Use of Articles in the Pachyonychia Congenita Bibliography

The articles in the PC Bibliography may be restricted by copyright laws. These have been made available to you by PC Project for the exclusive use in teaching, scholarship or research regarding Pachyonychia Congenita.

To the best of our understanding, in supplying this material to you we have followed the guidelines of Sec 107 regarding fair use of copyright materials. That section reads as follows:

Sec. 107. - Limitations on exclusive rights: Fair use
Notwithstanding the provisions of sections 106 and 106A, the fair use of a copyrighted work, including such use by reproduction in copies or phonorecords or by any other means specified by that section, for purposes such as criticism, comment, news reporting, teaching (including multiple copies for classroom use), scholarship, or research, is not an infringement of copyright. In determining whether the use made of a work in any particular case is a fair use the factors to be considered shall include - (1) the purpose and character of the use, including whether such use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the amount and substantiality of the portion used in relation to the copyrighted work as a whole; and (4) the effect of the use upon the potential market for or value of the copyrighted work. The fact that a work is unpublished shall not itself bar a finding of fair use if such finding is made upon consideration of all the above factors.

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.
Ichthyosis
Etiology, Diagnosis, and Management

John J. DiGiovanna1,2,3 and Leslie Robinson-Bostom2,4

1 Division of Dermatopharmacology, Brown Medical School and Rhode Island Hospital, Providence, Rhode Island, USA
2 Department of Dermatology, Brown Medical School and Rhode Island Hospital, Providence, Rhode Island, USA
3 Basic Research Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA
4 Department of Pathology, Rhode Island Hospital, Providence, Rhode Island, USA

Contents

Abstract .................................................................................................................................................. 81

1. Etiology ........................................................................................................................................ 82
   1.1 Hereditary Ichthyoses .................................................................................................................. 82
       1.1.1 Congenital Autosomal Recessive Ichthyosis ........................................................................... 83
       1.1.2 Epidermolytic Hyperkeratosis .............................................................................................. 83
       1.1.3 Ichthyosis Vulgaris .............................................................................................................. 83
       1.1.4 Ichthyosis Bullous of Siemens ............................................................................................. 85
       1.1.5 X-Linked Ichthyosis ........................................................................................................... 85
       1.1.6 Erythrodermatodermia ........................................................................................................ 86
       1.1.7 Sjögren-Larsson Syndrome ................................................................................................ 86
       1.1.8 Netherton's Syndrome ....................................................................................................... 87
       1.1.9 RSF's Disease ...................................................................................................................... 87
       1.1.10 Tay-Sachs Syndrome - Trichothiodystrophy ...................................................................... 87
   1.2 Acquired Ichthyosis ................................................................................................................... 88

2. Diagnosis ...................................................................................................................................... 88
   2.1 Clinical Diagnosis ...................................................................................................................... 88
       2.1.1 History/Family History/Pattern of Inheritance ...................................................................... 89
       2.1.2 Physical Examination ......................................................................................................... 89
   2.2 Laboratory Diagnosis ............................................................................................................... 89
       2.2.1 Clinical Pathology .............................................................................................................. 89
       2.2.2 Anatomic Pathology .......................................................................................................... 90

3. Management .................................................................................................................................. 90
   3.1 Topical Therapy ....................................................................................................................... 91
       3.1.1 Hydration and Lubrication .................................................................................................. 91
       3.1.2 Keratolytics ...................................................................................................................... 91
   3.2 Systemic Treatment ................................................................................................................ 92

4. Conclusion ................................................................................................................................... 93

Abstract
The ichthyoses are a heterogeneous group of disorders with both inherited and acquired forms. Clinical presentation, pattern of inheritance, and laboratory evaluation may establish a precise diagnosis, which can assist in prognosis and genetic counseling.

Congenital autosomal recessive ichthyosis (CARI) usually presents at birth, often as a collodion baby. CARI can progress into any one of a spectrum of disorders. Lamellar ichthyosis is characterized by dark, plate (armor)-like scale. This disease is often caused by mutations in the gene encoding the enzyme transglutaminase 1. Congenital ichthyosiform erythroderma is another phenotype within CARI, marked by generalized redness and fine white scale.

Epidermolytic hyperkeratosis is an autosomal dominant disorder characterized by hyperkeratosis and blistering, and at least six clinical phenotypes have been described. It may be due to mutations in the gene encoding the intermediate filament proteins keratin 1 and 10.
Ichthyosis vulgaris is the most common ichthyosis, and is inherited in an autosomal dominant pattern. Involvement is generally mild and may vary greatly with climate and humidity. X-linked ichthyosis, due to a defect in the enzyme steroid sulfatase, affects males with generalized scaling that usually begins soon after birth. There may be associated corneal opacities that do not affect vision.

Sjögren-Larsson syndrome is an autosomal recessive ichthyosis associated with progressive spastic paralysis and mental retardation. This condition is caused by mutations in the gene for fatty aldehyde dehydrogenase. Refsum's disease, due to accumulation of phytic acid, results in ichthyosis and progressive neurologic dysfunction.

The erythrodermatodermas are characterized by hyperkeratosis and localized erythema. Erythrodermatodermia variabilis is autosomal dominant and characterized by generalized or localized hyperkeratosis and migratory red patches. Mutations in the genes encoding the gap junction proteins, connexins, underlie this disorder.

Netherton's syndrome is an autosomal recessive disorder characterized by ichthyosis, a hair shaft abnormality and atopy. The ichthyosis may present at birth with erythroderma or in some cases a colloidon presentation. However, a frequent characteristic skin manifestation is ichthyosis linearis circumflexa. Netherton's syndrome has been found to be due to an abnormality in a serum protease inhibitor. Acquired ichthyosis can have a variety of underlying causes including neoplastic, infectious, drugs, endocrine, metabolic, autoimmune, malabsorptive states, and hereditary. Topical, and in more severe cases, systemic, therapy are useful in managing this array of disorders of cornification.

The term ichthyosis is derived from the Greek word 'ichthys' and in general refers to a group of scaly skin disorders. However, the term is also used to refer to specific diseases such as ichthyosis vulgaris or lamellar ichthyosis. Scaling in ichthyosis covers a very broad spectrum, from severe to mild, where it blends into the realm of 'dry skin'. Xerosis is the term used to describe dry skin. Usually xerosis refers to the 'normal' or non-pathologic state. However, it is also used to describe dry skin that occurs in those patients with specific disorders. Ichthyosis vulgaris is generally considered among the mildest presentations of ichthyosis. Within the scope of ichthyosis vulgaris, there are patients with very mild involvement that overlaps with xerosis. Even in patients with a specific, diagnosed disorder, such as ichthyosis vulgaris or X-linked ichthyosis, there may be a wide range of severity and variability in severity over time.

1. Etiology

Ichthyoses are a heterogeneous group of disorders with both inherited and acquired forms. While the severe forms of hereditary ichthyosis usually present at birth, several types of hereditary ichthyosis may develop later in life. A specific diagnosis of ichthyosis in an individual or within a family is important for both prognosis and genetic counseling. Several features are useful in establishing a diagnosis. These include both clinical and laboratory features.

A major function of the epidermis is to produce the stratum corneum, which is composed of corneocytes surrounded by intercellular matrix. This configuration has been viewed as a 'bricks and mortar' array, with the protein-enriched corneocytes being the bricks surrounded by the intercellular mortar of hydrophobic, lipid-enriched membrane bilayers.[1] It is thought that the keratin-laden corneocytes account for the resilient and water retention characteristics of the stratum corneum while the lipid rich matrix is the barrier to water loss. The stratum corneum is the focal point of the abnormality in all ichthyoses. Rather than a simple, inert structure, it is a complex, dynamic interface between the organism and the environment.[2] This most superficial skin layer is the interface with the environment and is heavily influenced by environmental conditions. Ichthyosis can be a manifestation of increased stratum corneum production (hyperproliferation), as occurs in epidermolytic hyperkeratosis, or abnormal corneocyte shedding (disahesion), as occurs in lamellar ichthyosis. Ichthyosis is exacerbated by cold, dry climates and improves in humid environments. Occasionally the disease can have symptoms masked in a warm, humid climate only to undergo severe exacerbation, or even first present with symptoms, when the individual moves to a cold, dry climate.

1.1 Hereditary Ichthyoses

Hereditary ichthyosis can be present at birth or can develop later in life. A family history and pedigree is an important part of the evaluation of patients with ichthyosis and can be helpful in identifying the pattern of inheritance. A history of parental consanguinity suggests a recessive inheritance. Alternatively, a history of an affected parent and sibling would suggest autosomal dominant inheritance. Occurrence in males related through the maternal side of the family would suggest X-linked ichthyosis. Table I lists a number of hereditary ichthyosiform dermatoses with their prominent features, sorted by pattern of inheritance.[3] This table may be helpful where the pedigree is informative.
The nomenclature used to identify different ichthyoses can be confusing and has changed over time. Earlier, the terms ‘bullous congenital ichthyosiform erythroderma’ and ‘nonbullous congenital ichthyosiform erythroderma’ were in common use. These names derived from the clinical appearance during the newborn period in order to distinguish infants with generalized erythroderma who had blistering from those who did not have blistering. Today the term ‘epidermolytic hyperkeratosis’ is generally used instead of ‘bullous congenital ichthyosiform erythroderma’. The term ‘nonbullous congenital ichthyosiform erythroderma’ had included a variety of clinical phenotypes. In 1985, our understanding of these diseases, and also their terminology, was refined by distinguishing two subsets of patients who had autosomal recessive ichthyosis: lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. Today, many authors have dropped the ‘nonbullous’.

1.1.1 Congenital Autosomal Recessive Ichthyosis

Conceptually, congenital autosomal recessive ichthyosis is a useful term that encompasses several clinical phenotypes, each of which may be difficult to precisely diagnose on the basis of appearance, but which share congenital onset and pattern of inheritance. Within this group there are two well defined clinical phenotypes: lamellar ichthyosis (figure 1) and congenital ichthyosiform erythroderma (figure 2). Lamellar ichthyosis usually presents at birth with the severe phenotype of a collodion baby. Over the first few days the membrane is shed and over time the child develops dark, plate (armor)-like or lamellar scale. Lamellar ichthyosis is often caused by mutations in the gene encoding the enzyme transglutaminase 1 (TGM1). Congenital ichthyosiform erythroderma can also have a collodion presentation. Children with congenital ichthyosiform erythroderma often have an appearance of generalized redness with fine white scale. Some individuals with congenital ichthyosiform erythroderma may also have mutations in TGM1. There are many individuals with congenital autosomal recessive ichthyosis who have phenotypes intermediate between lamellar ichthyosis and congenital ichthyosiform erythroderma, and these may have different underlying molecular defects. There may be several different genetic loci underlying these clinically similar disorders. It is important to recognize that in spite of the severe appearance of a collodion baby in the newborn period, this phenotype progresses to a spectrum of disorders ranging from the severe lamellar ichthyosis to the extremely mild ‘self-healing’ collodion baby.

1.1.2 Epidermolytic Hyperkeratosis

Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma) is an autosomal dominant disorder characterized by hyperkeratosis and, often, blistering (figure 3). The clinical manifestations of epidermolytic hyperkeratosis vary widely and at least six clinical phenotypes have been described. Epidermolytic hyperkeratosis is unusual among the ichthyoses in that it has a diagnostic histologic picture. While there are differences in clinical appearance, all share similar histology. Approximately two-thirds of cases have been found to be due to mutations in the gene encoding keratin 1 or keratin 10. Epidermolytic hyperkeratosis has a high frequency of spontaneous mutation, which presents histologically and clinically as epidermolytic hyperkeratosis without a family history. In this circumstance, the
<table>
<thead>
<tr>
<th>Mode of inheritance</th>
<th>Diagnosis</th>
<th>Onset</th>
<th>Characteristic clinical features</th>
<th>Associated features</th>
<th>Etiology</th>
<th>Skin histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td>Ichthyosis vulgaris</td>
<td>Infancy/childhood</td>
<td>Fine or centrally tacked down scale with superficial fissuring. Relative flexural sparing, worse on lower extremities. Hyperlinear palms/soles</td>
<td>Keratosis pilaris, atopy</td>
<td>Unknown, decrease or absent filaggrin or its precursor pro-filaggrin</td>
<td>Hyperkeratosis, may have decreased or absent granular layer</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma)</td>
<td>Birth</td>
<td>Heterogeneous. May have verrucous, firm, hyperkeratotic (hystric) spines, often linearly arrayed in flexural creases, blisters, may have erythroderma and or palm plantar keratoderma</td>
<td>Frequent skin infections, characteristic pungent odor</td>
<td>Mutations in gene encoding keratin 1 or keratin 10. In Vörmel type (confined to palms/soles) keratin 9</td>
<td>Hyperkeratosis, vacuolated degeneration of the epidermal granular (and often deeper) layer; large, irregular keratohyalin granules</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Ichthyosis bullosa of Siemens</td>
<td>Birth</td>
<td>Redness and blistering at birth. Later develop hyperkeratosis, accentuated over flexures. Molting: collarette-like lesion where uppermost epidermis has been lost</td>
<td>Mutations in gene encoding keratin 2a</td>
<td>Hyperkeratosis and epidermal vacuolization, similar to epidermolytic hyperkeratosis but confined to the granular layer</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Erythrokeratodermia variabilis: generalized type</td>
<td>Birth</td>
<td>Generalized hyperkeratosis and figurate, migratory red patches</td>
<td>Red patches move over minutes to hours, may be triggered by changes in temperature</td>
<td>Mutations in gene encoding connexin 31 or 30.3</td>
<td>Hyperkeratosis, acanthosis, papillomatosis, capillary dilatation; epidermis may have 'church spire' appearance</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Erythrokeratodermia variabilis: localized type</td>
<td>Variable</td>
<td>Localized hyperkeratotic plaques with figurate, migratory red patches</td>
<td>Hyperkeratotic plaques may be induced by trauma. Considerable intrafamilial variability</td>
<td>Mutations (usually deletions) in gene encoding steroid sulfatase</td>
<td>Hyperkeratosis, may have hypergranulosis, nonspecific</td>
</tr>
<tr>
<td>X-linked recessive</td>
<td>X-linked ichthyosis</td>
<td>Birth/Infancy</td>
<td>Fine to large scales, comma-shaped corneal opacities on posterior capsule, increased migration of beta-lipoproteins on electrophoresis</td>
<td>Cryptorchidism, female carriers may have corneal opacities and delay of onset or progression of affected pregnancies</td>
<td>Mutations in gene encoding transglutaminase 1, other disease causing loci mapped to chromosome 2q35-35 and 10p12-q12</td>
<td>Hyperkeratosis, acanthosis. Nonspecific</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Lamella ichthyosis</td>
<td>Birth, often collodion presentation</td>
<td>Large, plate-like, brown, scale over most of the body, accentuated on lower extremities. Ectropion, alopecia</td>
<td>Heat intolerance</td>
<td>May have mutations in gene encoding transglutaminase 1 and other disease causing loci mapped to chromosome 17p13.2-13.1</td>
<td>Hyperkeratosis, acanthosis, may show parakeratosis. Nonspecific</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Congenital ichthyosiform erythroderma</td>
<td>Birth, often collodion presentation</td>
<td>Fine, white scale, generalized erythroderma</td>
<td>Heat intolerance</td>
<td>Mutations in gene encoding transglutaminase 1 in few, other disease causing loci mapped to 3p21 and 17p13.2-13.1</td>
<td>Hyperkeratosis, acanthosis, may show parakeratosis. Nonspecific</td>
</tr>
</tbody>
</table>
Table 1 continued

disease is then transmitted as an autosomal dominant to future
generations. Spontaneous mutation can occur after fertilization,
as a postzygotic mutation, leading to mosaic involvement. These
patients present with streaks of hyperkeratosis of the skin distrib-
uted along Blaschko’s lines. In this clinical presentation, fre-
quently there is involvement of the germ line, and the disease is
then transmitted with the full clinical phenotype, which is usually
more extensive and severe.

1.1.3 Ichthyosis Bullosa of Siemens
Ichthyosis bullosa of Siemens is an autosomal dominant dis-
order that is similar to epidermolytic hyperkeratosis. The disease
is also characterized clinically by hyperkeratosis and blistering;
however, in contrast to epidermolytic hyperkeratosis, this occurs
more superficially within the epidermis. The superficial location
of the pathology can result in areas of skin where the stratum
corneum has been lost while leaving the remainder of the epider-
mis in place. Clinically this has been called molting. While the
histologic changes of epidermolytic hyperkeratosis include vac-
ular degeneration throughout the viable supra-epidermal layers,
in ichthyosis bullosa of Siemens this change is confined to the
granular layer. While the underlying defect in epidermolytic hy-
perkeratosis is a mutation in the differentiation keratins 1 or 10,
in ichthyosis bullosa of Siemens the defect is in keratin 2e, which
is expressed in the granular layer, consistent with both the clinical
and histologic manifestations observed.13

1.1.4 Ichthyosis Vulgaris
Ichthyosis vulgaris is the most common ichthyosis with an
incidence as high as 1 in 250.14 It is inherited in an autosomal
dominant pattern. Involvement is usually mild (figure 4) and of-
ten occurs in association with atopy, hyperlinear palms, and ker-
atosis pilaris. Involvement is usually greatest over the lower ex-
tremities. In humid climates, individuals with ichthyosis vulgaris
may have ‘normal’ appearing skin, only to become dry and scaly
in cold, dry environments. The etiology of ichthyosis vulgaris is
not known. However, there is reduced or absence of keratohyalin
granules in the epidermis. Even when present on light micros-
copy, keratohyalin granules in ichthyosis vulgaris are abnormal
on electron microscopy.15 In addition, there is a decrease or ab-

cence of profilaggrin, a major component of keratohyalin gran-
ules.16,17

Because there is no firm diagnostic criteria, nor any objective
test to diagnosis ichthyosis vulgaris, this clinical phenotype could
be the result of several different underlying disorders that could
have different molecular basis.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Features</th>
<th>Laboratory Findings</th>
<th>Genetic Basis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive Lamella ichthyosis/ Congenital ichthyosiform erythroderma overlap</td>
<td>Usually birth, often collodion presentation</td>
<td>Heterogeneous: scale may be fine to large with various extent of erythroderma</td>
<td>Heat intolerance</td>
<td>Unknown</td>
</tr>
<tr>
<td>Autosomal recessive Netherton's syndrome</td>
<td>Birth, may have collodion presentation</td>
<td>Ichthyosis linearis circumflexa or similar to congenital ichthyosiform erythroderma, trichorrhexis invaginata</td>
<td>Atopy, high serum levels of Immunoglobulin E, may have aminoaciduria</td>
<td>Mutation in gene encoding serine protease inhibitor LEKTI</td>
</tr>
<tr>
<td>Autosomal recessive Refsum's disease</td>
<td>Ichthyosis develops in adulthood</td>
<td>Progressive neurologic dysfunction, skeletal, cardiac and renal abnormalities</td>
<td>Retinitis pigmentosa</td>
<td>Mutations in gene encoding phytanic acid oxidase (phytanoyl-CoA hydroxylase)</td>
</tr>
<tr>
<td>Autosomal recessive Sjögren-Larsson syndrome</td>
<td>Ichthyosis apparent at birth</td>
<td>Generalized coarse hyperkeratosis, spastic diplegia, mental retardation, retinal glistening white dots</td>
<td>Short stature, seizures</td>
<td>Mutations in gene encoding fatty aldehyde dehydrogenase</td>
</tr>
<tr>
<td>Autosomal recessive IBIDS (trichochothyroderma, Tay's syndrome)</td>
<td>Ichthyosis apparent at birth, may have collodion presentation</td>
<td>Ichthyosis, brittle hair, intellectual impairment, decreased fertility, short stature</td>
<td>Hypogonadism, abnormally low sulfur content of hair, hair shaft abnormalities</td>
<td>Unknown</td>
</tr>
<tr>
<td>PIBI(D)S</td>
<td>Ichthyosis mild and not congenital</td>
<td>Similar to IBIDS but with photosensitivity and usually without hypogonadism</td>
<td>Abnormally low sulfur content of hair, hair shaft abnormalities</td>
<td>Mutations in DNA repair genes ERCC2/XPB or ERCC3/XPD</td>
</tr>
</tbody>
</table>

CoA = coenzyme A; IBIDS = ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature; LEKTI = lympho-epithelial Kazal-type-related inhibitor; PIBI(D)S = photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature (usually without hypogonadism).
1.1.5 X-Linked Ichthyosis

X-linked ichthyosis may present with scaling in newborns and involvement is usually more severe and extensive than ichthyosis vulgaris (figure 5), generally involving most or all of the skin surface area. It is a recessive disorder that occurs with a frequency of 1:2000–6000 in males.[3] Adult patients may have comma shaped corneal opacities, which do not affect vision. This disorder is known to be due to a defect in the enzyme sterol sulfatase, which catalyzes the hydrolysis of cholesterol sulfate. In affected pregnancies, the absence of steroid sulfatase in the fetal placenta is associated with failure of labor to initiate or progress normally. Cholesterol sulfate levels are elevated in serum, epidermis and scale.

1.1.6 Erythrokeratodermia

The erythrokeratodermae are a group of disorders characterized by hyperkeratosis and localized erythema. While two clinical phenotypes, erythrokeratodermia variabilis and progressive symmetric erythrokeratodermia, can be delineated, they have overlapping features.

Erythrokeratodermia variabilis is an autosomal dominant disorder that usually presents at birth or within the first year of life. Patients with erythrokeratodermia variabilis can have generalized involvement with persistent, brown hyperkeratosis. In contrast, a localized type is characterized by sharply demarcated, hyperkeratotic plaques, which can remain fixed. Both types have sharply demarcated, migratory, red patches, which may be triggered by trauma or a change in temperature. There may be palmar/plantar hyperkeratosis. Missense mutations in the connexin gene GJB3 have been found in four families with erythrokeratodermia variabilis.[18,19] This gene encodes connexin 31, a gap junction protein, suggesting defective intercellular gap junction mediated communication as the underlying pathophysiology.

Progressive symmetrical erythrokeratodermia is characterized by erythematous, hyperkeratotic plaques, which are distributed symmetrically over the extremities, buttocks and often the face. The migratory erythema of erythrokeratodermia variabilis is absent. The disorder is inherited as an autosomal dominant trait, but with incomplete penetrance.

1.1.7 Sjögren-Larsson Syndrome

Sjögren-Larsson syndrome is an autosomal recessive condition of congenital ichthyosis with progressive development of spastic paralysis and mental retardation. Patients with this ichthyosis often have pruritus. One characteristic ocular finding that patients may have is the presence of glistening white dots in the macula of the retina. This syndrome is associated with abnormal fatty alcohol metabolism.

Fatty alcohol:nicotinamide adenine dinucleotide (NAD) + oxidoreductase (FAO) is an enzyme with two proteins, which sequentially catalyze the oxidation of fatty alcohol to fatty aldehyde and then fatty acid. The fatty aldehyde dehydrogenase com-
ichthyosis vulgaris is on the leg shows scaling and, in this patient, keratosis pilaris. Typically, involvement is greater over the lower extremities and there is no erythroderma.

ponent is affected in Sjögren-Larsson syndrome and mutations have been found in the fatty aldehyde dehydrogenase gene. Prenatal diagnosis has been accomplished by enzyme assay and is now possible based on mutation analysis.

1.1.8 Netherton’s Syndrome

Netherton’s syndrome is a rare, autosomal recessive disorder characterized by ichthyosis, a hair shaft abnormality, and atopy. The disorder may present at birth with erythroderma or, in some cases, a collodion phenotype. However, a frequent and characteristic finding is ichthyosis linearis circumflexa. This is a distinctive presentation of polycyclic, serpiginous, erythrodermatous plaques, punctuated at the margins by a characteristic double-edged scale. In some patients the ichthyosis resembles lamellar ichthyosis or congenital ichthyosiform erythroderma. Trichorrhexis invaginata (bamboo hair), an abnormality of the hair shaft, is present in most patients. However, only a small percentage of hairs may be affected. This hair structure abnormality appears as a ball and socket deformity on light microscopy. Atopy is common and high serum levels of immunoglobulin E may occur. Mutations in serine protease inhibitor, Kazal type 5 (SPINK5) have been found in families with Netherton’s syndrome. SPINK5 encodes a serine protease inhibitor (lympho-epithelial Kazal-type-related inhibitor [LEKTI]), supporting a role for this protein in epidermal barrier function and immunity.

1.1.9 Refsum’s Disease

Refsum’s disease (phytanic acid oxidase deficiency, heredopathia atactica polyneuritisformis) is a rare autosomal recessive disorder of lipid metabolism resulting from a deficiency of phytanic acid oxidase. The clinical features include retinitis pigmentosa, mixed sensorimotor polyneuropathy and cerebellar signs. Cranial nerve dysfunction, papillary dysfunction, electrocardiographic changes, cardiomyopathy, renal tubular dysfunction and epiphyseal dysplasia may be present. Ichthyosis resembling mild ichthyosis vulgaris with fine scale on the lower trunk and limbs clinically coincides or develops after the neurologic and ophthalmologic signs in a variable number of adults. Lamellar type scale may develop in untreated cases. Scandinavians and other Northern European populations are most frequently affected.

Phytanic acid is a branched-chain fatty acid which is exclusively derived from exogenous dietary sources, primarily chlorophyll-containing foods and to a lesser extent dairy products and ruminant fats. Deficiency of phytanic acid oxidase results in accumulation of phytanic acid in tissues and body fluids. It replaces other fatty acids in tissues and binds to sterols. This leads to formation of lipid vacuoles in the basal and supra-basal layers of the epidermis. Phytanic acid and other chlorophyll metabolites bind to the retinoid X receptor (RXR). Phytycan acid can bind RXR similar to 9-cis-retinoic acid, the natural RXR ligand, however the role of this pathway in the pathogenesis of Refsum’s syndrome has not been elucidated.

1.1.10 Tay’s Syndrome – Trichothiodystrophy

Tay’s syndrome is described clinically by the acronym: (I) ichthyosis, (B) brittle hair, (I) intellectual impairment, (D) decreased fertility, and (S) short stature (IBIDS). IBIDS is rare and heterogeneous with an autosomal recessive inheritance pattern and a worldwide distribution. Patients may present at birth with a collodion membrane that evolves into generalized ichthyosis characterized by variable fine translucent scaling to large yellow brown hyperkeratosis. Flexural sparing may occur. Additional features may include palmoplantar hyperkeratosis and nail dystrophy. Ectropion is usually absent. Low birth weight, progeria-like facies with lack of subcutaneous fat, prominent ears and chin recession, short stature and delayed psychomotor development is common. Cryptorchidism occurs in males and impaired sexual maturation in females. The sparse, brittle hair
demonstrates alternating bright and dark (tiger tail) bands under polarization. The hair has a low sulfur content from a decrease in sulfur containing amino acids (trichothiodystrophy). A variety of hair shaft abnormalities may be present including trichoschisis, pili torti, and trichorrhexis nodosa. There may be an undulating contour of the shaft and absent or defective cuticle visualized by scanning electron microscopy.\textsuperscript{[27]}

PIBIDS syndrome (photosensitive trichothiodystrophy) is characterized by photosensitivity in addition to the other clinical findings of IBIDS syndrome. The ichthyosis is milder than in IBIDS and is not present at birth. Hypogonadism is usually absent. These patients have a deficiency of DNA excision repair which in the majority of cases is identical to that observed in xeroderma pigmentosum (XP) complementation group D (ERCC2/XPD).\textsuperscript{[28]} Mutations in the xeroderma pigmentosum complementation group B gene (ERCC3/XPB) have been reported in a few patients.\textsuperscript{[29]} There are patients in the PIBIDS group who have as yet unidentified mutations. One patient was recently described with a mutation of TTD-A.\textsuperscript{[30]} While exaggerated development of skin cancers is observed in patients with XP, this does not occur in patients with PIBIDS syndrome.

1.2 Acquired ichthyosis

Acquired ichthyosis can have a variety of underlying etiologies, including neoplastic, infectious, drugs, endocrine, metabolic, autoimmune, malabsorptive states and hereditary (table II).\textsuperscript{[31]}

The most common malignancy associated with acquired ichthyosis is Hodgkin’s lymphoma.\textsuperscript{[32,33]} However, non-Hodgkin’s lymphoma\textsuperscript{[34,35]} and other malignancies including mycosis fungoides,\textsuperscript{[36]} multiple myeloma,\textsuperscript{[37]} carcinoma of the breast,\textsuperscript{[38,39]} lung and cervix,\textsuperscript{[40]} and Kaposi’s sarcoma\textsuperscript{[41-43]} have been associated with acquired ichthyosis. Sarcomas,\textsuperscript{[44,45]} melanoma, and other neoplastic conditions\textsuperscript{[46-48]} have also been associated with acquired ichthyosis. When ichthyosis develops in association with malignancy, the skin manifestations usually follow the course of the malignancy. The skin manifestations can clear with effective cancer treatment and may be a marker of recurrence. A case of lymphomatoid papulosis was reported to precede the diagnosis of acquired ichthyosis by 2 years.\textsuperscript{[49]}

Acquired ichthyosis has been observed in association with infections including leprosy, HIV and human T-lymphotropic virus 1 and 2.\textsuperscript{[50-53]} The disorder has been observed in up to 30% of patients with AIDS.\textsuperscript{[51,54]} Sarcoid can cause acquired ichthyosis, and the presence of noncaseating granulomas in the dermis can be diagnostic.\textsuperscript{[55-57]} Acquired ichthyosis has been observed with metabolic diseases (e.g. chronic liver disease, chronic renal failure, essential fatty acid deficiencies, pancreatic insufficiency) and endocrine disorders (e.g. hypothyroidism, hyperparathyroidism,\textsuperscript{[58]} hypopituitarism). Connective tissue disease, including systemic lupus erythematosus,\textsuperscript{[59,60]} dermatomyositis,\textsuperscript{[61,62]} mixed connective tissue disease and eosinophilic fasciitis,\textsuperscript{[63]} have been associated with acquired ichthyosis. It can be associated with graft versus host disease after bone marrow transplantation,\textsuperscript{[64,65]} Cholesterol lowering agents (nicotinic acid, triparanol) and other drugs have also been implicated (table II).\textsuperscript{[66-71]}

2. Diagnosis

2.1 Clinical Diagnosis

Several forms of ichthyosis can be diagnosed on clinical features, and in a few, the diagnosis can be confirmed with laboratory testing. However, because of substantial heterogeneity within many forms of ichthyosis, the clinical diagnosis will be elusive in some patients. A number of clinical features are useful for diagnosis. These include personal and family history, pattern of inheritance, age of onset, quality and severity of scale, pres-
Table II. Acquired ichthyosis

**Neoplastic**
- Anaplastic large-cell lymphoma
- Carcinoma of breast
- Carcinoma of cervix
- Carcinoma of lung
- Hodgkin's lymphoma
- Kaposi's sarcoma
- Leiomyosarcoma
- Malignant melanoma
- Multiple myeloma
- Mycosis fungoides
- Non-Hodgkin's lymphoma
- Polycythemia rubra vera
- Rhabdomyosarcoma

**Infectious**
- Leprosy
- HIV
- Human T-lymphotrophic virus

**Endocrine**
- Hyperparathyroidism
- Hypopituitarism
- Hypothyroidism

**Metabolic**
- Celiac disease
- Chronic hepatic disease
- Chronic renal failure
- Essential fatty acid deficiency
- Malabsorption
- Malnutrition
- Pancreatic insufficiency

**Autoimmune/connective tissue**
- Dermatomyositis
- Eosinophilic fasciitis
- Systemic lupus erythematosus

**Drugs**
- Allopurinol
- Butyrophenone
- Climetidine
- Clofazimine
- Disylazine
- Dixyrazine
- Ethionamide
- Hydrochlorothiazide
- Kava
- Lithium salts
- Maprotiline
- Nicotinic acid
- Riboflavin
- Triparanol

**Miscellaneous**
- Haber's syndrome
- Post bone marrow transplantation
- Sarcoidosis

ence/absence and degree of erythroderma, abnormalities in other skin (e.g. ectropion, ecabium) and adnexal structures (e.g. alopecia, hair follicle or shaft abnormality), and involvement of other organ systems.

### 2.1.1 History/Family History/Pattern of inheritance

Many aspects of a patient's history contribute to formulating a diagnosis. These include:

- age and presentation at onset (collodion presentation in lamellar ichthyosis/congenital ichthyosiform erythroderma; blistering in epidermolytic hyperkeratosis)
- history of infections (epidermolytic hyperkeratosis)
- pruritus (Sjögren Larsson syndrome)
- involvement of other organs (neurologic involvement/mental retardation in Sjögren-Larsson syndrome).

Hyposidrosis and heat intolerance are common in lamellar ichthyosis and congenital ichthyosiform erythroderma. A family pedigree may clarify the pattern of inheritance and suggest the diagnosis. For example, a pedigree consistent with X-linked inheritance can be very helpful in suggesting the diagnosis. Once suspected, ophthalmologic exam, demonstrating comma shaped opacities of the posterior capsule, can further support the diagnosis. In some patients, abnormal lipoprotein migration on serum protein electrophoresis can, for a very astute observer, suggest the diagnosis. Finally, assessing steroid sulfatase levels, which can be measured in the serum, can establish the diagnosis with certainty.

### 2.1.2 Physical Examination

Physical examination findings that can help formulate diagnosis include:

- quality and quantity of scale (e.g. fine vs lamellar);
- presence of erythema (e.g. congenital ichthyosiform erythroderma);
- extent and distribution of involvement (e.g. worse over joints in epidermolytic hyperkeratosis);
- character and thickness of hyperkeratotic horn;
- presence or absence of palmar and plantar thickening.

Blistering and infection are common in epidermolytic hyperkeratosis. Ectropion, ecabium and alopecia are common in lamellar ichthyosis. Spastic paralysis and mental retardation are seen in Sjögren-Larsson syndrome, and features of atopy are seen in Netherton’s syndrome.

### 2.2 Laboratory Diagnosis

#### 2.2.1 Clinical Pathology

Several types of laboratory information can be helpful in establishing a specific diagnosis of ichthyosis. In X-linked ichthyosis, due to steroid sulfatase deficiency, cholesterol sulfate levels
are elevated in the serum, epidermis and scale. There may be increased mobility of β-(low density) lipoproteins on lipoprotein electrophoresis, which may suggest the diagnosis. The diagnosis of X-linked ichthyosis is usually confirmed by finding elevated serum cholesterol sulfate levels in serum.

In patients with a clinical presentation suggestive of Sjögren-Larsson syndrome, FAO activity can be measured in fibroblasts. In addition, the diagnosis can be confirmed by mutational analysis, identifying the mutations in the fatty aldehyde dehydrogenase (FALDH) gene.

The diagnosis of lamellar ichthyosis can be confirmed in some cases by identification of mutations in TGM1, the gene that encodes the enzyme transglutaminase 1. However, it is not certain that all individuals with TGM1 mutations have the severe phenotype of lamellar ichthyosis, since there may be some individuals with congenital ichthyosiform erythroderma who have mutations in the same gene.

In about three-quarters of cases of epidermolytic hyperkeratosis, mutations can be found in the genes that encode the proteins keratin 1 and 10. The keratin 1 and 10 proteins are important to the structural integrity of supra-basilar keratinocytes. Similarly, mutations in the gene-encoding keratin 2e are found in ichthyosis bullosa of Siemens. Molecular defects in other keratins have been associated with a variety of dermatologic disorders.

For a variety of ichthyoses, in families where a mutation is identified and a genetic diagnosis is established, prenatal diagnosis may be performed if desired. There are a number of specialized laboratories that are capable of performing mutational analysis; a listing is available on the Internet (at www.genetests.org).

Patients with Netherton’s syndrome may have elevated serum levels of immunoglobulin E. In Refsum’s disease, there is an accumulation of phytic acid in tissues and body fluids. Serum phytic acid levels are greatly elevated in all patients and diminished activity of phytic acid oxidase can be measured in fibroblast cultures. The cerebrospinal fluid has an increase in protein concentration without pleocytosis.

### 2.2.2 Anatomic Pathology

The histologic features in most forms of ichthyosis are not specific and, therefore, are suggestive rather than diagnostic. For example, classic lamellar ichthyosis may simulate biopsies obtained from the normal palm or sole. Congenital ichthyosiform erythroderma demonstrates nonspecific psoriasiform hyperplasia with overlying parakeratotic scale. In ichthyosis vulgaris and most forms of acquired ichthyosis, an absent or decreased granular cell layer is usually observed. While in acquired ichthyosis associated with sarcoidosis, sarcoïdal granulomata (naked tubercles) are seen.

The histologic features of epidermolytic hyperkeratosis are characteristic and diagnostic. Bullous and normal-appearing skin show similar features. The stratum corneum is tremendously thickened and the supra-basilar malpigian layer shows varying sized clear spaces surrounding keratinocyte nuclei and indistinct cell boundaries (vacuolar degeneration) [figure 6]. There is hyper-granulosis with irregularly sized and shaped trichohyalin-like and keratohyalin-like granules. Electron microscopy reveals clumped tonofilaments containing the terminal differentiation keratin intermediate filaments keratin 1 and 10. The light microscopic features of ichthyosis bullosa of Siemens are similar to epidermolytic hyperkeratosis but the findings are primarily confined to the upper epidermis.

### 3. Management

In addition to the visible cosmetic concerns, patients with ichthyosis can have pruritus, thickening of the skin with cracking and fissuring, decreased range of motion at joints, decreased tactile sensitivity of the fingers, and skin infection. Some patients have hypohidrosis with heat intolerance. The symptoms of ichthyosis can vary between patients and even within the same patient over time. Therefore, it is important to tailor therapy to the individual patient.

There are a number of concepts that can be useful in guiding therapy. In general, scaly skin is characterized by an abnormal barrier function, and increased transepidermal water loss. This skin is prone to enhanced penetration of drugs, tendency
towards irritation, and poor retention of moisture. When dryness and scaling are minimal, hydration and lubrication can often easily improve barrier function and decrease scaling. However, as scaling becomes more severe, it becomes substantially more difficult to restore ichthyotic skin towards normal. As the stratum corneum thickens, there may be cracking, fissuring and decreased range of motion around joints. There are three key mechanisms that govern the action of most agents used in the treatment of ichthyosis: hydration, lubrication, and keratolysis. Many treatments act through all three mechanisms.

The barrier function of the skin is impaired in the ichthyoses, and in conjunction with excessive scale, this can lead to enhanced susceptibility to skin infection and difficulty in easily recognizing the manifestations of skin infection. The hyperkeratosis and easy blistering skin of epidermolytic hyperkeratosis is prone to heavy bacterial colonization and recurrent infection with bacteria and other organisms, which can lead to enhanced blistering. Management with topical and, when necessary, systemic antibiotics may be required to manage these infections. The usual scaling of many ichthyoses may mask the development of dermatophyte infections, which can become widespread. A high index of suspicion for skin infection can facilitate early diagnosis and institution of appropriate management.

Certain ichthyoses require management specific for the disorder. Netherton’s syndrome includes findings of ichthyosis and also of atopy, such as atopic dermatitis. Because of the abnormal barrier function in this ichthyosis, treatment of atopic dermatitis may result in enhanced absorption of topical medications. Abnormally high blood levels of tacrolimus have been observed after topical application of the drug for the treatment of atopic dermatitis in patients with Netherton’s syndrome. Refsum’s disease requires management with specialized diet free of chlorophyll, phytol, phytic acid and their precursors. Dietary restriction of these agents can lead to reduction in levels of phytic acid in blood and clinical improvement. Plasmapheresis performed once or twice a month can remove phytic acid from the body and can allow liberalization of dietary restriction.

The following resources can be helpful in the management of ichthyosis.

- The National Registry for Ichthyosis and Related Disorders is funded by the National Institutes of Health to identify and enroll individuals affected with the ichthyoses in an effort to improve diagnosis and treatment of these disorders and is located at the University of Washington, Dermatology/Box 356524, R.BB1353, 1959 NE Pacific St., Seattle, WA 98195-6524 (Tel: 1-800-595-1265, http://www.skiregistry.org/, Email: info@skiregistry.org).

- The Foundation for Ichthyosis and Related Skin Types is an organization providing support and information for affected individuals, family members, and friends. It can be reached at F.I.R.S.T., 650 N. Cannon Avenue, Suite 17 Lansdale, PA 19446 (Tel: 215-631-1411, http://www.scalyskin.org/, Email: info@scalyskin.org).

- A useful resource for information about the availability of genetic evaluation and testing, in addition to information about inherited disorders is located at their website (www.genetests.org).

3.1 Topical Therapy

3.1.1 Hydration and Lubrication

Hydration through humidification or bathing is extremely beneficial for ichthyotic skin. Individuals with mild forms of ichthyosis such as ichthyosis vulgaris may have minimal to no symptoms in humid climates while developing scaling, pruritus and atopic eczema in dry, cold climates. Some patients with milder phenotypes of X-linked ichthyosis may also have minimal symptoms in humid climates. Therefore, in cold, winter months, humidification of the home, school and work environments is important.

Bathing, with soaking for prolonged periods, can be one of the most effective methods for symptomatic improvement. Soaking softens stratum corneum such that the thickened, hyperkeratotic horn can be more easily removed. During soaking, many patients will use mechanical debridement with roughly textured sponges (e.g. loofa) and abrasives (e.g. Buff Puff™), or other creative tools to mechanically remove thick areas. Lubricating bath oils can be added to the water to help ‘seal in’ moisture that is absorbed during bathing. Care should be taken to avoid injury with bath oils because some can lead to a slippery tub surface. At the end of bathing, lubricating creams and ointments should be applied generously while the skin is still wet or moist. If the skin is allowed to dry and the humidified environment is lost, much of the absorbed moisture evaporates and will be lost.

3.1.2 Keratolytics

Keratolytic agents are used to decrease keratinocyte adhesion promoting desquamation of the stratum corneum and increase water binding thereby enhancing hydration of the skin. There are numerous commercially available formulations of these agents including α-hydroxy acids (lactic acid, glycemic acid, etc.), salicylic acid, urea and propylene glycol. In addition, many dermatologists prescribe keratolytic preparations that they have formulated according to their own recipes.

Salicylic acid is the oldest keratolytic and is used in concentrations ranging from 0.5–60%. Percutaneous absorption of ad-

1 Use of tradenames is for product identification only and does not imply endorsement.
ditional agents is enhanced when formulated in the same base. Urea in concentrations of 5–10% in a variety of bases is beneficial in the management of ichthyosis. Preparations including lactic acid can also be very effective for ichthyosis. Anecdotally, many patients consider the prescription brand Lac-Hydrin® with a specifically developed vehicle more effective than generic or compounded preparations of lactic acid. Aqueous propylene glycol in concentrations at 40–60% under occlusion may also be effective in softening hyperkeratotic skin of patients with ichthyosis.[83]

The impaired barrier function of the skin in ichthyosis should be considered when using topicals over large areas of body surface. Transcutaneous salicylate intoxication is a rare event that can occur after application to large body surface areas. It occurs more frequently in children because of greater body surface area per unit weight than adults. Signs and symptoms include fever, dyspnea with respiratory alkalosis, oculargic crisis, coma, and even death. This has been reported with concentrations as low as 10% salicylate and urea ointment.[84,85] The impaired barrier function of ichthyosis is important in Netherton’s syndrome, where enhanced absorption of the topically applied immunomodulator tacrolimus has been observed.[80]

Other topical modalities which have been described to have variable efficacy in the treatment of ichthyosis include calcipotriol ointment and topical N-acetylcysteine.[86-88] In two patients with Sjögren-Larsson syndrome, topical calcipotriol also resulted in a substantial clinical effect.[89] In a 12 week study, patients with congenital ichthyosis used calcipotriol ointment (calcipotriol 50 μg/g ointment; average 59.3 g ointment/week) without significant change of serum calcium levels.[87]

In patients with lamellar ichthyosis, two randomized, double-blind, vehicle-controlled (right vs left), comparative studies demonstrated moderate improvement with topical calcipotriol ointment.[87,88] A weekly dose below 100–120 g is recommended, therefore, if twice daily application is utilized, approximately 15–20% of an adult body can be treated. In The Netherlands, topical 13-cis-retinoid acid cream was used for 4 weeks in seven patients with classic lamellar ichthyosis and one patient with ichthyosis vulgaris.[90] Clinical response was noted in two of the patients with classic lamellar ichthyosis. Adverse effects included mild irritation. Induction of cytokerotin 4 and 13 was observed in some patients after therapy. These cytokerotins are normally present in the fetal epidermis.[90] The topical receptor selective retinoid tazarotene (0.05% gel) was evaluated in a heterogeneous group of 12 patients with congenital ichthyosis. Seventy-five percent of patients responded favorably resulting in remission lasting up to 2 months. No therapeutic effect was seen in patients with ichthyosis bullosa of Siemens. Local irritation was the only adverse effect observed.[91]

One exciting potential therapeutic option for the future is gene transfer. Recently, models for gene delivery to the skin have been studied in recessive X-linked ichthyosis and lamellar ichthyosis.[92,93] Major technical problems remain to be solved including the tendency for cells to lose the inserted corrective gene.

3.2 Systemic Treatment

Systemic retinoids have been found to be useful in a variety of disorders of cornification including several different ichthyoses such as lamellar ichthyosis, congenital ichthyosiform erythroderma, epidermolytic hyperkeratosis, and erythrokeratodermia variabilis.[94] In the more severe ichthyotic disorders such as lamellar ichthyosis and congenital ichthyosiform erythroderma, systemic retinoid therapy can lead to significant physical and psychosocial benefits.[94,95] There is usually substantial improvement in skin function, including a decrease in scale and improved heat tolerance and sweating. In patients prone to ectropion, there may be improvement in existing ectropion and a decrease in the tendency towards future ectropion development. Patients with epidermolytic hyperkeratosis can experience a decrease in hyperkeratosis, lesion extent, and frequency of secondary infection. Treatment of epidermolytic hyperkeratosis should be started at a low dosage and slowly increased as tolerated, because at high doses blistering can be increased. A recent study observed that retinoid therapy was particularly effective in epidermolytic hyperkeratosis patients with mutations in the gene encoding keratin 10 compared with those with mutations in the gene encoding keratin 1.[96] The skin of many patients with epidermolytic hyperkeratosis is heavily colonized with bacteria and skin infection is common, and may be associated with an increase in blistering. This may be controlled with antibacterials. Some patients with epidermolytic hyperkeratosis may experience disease improvement with age.

Lamellar ichthyosis may respond more completely to the aromatic acitretin, compared with isotretinoin. When using isotretinoin, administration can begin at 0.5 mg/kg/day and adjusted as needed. In some patients doses as high as 2 mg/kg/day may be required. Acitretin is usually given at lower doses and may be started at 10–25 mg/day. Desquamation usually begins about 1–2 weeks after initiating systemic retinoid therapy. Prior to initiation of systemic retinoid therapy, a baseline laboratory assessment, including complete blood count, liver function tests, fasting cholesterol and triglycerides, and pregnancy testing for women of childbearing potential, is performed. Laboratory monitoring should be continued on a regular basis. Strict contraceptive counseling is essential for women at risk for pregnancy. Women who may want to consider a future pregnancy should be aware that acitretin
may persist after discontinuation of the drug and pregnancy should not occur for at least 3 years after stopping the drug.\(^\text{[97]}\)

In contrast to acitretin, after the discontinuation of therapy, isotretinoin is eliminated from the body more quickly. It is considered safe for a woman to conceive after waiting a period of at least 1 month after therapy with isotretinoin has ended.\(^\text{[98]}\)

In the treatment of ichthyosis, improvement does not persist very long after the discontinuation of therapy, which often leads to the retinoid therapy being continued long-term. Long-term treatment involves a higher risk of chronic skeletal toxicity such as calcification of tendons and ligaments, hyperostoses and osteoporosis, which may require periodic monitoring.\(^\text{[99]}\) A periodic skeletal survey can monitor for skeletal toxicity and can include a lateral view of the cervical and thoracic spine, lateral view of the calcaneus (heel), and posteroanterior view of the pelvis. For patients at risk for osteoporosis, densitometry studies can be used for periodic monitoring. Chronic toxicity may be minimized by keeping the total retinoid dose as low as possible. The dose of retinoid may often be lowered with the use of combination therapy including keratolytic, hydrating and lubricating topicals. Treatment of younger patients who are still growing adds a risk for the additional toxicity of premature epiphyseal closure. While it is possible for children with severe disorders to be safely treated, the dose should be as low as feasible and growth should be monitored with a standardized growth chart.\(^\text{[95]}\)

Novel systemic therapies are needed for this group of severe disorders. One new oral therapy being studied is the cytochrome P450 inhibitor liarozole. This drug inhibits the 4-hydroxylation of retinoic acid, resulting in increased tissue levels of retinoic acid. Twelve male patients treated with oral liarozole, 150mg twice daily in an open study\(^\text{[100]}\) had marked improvement of ichthyotic skin lesions. Clinical adverse effects were reminiscent of those with synthetic retinoids.

4. Conclusion

Recently, there have been substantial advances in understanding the mechanisms underlying the ichthyoses. Armed with this new understanding of the disease processes there is great hope for the development of specific, rational therapies targeting the abnormal pathophysiologic mechanisms. A new era in treatment of these severe disorders is overdue.

Acknowledgements

Dr DiGiovanna has received travel and speaking honoraria and clinical research support from Hoffman-LaRoche, and clinical research support from Allergan, who market retinoid drugs.


Correspondence and offprints: Dr John J. DiGiovanna, Division of Dermatopharmacology, Department of Dermatology, Brown Medical School and Rhode Island Hospital, 593 Eddy Street, Providence, JBS-1, RI 02903, USA.
E-mail: John_DiGiovanna_MD@brown.edu