MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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INHERITED DISORDERS OF KERATINIZATION IN MAN

NORMAL KERATIN AND KERATINIZATION: TERMINOLOGY

"Keratin" means one thing to the biologist, another to the morphologist, and a third to the biochemist. The biologist regards keratin as a complex mixture of debris resulting from dessication of epidermal cells and their derivatives, and definitely not as a single chemical entity. This mixture may have the hardness of a tiger's claw, the complex organization of a feather, or the social stigma of a flake of dandruff. Other keratin derivatives include: Hair, horn, nail, quill, hoof, beak, scale, and outer layer of skin; I shall consider in detail only the latter.

Cohen, Jack. Feathers and Patterns, in *Vol. 5 Advances in Morphogensis*, ed. by M. Abercrombie and J. Brachet. Academic Press, NY, 1966, pp 1-38.

The morphologist focuses on a different set of phenomena with his light or electron microscope and defines keratinization even more inclusively. He emphasizes that cells of the vaginal and oral mucous membranes also produce tonofibrils and then dehydrate as they move toward the surface. But unlike the horny layer of epidermis these cells rarely cement together in a tightly coherent membrane. Among other peculiarities, they fail to synthesize keratohyaline granules and often contain visible nuclei when shed. Clinicians have successfully exploited several features of mucous membrane keratinization, especially the exquisite responsiveness to estrogens in females. Gynecologists have long used the proportion of fully keratinized cells in vaginal smears as one index of hormonal status in their patients.

Zelickson, A.F. and J. F. Hartman. An Electron microscopic study of normal human non-keratinizing oral mucosa. *J. Invest. Dermatol. 38: 94, 1962.*

Ta-Jung, L. and L. Su-thin. The Vaginal Cytogram. *JAMA 185:844, 1963.*

To the biochemist, keratin clearly belongs in the class of fibrous proteins with helical primary structure. X-ray diffraction analysis, chromatographic separations, and other physical methods have built remarkably detailed models of wool and hair keratin. These keratins differ in important respects from epidermal horny layer protein, however, and one must critically examine generalizations based on wool structure before applying them to skin. I will summarize these studies below, but here I should mention some of the outstanding distinctions: (1) horny layer contains much lower levels of sulfur-containing amino acids. The cell envelopes contain the largest amounts. (2) hair keratinizes without a granular layer. Although the inner root sheath develops very similar basophilic granules called trichohyaline, the major portion of the hair cortex does not. (3) horny layer desquamates at a fixed level above the zone in which it keratinizes while hair cortical cells remain rigidly cemented together. In spite of these differences, the fibrillar structure embedded in a protein matrix may be a common feature with only minor variations accounting for staining and other differences.

Fraser, R.D.G. Keratins, *Scientific American 221: 86-96, 1969.*

Crounse, R.G., Epidermal keratin and epidermal prekeratin. *Nature 211: 1301-1302, 1966.*

Montagna, W. The Structure and function of skin. Academic Press 2nd ed., NY 1962 pp 174-240.

EVOLUTION:

Keratin may have first appeared in the horny teeth of primitive vertebrates such as jawless lampreys. Lacking an impermeable body envelope, the first vertebrates to venture on land must have required very humid conditions for survival. The mud skipper, a partially terrestrial fish that survives today in heavy swamps, illustrates adaptations that may have been characteristic at this stage of development. It lacks keratin on its body surface but forms it at the base of the ventral fins. Later mutations leading toward a fully keratinized epidermis may have conferred advantage by reducing evaporative water losses. New forms able to exploit drier terrain may have emerged as a consequence.

With the rise of the amphibians a true stratum corneum became more general. The modern survivors of this class form a thin horny layer, sometimes one cell diameter in thickness, composed of flattened nucleated cells. No granular layer develops in the skin of these creatures, however. Although electron micrographs show intracellular keratin filaments resembling those in mammals, the filaments are rather loosely stabilized by crosslinks. They stretch easily from a spiral coil of modest pitch (the α helical pattern) to a much more extended or β pattern.

Both amphibians and reptiles periodically slough the entire stratum corneum instead of continuously losing indivisual cells or flakes as do mammals. Details of the control mechanisms for this process have not come to light, but the thyroid and other endocrine glands exert some influence over the moulting process, at least in amphibia. Parakkal and Matoltsy detected simultaneous synthesis of mucus and keratin in the mid-epidermis of frogs, and suggested that persistance of this pluripotential feature might explain mucous metaplasia due to excess vitamin A and squamous metaplasia in its absence in mammalian epithelia. Similar suggestions had come from Wislocki et al much earlier. Mucus synthesis competing with keratin elaboration might also explain moulting in amphibia.

Modern reptiles generate scales with very complex histological organization. Grossly, the patterns vary widely, with a range that stretches from the primitive box-like carapace of the turtle to the highly differentiated hinged scale of lizards and snakes. Since mammals may have diverged from preceding forms much earlier than reptiles and the birds may have branched off later still, the fascinating intricacies of scale and feather formation will not concern us in this discussion.

Spearman has suggested that mammalian stratum corneum emerged as an exaggeration of very minor features in the skin of the early protoreptiles. The flexible mammalian horny layer may have appeared first around hair follicles located at the rear edges of horny scales in these primitive mammal-like forms. Rats and other rodents still possess tail-scales with hair follicles in the interscale regions. A prominent granular layer develops in the epidermis surrounding these hair follicles, and this type of horny layer, formed from a granular layer, may have gradually replaced the original reptilian scales as hair follicles increased in numbers and covered more of the body surface. Mammalian speciation generated a number of secondary modifications including thick fur appropriate to terrestial cold climates, the hairless, parakeratotic epidermis of whales, and the dense compact horny layer in large tropical mammals such as the rhinoceros, elephant, and hippopotamus. In hair-covered animals like sheep the surface epidermis became thin. Hair-covered surfaces in these animals have a two or three-cell thick horny layer while more exposed surfaces are thicker.

It comes as no surprise to find that man's later emergence into relatively

hairless nudity was accompanied by a compensatory increase in epidermal thickness. Kligman found an average of seven or eight cells for the depth of the prickle-cell layer, and about fifteen much thinner ones in the horny layer. From an esthetic viewpoint I doubt if many of us would choose to reverse the trend away from hirsutism (though current fashion decrees that we make the most of what's left). But those who treat skin cancer and the other unpleasant late effects of ultraviolet-induced damage sometimes wonder where the evolutionary advantage lay.

Spearman, R.I.C. The evolution of mammalian keratinized structures. In *The Mammalian Epidermis and its derivatives. Symposium 12*, Ed. F. J. Ebling *Zool Soc Lond, 1964.*

Spearman, R.I.C. The keratinization of epidermal scales, feathers, and hairs. *Biol. Rev. 41:59-96, 1966.*

Mercer, E.H., *Keratin and Keratinization.* Pergamon, NY, 1961, pp49-52.

Parakkel, P.F. and A.G. Matoltsy. A study of the fine structure of the epidermis of *Rana Pipiens. J. Cell. Biol. 20:85-94, 1964.*

Kligman, A.M. The biology of the stratum corneum in *The Epidermis*, eds. W. Montagna and W. C. Lobitz. Academic Press, NY, 1964. pp 387-430.

Wislocki, G.B., D. W. Fawcett, and E. W. Dempsey. Staining of stratified squamous epithelium of mucous membranes and skin of man and monkey by the periodic acid-Schiff method. *Anat. Rec. 110:359-375, 1951.*

STRUCTURE:

The structure of normal epidermis falls naturally into four layers for purposes of discussion: (1) the basal layer, (2) the prickle-cell or malpighian layer (3) the granular-cell layer (or merely granular layer) and (4) the horny layer. The stratum lucidum occasionally seen on the palms and soles between the granular and horny layers appears to be an artifact of stains used for light microscopy. Electron microscopy shows only a more loose-textured appearance in this region when compared with the more compact layers above.

(1) The basal layer lies on and may contribute to the synthesis of a basement membrane. Microscopic sections show a pattern of interlacing reticulin fibers embedded in a mucopolysaccharide matrix. Evidence of this contribution has been gathered in studies on amphibian and bird epidermis, but may explain certain peculari-ities of human histopathology as well. As one example, it might account for the clear zone of normal connective tissue frequently found interposed between the epidermis and pathologic alterations in the dermis.

Hay, E.D. Secretion of a connective tissue protein by developing epidermis in *The Epidermis* eds. Montagna and W. C. Lobitz. Academic Press, NY, 1964. pp 97-114.

Fell, H.B. The experimental study of keratinization in organ culture *ibid.* pp 61-81.

Ordinarily, only the basal cells of the epidermis undergo nutosis. Here the first intracellular fibrillar material appears. These fibrils can be followed to the edge of the cell where they insert into highly differentiated thickenings of the cell membrane called desmosomes. These look and perhaps act like magnetic joints with several partly intracellular and partly extracellular layers. They may develop at areas of greatest stress but are clearly capable of fluid movement at the cell's periphery as it ascends through the epidermis. Half-desmosomes attach the basal layer to the basement membrane.

Brody, I. An electron-microscopic study of the junctional and regular desmosomes in normal human epidermis. *Acta Derm-venereol. 48: 290-302, 1968.*

Campbell, R.D. Desmosome formation: An hypothesis of membrane accumulation. *Proc. Nat. Acad. Sci. 58: 1422-1427, 1967.*

(2) The prickle-cell layer forms a mosiac of cells in which a three-dimensional network of tonofibrils develop. These appear doubly refractile under the polarizing microscope, which best demonstrates their criss-cross pattern with insertions at desmosomal thickenings.

Nieuwmeijer, A.H. Tonofibrils in bullous dermatoses: A histo- and cyto-pathologic study. *Dermatologica 106:379, 1953.*

The tonofibrils contain much smaller filaments which may range in size from 60 to 80 Å, with the average around 75 Å. Australian investigators claim to have further resolved these filaments into even finer protofibrils of 20 Å diameter in hair and wool, though not in skin. The protofibrils are laid down in a geometrically regular array with a tantalizing resemblance to the 9 plus 2 organization of the fibrils seen in cross sections of flagella.

Filshie, B.K. and G.E. Rogers The fine structure of α-keratin. *J. Mol. Biol. 3:784-786, 1961.*

This interpretation has been critized because of several methodological uncertainties: (1) The protofibrils approach the limits of electronmicroscopic resolution. (2) Variations in the plane of section away from 90° to the axis of the protofibril may distort the optical image, and (3) doubts continue regarding the specificities of the heavy metal stains used in these studies.

Johnson, D.F. and J. Sikorski. Molecular and fine structure of alpha keratin. *Nature 194:31-34, 1962.*

Dobb has found independent evidence for 20 Å fibrils in negatively stained partially disintegrated wool, and Rogers and Clarke detected them in hair follicle homogenates.

Dobb, M.F. The structure of keratin protofibrils. *J. Ultrastructure Res. 14:294-299, 1966.*

Rogers, G.E. and R. M. Clarke. An approach to the investigation of protein biosynthesis in hair follicles. in *The Biology of Skin and Hair Growth,* eds. A. G. Lyne and B. F. Short. Elsevier, NY, 1966. pp. 329-343.

Millward has recently cast doubt on Dobb's interpretations by finding fibrils of similar diameter in "control" or wool-free preparations, apparently due to ubiquitous cellulose contamination.

Millward, G.R. Cellulose contamination: A possible source of error in the interpretation of previous experimental evidence for the α-keratin fibril. *J. Cell. Biol. 42:317-320, 1969.*

Fraser's recent studies support the Filshie and Rogers concept, however, from an independent direction. His optical filtering technique averages a large number of electron microscopic cross sectional images and produces data that agrees with the Australian model, as well as with similar ones built on x-ray diffraction results. He proposes that the basic 75 A fibril consists of smaller filaments in an annular ring surrounding a central core.

Fraser, R.D.B. op cit.

The 75 Å fibril seems to be a remarkably consistent feature of keratin, present in all mammalian derivatives examined so far, ranging from quills of the spiny ant-eater to prehistoric mammoth hair. It is also seen in mammalian horny layer.

(3) The granular-cell layer forms toward the top of the prickle-cell layer in a region just beneath the stratum corneum, a zone two or three cells deep in most regions. Here coarse, irregular, deeply basophilic granules develop in most mammals. These were first noticed by Langerhans in 1893 and named by Waldeyer a few years later. Their presence seems essential for production of a normal, flexible stratum corneum, and their appearance in cells surrounding the hair follicle may have marked a major evolutionary step toward that end, but no organelle has generated more interest and speculation among skin biologists. Brody's electron micrographs show that these granules begin as dense regions between the tonofibrils, growing larger and becoming dispersed as the cell reaches the stratum corneum. Here they stain densely with heavy metals as a matrix in which lighter tonofibrils are embedded.

Brody, I. Differential staining methods for the electronmicroscope. *The Epidermis* loc cit pp 251-272.

Montagna, William. *The Structure and Function of Skin*, 2nd ed., Academic Press, NY, 1962, pp 62-67.

The granules resist the proteolytic effects of alkaline pH, trypsin, and hydrogen-bond breaking effects of urea better than other parts of the granular cell, as indeed they should if they cement together the embedded fibrils.

Matoltsy, A.G. and M. Matoltsy. A study of morphological and chemical properties of keratohyaline granules. *J. Invest. Derm. 38:237-247, 1962.*

Synthesis of matrix probably begins in the basal layer just as synthesis of fibrillar material does, in spite of the accepted doctrine that earlier suggested separation in their sites of synthesis.

Mercer op cit p 228 ff.

Fraser has recently found that careful fractionations of wool root cells allowed him to detect simultaneous synthesis of both components at all levels

without the sharp distinctions previously proposed.

Fraser, I.E.B. The proteins of keratin and their synthesis I. proteins of prekeratin and keratin. *Aust. J. Biol. Sci. 22:213-230, 1969.*

Fraser, I.E.B. The proteins of keratin and their synthesis II. incorporation of [^{35}S] cystine into prekeratin and keratin proteins. *Aust. J. Biol. Sci. 22:231-238, 1969.*

Keratohyaline granules preferentially incorporate histidine - H^3, and most of the bound H^3 can be removed by selective extraction of the granules. In the hair follicle, sulfur-containing amino acids localize rather precisely in the region of highest matrix-synthesizing activity, an area analogous to the granular layer in skin. But sulfur-35-labelled aminoacids label only the cell membrane region in epidermis, and show no affinity for keratohyaline granules.

Fukuyama, K., and W. L. Epstein Ultrastructural autoradiographic studies of keratohyaline granule formation. *J. Invest. Derm. 49:595-604, 1967.*

Cox, A.J. and E.P. Reaven Histidine and keratohyaline granules. *J. Invest. Derm. 49:31-34, 1967.*

Fukuyama, K., M.M. Buxman, and W. L. Epstein. The preferential extraction of keratohyaline granules and interfilamentous substances in the horny cell. *J. Invest. Derm. 51:355-364, 1968.*

Fukuyama, K. and W. L. Epstein Sulfur-containing protein and epidermal keratinization. *Clin. Res. 16:256, 1968 (abstract)*

Psoriatic epidermis, which matures without producing a granular layer, incorporates little or no labelled histidine into a protein fraction which is rich in histidine when isolated from normal skin.

Gumucio, J., C. S. Feldkamp and I.A. Bernstein Studies on localization of "histidine-rich" peptide material present in epidermis of the newborn rat. *J. Invest. Derm. 49:545-551, 1967.*

Voorhees, J.J., S. G. Chakrabarti, and I.A. Bernstein. The metabolism of "histidine-rich" protein in normal and psoriatic keratinization. *J. Invest. Derm. 51:344-354, 1968.*

These findings strongly suggest that part of the keratohyaline granule, and the interfibrillar matrix presumably derived from it, contain protein poor in sulfur but rich in histidine. As a consequence, the disulfide cross-links prominent in hair keratin may be replaced in skin by matrix proteins which cement the fibrils with bonds of other types. These may include hydrogen bonds and electrostatic interactions. The flexibility and controlled desquamation of skin may follow in part from the weaker character of these bonds when compared with covalent disulfide links.

The two-phase, fibril-plus-matrix, theory of keratinization was rendered even more attractive by recent studies with glutaraldehyde fixation. Following this procedure, selective extraction of keratohyaline and interfilamentous material in the stratum corneum laid bare a number of structures whose persistance at those levels had been doubted. An extensive network of previously masked fibrils as well

as surviving desmosomes appeared in the electron micrographs.

Fukuyama, K., M.M. Buxman, and W. L. Epstein op cit.

(4) The horny layer. This filmy shroud averages only 15μ in thickness over most of the body, barely more than two red cell diameters in thickness, yet it could not be more essential for life.

The toughest part of this tough membrane is the individual horny cell envelope. Matoltsy found that 95% of powdered callus dissolved at pH 13, but the cell membranes resisted this treatment and yielded only to prolonged acid hydrolysis. I noted earlier that the membrane contains large amounts of cystine, suggestive of s-s crosslinks, and proline. Proline cannot support an α-helical tertiary structure and its presence in large amounts suggests that the membrane proteins are highly amorphous.

Matoltsy, A.G. and M.N. Matoltsy, The membrane protein of horny cells. *J. Invest. Derm. 46:127, 1966.*

Lipids account for one third of this membrane fraction. Smaller amounts of carbohydrate are found.

Matoltsy, A.G. and P.F. Parakkal Keratinization in *Ultrastructure of Normal and Abnormal Skin*, ed. by A. S. Zelickson, Lea and Febiger, Philadelphia, 1967. pp 76-104.

This extremely resistant cell envelope condenses against the delicate plasma membrane with which it later fuses. Jarrett has speculated that a slightly higher pO_2 in the peripheral cytoplasm may induce synthesis of this distinctive material.

Farbman, I.A. Plasma membrane changes during keratinization. *Anat. Rec. 156:269-282, 1966.*

Jarrett, A., R.I.C. Spearman, P.A. Riley, and A.K. Cane. The distribution of epidermal phospholipids and their relation to alkaline phosphatase activity of the granular layer. *J. Invest. Derm. 44:311-319, 1965.*

To summarize this structural and developmental description, the evidence considered so far suggests that the horny cell is a tiny, dessicated sack with an exceedingly tough wall and rather mixed contents. Besides the stress on synthesis of fibrous protein, I should emphasize the important evidence for simultaneous antolysis. Hydrolytic enzymes degrade much of the cell's interior to small molecules, many of which contribute a critical hygroscopic property to the stratum corneum, without which its smooth, plastic movement might be impossible.

Jarrett, A., et al *ibid.*

Jarrett, A. Histochemistry of keratinization, in *The Mammalian Epidermis and its Derivatives. op cit pp 55-66.*

PHYSIOLOGY: Permeability

Although the horny layer resists the passage of most molecules, charged or neutral, with impressive tenacity, its permeability is measurable and clinically important. Several conclusions can be drawn from the pioneering studies of Irwin Blank and his colleagues.

(1) Both steady-state penetration and insensible outflow involve movement directly across the layered membranes of the flattened horny cells rather than along tortuous intercellular boundaries or through sweat ducts. Large, highly polar steroid molecules may represent a partial exception to the rule followed by most substances, however. They diffuse so slowly across intact horny layer that the tiny amounts reaching the skin through so-called shunt pathways (like ducts of appendages) may constitute a major fraction of the whole.

(2) Polar groups and molecular dimensions both have major effects on the passage of material through the normal horny layer. The membrane lipids determine much of this behavior, for the absorption rates of polar and non-polar substances approach each other if delipidated stratum corneum is tested. Blank feels that non-polar molecules diffuse more rapidly because they dissolve in, and move through, a lipid layer in stratum corneum, while polar compounds diffuse through much thinner film of bound water in which their (thermal) activation energy increases with the number of charged groups per mole. Delipidation replaces both types of pathway with broad, solvent-filled channels which allow all classes to pass freely. DMSO and other highly polar, non-aqueous solvents extract both lipids and water soluble molecules; they hasten absorption by a similar mechanism.

(3) Either polar or non-polar solvent extractions alone extract far less material and reduce permeability less, than do both together. Lipids and water-soluble materials must interact together and with structural protein in order to retard dissolution of the complex. After one component has been thoroughly extracted, the others follow much more readily.

(4) It is intriguing to correlate Blank's interpretations with those of Matoltsy, *et al.* He confirmed the destructive effect of lipid solvents on barrier function and showed that buffer extraction of cytoplasmic proteins caused little change without prior lipid removal. His most interesting experiments attempted to distinguish between changes in permeability following attack on cell envelope protein versus those directed against intracellular protein. Peracetic acid oxidation of the cell envelope was the most effective procedure.

A picture emerges from these studies of a physiologic barrier to penetration whose design closely resembles that of such clever, man-made, protective layers as the suits worn by lunar astronauts. These cloth suits must weigh little, yet prevent penetration by high-speed micrometeorites. They are made from 40 or more exceedingly thin laminae, compressed to a thickness not much more than ordinary cloth. This is about the number of layers traversed by a molecule in penetrating man's stratum corneum. Thus NASA mimics Nature.

Blank, I.H. and R.J. Scheuplein The epidermal barrier in *Progress in Biological Sciences in Relation to Dermatology Vol. 2*, ed. by A. Rook and R.H. Champion. Cambridge U. Press, Cambridge, 1964 pp 245-261.

The New York Times for Monday, July 21, 1969. p 14, Late City Edition

Blank, I.H. Penetration of low-molecular-weight alcohols into skin I. effect of concentration of alcohol and type of vehicle. *J. Invest. Derm. 43:415, 1964.*

Scheuplein, R.J. Mechanism of percutaneous absorption I. routes of penetration and the influence of solubility. *J. Invest. Derm. 45:334, 1965.*

Scheuplein, R.J. Mechanism of percutaneous absorption II transient diffusion and the relative importance of barrier routes of skin penetration. *J. Invest. Derm. 48:79, 1967.*

Blank, I.H., R. J. Sheuplein, and D.J. MacFarlane Mechanism of percutaneous absorption III the effects of temperature on the transport of non-electrolytes across the skin. *J. Invest. Derm. 49:582-589, 1967.*

Scheuplein, R.J. and L. J. Morgan. Bound water in keratin membranes measured by a microbalance technique. *Nature 214:456-458, 1967.*

Scheuplein, R.J., I.H. Blank, G.J. Brauner, and D.J. MacFarlane Percutaneous absorption of steroids. *J. Invest. Derm. 52:63-70, 1969.*

Matoltsy, A.F., A.M. Downes, and T.M. Sweeney. Studies of the epidermal water barrier II investigation of the chemical nature of the water barrier. *J. Invest. Derm. 50:19-26, 1968.*

Baker, H. The effects of DMSO, DMF, and DMA on the cutaneous barrier to water in human skin. *J. Invest. Derm. 50:283-288, 1969.*

Tensile Strength

Tensile strength of the human abdominal horny layer at 65% relative humidity is ten-to twenty-fold greater than newspaper, but only a third of the value for ordinary typewriter paper and less than 2.5% of that for saran wrap. The collagenous dermis is far stronger, of course, with the result that our knees are scraped long before they are lacerated.

Kligman, A.M. *op cit.*

Cohesion

The question of why cells stick together continues to excite debate. Aside from desmosomes which seem to persist throughout the epidermis into the stratum corneum, intercellular glues of various sorts have been proposed. To be a candidate, any substance or mixture must hold unshakably for most of its functional life, then suddenly crumble to dust and shed its parent squame in single file, without allowing it to stick to its neighbors as visible flakes.

Material in the intercellular spaces stains as would protein-bound neutral and acidic mucopolysaccharides. Brody has detected unsuspected structural features in the intercellular spaces of the horny layer. While no one knows precisely how keratinocytes synthesize their surface coats, several electron microscopists have argued that certain small intracellular granules containing lamellated membranes make an indispensable contribution. Mercer and others find no stainable carbohydrate in these "membrane coating granules", and instead of contributing cementing substances, they propose they may release the lysosomal enzymes needed for controlled autolysis and shedding.

Kligman, A.M. The biology of the stratum corneum *op cit.*

Braun-Falco, O. The pathology of blister formation in *The Yearbook of Dermatology 1969*. ed. by A. W. Kopf and R. Andrade. Yearbook Medical Publishers, Chicago, 1969, pp 6-42.

Mercer, E.H., R.A. Jahn, and H.I. Maibach. Surface coats containing polysaccharides on human epidermal cells. *J. Invest. Derm. 51:204-214, 1968.*

Wolff, K. and E. Scheiner. An electronmicroscopic study on the extraneous coat of keratinocytes and the intercellular space of the epidermis. *J. Invest. Derm. 51:418-430, 1968.*

Brody, I. Intercellular space in normal human stratum corneum. *Nature, 209:472-476, 1966.*

Matoltsy, A.G. and P.F. Parakkal. Keratinization *op cit.*

Pliability

Irwin Blank's experiments established beyond question that water is the single most effective plasticizer of stratum corneum.

Blank, I.H. Factors which influence the water content of the stratum corneum. *J. Invest. Derm. 18:433-440, 1952.*

Flesch and Esoda later found a reduced binding affinity for water in a number of dermatologic disorders and suggested this followed loss of small, water-soluble molecules with hygroscopic properties.

Flesch, P. and E.J.C. Esoda. Deficient water binding in pathological horny layers. *J. Invest. Derm. 28:5-13, 1961.*

Middleton recently introduced subtle new distinctions into the simple model of horny layer structure described above. Instead of a lipoprotein bag containing osmotically active molecules, his data requires that several classes of sites must exist. He found that extensibility in isolated horny sheets fell sharply after gentle extraction of water-soluble substances, but that overall water binding capacity in the same sheet fell only slightly. His work favors the thesis that pliability depends on one or a few compartments of bound water and may involve only a small fraction of the total.

Middleton, J.D. The mechanism of water binding in stratum corneum *Brit. J. Derm. 80:437-450, 1968.*

Side-chain amino groups bind a major share of the moisture in wool, whose cells contain little hygroscopic material. Hydrophilic side-chains showed much lower affinity.

Leeder, J.D., and I.C. Watt The role of amino groups in water absorption by keratin. *J. Phys. Chem. 69:3280-3284, 1965.*

Recordings of water loss from stratum corneum during controlled temperature rise shows a reproducible series of peaks, which have been interpreted as classes of binding sites requiring differing amounts of energy for release of bound molecules. One such peak is missing in psoriatic epidermis, suggesting that these sites may be altered in disease.

Bulgin, J.J., and L.J. Vinson. The use of differential thermal analysis to study the bound water in stratum corneum membranes. *Biochem. Biophys. Acta. 136:551, 1967.*

Two Dutch workers have recently published results of incisive yet simple experiments that banish several uncertainties in stratum corneum physiology. Using the data of Spier and Pascher, who catalogued the water-soluble material in normal horny layer, they measured the water-binding capacity of each identifiable salt, suger, amino acid, and purine, as well as other types of compounds. (Five to ten percent of the water-soluble material has not been identified).

Table I. Composition of a mixture in which all known water-soluble substances of the horny layer are present (based on data of Spier and Pascher, 1959). All values represent mg. per 100 g. of skin scrapings.

alanine	754	creatinine	13
arginine-HCl	363	citric acid	20
aspartic acid	648	glucosamine	26
citrulline	1285	glucose	215
glutamic acid	290	glycogen	18
glycine	870	1 N KOH	10.98 ml
histidine-HCl	860	lactic acid	1606
leucine	416	formic acid	0.03 ml
lysine-HCl	232	$MgCl_2$-6 H_2O	226
ornithine-HCl	255	Na_2HPO_4-2 H_2O	63
phenylalanine	193	1 N NaOH	23.3 ml
proline	203	NH_4Cl	107
serine	2515	pyrrolid-2-one-5-carboxylic acid	1840
threonine	512	ribose	50
tryptophane	106	urea	550
tyrosine	309	uric acid	30
valine	280	urocanic acid	560
$CaCl_2$-H_2O	942		

modified from: Smeenk and Rijnbeek, 1969.

They then mixed these in physiological proportions and measured binding by the mixture and by a sample of extracted (natural) material.

Table II. Water-binding capacity of individual amino acids of the horny layer.(as % of dry weight bound at 95% relative humidity).

alanine	1	ornithine-HCl	225
arginine-HCl	142	phenylalanine	0
aspartic acid	1	proline	2
citrulline	11	serine	1
glutamic acid	0	threonine	1
glycine	7	tryptophane	2
histidine-HCl	2	tyrosine	1
leucine	1	valine	2
lysine-HCl	243		

Basic amino acids with side-chain amino groups bound most water, but the physiologic mixture bound far more than would have been predicted from calculations based on the final concentrations of individual substances.

Table III. Water-binding capacity of mixtures of various substances of the horny layer. (as % of dry weight bound at 95% relative humidity).

synthetic mixture of amino acids in proportions present in horny layer (pH 5.58 after water uptake)	268
synthetic mixture of all other known water soluble substances of the horny layer (pH 4.50 after water uptake)	404
mixture of all known substances of the horny laer in physiological proportions (pH 5.20 after water uptake)	288
natural extract of the horny layer (pH 5.25 after water uptake)	309

Their values for the physiological mixture fell remarkably near those for the horny layer extract (288% of dry weight versus 309%) and their pH measurements after water regain were nearly identical (5.20 versus 5.25).

While illuminating, these results have not provided quantitative answers to certain critical questions: How much *in vivo* hydration can be accounted for by extracted substances and how much depends on intracellular interactions? Are hygroscopic substances a major or minor factor in softening skin?

Smeenk, G.,and A.M. Rijnbeek. The water-binding properties of the water-binding substances in the horny layer. *Acta Derm.-Venereol. 49:476-480, 1969*

Spier, H.W., and G. Pascher. Physiologie der Hautoberflache in *Aktuelle Probleme der Dermatologie, vol.1* Karger, Basel, 1959.

BIOCHEMISTRY: High- and Low-sulfur Fractions in Wool

General references: Fraser, R.D.B., *op. cit.*

Crewther, W.G., R.D.B. Fraser, F.G. Lennox, and H. Lindley The chemistry of keratins in *Advances in Protein Chemistry vol 20* ed by C.B. Anfinsen, Jr., *et. al.* Academic, NY, 1965 pp. 191-346.

Lundgren, H.P., and W.H. Ward Levels of molecular organization in α-keratins. *Arch. Biochem. Biophys. Suppl 1:78-111, 1962*

Mercer, E.H. *Keratin and Keratinization* Pergamon, NY, 1961

Extraction methods used in the study of wool proteins have liberated two major components that differ widely in composition and properties. The A or low-sulfur protein derives from fibrils. It contains 1-2% sulfur and can be reconstituted from solution to yield oriented fibers or films that diffract x-rays in an α pattern. Optical rotatory dispersion measurements show values of 60% helix or so in non-aqueous solvents. The B or high-sulfur protein derives from the interfibriller region, contains 6-8% sulfur, and appears amorphous or randomly coiled by x-ray or ORD.

The A Proteins

Low-sulfur A proteins produce two major bands and a number of minor ones when derivitized and run in electrophoretic systems. One of these components proved to be an associating mixture composed of monomer and (mostly) trimer in aqueous buffer, but mostly dimer in 8 M urea. The molecular weight of the smallest subunit was 23,000.

Jeffrey, P.D. The molecular weight in 8 M urea of a low-sulfur protein from wool. *Biochemistry 7:3345-3351, 1968*

Jeffrey, P.D. An associating low-sulfur protein from wool. *Biochemistry 7:3352-3360, 1968*

O'Donnell found N-terminal serine and pyrrolid-2-one-5-carboxylic acid in his end-group analyses, identifying a minimum of two subunits. Other data suggested that these sub-units were themselves heterogeneous, or at least variable at certain loci.

O'Donnell, I.J. Pyrrolid-2-one-5-carboxylic acid as an N-terminal group in a low-sulfur protein of wool. *Aust. J. Biol. Sci. 21:1327-1330, 1968.*

Crewther and Harrap further refined the structural model for the low-sulfur subunit. They obtained material considerably enriched in helical segments after digestion with pronase. The digested material formed two major new bands on electrophoresis and contained more of the amino acids capable of forming α-helices (glut,leu, lys, asp, and ala) and less of those that favor random coiling (gly, pro,ser, and cys). Other data suggested that the parent subunit may have been 20 Å by 180-200 Å in size, and may have contained both helical and non-helical regions. They suggested that the cystine and other "random" amino acids may lie within the non-helical regions, which may be located in one or two short sections of the molecule. O'Donnell proposed that one such region lies as a tail at the N-terminus, where the frequency of cystine rises to that in the B or high-sulfur proteins.

The overall pattern of primary structure in both A and B proteins seems to consist of an underlying basic sequence with moderate degrees of heterogeneity superimposed. This situation is familiar from studies of immunoglobulin heavy chains, as well as many other proteins.

Crewther, W.G, and B.S. Harrap. The preparation and properties of a helix-rich fraction obtained by partial proteolysis of low-sulfur SCMK from wool. *J. Biol. Chem. 242:4310-4319, 1967.*

O'Donnell, I.J. Studies on reduced wool IX The N-terminal sequence of a fragment produced by cleavage of component 8 with cyanogen bromide. *Aust. J. Biol. Sci. 22:471-488,1969.*

The analogous human hair proteins were studied by Shechter, *et. al.*, who compared the migration on disc gel electrophoresis of low-sulfur fractions from human, monkey, dog, guinea pig, and rabbit hair. Although 5 of 18 bands moved a similar distance in all the samples, complexity of the patterns and low yields of soluble proteins from his extraction procedures make interpretation hazardous.

Shechter,Y.,J.W. Landau, and V.D. Newcomer. Comparative disc electrophoresis of hair kerateines. *J. Invest. Derm. 52:57-62, 1969.*

The B Proteins

One peculiar feature of the high-sulfur proteins has attracted the attention of investigators almost from the start. Molecular weight seems to rise with increasing sulfur content. To explore this surprising property Gillespie studied the wool of sheep that had been given sulfur-containing amino acids in large amounts. These animals formed wool containing larger amounts of the subunits highest in sulfur, and even formed some new proteins with very high cystine levels, but none of the fractions *also found in controls* changed in composition. No one has suggested a similar effect of diet on keratinized structures in man save for the body-wide abnormalities in very severe malnutrition.

Gillespie, J.M., A. Broad, and P.J. Reis. Further study on the dietary- regulated biosynthesis of high-sulfur wool proteins. *Biochem. J. 112:41-49, 1969*

Sims, R.T., and P.T. Hall. X-ray emission microanalysis of the density of hair protein in kwashiorkor. *Brit. J. Derm. 80:35, 1968*

Molecular weights for these amorphous, non-association proteins vary form 22 to 27,000, depending on sulfur content. Their separation into 8 or more bands on disc electrophoresis seems likely also to depend on sulfur content, since the net charge of a protein after its sulfhydryls have been blocked with the usual agents rises with the number of new groups introduced.

Gillespie has recently described a homologous sequence of atleast 21 amino acids and a 7-membered N-terminal peptide common to 5 types of wool and in bovine hair. He also found large amounts of "random" amino acids in these proteins. Cys, ser, threo, gly, pro, and glut made up over 75% of the residues, while his and lys were practically absent. It should be noted that these data indicate the widest possible differences between the matrix protein of hair or wool and that of epidermis. In skin, his is a major residue in the granular matrix; in wool his is absent and cys dominates.

Gillespie, J.M., T. Haylett, and H. Lindley. Evidence of homology in a high-sulfur protein fraction (SCMK-B_2) of wool and hair α-keratins. *Biochem. J. 110:193-200,1968.*

While firm evidence of underlying homogeneity in the high-sulfur proteins seems to be emerging from the work of Gillespie and others, some groups continue

to uncover disturbing signs of microheterogeneity in supposedly pure chromatographic fractions. This finding may either indicate the presence of a large number of separate but closely related proteins in each hair, with functional roles that are currently wholly obscure, or differences in synthesis between neighboring follicles, perhaps due to different circulatory or nutritional input. Random somatic variation or "wobble" during transcription are less attractive possibilities.

Swart, L.S., F.J.Joubert, and A.J.C. Strydon. Apparent microheterogeneous nature of the high-sulfur proteins of α-keratins. *Text. Res.J. 39:273-279,1969*

In summary, biochemical information is still far from complete at the level of subunit composition and structure. Much more needs to be done before information relevant to human skin, or even hair, disorders becomes available.

X-ray Diffraction Studies

Earlier proposals based on x-ray diffraction studies and the proposals of Pauling and Crick are summarized in the general references.

Two or three strand α-helical protofibrils could certainly account for both x-ray and chemical data, and the discovering of non-helical bubbles and/or tails has helped explain the relatively high content of random coil in these proteins.

If current theories are correct, most mammalian keratins may differ from each other in the mode of packing of their microfibrils and in the composition of their matrix, and in these respects only.

Fraser, R.D.B., *op. cit.*

Fibrous Proteins of Epidermis

Baden and Bonar isolated an α-fibrous protein from epidermis and documented many of its characteristics. They were unable to obtain subunits having a molecular weight less than several million, however, despite vigorous treatment with s-s bond-splitting reagents, urea, and alkaline condition. They could not duplicate Rothberg's findings with proteolytic digestion without having the protein lose helical content. They concluded that bonds linking the subunits in wool had little in common with those of skin.

Results of earlier approaches using dilute alkali solubilization must be viewed with caution since repticle bonds are sensitive to base; and this treatment may have produced very heterogenous mixtures.

Baden, H.P. and L. Bonar The α-fibrous proteins of epidermis. *J. Invest. Derm. 51:478-483, 1968.*

Rothberg, S. and G. D. Axilrod Enzymatic solubilization of insoluble proteins at neutral pH. *Science 156:90, 1967.*

A group of German workers has recently found decisive evidence for smaller subunits following gentle extraction procedures with nonaqueous solvents in epidermis. Using a two step procedure they first analyze water soluble proteins, then extract non-water soluble ones using 2-chloroethanol, a polar solvent. The dissolved proteins can be separated from accompanying lipids and fractionated by electrophoresis. This approach is an interesting one from theoretical as well as practical viewpoints, since it tends to extend the findings discussed under Permeability. These implied that sequestered lipids were exposed to extraction after removal of water soluble compounds. The same must be true of a class of structural proteins. Studies using modifications of these methods are in progress in my laboratory.

Krebs, A., K. Sellei, and H. Schaltegger Disc-elektrophoretische untersuchungen der wasserlöslichen und <<strukturellen>> Proteine in normaler und psoriatischer Epidermis. *Dermatologica 138:129-143, 1968.*

Cellular Kinetics: rate of cellular turnover

While early workers found that turnover times varried from 13-100 days in various mammals, a number of experimental approaches have established 28 days as the mean period required for a human basal cell to ascend, cornify, and be shed. The cell spends about one-half of this period in the mialpighan layer and one-half in the horny layer.

Rothberg, S., R. R. Crounse, and J. L. Lee. Glycine-C^{14} incorporation into proteins of normal stratum corneum and abnormal stratum corneum of psoriasis. *J. Invest. Derm. 37:497-504, 1961.*

Van Scott and his colleagues have further defined the several factors that control horny layer formation. These include: (1) size of the germinative population. This is three cells thick in psoriasis instead of a single cell layer ordinarily. (2) length of mitotic and interphase cycles. These are shortened to 1/3 normal in psoriasis. (3) length of generative basal line versus length of surface line. Extreme psoriatic papillomatosis increases the germinative population beneath each unit area of surface.

Van Scott, E.J. and T.M. Ekel. Kinetics of hyperplasia in psoriasis. *Arch. Derm. 88:373-381, 1963.*

Weinstein, G.D. and E.J. Van Scott. Autoradiographic analysis of turnover times in normal and psoriatic epidermis. *J. Invest. Derm. 45: 257, 1965.*

Van Scott and Flaxman have attempted to define the maximum depth attainable by the malpigham layer before cornification begins and have speculated that a critical O_2 tension may determine the onset of this sequence.

Van Scott, E.J. and B. A. Flaxman Environmental control of epithelial cells in vivo and vitro in *Epithelial-Mesenchymal Interactions.* Ed. by R. Fleischmajer and R. E. Billingham, Williams and Wilkins Baltimore, 1968 pp 280-298.

Jarrett has suggested that the keratinocyte's cellular envelope forms its particularly dense coat because of a slightly higher $^{0}2$ tension as noted above.

Jarrett, A., R.I.C. Spearman, P.A. Riley and A. Cane *op. cit.*

Separate discoveries by Bullough and by Cohen have recently opened exciting vistas for understanding basic mechanisms of epidermal growth and differentation. Bullough has described a tissue-specific, but species-nonspecific, water soluble inhibitor of epidermal mitosis. Material extracted from skin thus works only on skin, but mouse extract suppresses human material, etc. This substance, called epidermal chalone, is a non-dialysable, heat-stable protein or glycoprotein with a molecular weight between 30,000 and 40,000.

Bullough, W.S., E.B. Lawrence, O.H. Iverson, and K. Elgjo The vertebrate epidermal chalone. *Nature 214:578, 1967.*

Boldingh, W.H. and E.B. Laurence Extraction, purification and preliminary characterisation of the epidermal chalone: a tissue specific mitotic inhibitor obtained from vertebrate skin. *European J. Biochem. 5: 191-198, 1968.*

Effects of other vitamins and hormones are more controversial and less likely to be direct.

Ebling, F.J. and A. Rook *op. cit.*

Cohen studied a growth stimulatory factor obtained from salivary gland. A second substance active in stimulation of nerve growth can also be isolated from this tissue, and its physiological significance is uncertain.

Cohen, S. The stimulation of epidermal proliferation by a specific protein (EGF) *Devel. Biol. 12:394, 1965.*

The Cell Cycle

While most basal cells presumably scatter at random through the several stages of mitosis and DNA synthesis, Gelfant has described a population that seems to be arrested in G_2. Injury mobilizes these cells directly into mitosis, providing a unique reservoir for repair. This population has been demonstrated in mouse, but not in human skin.

Gelfant, S. Patterns of epidermal cell division I. genetic behavior of G_1 cell population. *Exper. Cell. Res. 32:521-528, 1963.*

SKIN ORGAN CULTURE

Organ culture of human skin requires several special factors for normal differentiation. A dermal substrate seems indispensable to completely normal keratinization by microscopic criteria. Although Flaxman has demonstrated oriented partial maturation with glass or plastic substrata, his cultures did not form keratohyaline granules or lose nuclear staining as in orthokeratosis. In dispersed cell cultures keratinocytes rapidly de-differentiate and become indistinguishable from fibroblasts. The dermal substrate need not be living. It may be killed by freeze-thaw cycles, separated

and recombined, or obtained from unrelated human donors.

Flaxman, B.A., M.A. Lutzner, and E.J. Van Scott. Cell maturation and tissue organization in epithelial outgrowths from skin and buccal muccosa in vitro. *J. Invest. Derm. 49:322-332, 1967.*

Briggaman, R.A. and C. E. Wheeler. Epidermal-dermal interactions in adult human skin: the role of dermis in epidermal maintenance. *J. Invest. Derm. 51:454-465, 1968.*

Reaven, E.P. and A.J. Cox. Behavior of adult human skin in organ culture II effects of cellophane tape stripping, temperature, oxygen tension, pH, and serum. *J. Invest. Derm. 50:118-128, 1968.*

Amino-sugars and larger polysaccharides influence maturation of keratinizing cells. Glucosamine is particularly effective in inducing growth of a granular layer. Other substances, such as vitamin A, reduce granular layer formation, increase ^{35}S uptake, and lead to appearance of mucoproteins.

Hambrick, G.W., S.I. Lamberg, and R. Bloomberg Observations on keratinization of human skin in vitro. *J. Invest. Derm. 47:541-550, 1966.*

INHERITED DISORDERS OF KERATINIZATION

History

The word ichthyosis derives from Greek elements meaning "fishy condition", but was not used in ancient medicine or until the time of Alibert, (1768-1837). Wilson suggested that ancient authors applied the term for horny excrescences to this group of disorders.

The first accurate description of a patient with ichthyosis vulgaris came from Panarolus of Rome who in 1654 described an otherwise healthy lady whose skin was "everywhere covered with scales".

for references see Costello, M.J. and R.C. Gibbs. *The Palms and Soles in Medicine.* Thomas, Springfield, 1967 pp 248.

General Considerations.

Conspicious and visible scaling differentiates this group of inherited skin disorders from ordinary dry skin brought on by excessive bathing or exposure to dry winter weather. Unfortunately for patients as well as physicians, the literature in this field has attracted a disproportionate number of scholarly reviews and schemes of classification and too little clinical research.

Exceptionally valuble contributions have come from several groups, however. Wells and Kerr provided a clear guide to inheritance and terminology and first clearly drew the clinical distinctions separating sex-linked and autosomal dominant ichthyosis.

Frost and Van Scott further refined our concepts by analysing epidermal cellular kinetics in several of these disorders. Understanding of the role of hyperproliferation has also allowed clearer classification.

The classifying impulse should not be dismissed as unimportant, of course, since new therapies with cytotoxic agents and specific antikeratinizing drugs depend on understanding pathogenesis. As a practical matter, our knowledge should now allow the physician to diagnose practically all patients in a meaningful way if he follows four steps. He should (1) look carefully at the type of scale, (2) notice its distribution, and (3) obtain a thorough family history. The fourth step may be unnecessary in most patients, but the puzzling case with mixed features deserves a skin biopsy.

Four major disorders account for all but a tiny minority of patients with ichthyosis. These are (1) autosomal dominant ichthyosis vulgaris, (2) sex-linked recessive ichthyosis, (3) autosomal dominant epidermolytic hyperkeratosis (4) and lamellar ichthyosis, the last inherited as an autosomal recessive. All but 5 of 637 patients studied in a large-scale case-finding study could be placed in one of these four categories.

Much rarer disorders include (1) harlequin fetus, an almost uniformly fatal variant due either to a sporadic dominant or to an unusually severe lamellar ichthyosis (2) psoriasiform ichthyosis, which may represent an exfoliative psoriasis of childhood.

The collodion baby syndrome refers to a newborn whose skin is tense, shiny, and dries readily to an inelastic, easily cracked membrane. Several disorders may present in this manner, so that it may be unwise to offer a prognosis unless the family history makes the diagnosis obvious. Sex-linked ichthyosis, epidermolytic hyperkeratosis, or lamellar ichthyosis may all present in this way, although a fourth possibility should always be considered. A few babies develop normal unaffected skin and have no late symptoms after shedding their membranes.

A few other rare disorders will be mentioned briefly. Ichthyosis is a variable or regular feature in all of them and has interesting implications in some.

Wells, R.S. and C. B. Kerr Genetic classification of ichthyosis. *Arch. Derm. 92:1-6, 1965.*

Wells, R.S. and C.B. Kerr. The histology of ichthyosis. *J. Invest. Derm. 46:530-535, 1966.*

Wells, R.S. and M.C. Jennings X-linked ichthyosis and ichthyosis vulgaris. *JAMA 202:485-488, 1967.*

Frost, P. and E.J. Van Scott Ichthyosiform dermatoses: Classification based on anatomic and biometric observations. *Arch. Derm. 94:113-126, 1966.*

Ebling, F.J. and A. Rook Ichthyosis in *Textbook of Dermatology Vol. II* ed. by A. Rook, D.S. Wilkinson, and F.J. Ebling, F.A.Davis, Philadelphia 1968, pp 1027-1042.

Esterly, N.B. The ichthyosiform dermatoses *Pediatrics 42:990-1004, 1968.*

Table IV. The Four Major Types of Ichthyosis

	ICHTHYOSIS VULGARIS	*SEX-LINKED ICHTHYOSIS*	*EPIDERMOLYTIC HYPERKERATOSIS (Bullous CIE)*	*LAMELLAR ICHTHYOSIS (Non-Bullous CIE)*
INHERITANCE	autosomal dominant	x-linked recessive	autosomal dominant	autosomal recessive
ONSET	over 3 months	birth to 1 year	birth to 6 months	birth
SEVERITY	mild	mild. cosmetic disability moderate due to dirty appearance.	severe	moderate

Table V. The Four Major Types of Ichthyosis: Distribution

	ICHTHYOSIS VULGARIS	*SEX-LINKED ICHTHYOSIS*	*EPIDERMOLYTIC HYPERKERATOSIS (Bullous CIE)*	*LAMELLAR ICHTHYOSIS (Non-Bullous CIE)*
FACE	forehead, cheeks	ears, preauricular	lower face	upper face
NECK	spared	heavily involved, dark		ectropion
TRUNK	back	abdomen		
FLEXURES	spared	1 in 5 heavily involved	heavily involved, moist, odor from bacteria	involved
KNEES ELBOWS	accentuated keratosis	confluent with remainder		
PALMS	increased markings	normal	involved	involved
SOLES	painful fissures	normal		
KERATOSIS PILARIS	1 in 3	normal	normal	normal
EYES	normal	punctate corneal opacities	normal	ectropion conjunctivitis

Table VI. The Four Major Types of Ichthyosis: Course

	ICHTHYOSIS VULGARIS	*SEX-LINKED ICHTHYOSIS*	*EPIDERMOLYTIC HYPERKERATOSIS (Bullous CIE)*	*LAMELLAR ICHTHYOSIS (Non-Bullous CIE)*
SCALE APPEARANCE	small, fine, white, flat	large, yellow-brown flat, moulting noted	warty, yellow-brown, elevated	large, dark brown, flat
COURSE	improve with age	worsen with age	may improve	same or worse
SEASONAL CHANGES	improve in summer	improve in summer	little change	improves

Table VII. The Four Major Types of Ichthyosis: Pathology

	ICHTHYOSIS VULGARIS	*SEX-LINKED ICHTHYOSIS*	*EPIDERMOLYTIC HYPERKERATOSIS (Bullous CIE)*	*LAMELLAR ICHTHYOSIS (Non-Bullous CIE)*
HORNY LAYER	increased	increased	massive increase	increased
GRANULAR LAYER	thin	thick	vacuolated granular cytoplasm	irregular
PRICKLE-CELL LAYER	normal	thick epidermal rete increased	marked thickening	irregular

Autosomal Dommant Ichthyosis

Incidence: Dommant ichthyosis vulgaris occurs with relatively high frequency in English-speaking countries. Two groups noted that approximately 0.8% of their patients fell into this category.

Zakon, S.J., H.F. Garrard, and R.E. Ihrke The most common dermatoses in clinical practice. *Quart. Bull. Northwest U. Med. Sch. 23:229, 1949.*

Perlman, H.H. The incidence of dermatoses among infants and children as seen in the outpatient clinic at a skin hospital in a large city. *J. Pediat. 42:700, 1953.*

Its overall incidence in the population ranges from 1.1 per thousand in the Faroe Islands to 4 per thousand among school children in Berkshire, England.

Lomholt, G. *Psoriasis: Prevalence, spontaneous course and genetics.* Gad., Copenhagen, 1963. p. 204.

Wells, R.S. and C.B. Kerr. Clinical features of autosomal dominant and sex-linked ichthyosis in an English population. *Brit. Med. J. I:947-958, 1966.*

Clinical Features: These are summarized in tables IV-VII. Dominant ichthyosis rarely presents at birth or in the neonatal period but usually develops before age 4. The scaling increases until puberty then gradually improves with age. At the mildest extreme the patient may notice only rough, dry skin during the winter. The hair and nails are never affected, though fine white branny scale may appear on the scalp as it does on other areas. The distribution favors extensor surfaces and almost invariably spares the flexures.

Many patients have keratotic plugging of hair follicles (keratosis pilaris) and a profusion of irregularly criss-crossing creases on the palms and soles.

Discrete, shiny hyperkeratoses on knees and elbows may also be helpful in making the diagnosis. The skin is unusually susceptible to solvents which produce further drying or primary irritant reactions. A frequently quoted clinical pearl emphasizes the high incidence of asthma, hayfever, and atopic dermatitis in these patients and their families although the association is difficult to account for.

Histology: Light and electronmicroscopic studies agree that the granular layer is reduced and the stratum corneum hyperkeratotic Lamellated membrane-coating granules were also greatly reduced, a finding which correllates generally with reduced desquamation.

Wilgram, G.M., J.B. Caulfield and E.B. Madgic An electron microscopic study of genetic errors of keratinization in man, in *The biology of Skin and Hair Growth* ed. by A.G. Lyne and B.F. Short, Elsevier, NY, 1965. pp 251-266.

Pathogenesis: Rothman and Felsher first appreciated the critical distinction between scaling disorders caused solely by retention of keratinized cells, and those due to their overproduction.

Rothman, S., and Z. Felsher. Insensible perspiration and the keratinization process. *Proc. Soc. Exper. Biol. Med. 56:139-141, 1944.*

They correctly emphasized the role of scale retention in this disorder, a view supported more recently by autoradiographic and biometric studies.

Frost, P. and E.J. Van Scott *op. cit.*

Frost, P., G.D. Weinstein, and E.J. Van Scott The ichthyosiform dermatoses II autoradiographic studies of epidermal proliferation. *J. Invest. Derm. 47:561-567, 1966.*

Fisher, L.B. and G.C. wells The mitotic rate and duration in lesions of psoriasis and ichthyosis. *Brit. J. Derm. 80:235-240, 1968.*

Rothman and Felsher reached their conclusions partly on the basis of evidence favoring an association between increased shedding and accelerated insensible water loss from affected skin. Recent studies have confirmed this relationship for

grossly hyperproliferative disorders such as psoriasis, but more careful measurements have shown that patients with the arch-typal disease of scale retention *also* have elevated trans-epidermal water loss (TEWL), but in amounts undetectable with the methods of twenty years ago. While it is notoriously difficult to evaluate large percentage changes in very small numbers such as these, Grice and Bettley have published data that suggests that ichthyotics lose insensible perspiration at twice the normal rate.

Grice, K.A. and F.R. Bettley. Skin water loss and accidental hypothermia in psoriasis, ichthyosis, and erythroderma. *Brit. Med. J. 4: 195-198, 1967.*

Table VIII. Comparison of trans-epidermal water loss (TEWL) in ichthyotics and normals.

		Mean TEWL	Mean daily loss
Ichthyotics	N=7	0.71 mg/cm^2/he SD 0.29	348 $\pm$ 124 ml
Normals	N=47	0.35 mg/cm^2/hr SD 0.09	151 $\pm$ 44 ml

Modified from: Grice and Bettley, 1967.

Although direct measurements of water *content* or its distribution among possible compartments are lacking, these increases in rate of *loss* suggest that ichthyotic skin is indeed just as dry as it looks, and feels. These findings also bear upon pathogenesis quite directly. For if horny layer remains flexible and resilient only as long as bound water occupies certain sites, drying will lead to cracks, tears, and crevices dotted with scale. Dessication may also lead to reduced intercellular proteolysis, so that scale collects, but is then shed in a normal manner. The cause of the reduced granular layer is more speculative and difficult to justify without detailed knowledge of normal composition.

A recent report mentioned accentuated ichthyosis developing in a previously denervated area of skin. The author detected reduced cellular turnover in the denervated area, possibly due to further reduction in epidermal hydration there. The injury definitely abolished sweating in this area of skin, and may additionally have reduced blood flow, although direct flow measurements were not performed.

Petrone, G.S. Accentuation of ichthyosis vulgaris in denervated skin. *Arch. Derm. 100:42-45, 1969.*

These studies suggest to me that a water-binding, perhaps structural protein or lipoprotein, must be at fault in ichthyosis vulgaris. This substance may normally prevent loss of both water and small hygroscopic molecules, and its lack may allow both to become depleted. The distribution of involvement, with most noticeable changes on extensor surfaces and the more moist flexures spared, suggests that the defective protein exerts its influence only secondarily by allowing dessication to occur. Otherwise the surface should be more evenly involved. The exaggerated irritation caused by solvents and detergents in these patients, and their wintertime exacerbations reinforce this thesis.

Therapy: Mild seasonal kerosis rarely needs more than a bland emollient, but

the more severly affected patients may suffer moderate discomfort, particularly in winter. Large oral doses of vitamin A transiently improve some patients, although few are deficient. No studies suggesting a link between abnormal retinol metabolism and ichthyosis have appeared since the unconfirmed report of Fischer in 1955, who found lowered blood levels and a blunted rise after oral administration of the vitamin.

Fischer, J.P. quoted in Ebling, F.J. and A. Rook *op. cit. p 1028.*

Topical retinoic acid produced burning and irritation without noticeably improving these patients, in contrast to its impressive benefits in patients with the hyperproliferative varities.

Frost, P. and G.D. Weinstein Topical administration of vitamin A acid for ichthyosiform dermatoses and psoriasis. *JAMA 207:1863-1868, 1969.*

The most consistently effective therapy for this frustratingly chronic disorder is one which restores moisture for the longest period to the dry epidermis. Baths, lipid films provided by emollient lotions, and mild keratolytics keep many patients free of scale, when they take time to use them. More interesting, however, are the results with topically applied sodium chloride and urea.

Both definitely increase the pliability of stratum corneum, probably in part by binding water within the uppermost cells which they penetrate readily due to favorable charge/size relationships. Urea passes most membranes so quickly that it is osmotically inactive in an aqueous environment. But even ordinary horny layer impedes its passage more than most tissues because both greater numbers of laminae and fewer free water molecules are present. Table II, line 2 indicates that a mixture of inorganic salts (and other soluble substances besides amino acids) has the highest water-binding capacity of any mixture studied, and it seems reasonable to suggest that supplementing skin with molecules of this class would prove most effective.

Urea may outperform inorganic salts for several reasons aside from its more rapid ingress. By displacing hydrogen bonds that may account for a part of cellular cohesiveness, it hastens shedding of accumulated scale. It also exposes previously bound carbonyl groups to hydration by available water molecules. Other consequences such as denaturation and destabilization of membranes are difficult to estimate.

Whatever the mechanism, Swanbeck has recently measured the surprisingly effective results of urea applications in normal and affected horny layer. After immersion in 5 M urea and exposure to 85% relative humidity, ichthyotic specimens absorbed and retained nearly twice the amount of water taken up by normal callus treated in the same manner. After immersion in distilled water the positions were reversed: Callus absorbed 11% and scales nothing.

Although his experimental design can be criticized for failing to compare normal *horny layer* with ichthyotic horny layer (callus differs from horny layer in significant respects) the differences are likely to be real. A clinical study reported simultaneously showed far greater improvement on the urea-treated side than on the control side.

Swanbeck, G. A new treatment of ichthyosis and other hyperkeratotic conditions. *Acta. Derm. - Venereol 48:123-127, 1968.*

Table IX. Uptake of Water at 85% Relative Humidity (as % of dry weight*)

TREATMENT	SAMPLE	
	Normal callus from sole	Ichthyotic scale
1 M urea (6% w/w)	14.3	-
5 M urea (30% w/w)	34.2	57.9
35% glycerol	20.0	-
glycerol + 6 M Urea	26.0	-
distilled water	11.3	0

*dry weight determined by weighing the specimen after drying for 24 hours in a dry atmosphere, following water uptake.

Modified from: Swanbeck, 1968.

Sex-Linked Recessive Ichthyosis

Incidence: Wells and Kerr estimated that 1 in 6000 male births involved a child with this disorder. About 1/3 of all males with ichthyosis had this form in a large survey of skin disease in the five English counties around Oxford.

Wells, R.S., and C.B. Kerr. Clinical features of autosomal dominant and sex-linked ichthyosis in an English population. *Brit. Med. J. 1: 947-950, 1966.*

Clinical Features: These are summarized in tables IV-VII. The disease presents at birth or immediately afterward in about 1/3 of the cases and is the most common cause of the collodion baby syndrome in male infants. Other children begin to peel shortly after birth without having had a preceding membrane.

Affected areas change in a characteristic sequence with age. In childhood affected boys have heavy, brown-gray scaling of the scalp, neck, and sides of the face. The pigmented scales gives the patient a perpetually dirty look, rather reminiscent of a small, soiled lad named "Pig Pen" in Charles Schultz's comic strip. Later on these areas improve, but scaling then intensifies on the thighs, lower abdomen, and flexural regions.

The flexures are conspicuously worse than surrounding skin in 1/3 of the patients while they remain clear in the dominant variety. The scales are larger and darker in x-linked than in the dominant form, and brief seasonal episodes of increased shedding (moulting) may occur.

Although it spares the nails and does not involve the hair primarily, it may cause rather severe scaling of the scalp in childhood, and occasionally produce a spotty alopecia or retard the onset of hair growth in infancy.

Female carriers rarely have symptomatic skin changes. (one mildly affected hemizygous woman has been reported) The most interesting sign of the hemizygous state is asymptomatic deep corneal stippling found in 3 of 8 women examined.

Table X. Eye Changes Found in Major Varieties of Ichthyosis.

	ECTROPION	*DEEP CORNEAL OPACITIES (GRADE)*				
		NONE	*1*	*2*	*3*	*4*
ICHTHYOSIS VULGARIS (N=37)	-	32	5	-	-	-
X-LINKED ICHTHYOSIS (N=17)	-	-	-	1	9	7
X-LINKED ICHTHYOSIS CARRIERS (N=8)	-	1	4	3	-	-
LAMELLAR ICHTHYOSIS (N=16)	13	16	-	-	-	-
EPIDERMOLYTIC HYPERKERATOSIS (N=11)	-	11	-	-	-	-
NORMAL CONTROLS (N=100)	-	91	9	-	-	-

Modified from: Sever, et. al. 1968.

Sever, R.J., P. Frost, and G.D. Weinstein Eye changes in ichthyosis. *JAMA 206:2283-2286, 1968.*

Histology: The horny layer demonstrates both hyperkeratosis and parakeratosis (retained nuclear fragments in the stratum corneum) in stained sections. One finds a thickened granular layer in contrast to the diminished one in dominant ichthyosis, and a prickle-cell layer of increased depth. Around dermal vessels there are collections of lymphocytes and other chronic inflammatory cells, though these changes are spotty. To my knowledge, no one has turned an electron microscope on one of these patient's biopsies.

Wells, R.S. and C.B. Kerr The histology of ichthyosis. *J. Invest. Derm. 46:530-535, 1966.*

Pathogenesis: Factors similar to those discussed for the dominant variety may also figure in this disorder, but several points require special consideration. The deep corneal opacities found in affected men and in a few hemizygous women imply that tissues derived from embryonic mesoderm may express the defect in limited ways along with ectoderm.

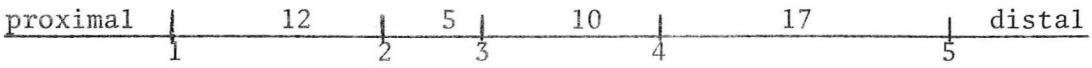
The inheritance pattern suggests that the defect will finally be found not in a structural protein as in most dominant defects, but in an enzymatic protein as in most recessive ones. That symptoms and signs are found in a small proportion of the women is not surprising, and may be confidently explained by the Lyon hypothesis.

Some guesses about pathogenesis may be made on the basis of the collodion baby phenomenon. Since the baby forms an abnormal stratum corneum *in utero* one can hardly suggest that drying or other environmental stress acts as a proximate cause

for the hyperkeratosis as was proposed for dominant ichthyosis.

Sex-linked ichthyosis has proven useful in mapping part of the human x-chromosome, where it conveniently bridges a broad gap between Xg blood group and G-6-PD.

Figure I. Map of the short arm of the human x-chromosome around x-linked Ichthyosis. (distances in centimorgans)



1. hemophilia A
2. deutan color vision
3. G-6-PD
4. X-linked ichthyosis
5. Xg blood group.

Modified from: Kerr, Wells, and Sanger, 1964.

Kerr, C.B., R.S. Wells, and R. Sanger X-linked ichthyosis and the Xg groups. *Lancet 2:1369-1370, 1964.*

Adam, A., L. Ziprkowski, A. Feinstein, *et. al.* Ichthyosis, Xg blood groups and protan. *Lancet 1:877, 1966.*

Wells, R.S., M.C. Jennings, R. Sanger, and R.R. Race. Xg blood groups and ichthyosis. *Lancet 2:493-494, 1966.*

Therapy: refer to dominant ichthyosis

Lamellar Ichthyosis (Non-bullous congenital Ichthyosiform Erythroderma)

Incidence: This disorder is a rare cause of ichthyosis. Wells and Kerr found only 1 in 260 patients in their survey, and Lentz and Altman counted only 103 case reports in the world's literature. Consanguinity is common in affected families, as is often found in diseases due to rare recessive alleles.

Lentz, C.L., and J. Altman Lamellar ichthyosis. The natural clinical course of the collodion baby. *Arch. Derm. 97:3-13, 1968.*

Clinical Features: This category harbors a spectrum of conditions given separate names in the past. A few infants desquamate their collodion wrapper in lamellar sheets soon after birth and thereafter enjoy a normal epidermis. In another group the redness and scaling persist and become generalized, only to improve with age. At its most severe, the infant's horny, brittle skin gapes wide with each new movement, emitting a thin, blood-tinged discharge. In these cases hands and mouth are immobile and useless, and the leathery skin of the chest may restrict breathing. Survival longer than a few days is unusual.

In the moderately severe group the child's face is red and taut during the early years but improves with age. Ectropion and eclabium are common and distinguish this disorder from x-linked ichthyosis in affected boys. The forehead and upperface appear most involved in lamellar, while the lateral cheeks and neck scale more severely in x-linked. There may be a flattened nose and the external ears may appear glued to the scalp.

Large, dark scales are seen, again resembling the x-linked variety, a resemblance that includes the pattern of distribution on flexures, body, and scalp. Palms and soles may be thickened and inflexible, and nails are sometimes ridged and pitted as in psoriasis.

Bloom, D. and M.S. Goodfried Lamellar ichthyosis of the newborn. *Arch. Derm. 86:336-342, 1962.*

Shelmire, J.B., Jr. Lamellar exfoliation of the newborn. *Arch. Derm. 71:471-475, 1955.*

Histology: No distinctive changes are seen. The biopsies resemble those from sex-linked ichthyosis: focal parakeratosis, and a normal or thickened granular layer. A great many follicles show keratotic plugging.

Nix, T.E., H.W. Kloepfer, and V.J. Derbes: Ichthyosis, lamellar exfoliative type. *Derm. Trop. 2:142, 1963.*

Pathogenesis: Both this disorder and epidermolytic hyperkeratosis are marked by a considerable increase in the rate of epidermal cell turnover. Using glycine-^{3}H on Thymidine-^{3}H, the number of cells labelled per centimeter of surface line rose about 3-fold in lamellar ichthyosis and slightly higher in epidermolytic hyperkeratosis (see table XI).

Table XI. Cellular Kinetics in Ichthyosis

	Labelled cells/cm surface line	*Cell transit time (days) through epidermis*
NORMAL CONTROLS (18)	86 ± 21	12-14
ICHTHYOSIS VULGARIS (4)	70 ± 7	10-14
LAMELLAR ICHTHYOSIS (3)	230 ± 36	4- 5
EPIDERMOLYTIC HYPERKERATOSIS (3)	294 ± 85	4

Modified from Frost, Weinstein, and Van Scott, 1966.

Therapy: These results suggest that lamellar ichthyosis, like psoriasis, might respond to cytotoxic agents. One such patient has been reported who cleared dramatically on Methotrexate.

Esterly, N.B. and E. Maxwell Non-bullous congenital ichthyosiform erythroderma: A case treated with Methotrexate. *Pediatrics 41: 120-122, 1968.*

Topical retinoic acid proved remarkably effective in this disorder as it has in each of the scaling disorders in which increased cellular turnover has been shown.

Frost, P., and G.D. Weinstein, 1969, *op. cit.*

One carefully studied patient responded to oral as well as topical retinoic acid. Her response was particularly interesting since neither 3 times the oral dose of retinol, nor topical retinol, had shown the slightest effect.

Thompson, J. and J.A. Milne. The use of retinoic acid in congenital ichthyosiform erythroderma. *Brit. J. Derm. 81:452-455, 1969.*

Epidermolytic Hyperkeratosis (Bullous congenital ichthyosiform erythroderma)

Incidence: Wells and Kerr had 7 of 276 patients with this unusual disorder.

Clinical Features: This disorder may present at birth as one of the causes of the collodion baby syndrome, but its manifestations are quite variable, and localized, or generalized mild forms are not uncommon. The distribution may be densely generalized, but usually predominates around joints and in flexures. The horny layer is thrown into irregular ridges of gray-brown, confluent, wart-like excrescences.

Bullae and redness become less frequent with age, and usually affect flexural areas. Bacterial overgrowth in the deep, sometimes moist crevices of the stratum corneum may be partly responsible for these bullae, and measures designed to suppress their growth may be helpful.

Hair and nails are normal, but palms and soles may be heavily hyperkeratotic.

Wilgram, G.F. and A. Weinstock. Advances in genetic dermatology. *Arch. Derm. 94:456-479, 1966.*

Reed, R.J., E.G. Galvanek, and R. R. Lubritz. Bullous congenital ichthyosiform hyperkeratoses. *Arch. Derm. 89:665-674, 1964.*

Histology: A highly distinctive microscopic picture draws together an otherwise baffling clinical variety seen in this syndrome. Cells of the upper prickle-cell and granular layers balloon outward with edema, within which clumped keratohyaline, dispersed granular material, and disordered tonofibrils lie in confusion. Despite these seemingly irremediable changes the thickened horny layer above appears relatively normal.

Wilgram, G.F. and J.B. Caulfield An electron microscopic study of epidermolytic hyperkeratosis. *Arch. Derm. 94:127-143, 1966.*

Pathogenesis: Frost and his co-workers demonstrated greatly accelerated epidermal turnover and reduced transit time in this disorder. An unusually compact horny layer transmits this greatly speeded turnover into large mounds and ridges of accumulated keratin that is such a distinctive clinical feature of this syndrome. Surely both of Rothman and Filsher's mechanisms are at work here.

The frequent occurrence of localized (nevoid) forms of this disorder deserves comment, although the reasons for a high frequency of somatic mutation at this locus during embryonic life are obscure.

Frost, P., G.D. Weinstein and E.J. Van Scott *op. cit.*

Therapy: refer to lamellar ichthyosis

Very Rare Causes of Ichthyosis

Familial Continual Skin Peeling: This very rare disorder has recently been noted in four of nine siblings and shown to involve definite hyproliferation with what seems to be compensatory shedding. Other than rapid transit and increased number of labelled cells no histologic abnormalities were seen. The mode of genetic transmission has not been established although the unaffected parents were first cousins in the reported family, suggesting recessive inheritance. The skin was not red and palms and soles were spared.

Kurban, A.K., and H.A. Azan. Familial continuous skin peeling. *Brit. J. Derm. 81:191-195, 1969.*

Ichthyosis Linearis Circumflexa: Fourteen cases (M=F) of a bizarre, familial, migratory, annular, polycyclic scaling dermatosis have been reported. All cases began soon after birth and the early accompanying redness faded with age. Palms, soles, nails, and hair were normal. Biopsies show a parakeratotic horny layer, increased thickness of the granular and malpigham layer and little more. An autosomal recessive mechanism seems likely.

Vineyard, W.R., L.R. Lampkin, and J.C. Lawler Ichthyosis linearis circumflexa. *Arch. Derm. 83:630-635, 1961.*

Stevanoric, D.V. and R.L. Pavic Dryskeratosis ichthyosiformis congenital migrans. *Arch. Derm. 78:625-629, 1958.*

Netherton's Syndrome. (NS): Nine cases (M/F=1/8) of combined ichthyosis and bamboo hair (trichorrhexis invaginata) have been reported since Netherton's paper in 1958. A diffuse,scaly erythroderma was present from birth with accentuation in the flexures. The hair abnormality presented clinically as sparse, short, easily broken hair. Invaginated nodules were obvious only on microscopic examination.

Spontaneous reversion of the hair structure to normal occurred by puberty in most patients, and slow improvement in the skin was also noted.

Five of the reported 14 patients with ILC have had hair abnormalities, and two further patients have just been presented who share features of ILC and NS. These two entities may be combined once the results of variable expressivity become clearer.

Netherton, E. A unique care of trichorrhexis nodosa-"bamboo hairs". *Arch. Derm. 78:483-487, 1958.*

Wilkinson, R.D., G.H. Curtis, and W.A. Hawk Netherton's disease. *Arch. Derm. 89:46-54, 1964.*

Altman, J. and James Stroud. Netherton's syndrome and ichthyosis linearis circumflexa. *Arch. Derm. 100:550-558, 1967.*

Erythrokeratodermia Variabilis: Highly variable expression of an autosomal dominant gene determines this disorder, which results in lesions of five types: (1) sharply demarcated hyperkeratotic plaques which may form bizarre patterns on the skin and (2) patches of redness which change from day to day and vary from pink to deep red in color. The disorder begins at birth or during the first year, and often improves at puberty. Palms and soles may be involved. The histologic changes resemble those seen in x-linked ichthyosis. Only palliative treatment is available. An abnormality involving vascular control seems likely.

Brown, J. and R.R. Kiesland. Erythrokeratodermia variabilis. *Arch. Derm. 93:194-201, 1966.*

Rudd's

~~Reed~~'s Syndrome: No consistent features have emerged from this hodge-podge category of patients with mental retardation, epilepsy, ichthyosis of various sorts, sexual infantilism, and a variety of gross congenital malformations. Most authors believe these cases represent coincidence of more common disorders of keratinization with other defects.

Esterly, N.B. *op. cit.*

Ebling, F.J. and A. Rook *op. cit.*

Sjögren-Larsson Syndrome: The two authors have concluded that this autosomal recessive trait originated in a single mutation in northern Sweden during the fourteenth century. Approximately forty cases with congenital generalized fine scaliness, mental retardation, and spastic diplegia have been reported. Nails, and hair are normal, but keratoderma of palms and soles occurs. Ophthalmologic examination is usually normal. The patient's spasticity is progressive and life span is shortened.

The histologic changes resemble those in x-linked ichthyosis.

Sjögren, T. and T. Larsson. A clinical and genetic study. Oligophrenia in combination with congenital ichthyosis and spastic disorders. *Acta. Psychiat. Neurol. Scand. Supple. 113 32:1, 1959.*

Heijer, A. and W.B. Reed. Sjögren-larsson Syndrome. *Arch. Derm. 92:545-552, 1965.*

Conradi's Disease (chondrodystrophia congenita punctata): Features of this very unusual dominant disorder include (1) Whirl and swirl pattern of (congenital) ichthyosis (2) skeletal defects with shortened limbs and flexion contractures. (3) lenticular opacities, (4) facial bony abnormalities-high arched palate and

flattened nasal bridge, and (5) stippled epiphyses on x-ray. This is a diagnosis often first made by the well-read radiologist. The skin changes are variable and not found in every case, but highly dramatic when seen. As the patient ages the hyperkeratinization remits and leaves only mild hypopigmentation and follicular atrophy.

Bodian, E.L. Skin manifestations of Conradi's disease. *Arch. Derm. 94:743-748, 1966.*

Refsum's Syndrome (heredopathia atactica polyneuritiformis): This rare neuroectodermal syndrome may be the most interesting of all, since it is, to my knowledge, the only inherited disorder of keratinization in which a precise enzymatic defect has been localized. Less than fifty cases of this autosomal recessive syndrome have been reported. Clinical features include (1) retinitic pigmentosa (2) peripheral neuropathy and (3) cerebellar ataxia. Less frequent manifestations include ichthyosis, hearing loss, anosmia, short metatarsals, and EKG changes.

Again, a single Swedish or Norwegian mutation may be suspected. The skin changes are mild, and difficult to relate to the biochemical defect, which involves failure to oxidize an unusual dietary branched-chain fatty acid, phytanic acid (3,7,11,15 tetramethyl hexadecanoic acid). However, calculations show that this lipid may well play havoc with lipoprotein membranes everywhere in the body, and may affect a variety of structures by this means.

Dietary limitation of phytanale sources is the only rational therapy. The skin rarely requires treatment.

Kahlke, W. *Refsum's syndrome in lipids and lipidosis.* ed by *G. Schettler* Springer Veilag, NY, 1966.

O'Brien, J.S. Cell membranes - composition: Structure: function. *J. Theoret. Biol. 15:307-324, 1967.*

Steinberg, D. *et. al.* Refsum's disease-a recently characterized lipoidosis involving the nervous system. *Ann. Intern. Med. 66:365, 1967.*