lunula) The lunula is created by light reflected off the nuclei in the keratogenous zone. The Nail Bed matrix also exists in monkeys and other mammals (rats). Figure 2, Human finger, longitudinal section, showing all the components of the nail unit. Figure 3 is a higher magnification showing that the nail plate matrix (NPM) produces the nail plate (NP) and the nail bed matrix (NBM) produces the nail bed (NB). The NBM cells are situated immediately distal to the NPM cells which produce the keratogenous zone cells that cover the NBM cells. Again seen as a separate entity on rats, Figure 4, a histological sections of a rat finger showing the NBMatrix by auto radiographic techniques as a distinct structure,(1). All three different species humans, primates and lesser mammals have a NBM situated in the same location.

Nail bed matrix stem cells

Evidence is provided, by the selective nuclear labeling of rat and monkey nail units [1], wherein the existences of NB matrix (NBM) cells are unrelated to the NP matrix (NPM) cells. The NB matrix is located (double headed arrow) distal to the lunula, Figure 5-A1. Higher magnification of the NBM, Figure 5-A2, shows a cluster of heavily labeled cells (double headed arrow) distal to the NPM and tucked under the keratogenous zone of the distal lunula (arrow down). These cells are interpreted as NB stem cells, making up the NB matrix (NBM). Note that there is no nuclear labeling in the rest of the NB, (double arrows up). These results clearly display that the NBMS cells are separate from the NPM and that there is a homology between the NB and the inner root sheath of the hair follicle.

Distal NB movement of the stem cells

Most clinicians do not recognize that the normal NB is a moving epidermis similar to the ear canal [2], vagina [3] and intestinal villi [4]. In the auto-radiographic study referred above [1], the courses of the NB Thymidine nuclear radio labeled cells were followed at 4 and 18 days after a single pulse. Four days later, the heavily labeled undivided NB cells were moving distally along the basement membrane, with no labeling distally (see Figure 5 B-1 and 5-B-2, arrows down). Note that the cells labeled in the NPM are forming the NP (curved diagonal arrow). The heavily labeled NBM cells do not contribute to the NP. Eighteen days later, Figure 5 C, some of the undivided heavily labeled ("transit

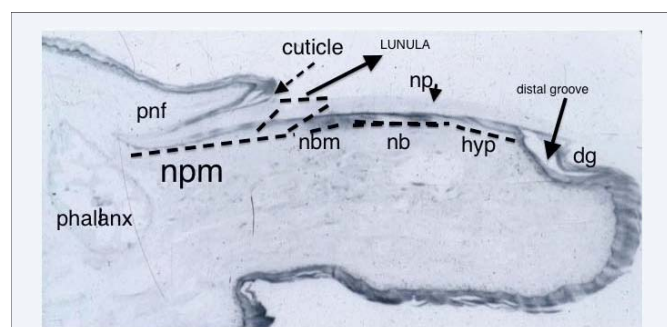


Figure 2 Human finger, longitudinal section. Showing actual nail unit components and the distal groove. Note that the NBM cannot be seen clinically because of the whitish lunula over it.

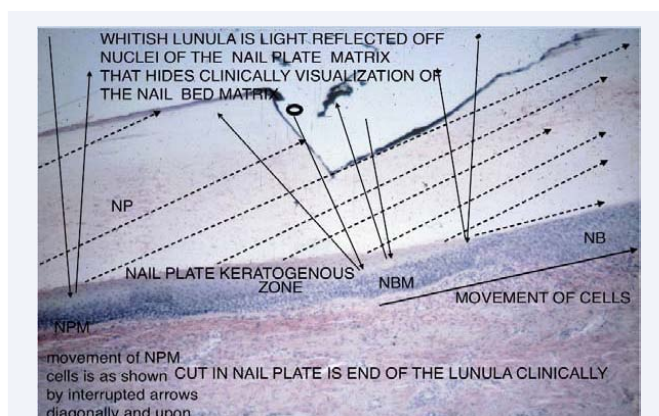


Figure 3 Human finger, higher magnification, longitudinal section, showing how the NPM cells produce the NP (interrupted diagonal arrows distally). The proximal areas produce the superficial portions of the NP, while the distal areas make the ventral portions of the NP (interrupted arrows diagonally). The NBM, not visibly clinically, because it is under the keratogenous zone of the most distal NPM. The retained nuclei, in this zone, reflects light and is clinically seen as the lunula (arrows up). The lunula then, blocks the visualization of the NBM. The cells of the NBM migrate over the basement membrane and produces the NB (long horizontal arrow) corneocytes. H and E X 36.

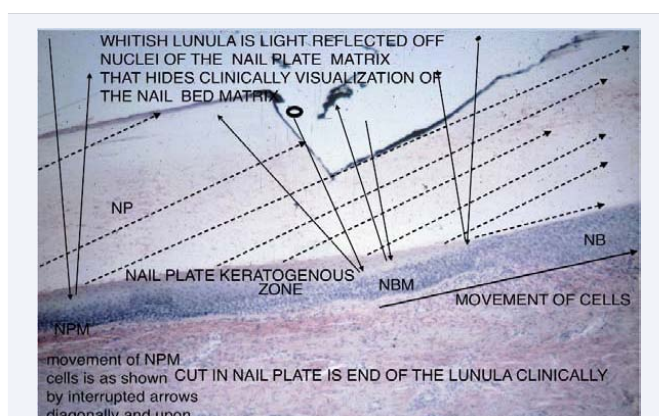


Figure 4 Rat fingernail unit. After 45 minutes of receiving titrated thymidine, observe that the nuclei have incorporated the radio-labeled nucleic acid into their nuclear DNA are very black (precipitated silver grains) in the NPM (large diagonal, with many smaller arrows) producing the nail plate (NP). The NP keratogenous zone (KZ) which extends beyond the proximal nail fold (PNF) is the whitish lunula (LU), seen clinically, (long arrow) proximally. The nail bed matrix (NBM) is a cluster of "darkly" nucleated cells separate from the NPM (four consecutive small arrows pointing distally) that are responsible for production the nail bed (NB). Note that there is no radioactive material uptake present in the NB nuclei distal to the NBM, (2 arrows up close together). H and E, X 22.

amplifying") NB cells have moved distally (arrows up) and have almost reached the hyponychium. Other NB cells have divided, differentiated, left the basement membrane and keratinized as they moved to the surface to become the corneocytes of the NB (arrows down). Larry Norton, utilizing auto-radiographic techniques, confirmed the movement of cells in the nail bed in human toes, [5].

Cellular proliferation studies using antibodies to Cyclin in human nail units; have shown that nail bed in its normal state expresses minimal cellular turnover in comparison to the NPM.

On the contrary, the NB expresses more epithelial activity in disease states. However, it never contributes to the NP [6].

Homology between the NB and the hair root sheath

Abundant literature documents the motion of stem cells in the hair bulge area and of the hair follicle in its normal cycle [7-9]. Figure 6 depicts the similarities between the nail and hair units in regards to the presence of stem cells, transit amplifying stem cells and their movement. In addition, the presence of the CEA within the internal root sheath of the hair [7-9], moves upwards toward the surface, as does the hair cortex, to which it is structurally in contact. The anatomic and developmental similarities of the NB and the inner root sheath of hair suggest a parallel evolutionary path, as does the hair cortex and the NP.

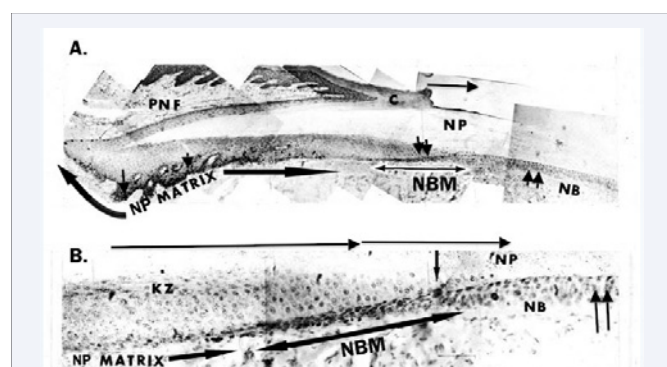


Figure 5a A1 – In this figure series, the movement of the radiolabeled thymidine will be followed up to 18 days. Monkey, finger; 45 minutes after the administration of 3H-thymidine. There is a heavy uptake of the radio labeled thymidine into the nuclei of the basal cells of the NP matrix (NPM) (separated small arrows down). Also, note the heavily tritium labeling of the NBM (double headed arrow) and (2 close together arrows down) under the keratogenous zone in the area of the lunula, (small arrow upper portion of figure pointing distally) . Note the absence of the radiolabel through the rest of the NB epidermis. H and E X 24. courtesy zaias (1). **A-2** – Higher magnification of the NBM area (double headed arrow), separate from the NPM. Note no nuclear labels distal to the NBM, H and E X 240. (courtesy zaias).

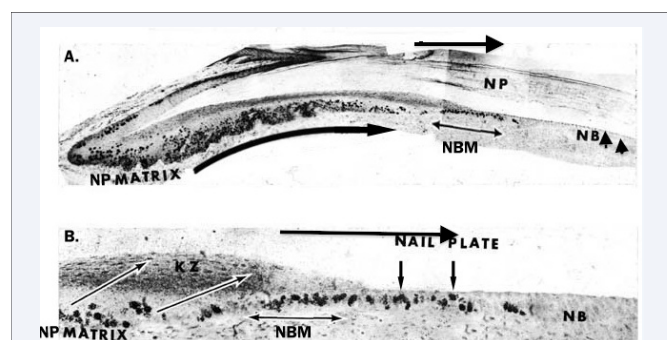


Figure 5b B-1 – Same as in fig 5-1, but 4 days later. Note that the NP matrix labels are cells becoming the onychocytes of the NP (two arrows diagonally up). The NB matrix (double headed arrow) shows little activity, a few nuclei, loaded with radio active thymidine are moving distally (two arrows down), while there is still no nuclear labels in the mature NB. H and E X24. (courtesy zaias). **B-2** – Higher magnification of the NBM , showing radiolabeled fully laden cells (undivided), moving along the basement membrane of the future NB epidermis, (arrows down), Hand E X 240. (courtesy zaias).



Figure 5c Same as in figs 5, but 18 days later. Note that, there are cells still radioactive laden that have migrated to the Hyponychium (arrows up) , while there are lighter (divided) labeled cells which have moved superiorly, toward the underside of the nail plate, (arrows down) toward the underside of the NP cells following the normal process of differentiation and keratinization of the NB. Hand E X 24. (courtesy zaias).

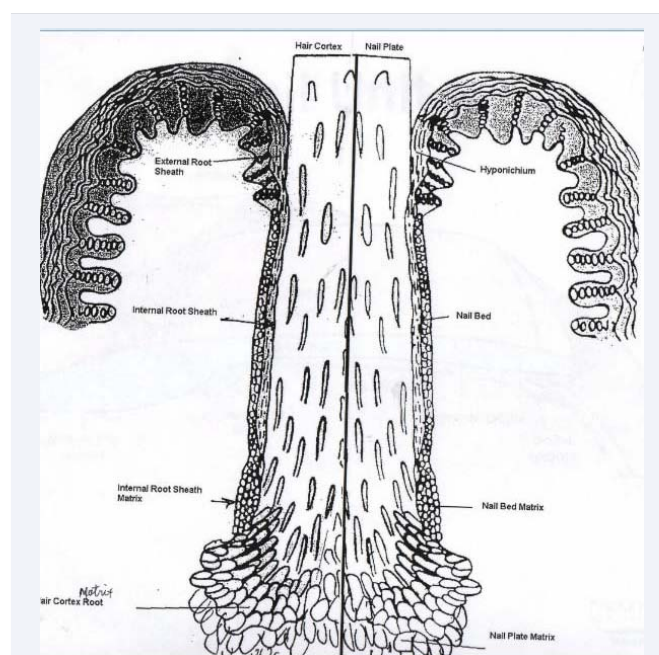


Figure 6 Diagrammatic drawing of the homology of the nail bed epidermis and the internal root sheath of the hair.

The normal NB (differentiation and keratinization) histology

The NB epidermis originates from the plantar and palmar embryonic skin. A review of the developmental process of the NB's differentiation and keratinization [10] will be useful. As the epidermal embryonic cells mature, near the tip of the digit, an area will develop that will be the future nail field (large arrow, separates the dorsum of finger skin from nail field 9 weeks in development the shorter is the future NB). Ten weeks in development, two additional structures develop. 1- Proximally, there is a wedge of stem cells penetrating the digit diagonally (large arrow Figure 7A). This will be the NP's primordial stem cells that will produce the future NP. Later in development this wedge will isolate tissue from the surface of the digit, above the NP primordium and create the future proximal nail fold at the dorsum of the digit's epidermis. 2- At the distal end of the dorsum of the finger, at the junction of the future NB hyponychium (HYP) and the palmar/

plantar skin, there is a structure termed the distal ridge (DR). The DR is the first zone of orthokeratosis (with a granular layer) keratinization. At fourteen weeks of development, Figure 7B, the orthokeratosis extends proximally and covers the surface of the digit (the future NB) up to the emerging NP. Thereafter, as the digit matures, the orthokeratosis (keratohyaline granular zone) of the NB appears to retreat distally, simultaneously as the NP grows distally, Figure 7C. Orthokeratosis disappears by 7-9 months in development, Figure 7D (arrows up) and is not expressed in the normal adult NB keratinization. Furthermore, all the genes available during embryonic times are capable of being expressed in adult life.

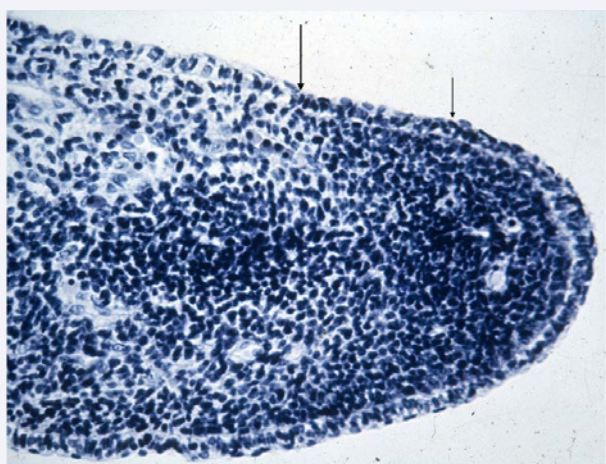


Figure 7a Developmental Histology of human finger nail at 9 weeks. All cells are still very undifferentiated, but there is sharply defined nail field between arrows down. Hand E X120. (courtesy Zaias).

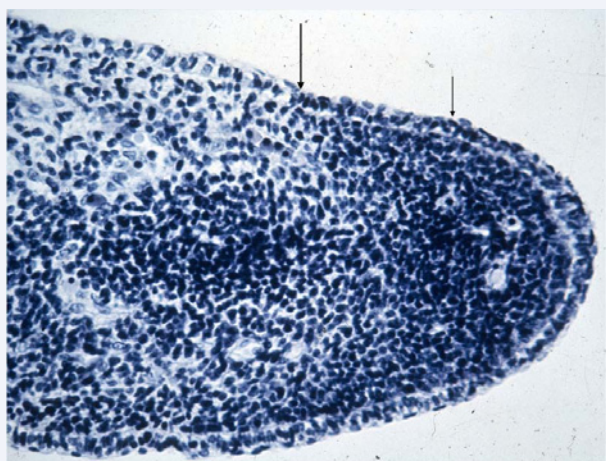


Figure 7b 13 week old embryo finger nail. The earlier nail field has differentiated and we see proximally where the proximal arrow, in figure 7A, a wedge of basophilic cells, the NP primordium, (NPP) (that will become the nail plate matrix), penetrating into the finger substance, creating the proximal nail fold (PNF). More distal, we see, under the first proximal horizontal arrow, the earliest distal portion of the NP Matrix or future lunula. The NB is exhibiting, for the first time, an epidermis that expresses orthokeratosis (keratin 15). Further distally the earliest distal groove is forming. The phalanx and the fingerprint pattern are forming. H and E, X 80 (courtesy Zaias).

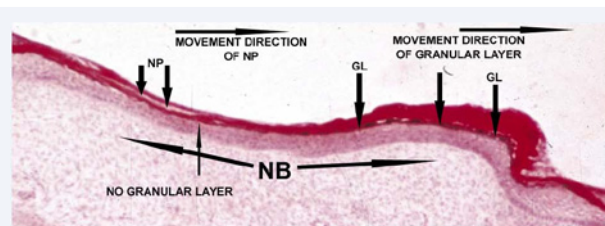


Figure 7c Human embryo finger at 20 weeks, clearly showing the orthokeratosis in the NB and HYP, which is retreating distally as the NP continues to move distally, (arrows down GL). The more proximal mature NB epidermis, that is under the NP (arrows down NP) is devoid of a granular layer and has already converted to the adult keratinization mode, without K15. H and E X 240. (courtesy Zaias).



Figure 7d A seven month embryo finger, showing an almost completely formed NP over an NB epidermis, now free of orthokeratosis. (arrows up). H and E X 12. (courtesy Zaias).

Normal gross anatomy

The normal adult nail bed anatomy consists of longitudinal, epidermal, down growing ridges, Figure 8 (NP avulsion show NB epidermal pattern – horizontal arrows). The lunula (large arrow head), overlays similar dermal plates forming epidermal down growths ridges, not rete, that fit in a tongue and groove fashion. Fig 8 is a diagrammatic drawing of the dermal topography of the NB. Figure 9 is a cross section of a normal adult NB, showing the Epidermal /Dermal unit (E/D) (outlined rectangle), which includes an epidermal plate and a dermal ridge. Disease or trauma may affect one or more units. Figure 10 depicts the possible appearance of the NB according to the cut of the histological section. The NB epidermis is derived from the epidermis of the tips of the fingers and toes and shares similarities to the fingerprint pattern [10].

The NB does not contribute to the NP

By autoradiography techniques [11] and the use of immunohistochemistry, [12], it was clearly shown that the NP is formed completely by the nail plate matrix (NPM) without any contribution from the NB.

Junction and attachment between NP onychocytes and NB corneocytes

In the absence of histological evidence of a “biologic lock” between the corneocytes of the NB and the onychocytes of the NP, Egawa, Kuroki, Inoues and Ono [13] described 14 normal subjects, in which they described carcinoembryonic antigen (CEA) glycoprotein which was produced by the corneocytes of the NB in contact with the onychocytes of the NP, Figure 11A (arrow). The histologic cut is depicted in Figure 10 B. The CEA is seen in the mid portion of the entire length of the NB corneocytes, which may serve a function of adhesion between the moving NP onychocytes, but not at the lateral areas of the NB, Figure 11B. The corneocytes of the NB meet the ventral onychocytes of the NP at an acute angle with the apex directed distally. This zone of contact is depicted in Figure 12, which is a diagram showing where the onychocytes of the lunula makes contact with the corneocytes of the NB. Note the CEA (in red color) on the surface of the NB corneocytes in contact with the NP onychocytes. These

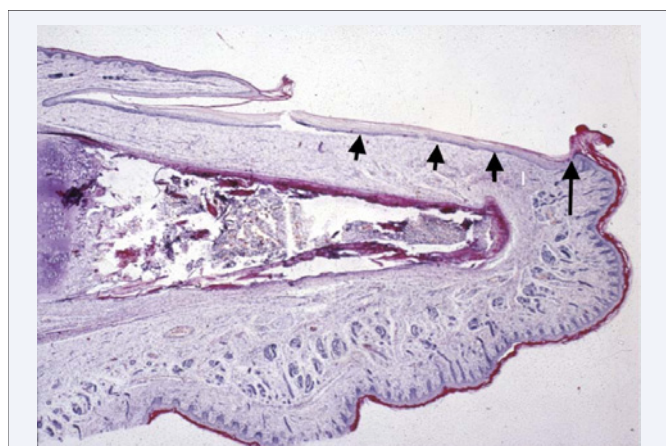


Figure 8 A human hallux with the NP removed to show the topography of the NB. Note the longitudinal ridges that appear parallel, which is seen in the fingerprint pattern of the volar skin (horizontal arrows). Lunula, thicker arrow.

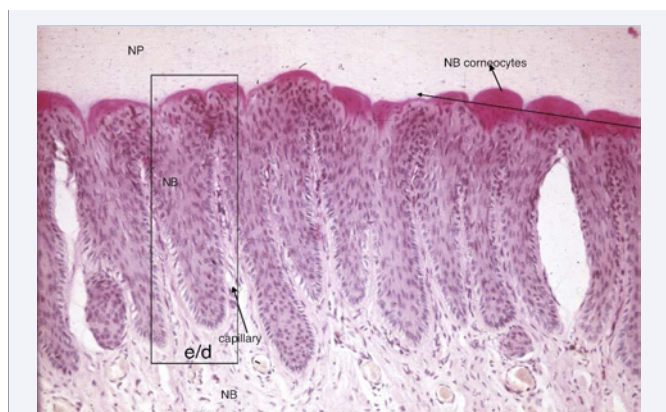


Figure 9 Human finger cross section of NB. Note the dermal ridges and epidermis fitting into the dermal ridges, in a tongue and groove fashion. The epidermal/dermal unit E/D (rectangle) unit. The width of the NB lesion is dependent upon on how many of these E/D units are involved. Clinically, Note the capillaries in the dermal ridges. The corneocytes of the NB ((long arrow) stain more intensely with Biebrich Scarlet than with Eosin. H and E X 26.

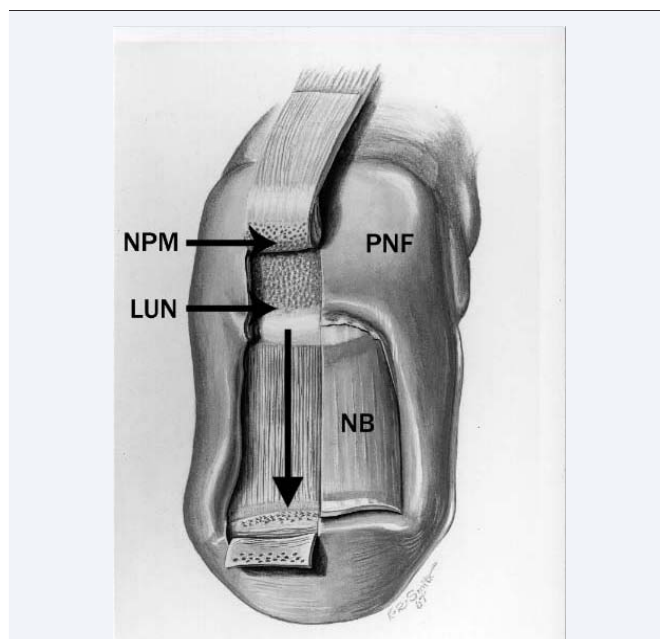


Figure 10 Diagrammatic drawing of the topography of the dermis in the nail bed.

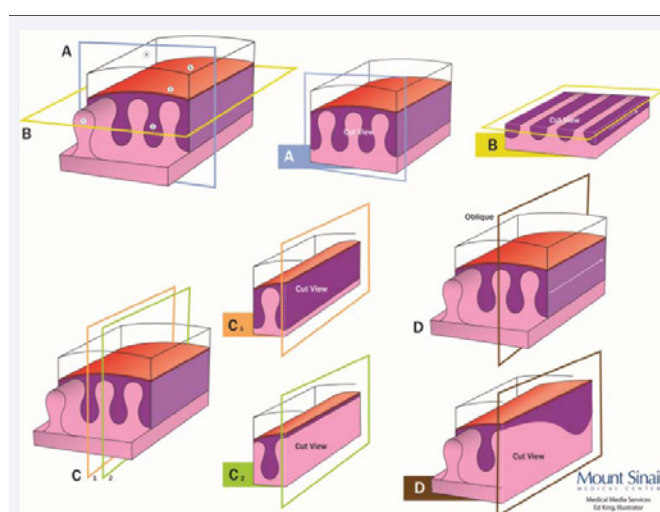


Figure 11 Diagrammatic drawings of potential views presented to the pathologist depending on the cut of the NB section.

investigators [13] also found CEA in the surfaces of the inner root sheath corneocytes of the hair follicle. Perhaps the CEA serves a similar function for the hair cortex cells and the inner root sheath cornified cells as does with the NB.

Synchronicity of the normal NB and NP movements

The fact that both the normal NP and NB move at the same speed was confirmed by auto radiographic techniques. A single pulse of cystine with dual radio for cytoplasm labeling of the NP was administered 5 days before the thymidine was pulsed for nuclear tagging of NB cells. Both of these labels remained at the same distance from each other through out the 18 day trajectory [13].

NB movements and minimal NB trauma

Figure 13 shows a finger with subungual hemorrhage and a mark on the NP. Both signs moved at the same pace during the time it took for the hemorrhage to clear distally. Another example of synchronous motion with minimal NB damage, is the splinter hemorrhage Figure 14A. It is often seen in patients with psoriasis [14] but also in a normal NB, where the hemorrhage runs along the dermal plates of the NB, Figure 14B. Notice that the small hemorrhage is completely encased in parakeratosis and will move distally with the NP.

NB synchronous distal motion with the NP in the successful treatment of Distal Subungual Onychomycosis (DSO)

In DSO, the fungus invades the NB from the hyponychium and the differentiation/keratinization process is altered to orthokeratosis. Clinically, the normally pinkish NB appears a grayish color, as seen thru the transparent NP. As the infection begins to resolve due to successful systemic antimycotic therapy, the non-infected NB emerges from its NBM without

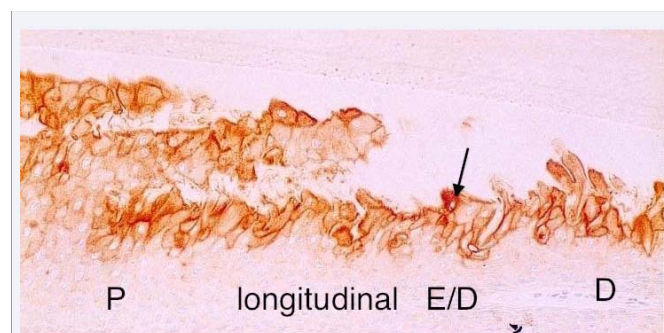


Figure 12a Human NB, midline and horizontal (superficial) cut thru the upper portions of the NB epidermis (see Figure 11 (B)). Note that the field shows 3 longitudinal NB epidermal ridges. The surfaces of the NB corneocytes stained orange with the CEA antigen. Immunohistochemistry X 420. (Courtesy of Egawa et al.).

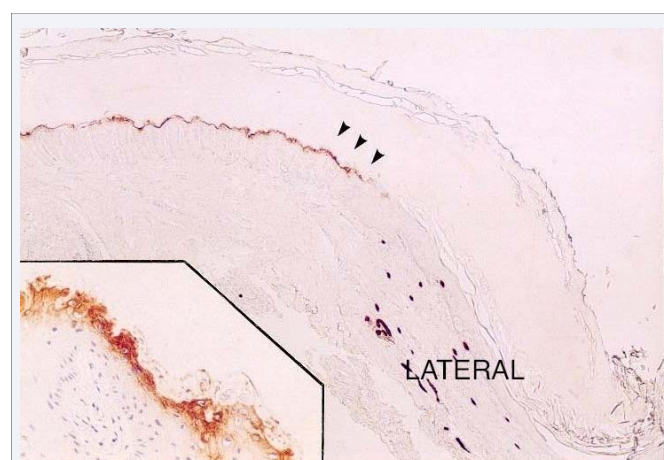


Figure 12b A human NB cross section, demonstrating the lack of CEA on the lateral borders of the NB. CEA Immunohistochemistry. X 420. (Courtesy Egawa et al.).

Cellular Dynamics of the Growing Nail Bed and Nail Plate as Revealed by Radioactive Labeling

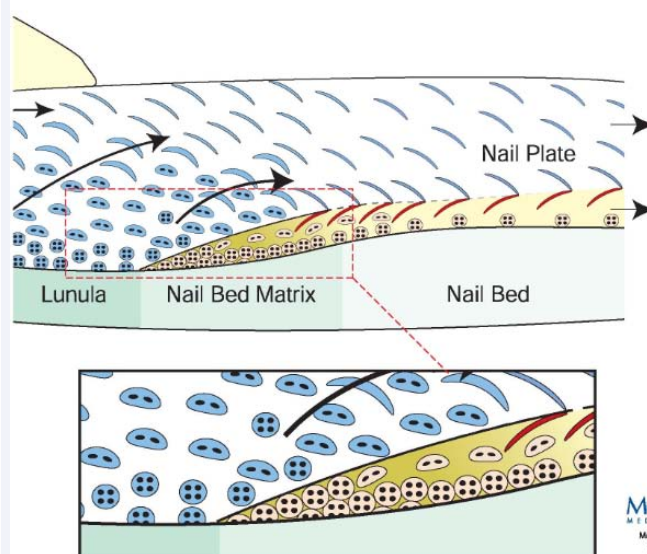


Figure 13 Diagrammatic drawing of the inter-phase between the onychocytes of the NP and the corneocytes of the NB as they make contact with each other at an acute angle. The red color indicates the presence of the CEA antibody on the NB corneocytes.

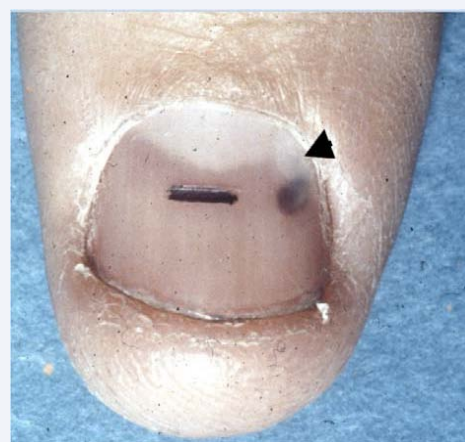


Figure 14 The photograph portrays minor NB trauma in which the NB hemorrhage and NP mark, will travel at the same rate.

orthokeratosis (gray color), and its normal pink color displaces the distally infected NB, Figure 15. This event is considered proof that the antimycotic chosen, is in fact, clinically effective [15].

Severe trauma to the NB makes the NB movement asynchronous with the np

When the NB is severely damaged, its distal motion is interrupted until the NB repair is completed, then it will begin moving at the same speed as the NP again. When the NP is avulsed, most of the NB epidermis is avulsed with the NP, but the NB and the NP matrices remain intact. In the adult with nail trauma, no activity is seen in the NB Matrix until the denuded NB epidermis

is replaced by epidermis from the lateral nail folds (LNF) which bridges the gap in the NB epidermis. During this time, the NB epidermis, derived from the LNF will express acanthosis and orthokeratosis. Once the entire NB is covered by epidermis the keratinization process switches back to non-orthokeratosis and the NB and NP move simultaneously again [16]. An example of severe trauma is shown in Figure 16, where a half of the NP is removed longitudinally, initiating the regeneration phenomenon. The NB and the NP are dotted with India ink and observed. This changes the differentiation/keratinization process from a non-orthokeratosis (not expressing K-10) to orthokeratosis (expressing keratin-10). The NB no longer moves distally and instead grows diagonally upwards. Notice the distal dots on the NB do not move until the newly formed NP abuts against them [17].

Keratin expression of the NB and nail unit

Identification of the keratin type of the different components of the normal nail unit was first described in 2000 [18] and confirmed in 2004 with normal and abnormal NB diseases [19]. Figure 17 shows a diagrammatic drawing in which each keratin



Figure 15a Image of a psoriatic patient with a splinter hemorrhage (arrow) in the hallux identical to Auspitz sign in the NB.

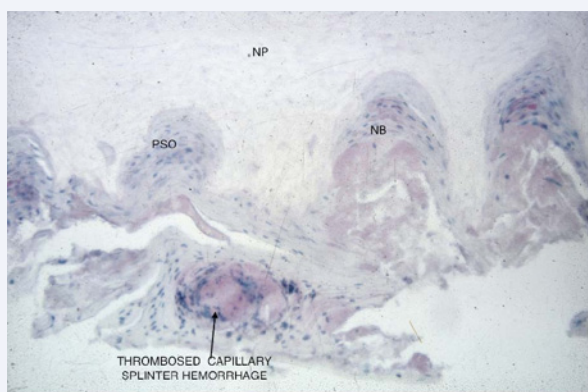


Figure 15b Cross section of Figure 15 (A). Splinter hemorrhage. Note the thrombosed capillary which has been sandwiched by the NB parakeratotic (psoriatic) corneocytes. H and E X 80.



Figure 16 Distal subungual onychomycosis, an infection of the NB corneocyte by *T. rubrum*. The NP has been marked to visualize the extent of the NB infection. With successful anti-mycotic treatment the marked nail plate and the normal NB will move at the same rate.

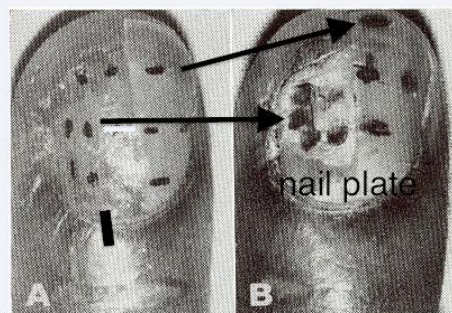


Figure 17 This figure shows that the severely injured NB does not have synchronous movement with the NP until the damage to the NB has been repaired. The finger nail plate was divided longitudinally into 2 halves. The left half of the nail plate (with the dark vertical line) in Fig A was manually avulsed, while the other side was left intact. A series of India ink spots were dotted on both sides (Fig A) and the movements of these dots were evaluated two weeks later (Fig B). In Fig B, all the dots moved distally without compression while the proximal dots moved distally with the newly developed NP. This image confirms that the NB does not move synchronously distally with the NP when severely injured or affected by some diseases. (Fig B was re-touched resulting in larger than normal size dots) (NZ NB Movements).

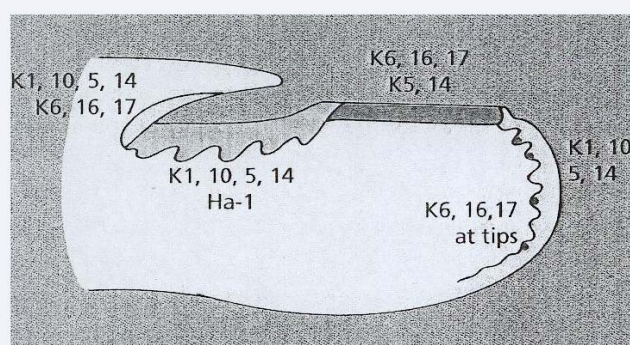


Figure 18 Diagrammatic drawing of the different keratin types in a normal nail unit. Notice the lack of K-10 which when expressed results in orthokeratosis. (courtesy de Berker et al).

type is identified dependent upon located. Observe that the NB favors K-5 and K-14 in the normal state. In contrast, K-10 is favored in abnormal NB states, with psoriasis being the exception. The NB never expresses any hard hair or nail plate keratin

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Cite this article

Zaias N (2014) The Nail Bed, Part I. The Normal Nail Bed Matrix, Stem Cells, Distal Motion and Anatomy. J Dermatolog Clin Res 2(1): 1008.