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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Current and Future Nail Research –
Areas Ripe for Study

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Key Words
Nail · Research · Keratins · Mouse models

Abstract
This discussion examines five common topics that affect nails adversely, onychomycosis, brittle nails, developmental nail disorders, chronic paronychia and onycholysis. What is known about these processes, what areas of research, old and new, might lead to improved understanding of the underlying basis of the problems and what prospects the future might hold are considered.

The charge of this discussion is to suggest areas of present and future research that may have an impact on the understanding and treatment of individuals with nail disorders. This is done in a broad context – for representatives of the pharmaceutical and cosmetics industries, chemists, pharmacologists, skin biologists and clinicians. To do so, one must consider what things affect nails adversely, what is known about these processes, what areas of research, old and new, might lead to improved understanding of the underlying basis of the problems and what prospects the future might hold.

What things affect nails adversely? If one excludes the systemic and cutaneous disorders that affect the nails indirectly, what remain are those processes that directly affect the nail or the structures that produce the nail, collectively known as the nail unit. I will focus on five specific problems in which the interaction of the nail and nail unit with the environment results in pathology, and where current and perhaps future studies should prove useful (table 1). This focus ignores many equally interesting and important clinical problems. Although these problems appear fairly different in their clinical presentation and presumed pathophysiology, I will try to tie them together into a rational approach for future studies.
**Table 1.** Specific clinical problems that suggest areas for nail research

- Onychomycosis
- Brittle nails
- Developmental/inherited defects
- Chronic paronychia and onycholysis

**Table 2.** Onychomycosis – problems

- Poor response
- Reinfection/recrudescence
- Inherited defect (?)

**Table 3.** Onychomycosis – solutions

- Long-term follow-up of present drugs
- New treatments
- Prophylaxis
  - Systemic
  - Topical
- Identify gene defects

**Fig. 1.** Refractory onychomycosis. a The nails of the gentleman did not respond to treatment with multiple systemic antifungal agents. b A different gentleman’s toenail onychomycosis recurred after initially responding to one of the new antifungals.

**Onychomycosis**

Dr. Scher has discussed onychomycosis in depth. Consider two groups of subjects with onychomycosis, those who do not respond to the drugs now available, and those with a strong family history of the disorder (table 2). Potential solutions to these problems are listed in table 3.

Let us assume the diagnosis is correct, that the subject has a true fungal infection of the nail, but that despite the new therapeutic options, he or she does not respond or responds only temporarily to treatment. The toenails of 2 such patients are shown in figure 1. The nails of the gentleman shown in figure 1a did not respond to treatment. A different gentleman’s toenail onychomycosis recurred after initially responding to one of the new antifungals (fig. 1b).

Unfortunately, although clinical studies defining the short-term efficacy of the new antifungal drugs abound, few good follow-up studies have been undertaken to determine the long-term outcome of these individuals. One must also consider the potential role of new treatments. This includes new agents and prophylaxis, both with intermittent pulses of
Brittle Nails

What holds the cells of the nail plate together, and what goes wrong to result in brittle nails (table 4)? Brittle nails is a nebulous term. Loosely speaking, the nail plate loses its resilience and falls apart. Usually one sees longitudinal cracking (fig. 2a) or splitting of the free end of the nail (fig. 2b). Why do we concern ourselves with such apparently trivial matters?

Forslind [1970] proposed that the biconvex curvature of the nail lends it strength (fig. 3a). He also showed that flattened keratinocytes in the nail are stacked like pancakes, with their thin diameter perpendicular to the surface, and with the intermediate filaments of the cells oriented perpendicular to the direction of growth (fig. 3b).

What about the proteins that make up the nail? The structural proteins of the nail can be divided into keratins and keratin-associated proteins [reviewed in Powell and Rogers, 1994] (table 5). Keratins were initially defined as proteins of the cornified layer of epidermis and of the hair and nail [Fraser, 1969]. As more has been learned about these proteins, the definition has been refined to

**Table 4.** Brittle nails – what holds the nail plate together?

<table>
<thead>
<tr>
<th>Biconvex curvature</th>
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<tr>
<td>Orientation of cells within the nail plate</td>
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<tr>
<td>Structural proteins</td>
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</table>

available systemic drugs to individuals who do respond to treatment, and with topical agents, as discussed by Prof. Marty. Such studies are scarce.

What is it about the 20–40% of individuals who do not respond to potent therapies and those who temporarily respond to treatment, only to see their infection recur? Perhaps the answer lies in the studies of Zaias et al. [1996], who published thirteen pedigrees supporting an autosomal dominantly inherited pattern of onychomycosis. Is there an inherited predisposition to onychomycosis? If so, what is/are the underlying gene defect or defects? If the inheritance pattern holds up to scrutiny, linkage analysis and positional cloning techniques should give valuable information about the underlying defect in these people and may explain those who do not respond to therapy or become reinfected after treatment.
proteins, type I (acidic) and type II (basic), that are expressed in all epithelia [reviewed in Fuchs, 1995]. Type I and type II keratins are characterized by structural, charge and immunologic differences. Over 30 keratins have been described, each the product of a specific gene. The keratins are numbered, based on subfamily type, primary structure, size and charge. One member of each keratin subfamily is coexpressed with its mate, a member of the other keratin subfamily. Which keratin pair is expressed varies as a function of the specific epithelium (e.g. epidermis vs. esophagus vs. oral mucosa) and the state of differentiation of the tissue (e.g. basal vs. suprabasal). As an example, keratins 14 (K14, type I, acidic) and 5 (K5, type II, basic) are expressed in the basal layer of all stratified epithelia. The keratins of the nail and hair can be divided into those keratins common to epidermis (the ‘soft’ keratins) and those keratins found primarily in hair and nail (the ‘hard’ keratins, table 5) [Heid et al., 1988].

The keratin-associated proteins are more numerous and much more complex (table 5). Most of the work on this heterogeneous group of proteins has been done with hair (wool) and

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**Table 5. Structural proteins of the nail plate**

<table>
<thead>
<tr>
<th>Keratins</th>
<th>Keratin-associated proteins</th>
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<tbody>
<tr>
<td>‘Hard’ keratins&lt;br&gt;Type I: Ha1–4 and x&lt;br&gt;Type II: Hb1–4 and x&lt;br&gt;Epithelial (‘soft’) keratins&lt;br&gt;Type I: K14, K16, K17&lt;br&gt;Type II: K5, K6</td>
<td>‘High-sulfur’ proteins&lt;br&gt;Ultrahigh sulfur (3 families, based on hair)&lt;br&gt;High sulfur (3 families, based on hair)&lt;br&gt;High glycine-tyrosine (2 families, based on hair)&lt;br&gt;Others: trichohyalin</td>
</tr>
</tbody>
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**Fig. 3.** What gives the nail plate strength? **a** The biconvex curvature of the nail plate lends it strength. **b** Cells of the nail plate are stacked like pancakes, with their thin diameter perpendicular to the surface, and with the intermediate (keratin) filaments of the cells oriented perpendicular to the direction of growth.
two ways, as matrix proteins in which keratin intermediate filaments are embedded within the cells of the nail plate and as intercellular 'glue' to hold the cells of the nail plate together. If one assumes the keratins are necessary for structural integrity of the nail unit and that the keratin-associated proteins serve a similar vital function in the nail unit and nail plate integrity, it is easy to envision the importance of these structural proteins in the context of brittle nails.

The expression and function of the structural proteins of the nail is an obvious area for investigation in brittle nails. A related area of investigation involves what the defects in brittle nails tell us about absorption of substances through the nail plate, and how this may be used to improve topical therapies.

**Developmental and Inherited Defects**

What do developmental and inherited nail dystrophies tell us about the structure and function of the nail and the nail unit? I will discuss only two congenital nail dystrophies – the nail-patella syndrome and pachyonychia congenita. Both are classified in the group of ectodermal dysplasias, in which inherited abnormalities are found in the skin, teeth or epidermal appendages.

Nail-patella syndrome is inherited as an autosomal dominant trait in which nail dystrophies associated with abnormalities of the patella and other bones, and of the kidneys are found (fig. 4a; OMIM No. 161200). Pachyonychia congenita is also inherited as an autosomal dominant trait in which pachyonychia (elevation of the distal nail plate to form a ski-slope-like appearance), palmar/plantar hyperkeratosis and follicular hyperkeratosis are seen (fig. 4b). In one subset of subjects, leukokeratosis of the oral mucosa is seen with pachyonychia congenita (OMIM No. 16700);
in a second subset, pachyonychia is inherited in association with natal teeth and cysts (OMIM No. 167210).

Here, we have two disorders in which nail dystrophy is seen in association with other problems. Nail-patella syndrome maps to the long arm of chromosome 9, and appears to be associated with mutations in the LIM-homeodomain protein, LMX1B. Mutations in the keratin intermediate filament proteins found in the nail unit have been identified in both types of pachyonychia congenita. The identification of mutations in regulators of development and in keratins found at the site of inherited abnormalities supports the vital role of developmental and structural proteins in the nail unit and suggests that their study will lead to better understanding of associated nail disorders.

**Chronic Paronychia and Onycholysis**

Let us now consider chronic paronychia, inflammation of the tissues surrounding the nail, and onycholysis, the separation of the nail plate from the nail bed beginning distally. After onychomycosis, these two entities are probably the most common nail problems encountered in clinical practice. In these two mirror-image disorders, the tissues surrounding the nail lose their attachment. In chronic paronychia (fig. 5a), the attachment of the proximal nail fold to the underlying nail plate by the cuticle is interrupted; formation of a real space from a potential space results. Irritants and water accumulate in the ‘cave’ beneath the proximal nail fold and result in inflammation, edema formation and ‘bolstering’ of the proximal nail fold, and increased separation of the nail fold from the nail plate, leading to a vicious cycle. Bacterial and yeast superinfection may result, but only as secondary complication.

**Fig. 5.** Chronic paronychia and onycholysis. a Chronic paronychia: the cuticle is lost, the proximal nail fold is edematous, resulting in a bolster-like appearance. Dorsal nail plate dystrophy is secondary to inflammation overlying the nail matrix. b Onycholysis: separation of the nail plate from the nail bed, beginning distally. From Nail Tutor, ver 2.0, copyright University of Washington.

In onycholysis (fig. 5b), attachment of the nail plate to the underlying nail bed is lost at the hyponychium. Water accumulates in the ‘cave’, beneath the nail plate, and secondary infection by bacteria and yeast occurs. As opposed to chronic paronychia, inflammation is rarely seen.

In both chronic paronychia and onycholysis, a potential space becomes a real space. What effects these attachments, and what goes wrong to result in these changes? Little is known. Yeast can often be cultured from be-
Table 6. Areas of future research

- Clinical investigation
- Structural studies
- Genetic analysis
- Animal models

neath the unattached proximal nail fold in paronychia or beneath the nail plate in onycholysis. Are these true infections? Is this a form of onychomycosis? The treatment of chronic paronychia and onycholysis with antifungals is controversial; experts disagree on the best methods, although there is agreement that regardless whether the yeast is primary or secondary, one must eliminate the organisms in order to correct the problem. My bias is that the yeast is a secondary colonizer. Work by Tosti et al. [1992] suggests that in paronychia irritants are responsible for the inflammation in the proximal nail fold. Thus, the primary focus of investigation should be on what seals the surrounding skin to the nail plate. These nail disorders require creative clinical investigation for better understanding. But again, therapies, both topical and systemic, are relevant.

How can these four clinical problems be tied together and suggest directions for fruitful research (table 6)? Obvious avenues of pursuit include creative clinical investigation and the study of structural proteins and inherited disorders of the nail unit. In addition, I wish to introduce the idea of animal models for research as a means of beginning to understand the underlying processes. I will focus on the mouse as an animal model.

The advantages of the use of inbred mice as animal models for skin research has been clearly stated by Sundberg [1994]. From such studies, valuable models of hair disorders have arisen [Sundberg and King, 1996], sug-

ghosting the possibilities of models for nail disorders. Although the mouse nail is small and is a claw, as opposed to a human nail, the appendage has striking gross and microscopic similarities to its human homologue. Initial studies have identified a number of spontaneous and induced mouse mutations, suggesting that this may prove a valuable animal model for understanding human disorders [Fleckman and Sundberg, unpubl.].

Finally, one must acknowledge the serendipity of research. Who could have predicted that the interest of a few scientists in bacterial enzymes that cut DNA at specific bases would lead to today's explosion in molecular genetics? As a basic scientist and a clinician I wish to emphasize the importance of research at all levels for understanding and treating nail disorders. It is as necessary to support good basic science as it is to apply the fruits of those investigations to clinically and cosmetically important matters.

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References


