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Structural and Biochemical Parameters of Congenital Ichthyosis

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INTRODUCTION

The word "ichthyosis" derives from the Greek "ichthys," or fish, and denotes the superficial resemblance of the skin surface of persons with extensive hyperkeratotic disease to that of a scaly creature of the deep. Fish scales, however, are of dermal derivation, thus are more akin to skeletal spines [1]. Ichthyosis in humans is a purely epidermal disease; more specifically, the surface epidermis is involved whereas mucous membranes and other ectodermally derived structures are usually spared.

The ichthyoses comprise a large family of entities, loosely divided into inherited and acquired. Inherited types may be further subclassified into congenital and late-onset variants; acquired ichthyosis may be spontaneous, drug-induced, or associated with metabolic, immunologic, or malignant disease.

In recent times, models for the study of these hyperkeratotic disorders have been developed involving animals with both spontaneous and induced ichthyotic disorders, and tissue and organ culture techniques of human epidermis. Skin samples have been intensively studied with the electron microscope and have yielded their cell membranes to sophisticated lipid analyses. Serendipitous discoveries of enzyme defects affecting lipid metabolism in several of the ichthyoses have opened entire new vistas for research; development of new ways of studying amniotic fluid cells and of safely performing skin biopsies in utero have allowed us to penetrate farther into the exciting field of epidermal differentiation, an area of medicine almost totally unexplored for lack of suffi-
cient direction and techniques. But its time has come, and the mysterious ter-
rain of the ichthyoses is gradually yielding to the astute observations of sci-
entists relentlessly pursuing fragmentary clues and molding them together into a
whole. Integration of "well-known facts" with less well-known observations
and unusual applications and experimental design will be our key to under-
standing.

INHERITED ICHTHYOSIS

To adequately set the stage for this discussion, we must review the 5 major
forms of inherited ichthyosis, their clinical appearances, onset, microscopic
and electron microscopic details, and any biochemical data or observations
which may ultimately suggest the pathogenesis of these diseases.

Ichthyosis Vulgaris

Ichthyosis vulgaris is dominantly inherited by males and females equally,
and has an incidence in the population of 1/300 [2]. The disease, absent at
birth, shows itself within 6 months to 3 years as an accumulation of thin
brownish scales primarily on extensor arms and legs. However, a dry, fine
scale may extend over the entire integument (Fig. 1). Palms and soles are
usually spared, unless atopic dermatitis, occurring in some 40–50% [2] of
cases, adds a follicular hyperkeratosis (keratosis pilaris) of the arms and legs,
and thickening of the skin of palms and flexures (lichenification) to the basic
scaling condition. Persons with ichthyosis have an increased transepidermal
water loss; thus hydration of the stratum corneum is a major therapeutic prob-
lem [3,4]. If atopic dermatitis is also present, the itching and concomitant
scratching, excoriation, and repeated superficial skin infections are super-
imposed.

Histologically, there is mild hyperkeratosis, or buildup of the stratum cor-
neum, a variably diminished or altogether absent granular layer, and a slight
chronic inflammatory infiltrate within the upper dermis [5]. It is claimed [6]
that on the ultrastructural level keratohyalin granules of the upper epidermis
are distinctly abnormal, of crumbly texture, and insufficient in number. No
morphologic abnormalities are otherwise apparent. Keratin filaments, them-
selves, and their orientation within the epidermis appear normal, and analyses
of stratum corneum steroids in ichthyosis vulgaris have not revealed a defect
[7]. Although the biochemical defect of this disease is unknown, the primary
abnormality is presumed to reside in the barrier layer of the upper epidermis,
thus directly implicating cell membrane functions of the stratum corneum. De-
spite the apparently incomplete or defective terminal keratinization of ichthy-
osis vulgaris epidermis, the mitotic rate is not elevated in the basal layer, nor
is the transit time through the epidermis increased [4]. As discussed below,

interference with some types of epidermal lipids will increase cell prolifera-
tion in the lower epidermis and thus increase transit time.

X-Linked Ichthyosis

X-linked ichthyosis, which has a frequency within the population of
1/6,000 males [8], may closely resemble ichthyosis vulgaris clinically, with
extensor scaling most prominent over the lower legs and arms. Scaling along
the inner canthus of the eyelids, sides of the neck, and prominent involvement
of the hips and lower trunk (Fig. 2), however, help to clinically differentiate
the X-linked variety [9]. As with ichthyosis vulgaris, the flexures, palms, and
soles are spared, as are the mucous membranes. Histologically the epidermis
is absolutely normal, save for the hyperkeratosis; electron microscopy is help-
ful only in ruling out lamellar and vulgaris forms [10].

Atopic dermatitis seldom accompanies the X-linked form, but, when it is
present, flexural, palm, and sole thickening, and keratosis pilaris may all be
present, as in ichthyosis vulgaris. In a recent survey (Hanihn, Buxman and
Shapiro, unpublished data) of 25 consecutive persons in an atopic dermatitis
Fig. 2. X-linked ichthyosis. The lower trunk and buttocks, often spared in vulgaris type, are markedly involved.

Clinic with both atop dermatitis and concomitant ichthyosis, only one out of 25 was found to have X-linked ichthyosis, rather than ichthyosis vulgaris, an incidence closely in agreement with published figures, derived clinically [9]. In this patient, electron microscopy was successful in designating his ichthyosis as "non-vulgaris type," and steroid sulfatase deficiency was subsequently confirmed by fibroblast culture and assay (see below). Sulfatase activity of the other 24 atopic ichthyotics was normal. Since X-linked ichthyosis is relatively benign in character, very little interest was invested in this condition until 2 years ago, when a serendipitous association was made of a disorder of low placental estradiol production, labor delay or failure, and steroid sulfatase-deficient placenta, with an ichthyosis of X-linked type [11]. Family studies confirmed both the close linkage between the ichthyosis and the steroid sulfatase deficiency, and the presence of the diagnostic eye findings in adult male ichthyotics (asymptomatic corneal densities in the Decemet membrane) [12]. Subsequently an extensive multicenter double blind study of patients presenting with ichthyosis proved beyond a shadow of doubt that patients with clinical X-linked ichthyosis all had sulfatase deficiency, whereas this enzyme was normal in all other major forms of ichthyosis [13,14]. Obligate heterozygote mothers of sulfatase-deficient boys occasionally manifested a forme fruste of the eye findings in the disease [15] although sulfatase levels were always within normal limits, even after cloning of individual fibroblast lines. The locus of X-linked ichthyosis was subsequently determined to be 10 centimorgans from the Xq blood group alleles, in a region of the X chromosome which escapes inactivation during lyonization [16,17]. Elucidation of the enzyme defect in X-linked ichthyosis is the first association of a specific gene defect with one of the major forms of ichthyosis. The only other ichthyotic disorder for which a gene defect is known is Refsum disease, a multisystem progressive disorder of phytic acid metabolism [18].

In the future, diagnosis of steroid sulfatase-deficient ichthyosis may be facilitated both by the recent development of a histochemical stain for the enzyme [19], which can be performed directly on frozen tissue sections, and by preliminary observations that sulfatase deficiency may be detected in extracted hair bulbs, stratum corneum scrapings, or circulating leukocytes [20]. Prenatal diagnosis of the condition is possible either by measuring estriol in maternal urine or by culture of amniotic fluid cells following routine amniocentesis [21]. Therapy for X-linked ichthyosis is currently limited to topical modalities, which are usually quite effective. Urea-containing and emollient creams soften the skin and mask scaling. Patients with this disease are unresponsive to and may worsen with use of either topical or systemic retinoids [22]; the known interference of vitamin A compounds with cholesterol metabolism [23] may aggravate the existing defect.

Lamellar Ichthyosis

Lamellar ichthyosis, one of the rarer forms of classic ichthyosis, is an autosomal recessive trait with an incidence of 1/300,000 in the population. The sexes are equally affected [2]. It seems to be somewhat more heterogeneous than the other ichthyoses in clinical and histologic manifestations. The condition is virtually always present at birth, and affected infants may have a thin collodion membrane (see below) which sheds several days or weeks later to expose an underlying ichthyosis, or a severe ichthyosis may be expressed directly. Clinically, 2 forms of the disease may be recognized. The first form, which has also been called congenital nonbullous ichthyosiform erythroderma, manifests universal thin, rather transparent large scales (Fig. 3), with underlying erythema, which may show rather significant improvement in the summer months [24]. Mild ectropion may be present, and the palms, soles and flexures are affected, although the mucous membranes remain normal. The second major form of lamellar ichthyosis is extremely severe from birth; marked ectropion improves somewhat with age; universally present huge thick brown opaque scales are especially severe over the face and scalp (Fig. 4). Relative
alopecia, possibly due to recurrent pyoderma of the scalp, may be present. Light and electron microscopic examination of both variants show them to be identical, with an acanthotic epidermis, a well-defined wide granular layer and massive hyperkeratosis [25]. Focal parakeratosis with some diminution of the granular layer has occurred in a few unpublished cases. Under the electron microscope, the living epidermis is normal in structure, aside from the changes noted above, but stratum corneum cells contain large lipid-like inclusions (Fig. 5), a finding which, in our experience, is quite diagnostic of lamellar ichthyosis (R. Dimond and M. Buxman, unpublished observations).

Epidermal transit time is increased in lamellar ichthyosis, in contrast to the normal transit times in ichthyosis vulgaris and X-linked types [14]. Thus, there are elements of both retention and proliferation hyperkeratosis.

Treatment of lamellar ichthyosis with topical agents has been uniformly unrewarding as the scales are so thick and are replaced at a rapid rate from below. In the past 3 years, however, remarkable success has been attained with synthetic retinoids, particularly 13-cis retinoic acid [22,26]. We have treated both clinical variants of lamellar ichthyosis with 13-cis retinoic acid, and have found that the type with thin transparent scales responds well, with 80–90% improvement with continued high dosage (2+ mg/kg/d). The more severe variant, however, responds less well, perhaps achieving 40–50% improvement, depending on maximum tolerated dose. Scalp involvement, in particular, is difficult to ameliorate. Significant improvement in ectropion, however, has been achieved and is accompanied by improvement in the appearance of the cornea on serial eye examinations during treatment. Somewhat satisfactory topical treatment has been achieved by using aqueous propylene glycol, 40–60% [27] or 5% lactic acid (Lacticare®) or other α-hydroxy acids [28]. Topical Retin-A® is effective but extremely irritating. Irritation is also caused by synthetic retinoids used topically. Urea-containing creams may assist with hydration and improve patient comfort [29], as in other forms of ichthyosis.

Epidermolytic Hyperkeratosis

Epidermolytic hyperkeratosis, a dominantly inherited disorder, occurs with about the same frequency as lamellar ichthyosis. Clinically, the affected are born with diffuse or linearly reddened skin, with accentuated skin creases. Bullae and erosions of the skin develop with little provocation and often become infected with staphylococci. The marked erythema present at birth gradually subsides and hypertrophic scaling increases with age; bullae cease to de-
velop by adulthood in 80% of cases [30]. Epidermal transit time is increased in epidermolytic hyperkeratosis, just as in lamellar ichthyosis.

Under the light microscope, in formalin-fixed specimens (Fig. 6), a distinctive swelling of the granular layer cells with degeneration, and perinuclear clear spaces as far down as the midsquamous layer are evident. Under the electron microscope, these changes are appreciated as clumping of the endoplasmic reticulum, ribosomes, keratin filaments, and keratinosomes about the nucleus, with failure of the filaments to associate with peripheral desmosomes. This pathologic finding, not unique to epidermolytic hyperkeratosis, is also found in other hyperkeratotic diseases such as epidermal nevi, ichthyosis hystrix, certain palmoplantar keratodermas and certain solitary keratoses [31,32]. These may represent forms frustes of epidermolytic hyperkeratosis.

Epidermolytic hyperkeratosis improves with age. There is partial response to orally administered retinoids [33] but topical therapy with emollients, hydroxy acids, and urea-containing compounds, similar to that used for lamellar ichthyosis, remains the mainstay of treatment.

**Collodion vs Harlequin Disease**

The collodion baby is classically regarded as an initial presentation of one of several types of ichthyosis. Larréque et al. [34] have systematically studied the outcome of 29 cases and have concluded that the vast majority ultimately develop lamellar ichthyosis, while a few may eventuate in X-linked or ichthyosis linearis circumflexa types. Rarely is normal skin present beneath the collodion layer [35]. As seen in Figure 7, the appearance of the collodion infant at birth is distinctive; a tight, shiny parchment-like membrane covers the entire integument, causing ectropion and eclabium and occasionally restriction of chest movement as well. Within several days of birth, the membrane starts to peel systematically, with the head last, revealing the underlying state of the skin. According to these investigators, and confirmed by Bloom and Goodfried [36], an abnormally high rate of infant death is found among collodion infants.

Microscopically, the collodion layer appears as a compact lamellar stratum corneum with even transition to normal-appearing stratum corneum. The upper collodion layer cells are reported to contain large PAS- and diastase-resistant granules [37]. Ultrastructurally the upper two-thirds of the epidermis contains large vacuolar inclusions, together with many organelles. It is debatable whether the collodion membrane represents a retained periderm which has failed to disintegrate properly in utero.

Harlequin ichthyosis has historically been regarded as a unique, single entity of extremely severe fatal universal ichthyosis in which the integument is hardly present as such, but is essentially replaced by armadillo-like scales with intervening fissures extending deep into the dermis. Viability of infants
Fig. 6. Formalin-fixed section of epidermolytic hyperkeratosis. Note extreme hyperkeratosis of stratum corneum, disorganized granular layer, and intracellular edema of upper Malpighian layer. (Orig. mag. x 400)

bearing this diagnosis is limited to a few days of life, with rare exceptions, although cause of death has not been at all clear in most instances [38].

Histologic descriptions of harlequin ichthyosis vary considerably [39,40]; most show massive hyperkeratosis and acanthosis with either thickening or diminution of the granular layer. A single case of this disease was initially reported to have a high proportion of β-keratin in the viable epidermis [40] but this has not been confirmed subsequently. Most recently [41], an infant exactly fitting the classic clinical harlequin description (Fig. 8) was noted by light and electron microscopy to have large lipid inclusions in the stratum corneum and masses of amorphous intercellular material between stratum corneum cells (Fig. 9). Keratinosomes could not be identified in this infant’s skin, evidence that etiology for this infant’s disease may be an epidermal lipid metabolic problem. The stratum corneum did have a vacuolar appearance; Fettrot stain for neutral lipid was strongly positive throughout the stratum cor-
It is, however, increasingly clear that in all known keratinization defects leading to ichthyosis, lipid metabolism is involved either directly or indirectly.

Other Forms of Ichthyosis

There are literally hundreds of reports concerning inherited syndromes which include ichthyosis as one of a host of clinical abnormalities. In Bazex syndrome, a follicular ichthyosiform disorder eventuating in follicular atrophoderma and basal cell carcinoma is associated with fine, sparse hair [42,43]; in Rud syndrome sexual infantilism and neurologic abnormalities are associated with ichthyosis [44]; ichthyosis of lamellar type may be combined with a neutrophil chemotactic disorder [45], neurosensory deafness and cataracts [46], or with mental retardation and variable spastic neurologic degeneration (Sjögren-Larsson syndrome). Netherton syndrome consists of an ichthyosis linearis circumflexa with defective hair shafts [47]. Mild ichthyosis with a whirl and swirl pattern may accompany Conradi disease, a heterogeneous disorder with stippling of the epiphyses, some degree of mental retardation, and other anomalies [48].

One multisystem degenerative disease associated with ichthyosis deserves special mention, however, since its pathogenesis involves intrinsic lipid metabolism of the epidermis. Refsum disease consists of a triad of ichthyosis, retinitis pigmentosa, and neurologic degeneration with cerebellar ataxia and polyneuritis. Onset is between 4 and 7 years, and the disease is progressive and fatal in the 4th or 5th decade of life [49–51]. A specific enzyme defect has been implicated in this disease complex: faulty α hydroxylation of phytanic acid. Microscopically, hyperkeratosis and slight acanthosis are present with moderate hypergranulosis; the striking feature is that of vacuoles near the dermoepidermal junction. The vacuoles stain black with Sudan black and oil red O, and by electron microscopy are seen to be large nonmembrane-bound lipid deposits within lower epidermal cells. Biochemically, these deposits consist of phytanic acid which accumulates in the epidermis because the oxidation defect esterified to cholesterol and phospholipids. Phytic acid depletes epidermal membranes of free cholesterol needed for proper keratinization and results in failure of degradation of the cells at the surface, and secondarily, possibly leads to the "high output epidermopoesis" noted in this form of ichthyosis. Elimination of phytol in the form of chlorophyll from the diet results in some clinical improvement.

ACQUIRED ICHTHYOSIS

Hyperkeratinization is a final common pathway through which numerous primary biochemical defects may be manifested. The acquired ichthyoses may be grouped into "incidental" ichthyosis, which may develop secondary to an
organic disease process or as a side effect of drug ingestion, and “experimental” ichthyosis in animals, either natural or intentionally induced.

**Ichthyosis with Concomitant Organic Disease**

The pathogenesis of ichthyosis with concomitant organic disease is elusive and has been variously ascribed to production of hormones by malignant tumors, interference with lipid or vitamin A metabolism, or immunodeficiency [52–55]. The ichthyosis of malignant disease manifests itself as a dry, xerotic epidermis with gradual worsening in parallel with the primary tumor, which may remit during therapy only to recur with relapse or metastasis. The condition is notably refractory to treatment with emollients.

Histologically, epidermal atrophy and diminution of the granular layer accompany an orthohyperkeratosis, and an inflammatory infiltrate is absent. Proliferation rate and transit time are normal, closely simulating those in benign ichthyosis vulgaris [56].

Although most frequently reported with Hodgkin disease and other lymphoproliferative malignancies, solid tumors may also be found, such as breast, cervical, colon or lung carcinoma, or, more rarely, sarcoma (Kaposi) or leiomyosarcoma [56–64]. A clinically similar ichthyosis may be seen with nonmalignant organic disease such as hypothyroidism [55], sarcoidosis [65], rarely in hypopituitarism or aminoaciduria [55,66] and has been reported with approximately a 10% frequency in untreated lepromatous leprosy [67]. Skin changes may precede detection of malignancy by as much as 7 years, although it is frequently coincidental with the clinical diagnosis.

**Ichthyosis Secondary to Drug Ingestion**

Ichthyosis-inducing drugs almost universally interfere with lipid metabolism [68]. The 3 primary drug families involved are triparanol [69], first introduced as a hypocholesterolemic drug, the butyrophenones [70], noted for their primary antipsychotic effects, and nicotinic acid [54]. Both triparanol and nicotinic acid are known to interfere with cholesterol synthesis although by different mechanisms. Degree of ichthyosis is dose-related, and invariably reversible after the drug is withdrawn. Triparanol ingestion may cause alopecia and nail dystrophy, in addition to cataracts; it was withdrawn from clinical use several years after its introduction.

Histologically, drug-induced ichthyosis closely resembles ichthyosis vulgaris, and usually is not severe enough to warrant drug withdrawal.

**Essential Fatty Acid Deficiency**

Essential fatty acid deficiency has been reported to occur spontaneously in infants fed low fat diets [71] and in adults suffering from fat malabsorption following extensive intestinal resection and intravenous feeding [72,73]. The condition may be duplicated exactly in experimental rats by feeding a diet poor in the essential fatty acids, linoleic and arachidonic. Linoleic acid has a ω 6 conformation (denotes position of the methylene group between the 6th and 7th carbon groups on the molecule). Arachidonic acid is simply a chain elongation of linoleic, with 3 unsaturated double bonds instead of the 2. The functions of essential fatty acids (EFAs) in the skin are diverse; they form an integral part of cell membrane structure; they exert feedback control on cholesterol metabolism; arachidonic acid is a precursor molecule for the prostaglandins, which regulate epidermal homeostasis and mitosis [74]. In animals fed a diet lacking EFAs, the paws and tail show cracking and fissuring of the skin within 2 weeks, and necrosis of the tail tip ensues. The epidermis then becomes hyperplastic and acanthotic, with an increase in the granular layer, and accelerated epidermopoiesis [75,76]. The barrier function of the epidermis is interrupted, as manifested by a 10-fold increase in transepidermal water loss [77]. All these changes are reversible with either restoration of EFAs to the diet or topical application of sunflower oil, rich in linoleic acid, to the skin surface. Systemic correction of the deficiency is not necessary with application of sunflower oil. A precipitous drop in transepidermal water loss precedes decrease in scaling of the skin. Improvement in water barrier function can be demonstrated to be solely due to linoleic acid and to γ linolenic, its desaturation product. Correction of barrier function can proceed even if prostaglandin synthesis is blocked. By contrast, application of pure arachidonic acid corrected scaliness and mitotic rate faster than it improved barrier function [78,79].

The effect of EFA deficiency on DNA synthesis and mitosis may be due to its interference with cholesterol synthesis, since it has been shown that cholesterol or its esters, if incubated with erythrocyte membranes, have a marked inhibitory effect on both incorporation of 3H-thymidine and mitosis [80,81]. Conversely, interference with cholesterol production may (as in hypervitaminosis A) increase mitosis and 3H incorporation, with resultant hyperkeratosis.

Recently, it has been demonstrated ultrastructurally that abnormal epidermal lipid deposition occurs in experimental EFA deficiency [77]. The keratinosomes of the upper epidermis, although formed in normal numbers, were essentially devoid of lipid content, and intercellular domains of the stratum corneum contained decreased amounts of processed lipid, along with fragments of the defective lamellae derived from these lipid-deficient keratinosomes. Linoleic acid has been demonstrated to be a major component of intercellular lipid in the stratum corneum and may be essential for “waterproofing” of the skin during cornification [82]. Alternatively, this fatty acid may play a pivotal role in metabolism of other epidermal lipids destined for the intercellular space.

The essential fatty acid-deficient mouse has been proposed as a general model for hyperproliferative hyperkeratotic diseases such as psoriasis and the ichthyosiform dermatoses [83].
A naturally occurring mutant mouse, the ichthyosis mouse, bearing the genotype ictic, has been proposed as a model for lamellar ichthyosis. Although the fit is not exact, and the defect may resemble a phenocopy rather than a true genotype analog, the ichthyosis mouse bears certain resemblances to the more severe recessive form of ichthyosis. The trait is inherited in the mouse as an autosomal recessive, and clinical and histologic presentation except for normal proliferation rate and transit time, are similar to the human disease [84]. In recombination experiments of normal and abnormal dermis and epidermis, the ichthyosis trait has been localized to a primary epidermal defect [85, 86]. However, certain differences may exist: there is marked growth retardation in the ichthyosis mouse, and females are frequently infertile [84]. Although persons with lamellar ichthyosis of the severe type are occasionally small for gestational age at birth and somewhat growth retarded, they are not known to be infertile. In addition, the affected mouse manifests short guard hairs about the face; an occasional animal is mute; sloughing of the thickened stratum corneum occurs periodically, rather than continuously, with greatly reduced viability of the animal during the sloughing period. All of these findings suggest a more pervasive metabolic defect than is found in the human form of the disease.

The inherited hyperkeratosis recently described as "infantile ichthyosis" is closely linked to the gene for albinism, and causes periodic exfoliation on Days 3, 7, 11, and 15 of life. Thereafter the integument is normal in appearance and histology [87]. Histologically, hyperkeratosis, and parakeratosis are evident until Day 15, after which they disappear. No increase in proliferation rate was detectable with autoradiographic techniques. Normal shedding from the surface of mouse epidermis first occurs about Day 10–11. The histology and neonatal restriction of expression of this ichthyotic trait suggests a closer relationship to the collodion baby than to any of the persistent ichthyoses of humans.

The immunologically deficient nude mouse, although it does not have abnormal skin, has offered a home for skin grafts from ichthyotic humans [88], thus allowing direct studies of hyperkeratotic diseases intrinsic to the epidermis. Both epidermis and whole skin from patients with lamellar ichthyosis have been successfully maintained in a histologically representative state for long periods of time on the nude mouse, providing virtually endless possibilities for diagnostic and therapeutic manipulation of this previously elusive disorder. Maintenance of ichthyosis skin in organ culture is also possible, and with improved methods of cell culture, clones of epidermal cells expressing ichthyosis traits may be as well used as fibroblast lines currently are.

**FUTURE STUDIES**

It is now possible to diagnose 2 of the inherited ichthyoses simply by amniocentesis and enzyme assay: X-linked ichthyosis [89] and Refsum disease [90]. Several other forms (eg harlequin and lamellar ichthyosis and epidermolysis hyperkeratosis) may be approachable by fetal skin biopsy, a technique now becoming available in a number of research centers, since they show rather distinctive histopathology. Although abnormal scales from fetuses with many forms of congenital ichthyosis theoretically should be present in amniotic fluid pellets (clumps of aspirated surface epidermal cells have been recovered from the lungs of autopsied ichthyotic infants), a recent attempt to diagnose epidermolysis hyperkeratosis in a 20-week fetus by amniotic fluid cytology was unsuccessful [91]. The condition subsequently was proven by direct fetal skin biopsy [91, 92].

The huge leap taken into the etiology of the ichthyoses represented by discovery of the connection between steroid sulfatase deficiency and X-linked ichthyosis has served to focus our attention even more strongly on cell membrane lipids as the most productive area in which to concentrate our research efforts in days to come. We hope our knowledge will soon increase by geometric proportions, as scientists from biochemistry, cell biology and genetics lend their expertise to the field of ichthyosis research.

**REFERENCES**


