THE NAIL
IN HEALTH AND DISEASE

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Acknowledgments

In his air-conditioned office, Dr. G. Matoltsy spoke softly to the two of us, third-year residents in Miami. Marvin Lutzner and I had to choose subjects that could be studied presently and could lay the foundation for our future dermatologic academic careers. The choices, after the twenty-minute chat, were narrowed to two:

1. A reevaluation of the developmental stages of the skin adnexa, including ultrastructure, with the use of the newly installed prize of Dr. Harvey Blank's department, an RCA EM-38 electron microscope; and
2. The other subject, simply referred to as "THE NAIL."

I am indebted to Marvin Lutzner's lightning reply, choosing the adnexa that day in 1960, for starting my interest in "THE NAIL."

Fidel Castro provided further impetus in keeping my interest on the nail by having Dr. Pardo-Castello reside permanently, until his death, in Miami and at the University of Miami Department of Dermatology. His encouragement culminated in my presentation in 1961 at the American Academy of Dermatology—the embryology of the human nail.

Albert Kligman's superb and stimulating teaching conferences solidly cemented my future interest in the nail.

I am also indebted to all the colleagues who began to refer patients with nail problems from which I amassed the material I studied under the auspices of my chairman, Harvey Blank, at the University of Miami Medical School.

In addition, I have had the cooperation of many dermatologists, in particular, Drs. F. Ronchese, Robert Baran and Orville Stone, who have allowed me to use their clinical photographs of nail disorders.

Finally, I am greatful to the National Institutes of Health for their support.

An apology is forthcoming to the original describers of interesting syndromes and nail abnormalities. In the majority of cases, the most recent, complete review reference, and not the original, is used on the subject matter.

N.Z.
Miami Beach, 1980

Preface

The primary intent of this book is to familiarize the medical practitioner with the "nail unit" in a way which will render, correctly and more easily, the diagnosis of nail diseases. At the same time, it serves to encourage the treatment and corrective measures of the abnormalities, if possible, based on anatomical and physiological knowledge.

The chapters on anatomy, regeneration, and nail formation are basic to the author's intent. The content of the references quoted represents information which is proven and *not* controversial material. In addition, my own material not previously published is included.

I would like to introduce the anatomical concept that the *nail unit* consists of four different epithelial structures, each with its own characteristics, yet all interrelated. These four constituents are the Proximal Nail Fold (PNF), the Matrix (M), the Nail Bed (NB) and the Hyponychium (HYP). A disease may occur in any number of or all nail unit structures. A clear understanding of the anatomy, histology, and tissue kinetics of each constituent will be necessary and is the key factor in interpreting the abnormal findings of each of these constituents as disease occurs. It follows, therefore, that treatment and corrective measures should include the knowledge of not only the nail but also of its relationship to the bony phalanx and the digit.

Thus, on seeing the clinical nail signs, focus at the site of origin, and do not be confused by the signs of the end result of the disease. Also, the reader can then have a chronological appreciation as to when and for how long the disease has occurred and is continuing.

It is also the intent of the author to compile as many facts about human as well as animal nails and claws so that this may be used as a reference text.

Contents

CHAPTER 1

Anatomy and Physiology

The "nail plate" on the dorsum of all fingers and toes shapes and greatly enhances the coordinated fine digital movements. Four differently keratinizing epithelial structures make up the nail unit. What is commonly termed the nail (nail plate) is the horny end product of the most important epithelial component, the matrix.

The nail plate is a roughly rectangular, transparent/translucent, flat, horny structure which moves with the horny layer of the nail bed to extend unattached as a "free edge" growing past the distal tip of the finger. The normally pink nail bed (its color is due to an enriched vascular network) is seen through the transparent nail plate (Fig. 1). Usually in the thumbs and commonly in other fingers and large toenails, a whitish, crescent-shaped "lunula" is seen extending from under the proximal nail fold (Figs. 1, 2, 3, 4). Thus there are two lateral and one proximal nail folds.

Looking at the thumb's profile, the reader will notice that the nail plate emerges from under the proximal nail fold at an angle to the surface of the dorsum of digit skin (Fig. 5). This angle, commonly referred to as Lovibond's angle,[1] should always be less than 180°. Only in abnormal states, e.g., clubbing, is this emergence angle greater than 180° (see Chapter 23).

Each nail component (Fig. 1)—the proximal nail fold (PNF), the matrix (M), the nail bed (NB) and the hyponychium (HYP)—is an epithelial structure, like skin and hair, having an epidermis with a "live" germinative cell layer that differentiates and becomes the horny layer, or end product, which is considered "dead." These four components can easily be differentiated histologically from each other and can be traced as the nail unit develops embryologically (see Chapter 4).

COMPONENTS OF THE NAIL

The Proximal Nail Fold (PNF)

This is an extension of the skin of surface fingers and toes which becomes a fold and lies superficial to the matrix, which is deeper in the finger and toe substance (Figs. 3, 6;

chapter 4. It has two epithelial borders, a superficial and a deep layer. Only the superficial layer can be seen from the exterior. The cuticle, the horny layer of the PNF, "rides" adherent on the surface of the nail plate for a short distance before being shed normally or cut away by a manicurist (Fig. 13). The superficial PNF layer is like the epidermis elsewhere but has its own characteristics; i.e., the skin distally from the distal interphalangeal joint to the nail plate is devoid of hair follicles and finger print pattern, and is thinner than the dorsum of digit skin (Fig. 2). An occasional sweat gland may be seen proximally rather than distally. Often visible (at the tip of the PNF) are capillary loops described as hallmarks of certain disease states, e.g., lupus erythematosus, dermatomyositis and phototoxic conditions; however, these capillary loops may be seen normally.

Histology

The ventral PNF skin is thinner than its superficial counterpart and appears not to have marked epidermal ridges. In this respect, it shows similarities with the eyelids and scrotal skin. It may be the portal of entry of irritating as well as allergic chemicals which may be causative in a complex environment-influenced set of circumstances in the disease known as chronic paronychia. The ventral PNF layer is continuous with the matrix epithelium. These can be differentiated by observing that the PNF has a granular layer while the matrix does not. The arrows in Figs. 7 and 8 are positioned at the junction of these structures (Figs. 3, 6, 7 and 8).

The Matrix (M)

Deeper in the substance of the digits is the most important of the nail unit constitutents, located millimeters from the dorsal mid-portion of the distal bony phalanx (Fig 6). The matrix epithelium is bordered proximally by the ventral PNF and distally by the nail bed (Figs. 13, 15). The pattern of its epithelial rete is rootlike and seems to have a firm attachment to its dermal papillary counterpart (Figs. 7, 8, 9). The histologic observations of the firm attachment of the matrix epithelium to the dermis are excellently described by Hashimoto.[2] The matrix basal cells have small villous structures which project into the dermis (Fig. 10, arrows down). From these basal cell projections, anchoring filaments are seen to form bundles which extend (arrow) from the basement membrane (BM) to collagen fibers in the dermis (arrow sets, Fig. 11). By light microscopy, the epithelial differentiation process is similar to that seen in the hair matrix. The end product, or horny layer, the nail plate is considered a "hard keratinous" structure.

Histology—The Differentiation Process

The matrix epithelium consists of basal cells which seem to have their vertical axis directed diagonally/distally, resulting in the nail's growing out rather than up from under the PNF (Figs. 9, 12; see Chapter 4). As they differentiate, matrix basaloid cells (Figs. 8, 9, 12) flatten their nuclei, which begin to fragment and take on a more eosinophilic cytoplasm; thus the keratogenous zone is formed (Figs. 9, 12). The cells lose most of the nuclear materials and nail plate cells, or onychocytes are formed. Nuclear fragments (Fig. 12) may be detected by DNA stains in the well-formed nail plate a considerable distance

from the matrix, but these disappear completely nearing the distal free edge. This implies that DNA-ases, as well as RNA-ases, are still operational in the "dead, horny end product." This is unique to the nail plate. It also explains the earlier observation by Mitchell[3] of why leukonychial spots, parakeratonic foli, which usually follow matrix trauma such as manicuring, are reduced in the surface area and may totally disappear by the time they reach the free edge of the nail plate. The matrix does not exhibit a keratonyaline granular layer. The nail plate is transparent, does not take eosin, but is strongly basic Fuchsin–positive (acid-fast positive).

The Lunula

Returning to the thumb, we observe the lunula (half-moon) to be whitish and opaque (Fig. 1, 3). As stated previously, the lunula is the most distal area of the matrix. Since it is the only visible area of the matrix, we must assume that the whole matrix is opaque white (Fig. 13). Not all fingers exhibit a lunula; most consistently, it is seen in the thumb and index finger (Figs. 2, 3). Cerebral hemispheric dominance (handedness) can be ascertained by a greater surface area of the lunula and nail plate of dominant thumb.[4,5]

Color. Many investigators have written about the whitish color of the lunula, but none has presented convincing data. Various facts are noted and may play a role in the explanation of the whitish appearance (Fig. 13):

(1) The nail plate is very transluscent and almost transparent. This results in a "pink" appearance to the nail bed as light going through the nail plate reflects off the vasculature of the nail bed (Fig. 13).

(2) The nail plate over the lunula (distal matrix) is thinner than over the nail bed.

(3) The whitish color of the lunula coincides with the presence and shape of the keratogenous zone (KZ) of the matrix. In this zone there is nuclear retention

(4) Accounts of a reduced vasculature supplying the matrix have been disproven by this author.

At a glance, it would seem that the whitish color of the lunula is produced by the same phenomenon of light diffraction that occurs in the distal free edge of the nail, onycholytic nails, leukonychial spots secondary to manipulation of the matrix, and proximal nail fold. In the lunula, the KZ cells (in themselves a denser object) appear whitish, exactly like leukonychial spots (white spots) a parakeratolic focus of onychocytes.

The lunula plays an important role in shaping the nail plate. This was demonstrated by Clark LeGros[6] (Fig. 14).

In addition, the lunula is the portion of the matrix to first differentiate during developmental times (see Chapter 2) (Fig. 17).

Thus it makes sense that the configuration of the genetically predetermined nail area (lunula) shapes the free edge of the nail plate. Failure to reconstruct the lunula's shape during trauma or during surgical intervention may result in nail plate dystrophy.

Melanocytes

In the Negro race, melanocytes normally are abundant in the matrix epithelium. The color of the nail plate varies from very light to very dark gray. Generally, the nail plate may pigment diffusely, but longitudinal bands of pigment are often seen. These represent foci of melanocytic hyperplasia and are not nevi (see Chapter 2).

The Nail Bed (NB)

The nail bed is defined as that area of the nail unit beginning at the lunula (Figs. 1, 2, 3, 6, 13, 15) and extending to the hyponychium (Figs. 3, 6, 18, 21). Most of the surface of the dorsum of the fingertip is covered by the nail bed. It has two characteristic features: (1) its epidermis and (2) the spatial arrangement of its epidermal and dermal ridges. The nail bed consists of epidermal ridges, not rete, aligned longitudinally and almost parallel to each other. These ridges extend from the lunula distally (Fig. 21) to the hyponychium and fit tongue-and-groove fashion between similarly arranged dermal ridges (Fig. 16, arrows up and down). The appearance of the nail bed after the removal of the nail plate (Fig. 19) suggests the effect of the fingerprint pattern (Fig. 20). It can easily be seen that small blood vessels along these dermal ridges (Figs. 16, 17, 19) affected by either disease processes or trauma are responsible for the so-called splinter hemorrhages known only to occur in the nail bed. The architecture of the dermal/epidermal relationship in the lateral margins of the nail bed shows more complex primary epidermal ridges with secondary smaller ridges (Fig. 17).

The epidermis of the nail bed is unique in that by light microscopy examination there is an obvious lack of mitosis in the basal cells and also in that the horny cell layer is scanty. The differentiation of the epidermis is similar to that of the inner root sheath of hair. As basal cells differentiate to the surface of the epidermis (Figs. 16, 17), they lose their nuclei and become nail bed horn cells. There is no granular layer visible by light microscopy; however, Hashimoto[2] has described a keratohyline granular zone in the normal nail bed of embryonic fingers 17 weeks in development (through electron microscopy). In disease states, a rich granular layer involving the nail bed is not infrequent. The horny layer of the nail bed is scant. Few horn cells are added to the underside of the nail plate. The nail horn cells stain eosinophilic in contrast to the unstained nail plate cells (Figs. 16, 17). The cells of the basal layer of the nail bed epidermis "move" from an area near the lunula to the hyponychium. On the way, some of these cells differentiate distally and result in horn cells all along the nail bed epidermis. This "movement" takes place at the same rate as nail plate growth (see Chapter 4).

Not uncommonly, fairly large epithelial buds have been seen in the nail bed and matrix and recently have been reported by Lewin.[7] These consist of solid outpocketing of basal cells which show no abnormalities. Melanyocytes normally are not found in the nail bed epithelium but may occur in the Negro race and, rarely, in Orientals.

The Hyponychium (HYP)

The hyponychium is the most distal nail unit component, extending from the nail bed and terminating at the distal groove (Figs. 3, 6, 18, 21). The epidermis making up the hyponychium is similar to plantar and volar epidermis. Its epidermal rete pattern is similar to that of palmar and plantar epidermis, as is its dermis papillary pattern. The gross hyponychium normally is not seen but can be observed in fingers of nail biters. Rarely, a congenital "extended hyponychium" is seen[8] (Fig. 22); this has also been reported and termed pterygium inversum unguis.[9,10] The stratum corneum of the hyponychium normally is seen accumulating under the distal free edge of the nail plate. The distal groove seems more prominent in fingers. A wide groove separates the hyponychium from the volar skin (Figs. 3, 6). In primates and lower animals, the distal groove may be very prominent. In the microbiologic disease states, the hyponychial horny layer is the portal of entry to the nail unit (see Chapters 8, 15).

THE DERMIS

The dermal component of the nail unit is unique in that it is limited by the underlying phalanx and there is no subcutaneous tissue. In the matrix area, the dermal architecture is classical with papillae accommodating the arbor-like ridges of the matrix (Figs. 7, 21). In the nail bed epidermal ridges (described previously and seen in Figs. 16, 17, 21) harbor the fine capillaries which, when disrupted, result in splinter hemorrhages commonly seen in normal and disease states. Specialized vascular tissues are also present in the digits. The glomus is one of these structures, particularly in the nail bed[11] (Fig. 15). In clubbed fingers, dense fibrovascular hyperplasis of the nail bed and particularly under the matrix is responsible for the characteristic exaggerated angle of the nail plate (Figs. 2, 6). The capillaries of the proximal fold have been studied extensively by capillary microscopy and attempts to diagnose various disease states by the pattern of these capillaries have been generally unsuccessful. Some capillary loops normally are seen at the proximal nail fold, but in general these are observed in disease states such as lupus erythematosus, scleroderma and dermatomyositis.[12] The connective tissue of the nail unit consists mostly of reticular dermis as well as ligaments and bone-associated connective tissue. There is no subcutaneous fat of deep dermis between the phalanx and the nail unit. Nerve endings and nerve trunks are also numerous, with specialized nerve structures such as Vater-Pacini corpuscles and Meissner corpuscles; however, these are noted to be more at the fingertip of the phalanx. There are no adnexal structures arising from the nail bed or hyponychium.

ULTRASTRUCTURE

The ultrastructure of the nail is known from relatively few studies. Hashimoto and associates[13,14] have described various embryo nail unit constituents (matrix, nail bed, etc.). Yet I cannot agree with the concepts formulated from these studies, e.g., the use of terms such as the dorsal nail matrix when reference is being made to the ventral component of the proximal nail fold and other new unwarranted terminology.

According to Hashimoto, the keratinization process of the human toenail plate cells from nail matrix was found to be identical with that of epidermal stratum corneum cells, particularly in the formation of the marginal band, or broad zone, and in the discharge of the membrane-coating granules (MCG's) that form the intercellular cement. However, MCG's were not responsible for additions to the broad zone. The most striking difference between the keratinization of the nail plate cells and epidermal stratum corneum cells is that in the nail the keratin fibrils (or keratin pattern) form by accretions of cytoplasmic filaments without the formation of keratohyaline granules. In this respect, the nail is identical with hair cortex.

Structures similar to MCG's were described by Matoltsky[15] from abnormal nail plate. The adult matrix of toenails has also been studied by Hashimoto.[16] Caputo and Dadati[17] studied the nail plate after treatment with thioglycolic acid. The authors concluded:)1) "The cell's cytoplasm consists of keratin fibrils combining in bundles and immersed in a nonstructural amorphous mass. These bundles lay in no precise direction but are arranged haphazardly within the cell," and (2) "The intercellular links, which are quantitatively numerous may present three aspects: (a) the tight junction, that is, complete contact between two opposite membranes, (b) intermediate junction type, that is, the space between the two membranes is unconstant (200–300A) and a dense nonhemogenous substance can be observed within it, separated from the cell membranes by two thin light

bands, and (c) desmosone-like type with fibrillar bundles which converge toward the cell membrane. However, the typical stratification after cementing substance is missing from these bonds."

These studies have not been able to confirm that there are three distinct layers on the nail plate. Scanning electron microscopy of the nail plate by Forslind and Thyrasson[18] differentiated a hard dorsal nail plate and a more plastic intermediate nail plate. The authors, however, did not realize that a section taken vertically through the nail plate is made up of cells of different ages: a much older superficial nail plate layer and a more recent lower layer of the nail plate. The nail plate is formed as a sheet from the apex of the matrix to the lunula, and the superficial layers are therefore produced by the apex cells while the lowermost layers of the nail plate are produced by the lunula. Thus, at a vertical cut, an older (earlier-produced nail plate) is present with a younger (later-produced) nail plate.

GROWTH

The nail plate consists of dead, cornified cells produced by the matrix. The basal-like cells of the matrix lose their nuclei, flatten and cornify, and are added to the already formed solid nail plate. The rate of growth of the nail plate is determined by the turnover rate of the matrix cells. Shortly after death, matrix cells do not incorporate tritiated thymidine in their nuclei and appear to be incapable of DNA synthesis and cell division; therefore, the nail does not grow. Previous observations relating nail growth after death were, in fact, erroneously reporting apparent growth caused by the severe post-mortem drying and shrinking of the soft tissues around the nail plate.

Fingernails grow faster than toenails. Nails of individual fingers of the same hand grow at different rates.[19] The average growth of the thumbnail is 0.10–0.12 mm daily. The rate growth is thought to be greater in the second to third decades with a slight decline thereafter.[20] Family tendencies favoring similar growth rates among individuals have been noted,[21] as well as increased growth during the summer and diminished growth in cold climates[22] (Fig. 23). Many systemic disorders affect nail growth by deceleration, and many manifest by thinning and grooving of the nail plate. This phenomenon is best appreciated weeks after the event has occurred. Acute viral infection states, such as mumps and measles, are most often reported to affect nails. Starvation has also been associated with reduction of nail growth. Increase in growth rate can be seen during pregnancy,[23] nail biting trauma[24] and regrowth after avulsion (Fig. 24).

The ingestion of gelatin has not been conclusively shown to specifically encourage nail growth or nail strength.

CHEMICAL COMPOSITION AND BIOCHEMISTRY

Little is known about the chemistry and biochemistry of nails. Earlier investigators studied mainly total contents of various organic and mineral components of normal as well as specific diseased nails. A brief listing is presented for reference (see Table I): sulfur;[25] total nonprotein nitrogen; urea nitrogen; ammonia nitrogen; uric acid[26] in gout; creatinine[26,27] in chronic renal failure; sodium[28] elevated in cystic fibrosis despite normal values in sweat; calcium elevated in older normals[29] and in traumatic states,[30] not abnormal in brittle nails;[31] phosphorus; zinc; magnesium; manganese; silicon; lead; boron; titanium; strontium; silver; aluminum;[29] copper,[29] elevated in Wilson's disease;[31-33] iron,[34]

cholesterol,[35] and sulfhydryl-disulfide groups have demonstrated in the nail. In early embryonic life, there is a very high concentration of sulfhydryl groups;[36] this concentration decreases as the fetus reaches the newborn age and stabilizes at about age three.[37] Disulfide groups are present in small amounts in embryonic nails and rapidly increase as term and infancy approach.[36,37]

Iron is also found in higher amounts in infants' nails as compared to those of 40- to 70-year-olds. During the 20th to 40th years, the amount of iron is less than during the 40th to 70th years. (These levels were determined colorimetrically.) In cystic fibrosis of the pancreas, abnormally higher levels of calcium, magnesium and sodium have been reported to reflect more accurately a homozygous patient than the sodium level alone.[38] Ungulic acid, a new ganglioside sulfate, has been isolated from the horse hoof.[39]

Recently, Baden[40] and colleagues have presented data concerning certain biochemical events related to nails and compared them to hair and stratum corneum.

From x-ray diffraction and electron microscopy studies, Forslind[18] relates the hardness of nails to cell arrangement, cell adhesion, and ultrastructure arrangement of the keratin fibrils.

Table I
Mineral Elements in Normal and Diseased Nail

	Neutron dosimetry (mg/gm NAIL)	
Aluminum	0.00000000045[29]	
Antimony		
Arsenic	[41]	Poisoning[47]
Boron	0.007–0.006[29]	
Bromine	[41]	
Calcium	0.671–0.806[29,44]	
	3.64 ± 1.77[28a]	9.96 ± 3.70 Cystic fibrosis[38a] Kwashiakor[48a]
Copper	0.029–0.089[29,44,45]	
Gold	0.00044 ± 0.0006[41,44]	
Iron	0.029–0.064[29,34]	30b
Lead	0.0097–0.024[29]	
Magnesium	0.1–0.121[29,44]	
	3.45 ± 1.5[38a]	4.72 ± 1.45 Cystic fibrosis[38a] Kwashiakor[48a]
Manganese	0.002 ± 0.001[29,45,46]	
Phosphorus	0.00008–0.00027[29]	
Potassium		Kwashihkor[48c]
Silicon	0.17–0.54[29]	
Silver	0.000000048[29]	
Sodium	2.4 ± 1.8[41,45]	
	3.34 ± 1.4[38]	9.12–3.20 Cystic fibrosis[38c] Kwashiakor[48c]
Strontium	0.00000016[29]	
Sulfur	36.6 ± 2.1[42,43]	
Titanium	0.000016[29]	
Zinc	0.106–0.154[29,41,44,49]	

[a]Fluorometrically
[b]Colormetrically
[c]Flame photometry

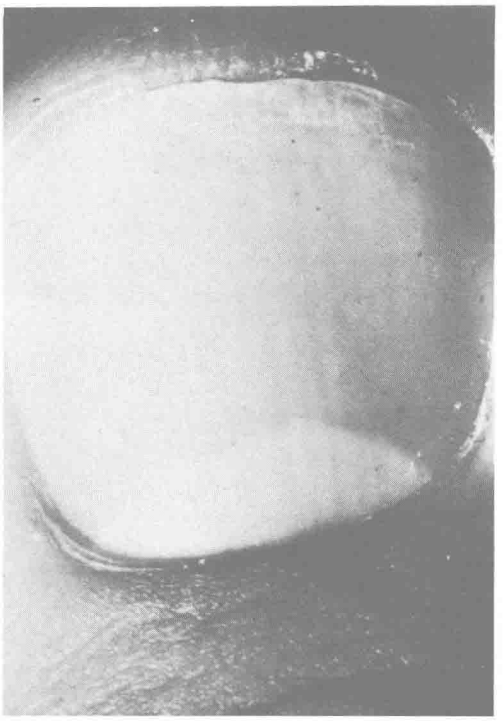

Fig. 1. Normal fingernail showing whitish lunula, pink nail bed.

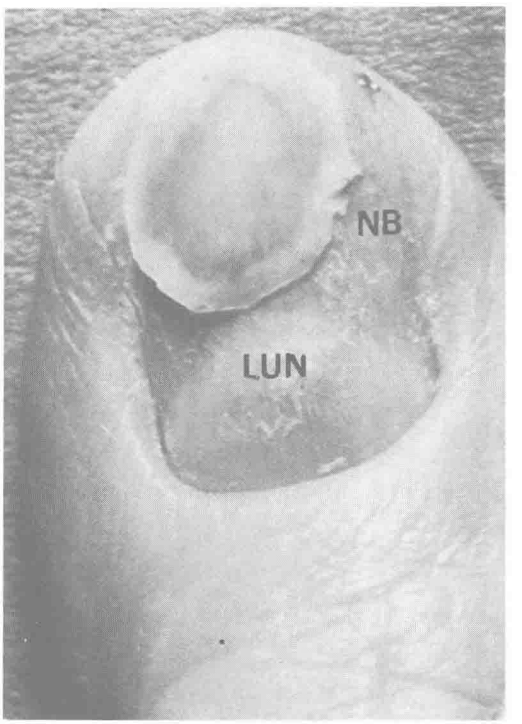

Fig. 2. Thumbnail. Nail plate remains as island attached to underlying nail bed. Lunula (LUN) can be seen as whitish, opaque structure. Nail bed (NB). Note lateral and proximal nail fold.

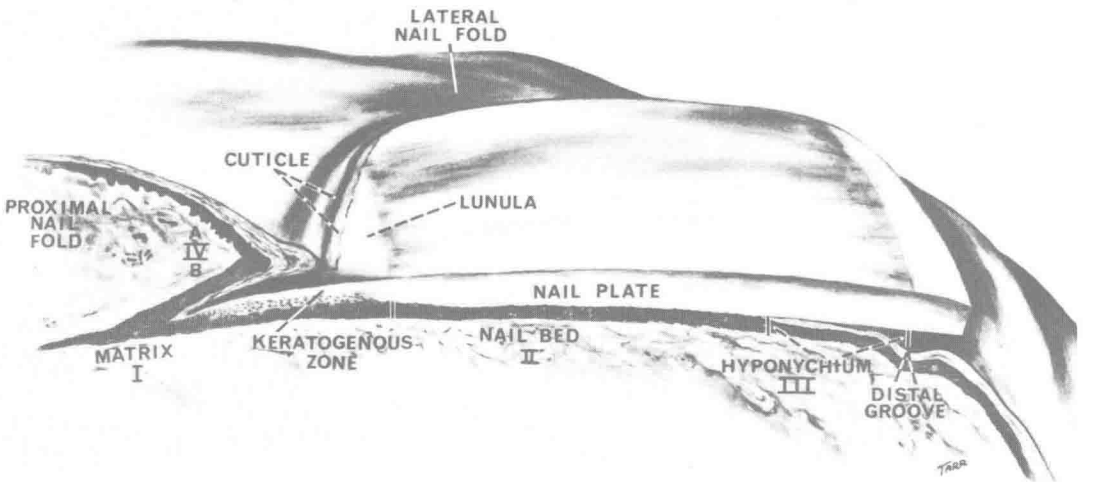

Fig. 3. Diagrammatic drawing of longitudinal section of fingernail showing four epithelial components: (1) matrix, (2) nail bed, (3) hyponychium, (4) proximal nail fold. (N. Zaias, *Arch. Derm. 87*: 37-53, 1963)

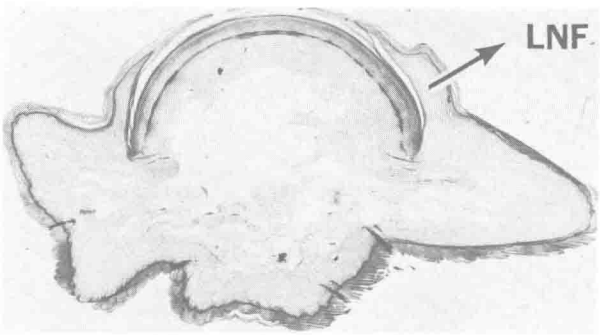

Fig. 4. Cross-section of finger at level of nail bed. Note lateral nail folds (LNF). H&E X12.

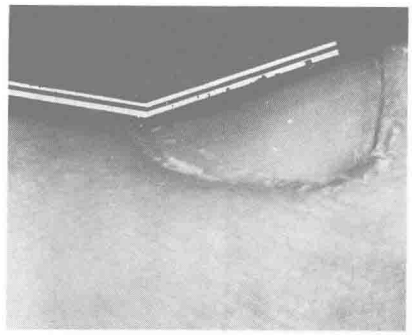

Fig. 5. Skin of proximal nail fold (PNF) should be on angle less than 180° with the emerging nail plate.

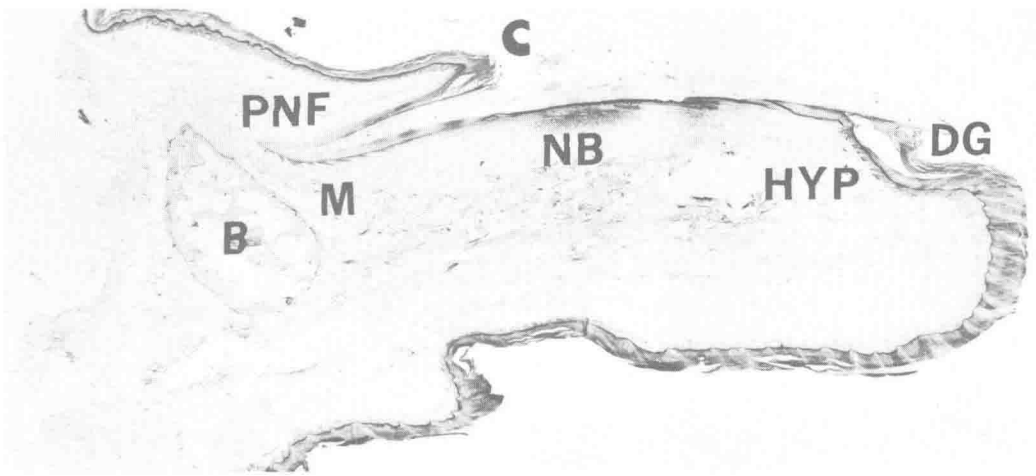

Fig. 6. Longitudinal section of fingernail. Note proximity of bone (B) to matrix (M) and that the cuticle (C), is the stratum corneum of the proximal nail fold (PNF). Note also that the distal groove (DG) exists in humans. H&E X12.

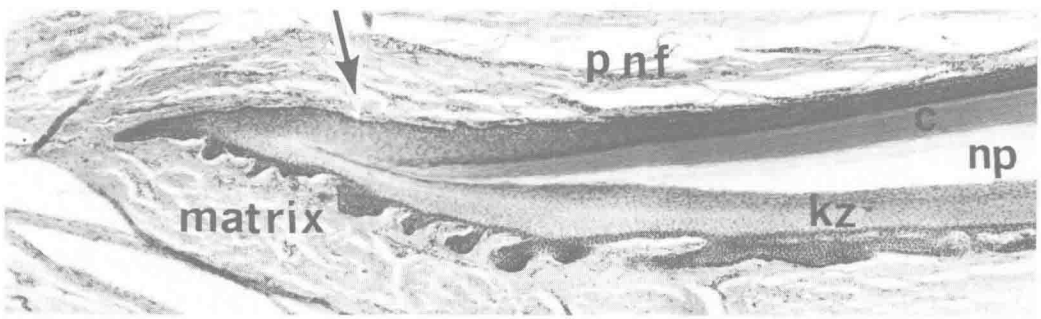

Fig. 7. Close-up from Fig. 6 of matrix area in which junction of proximal nail fold (PNF) and matrix (M) can be seen (arrow). Note rootlike epidermal rete of matrix. Keratogenous zone is seen. Nail plate (NP), cuticle (C). H&E X40. (N. Zaias, *Arch. Derm. 99*: 569, 1969)

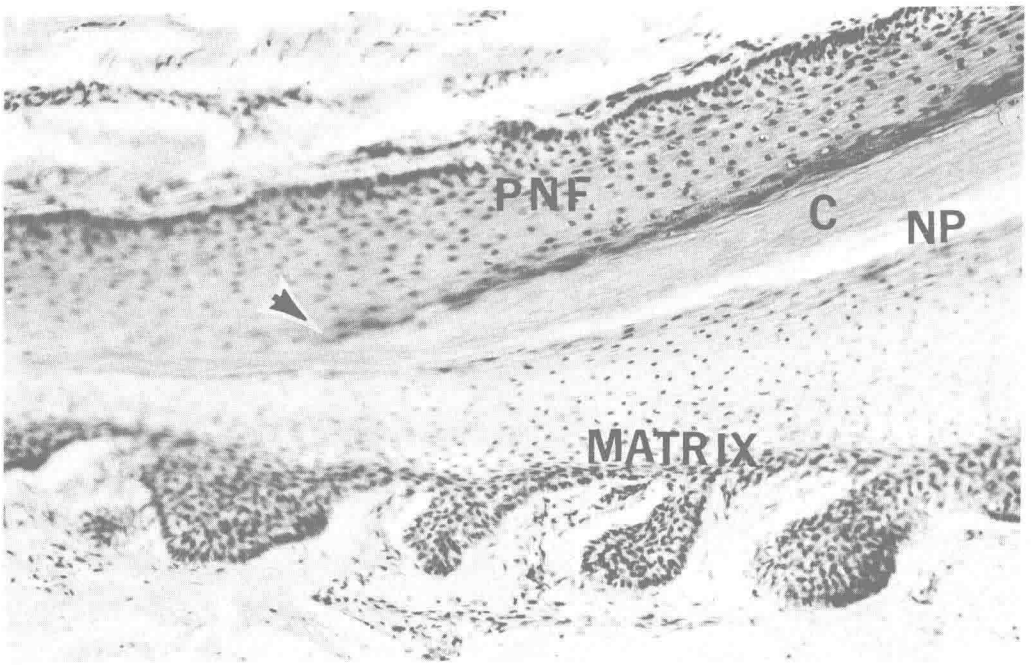

Fig. 8. Close-up of Fig. 7, (arrow) showing border of proximal nail fold (PNF) with matrix (M) (arrow). Granular layer of proximal nail fold epithelium disappears as matrix begins. Cuticle (C), nail plate (NP). H&E X150.

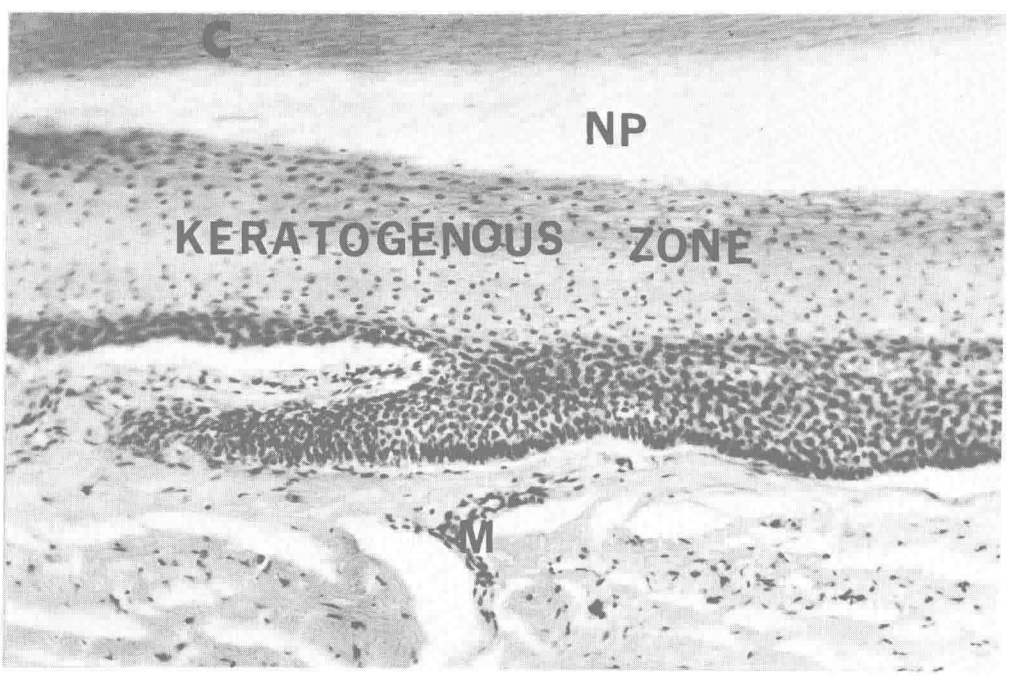

Fig. 9. Close-up of matrix in Fig. 7, near keratogenous zone (KZ), showing basal cells of matrix flattening or to becoming transparent nail plate (NP) cells, which do not take hematoxylin stain. H&E X140.