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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.

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# Pachyonychia Congenita (Jadassohn-Lewandowsky Syndrome): A Seventeen-Member, Four-Generation Pedigree With Unusual Respiratory and Dental Involvement

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Pachyonychia Congenita (PC) is an autosomal dominant syndrome of thick nails and other epithelial defects. A hospitalization for severe respiratory distress in a 3-year-old boy with PC and an affected father led to the discovery of 17 affected persons in a kindred spanning four generations. Nine relatives had varying degrees of upper respiratory tract obstruction, and eleven had dental aberrations.

We review PC and discuss other unusual findings in this kindred, ie, arthritis in four affected relatives and a discrepancy between expected and observed ratios of affected to unaffected offspring of mothers with PC.

**Key words: pachyonychia congenita; thick nails; Jadassohn-Lewandowsky syndrome; natal teeth, neonatal eruption of teeth; early, severe caries, early loss of carious teeth; leukokeratosis oris; follicular keratosis; laryngeal obstruction; hyperhidrosis; callouses, bullae, blisters; arthritis**

## INTRODUCTION

Pachyonychia congenita (PC), an autosomal-dominant ectodermal dysplasia, was first described by Jadassohn and Lewandowsky in 1906. A striking thickness and yellow-to-brown discoloration of the nails with pinched margins and upward tilt of distal tips should alert the physician to this diagnosis. Other ectodermal involvement is usually seen as well.

In 1968, Moldenhauer and Ernst reviewed 93 PC cases (including three of their own). Thick nails were present in 97%, follicular keratosis in 59%, plantar keratosis in 72%, and leukokeratosis oris in 57% of the cases. Other patients may have scalloped tongue edge, dental abnormalities, conduction deafness, palmar and plantar bullae formation in areas of pressure, hyperhidrosis, hair abnormalities, corneal

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opacification [Butterworth and Strean, 1962], hoarseness [Kumer and Loos, 1935], steatocystoma multiplex [Hodes and Norins, 1977], and natal teeth or early eruption of primary teeth [Gorlin and Chaudhry, 1958]. It has been stated that there is a tendency for the oral lesions to undergo malignant change [Rook, 1979].

At least two subclassifications have been proposed based on the presence or absence of various characteristics [Kumer and Loos, 1935; Schönfeld, 1980], but it is better to consider this entity as one syndrome with high penetrance and variable expressivity [Hodes and Norins, 1977].

The histopathological changes of nails, oral and lingual mucosa [Gorlin and Chaudhry, 1958], keratotic skin [Schönfeld, 1980], and larynx [Cohn, McFarlane, and Knox, 1976] appear to be fundamentally similar. Microscopically, there are perinuclear vacuolizations, acanthosis, parakeratosis, increased keratohyalin granules where appropriate, and a dermal perivascular lymphocytic infiltrate [Schönfeld, 1980]. Involvement of the larynx suggests that this is an epithelial dysplasia, not restricted to ectoderm [Cohn, McFarlane, and Knox, 1976].

Although hoarseness was observed as early as 1935 [Kumer and Loos], severe laryngeal involvement in PC has been reported only once before [Cohn, McFarlane, and Knox, 1976]. Thus, it was a noteworthy occurrence when a 3-year-old boy with PC required a second tracheostomy for marked laryngeal obstruction. We report a similar childhood course in his father and a remarkable pedigree of 17 affected members in four generations, some with unusual manifestations, most having evidence of laryngeal obstruction and early loss of secondary teeth. Prior to this, 150 cases of PC had been reported in the scientific literature [Schönfeld, 1980].

## REPORT OF PROPOSITUS

Within a 24-hour period, a 3-year-old boy with PC developed hoarseness, gagging, hemoptysis, stridor, respiratory distress, and cyanosis so severe that his father began artificial respiration. When he was intubated, the vocal cords were noted to be edematous and bloody; a tracheostomy was performed, and he was subsequently transferred to the pediatric intensive care unit of the University of California Davis Medical Center in a deteriorating condition presumably owing to aspiration pneumonia.

He was found to be an attractive, blonde, blue-eyed boy who was alert, though tachypneic and in moderate respiratory distress. He had a leukoplakia-like film on his tongue, buccal mucosa and hypopharynx, including a thickened, white, scalloped edge of the tongue. He had no hearing problem, and his eyes appeared normal. There was a follicular keratosis on both elbows and knees. Large yellow callouses were present on both feet (but no bullae). All nails were brown, greatly thickened and protruding dorsally. There were no other skin lesions (Figs. 1,3,5, and 7).

He improved rapidly under respiratory management and with antibiotic treatment and went home on the 6th day with a tracheostomy. Before discharge, he underwent direct laryngoscopy and bronchoscopy that showed thickening and erythema of the posterior commisure of the larynx. The subglottic region and trachea were essentially normal.

## PAST HISTORY

This boy was the first and only child of a nonconsanguineous white couple. The 22-year-old father had PC; the mother was 20. The boy was delivered by Cesarian

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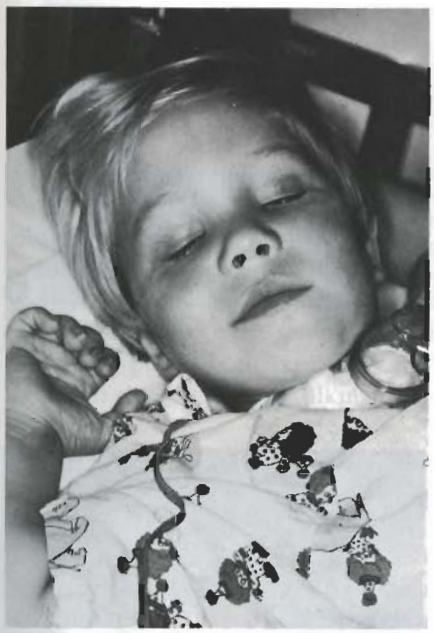

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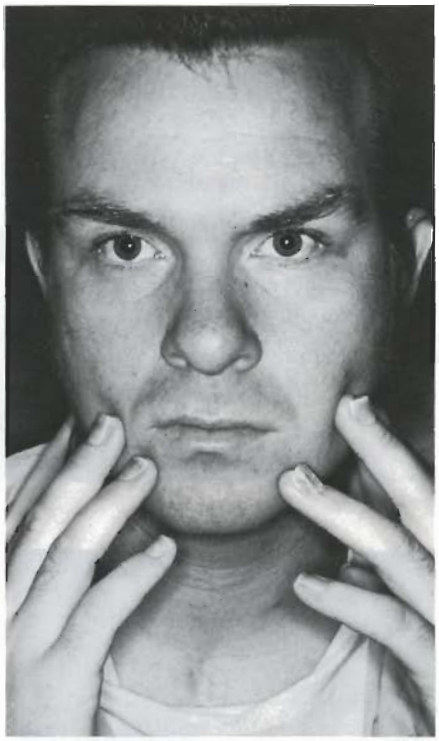

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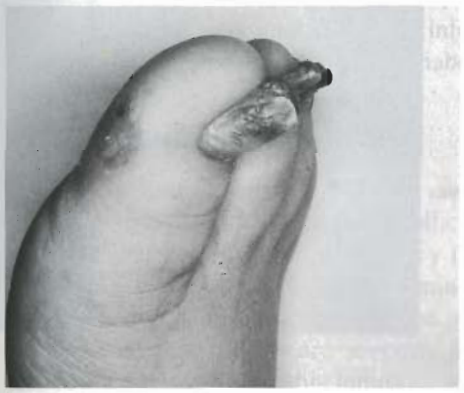

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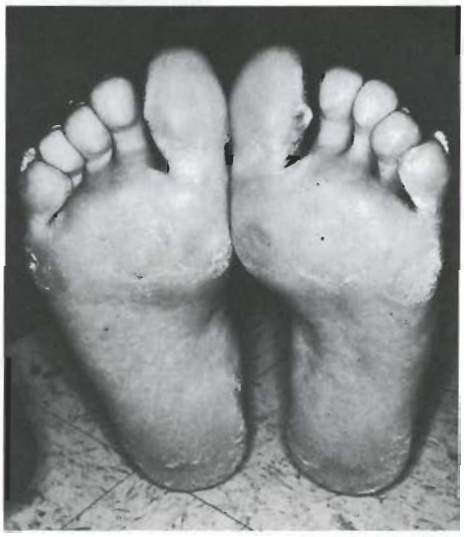

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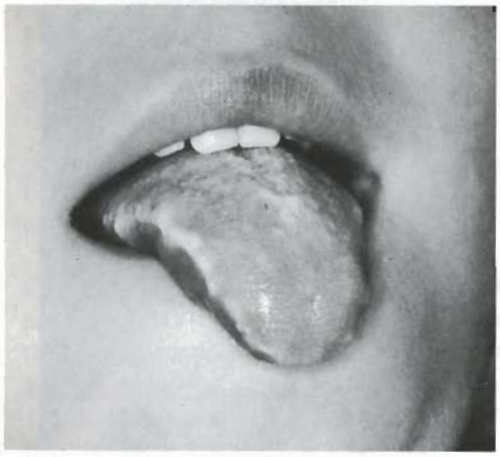
Fig. 1. Three-year-old boy (propositus) after tracheostomy for laryngeal obstruction. Note thick discolored nails.

Fig. 2. The boy's father at 25 yr with thick, discolored fingernails and a tracheostomy scar.

Fig. 3. The boy's foot with thickened, discolored nails and callous formation.

Fig. 4. The father's soles with marked callouses over the heels and heads of metatarsals and evidence of blister formation on toes. The yellow callouses are much more striking in real life than is depicted in a black and white photograph. The feet were moist from perspiration. Thickened, discolored toenails are partially visible in this view.



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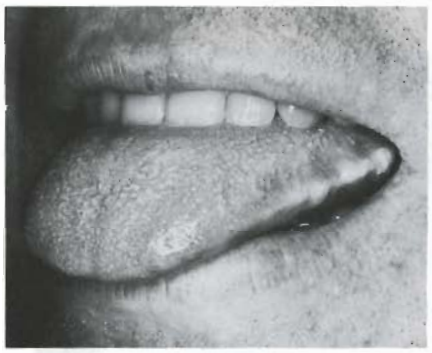

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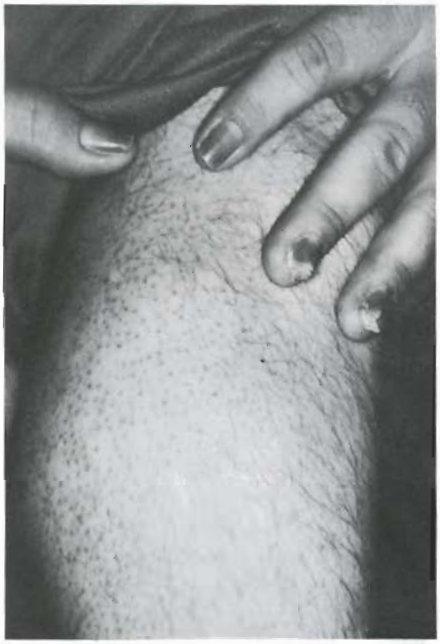

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Fig. 5. The boy's tongue with scalloped edge and leukokeratosis oris.

Fig. 6. Father's tongue with leukokeratosis oris and scalloped, white edge of tongue. All visible teeth have been capped because of the extensive caries commonly seen in affected members of this family.

Fig. 7. Follicular keratosis on the boy's elbow and knees.

Fig. 8. Follicular keratosis on the father's knee and pachyonychia.

section at 10 mo because of cephalopelvic disproportion. Birth weight was 4.53 kg (atypical for a family with no evidence of diabetes in mother). At birth, he appeared normal; an inguinal hernia was repaired at 1 mo.

His first three primary teeth erupted at 1 wk (early or prenatal eruption of primary teeth has been observed in PC). By 3 mo, he had all 20 primary teeth.

By 2 wk, his nails began to discolor and thicken. By about 4 mo, the initially yellow discoloration had become brown, and all nails were markedly thickened and "pinched in" at the edges. Distortion of shape and depth of color increased distally from the base of the nail.

In infancy, he was hospitalized for severe episodes of stridor and respiratory distress that eventually received the diagnosis of congenital tracheal stenosis and a tracheostomy at 6 mo. He did well while the tracheostomy was in place (18 mo) and for the year after its removal up until the present attack.

Generalized excessive sweating has been noted since about 2 or 3 mo. This is especially pronounced on palms and soles. Plantar callouses (rarely blisters) have occurred since he began walking at 1 yr.

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. All visible teeth
of this family.

## FAMILY HISTORY

The patient's father had almost identical signs of pachyonychia, leukokeratosis oris with scalloped tongue edge, plantar callouses (more severe than in son), and follicular keratosis on the extensor surface of the limbs (Figs. 2, 4, 6, 8). Since childhood, he has had a marked unexplained visual loss in his right eye.

The clinical history of the two is remarkably similar. The father also required a tracheostomy in infancy (Fig. 2).

With the father's assistance, we were able to contact by telephone five other affected relatives. Another unaffected, but knowledgeable, maternal aunt provided confirmation of facts and additional information (Fig. 9). Two paternal uncles and one paternal aunt of the father have diabetes mellitus.

## DISCUSSION

We present a kindred with 17 cases of PC in four generations. All affected members have had thickened nails, follicular keratosis, oral leukokeratosis, hyperhidrosis, plantar keratosis and a tendency to form blisters over pressure areas. Blisters will form on the feet with only 15 min of walking in warm weather. Many of the affected individuals considered this the most troublesome of all manifestations of PC; employment possibilities are severely limited. In addition, there are several other unusual aspects of PC in this family.

Severe laryngeal involvement, though reported before [Cohn, McFarlane, and Knox, 1976], seems to be unusually frequent in this family and has caused severe morbidity and near mortality. Nine persons have had severe recurrent upper respiratory symptoms requiring hospitalization; these were variously diagnosed as croup, bronchitis, or laryngitis. There were, in addition, three infant deaths attributed to pneumonia. Five affected individuals have chronic hoarseness. Two have required life-saving tracheostomies.

Many of the affected members have characteristics that have not been emphasized as a component of this syndrome. One of these is a propensity for early (under

Fig. 9. The 17 member, four generation PC kindred.

30) loss of secondary teeth. This appears owing to a marked caries and is not seen in unaffected relatives. This is noted in the majority of affected adults.

There is also early adult onset of mild-to-moderate large joint arthritis in four affected members (three sibs and the maternal grandfather). This may be coincidental, although it may be a pleiotropic manifestation of PC. Skeletal defects have been noted previously [Soderquist and Reed, 1968; Moldenhauer and Ernst, 1968]. Thus, all three germ layers might be affected in this syndrome, ie, ectoderm (nails, skin, hair, teeth, and oral mucosa), endoderm (laryngeal mucosa), and mesoderm (joints and laryngeal cartilage).

Other PC manifestations seen in this family include natal teeth or early eruption in at least three members, hair abnormalities (bushy eyebrows) in at least four members, and a scalloped tongue edge in association with leukokeratosis oris in at least three relatives. The number of affected persons with involvement of teeth, tongue, and hair probably is greater than noted because of limitations of knowledge of the six informants. There is no history of cancer, corneal blindness, deafness, skin cysts, increased occurrence of abortion, dyspareunia, or gross mental retardation in affected members of this pedigree.

The 17 affected relatives (9M and 8F) include two deceased adults who presumably died of heart attacks. Four affected children are 3 yr old or younger. The ratio of affected to unaffected offspring from affected parents (16:28) is a suggestive deviation (not statistically significant) from the 50:50 expectation in an autosomal dominant inheritance pattern and has not been noted before. There is an equal number of affected male and affected female parents (six each); the number of offspring produced by affected males (20) is not statistically different from the number produced by affected females (24). However, while affected males produced essentially the expected 1:1 ratio of affected to unaffected offspring (9 to 11), the affected females produced affected to unaffected offspring in a ratio of 7:17, which is a suggestively significant deviation from a 1:1 ratio. One neonatal death is not included in the ratios. Nail changes are evident several weeks after birth. The infants who died after this period were believed unaffected.

The distortion is difficult to explain in the reported absence of an increased incidence of abortions or impaired fertility and with reported near 100% penentrance in this syndrome. One could postulate that affected women have had increased numbers of early, unrecognized loss of affected embryos. Could there be a maternal humoral effect that compounds problems in affected offspring, or a reproductive tract mucosal or placental defect acting when both mother and embryo are affected as is the case in myotonic dystrophy and possibly in neurofibromatosis? Few other large PC pedigrees are available. It will be important to determine if in other pedigrees a similar distortion is seen before concluding significance from this observation.

The presumed origin of PC in this kindred is a mutation in the Dutch paternal great grandfather of the index case, although it is not possible to rule out illegitimacy (He was quite severely affected. On several occasions, he was offered a job as a freak in a circus side show). Many of the early cases described were also apparently spontaneous mutations, as congenital syphilis or other infections were blamed as causative.

Although most cases were identified by the highly penetrant pachyonychia, observations of index cases and affected relatives indicate that there is a wide range of severity with regards to involvement of other body tissues and their intensity and

Fig. 9. The 17 member, four generation PC kindred.

onset. Differences appear to be more pronounced between unrelated families than within kindreds. This is probably best explained on the basis of epistasis; however, linkage studies have not been done to be sure the same mutation is present in every affected family. Genetic heterogeneity cannot be excluded.

The basic pathogenetic process in PC is not known. Somatic cell studies are needed. Persons with this syndrome usually do not show any manifestations at birth, although some are born with one or more primary teeth. Visible changes in the nails usually are not seen until several weeks after birth, at which time primary teeth also may begin to erupt. Thus, the term "congenita" is somewhat of a misnomer. Perhaps an alternate label such as "Pachyonychia neonatorum" would be better.

The above pedigree increases the number of reported cases by 11.3% to a present total of 167. It is hoped that this paper and discussion will broaden the understanding of the complexity of this syndrome and will stimulate additional reports and appropriate research.

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