Netherton Syndrome
Netherton syndrome is a rare, autosomal recessive disorder characterized by the concurrence of ichthyosis, a structural hair shaft abnormality, and atopy. The usual cutaneous manifestation is ichthyosis linearis circumflexa, a distinctive condition of generalized hyperkeratosis and polycyclic and serpiginous erythematous plaques with a characteristic, migratory, double-edged scale at the margins. At birth, affected children may present with generalized erythroderma. Infants and children may have feeding problems, with poor absorption and failure to thrive. With atopic dermatitis, there may be pruritus, and scratching can lead to lichenification at the flexures. In some patients, the ichthyosis resembles lamellar ichthyosis or CIE. Histopathologic examination is not specific and may show features of hyperkeratosis, psoriasis, and atopic dermatitis. Most patients have a specific hair shaft abnormality called trichorrhexis invaginata, in which the distal hair segment is telescoped into the proximal one, forming a ball-and-socket-like deformity on microscopic examination. This is also known as “bamboo hair” and is due to abnormal cornification of the internal root sheath. Hair from multiple areas should be examined, because only 20 percent to 50 percent of hair may be affected, and the characteristic abnormality may be more commonly observed on eyebrow hair. Trichorrhexis nodosa and pili torti may also occur. The hair defects may not be detectable at birth, and may disappear with age. Atopy in these patients may manifest as atopic dermatitis, asthma, or severe food allergy (particularly to nuts), and marked elevations of serum immunoglobulin E may occur. In some patients, a generalized aminoaciduria, mild developmental delay, and impaired cellular immunity may also be present. Netherton syndrome has been found to be due to mutations in SPINK-5, a gene encoding LEKTI (lympho-epithelial Kazal-type related inhibitor). LEKTI is a serine protease inhibitor that is predominantly expressed in epithelial and lymphoid tissues, and may be important in the downregulation of inflammatory pathways. This discovery highlights the importance of the regulation of proteolysis in the overlap between epithelial barrier function and the hypersensitivity of atopy. Subsequently, LEKTI was associated with common atopy and atopic dermatitis. Prenatal testing for Netherton syndrome using molecular data has been successfully accomplished. Tacrolimus ointment, a topical immunosuppressant, is effective in common atopic dermatitis with minimal systemic absorption. However, Netherton syndrome is complicated by an abnormal skin barrier, allowing increased percutaneous absorption and associated risk for systemic toxic effects. This should be considered when using topical agents such as tacrolimus, where monitoring of serum levels may be necessary, and topical steroids, where iatrogenic Cushing syndrome has been reported.
Sjögren-Larsson Syndrome

In 1957, Sjögren and Larsson reported on 13 families from north Sweden with a syndrome of congenital ichthyosis, spastic paralysis, and mental retardation. Sjögren-Larsson syndrome is a rare, autosomal recessive disorder that presents at birth with an ichthyosis that may range from fine scaling to generalized hyperkeratosis. Erythema may be present at birth but tends to gradually clear by 1 year of age. Collodion-like membranes are rarely seen. The ichthyosis manifests as fine scale, large scale, or a thickening of the stratum corneum without scale and may be pruritic. Thickened areas may be yellow to brown in color and have a lichenified appearance with accentuated skin markings. The most involved areas are the sides and back of the neck, lower abdomen, and flexures. Hair, nails, and the ability to sweat are generally normal. During the first 2 to 3 years, neurologic manifestations of spastic diplegia or tetraplegia and mental retardation develop and can be accompanied by speech defects and seizures. A characteristic ophthalmologic finding is the presence of glistening white dots in the macula of the retina; these occur after 1 year of age and may not be present in all patients. Histologic findings of hyperkeratosis, papillomatosis, acanthosis, and a mildly thickened granular layer are non-specific. Electron-microscopic examination of the skin shows lamellar membranous inclusions in the granular and cornified cells.

Rizzo et al. linked SLS to fatty alcohol: NAD oxidoreductase (FAO) deficiency. FAO is a complex enzyme with two separate proteins that sequentially catalyze the oxidation of fatty alcohol to fatty aldehyde and subsequently to fatty acid. Further work identified the fatty aldehyde dehydrogenase (FALDH) activity in cultured fibroblasts from patients with SLS
component as the affected component of FAO in SLS. FALDH is a microsomal enzyme that catalyzes the oxidation of medium- and long-chain aliphatic aldehydes derived from metabolism of fatty alcohol, phytanic acid, ether glycerolipids, and leukotriene B4. Mutations found in the FALDH gene (ALDH10, recently renamed ALDH3A2) of three unrelated SLS patients confirmed the role for this enzyme in the etiology of this disorder and the importance of this pathway for normal desquamation. Most mutations are specific to families, although several common mutations suggest founder effect or favored sites for mutation. The identification of decreased fibroblast FAO activity in a family with atypical cutaneous findings (lack of ichthyosis or discrete plaques rather than generalized ichthyosis) has expanded the spectrum of clinical phenotypes associated with abnormal FAO activity.