F.I.R.S.T.
Foundation for Ichthyosis and Related Skin Types

ICHTHYOSIS FOCUS

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PRESS RELEASE

Award Honors Dermatologist's Innovative Research Into Ichthyosis

Raleigh, NC - Eugene J. Van Scott, M.D., a well known dermatologist and clinical professor at Hahnemann University in Philadelphia, PA, has been named the first recipient of the F.I.R.S.T. Award for landmark work in scaling disorders of the skin which includes a genetic skin disorder known as ichthyosis.

Ellen B. Rowe, M.S.W., president of F.I.R.S.T. board of directors, presented the award to Dr. Van Scott at the annual meeting of the Society for Investigative Dermatology held in Baltimore, MD on May 1, 1992.

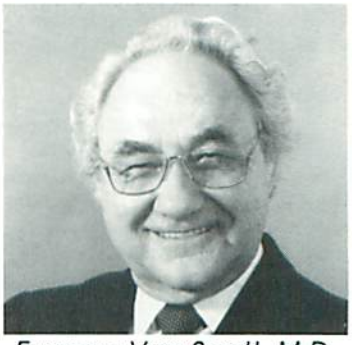
Dr. Van Scott began studying this disease during the 1950's and has published more than 160 articles. His excellent research has led to improved treatments for dry skin disorders and to an increased understanding of how skin cells divide and mature.

The medical advisory board of the Foundation of Ichthyosis and Related Skin Types voted unanimously to present this prestigious award to Dr. Van Scott. "The breadth and depth of his contributions to the treatment of ichthyosis and to understanding the fundamental processes of cell replication and maturation in cutaneous epithelia are already legendary," said Dr. Leonard Milstone, chairman of F.I.R.S.T.'s medical advisory board and a dermatologist at the Yale University School of Medicine.

Dr. Van Scott was instrumental in the development of new treatments and the discoverer of the beneficial effect of alpha hydroxy acids on the skin.

He began his work in the National Cancer Institute and was the first director of the dermatology branch of that institute. Dr. Van Scott was brought to NCI by Dr. Gordon Zubrod, who was then chief of intramural research and who thought that understanding controls of cell replication and maturation in the cutaneous epithelia might give clues to understanding controls operative in epithelial cancer.

Working with Dr. Van Scott at NIH in the early 60's when little was known about skin differentation, were Robert Auerbach, Kenneth Blalock, William Clendenning, Arthur Eisen, Gerald Weinstein and Phillip Frost. Their early research showed that cell division was increased



Eugene Van Scott, M.D.

in certain types of ichthyosis, while in others, scale formation was related to retention of dead cells.

Dr. Van Scott later moved to Temple University Medical School where he was joined by Dr. Ruey J. Yu in the discovery of the therapeutic benefits of alpha hydroxy acids. This group of acids includes glycolic acid, lactic acid, citric acid and malic acid. Van Scott and his coworkers determined that these acids normalize abnormally dry skin when added to creams and lotions.

Dr. Van Scott received his medical training at the University of Chicago, was scientific director at the National Cancer Institute in Bethesda, MD, and has served on the faculty at Temple University School of Medicine. He is currently a clinical professor of dermatology at Hahnemann University in Philadelphia, PA.

He is a member of the American Academy of Dermatology, American Medical Association, American Society for Clinical Investigation, American Society for Experimental Pathology, Society for Investigative Dermatology, and many others.

Dr. Van Scott and his wife reside in Abington, PA and have three children.

Network News

Cynnie Bates, chairman of the Regional Support Network, reports that all eight regions are functioning, exchanging addresses and telephone numbers, sharing information and providing local patient support. Cynnie wants to remind everyone to return their pink Participation Forms to the regional representatives. If you have misplaced your form, you can ask the F.I.R.S.T. office in Raleigh to send you another one. Region One (Northeastern states) is planning a support group meeting for May 23 in New York City at the Unitarian Church of All Souls located at the corner of Lexington Ave. and 80th St. The meeting will be held from 1 to 4 p.m. Children are invited, and child care will be provided for $2 per child. There is a $5 registration fee. Contact Lynne Alba at (215) 584-6366 for more details.

Trice Ovbey, Region Two, gave a 30-minute talk to physicians at Fort Bragg, NC on March 2. "I can't begin to tell you how nervous I was, only to find that everything went so smoothly. It surprised me," says Trice.

"I was amazed at how little some professionals know about ichthyosis and how interested they really are to find out more," says Trice. "Believe me, one on one, I can out talk the best of you. But put me in front of a group and forget it! But this was unbelievably fun and easy. So put the word out that you are available to speak to groups and let's educate the public. If I can do it, anyone can!" says Trice. Trice is the mother of three children: Tiffany, age 7 with normal skin; Tommy, age 3 with CIE; and Abby, only one, also with CIE. They live in Fayetteville, NC.

Region Three would also like to have a meeting. If you live in that area and could suggest a place to meet, please call Cathy Sipper at (205) 335-6827.

Cynnie says Indianapolis has been suggested as a spot for Region Four to meet. If this appeals to you and you would like to help plan the get-together, please contact Cynnie at (606) 276-0142. She recently moved and this is a new number.

Regions Seven and Eight are planning a joint meeting for later this year. If you are interested in attending, contact Heather Gattuccio at (503) 284-8946.

In this issue . . .

Tell Me Doctor

Q. I have ichthyosis vulgaris and would like to know if either of my two kids (neither of which has ichthyosis) could be carriers of the lamellar or other, more serious, types of ichthyosis?

A. Since we believe that each form of inherited ichthyosis is caused by a single, separate factor, your children would have no greater chance of carrying factors for the other types of ichthyosis than anyone else in the general population. Although ichthyosis vulgaris is a "dominantly" inherited trait, its expression is highly variable and many who have the factor do not clinically express it, or express it only under certain conditions (such as cold dry weather, etc. ...).

Q. How common are the various types of ichthyosis? I have lamellar ichthyosis and don't know anyone else in this city (Portland, Oregon) who has it. None of my doctors has ever seen anyone with it either and they don't know the first thing about it.

A. Hopefully this will change soon as we now have an active support group in Portland! F.I.R.S.T. published a list of the major forms of ichthyosis and their incidence a few years ago. If you would like a copy of the fact sheet, please request one from the F.I.R.S.T. office. Briefly, the prevalence of the four major types is as follows: Vulgaris: 1:250 (Meaning one person in every two hundred and fifty Americans has the vulgaris type); X-linked 1:2,000; CIE and Epidermolytic Hyperkeratosis, 1:100,000; and Lamellar, 1:200,000.

Q. I recently gave birth to a baby diagnosed as a "Harlequin baby" and was told by the pediatricians that this was fatal and my baby would die within a few days or weeks. The dermatologist we consulted said several babies like this have survived well into childhood recently and that treatment with new drugs has improved their outlook. What is true?

A. Prior to the late 1970's Harlequin Ichthyosis, the most severe of the recessive ichthyosis, was always fatal. The infants succumbed to infection, or severe restriction of eating and breathing due to the excessively tight skin around the mouth and chest. However, with new, well equipped neonatal units in large hospitals, and with new antibiotics to combat infection, we have been able to save most of these babies. One is 10 years old and doing well. Several have been treated with the new Vitamin A drug, Etretinate, with dramatic results. Two or three of these Harlequin babies have survived for a number of months and have had sudden unexplained crib death. We are collecting data on these and hope to be able to discover why. Another possibility is that of misdiagnosis. Since many types of ichthyosis are very rare, infants who actually have one of the other forms of ichthyosis may have tight skin when born (the so-called Collodion Baby). This goes on to peel nicely in a few weeks, and the true nature of the ichthyosis becomes apparent. These infants are sometimes improperly called "Harlequin" by hospital staff taking care of them. We recently had such a case here in Portland, and it was gratifying to be able to reassure the parents that their baby would indeed do very well and look much better after the tight collodion membrane peeled.

Melodie M. Buxman, M.D. is a dermatologist on the F.I.R.S.T. Medical Advisory Board. She has been writing this column for several years and will be happy to answer your questions. Please send your questions to the F.I.R.S.T. office and we will forward them to her. You may send them anonymously if you do not wish to be identified. Also, we will be glad to answer psychological, social, as well as medical questions that relate to skin. Mail your questions to FOCUS., P.O. Box 20921, Raleigh, NC 27619-0921.

Ellen Rowe

From the President...

The past few months have really flown by. Activity at the F.I.R.S.T. office has kept us all very busy. The more letters and phone calls we receive, the more I realize how important this organization is to those of us who have ichthyosis. When I hear stories of children who have been teased at school for "being dirty" and sent home to take a bath, I remember my own childhood and some painful experiences I lived through.

Simple things that most people take for granted can be major issues for those who have ichthyosis - like getting a haircut, for example. How do we explain all those flakes to the beautician? Will she refuse to cut my hair? This is just another form of discrimination, of ignorance, and F.I.R.S.T. continues to push for public awareness so that ichthyosis can be understood and accepted.

I can remember how miserable I was shopping for a prom dress. Those sleeveless, strapless gowns were so pretty - and so revealing. But, I was glad to have a date to the prom, and my mother and I found a beautiful yellow dress that was just right for me.

Feeling accepted, comfortable with who we are, what we look like, and living life to its fullest is a goal for all of us. The psychosocial problems we face are probably more difficult to overcome than the physical problems of having ichthyosis. I want to challenge everyone with ichthyosis to come to terms with this genetic disorder, accept it, and move on with the rest of your life. Let's not hide it any more. We can be proud of who we are and of the sensitivity we have for others who might also be a little different.

And remember, your contribution helps us help ourselves. Please send your donation to F.I.R.S.T. today!

Thanks, Ellen

Write Your Congressmen

By Frances McHugh
Vice-President

As we mentioned at our Williamsburg conference last summer, it is very important that F.I.R.S.T. supporters **write to their Washington representatives asking them to support a registry** and increase the budget of the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) to $300 million in FY 1993. Through NIAMS, Dr. Peter Steinert and Dr. Sherri Bale are conducting research on ichthyosis in their laboratory in Bethesda, MD. We are very happy about this, but feel that there is a dire need for a registry of people with ichthyosis as this may encourage additional research.

Many new things are happening in skin research at this time, and we want to make sure that ichthyosis research is considered, continued and expanded! Your letters do not have to be typewritten or fancy. This is your country and you write the way you talk. Some suggested addresses and salutations are as follows:

The Honorable John Doe
The United States Senate
Washington, DC 20510

Dear Senator Doe:

The Honorable John Doe
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Doe:

Some facts that you might mention are: 1) **You are very interested in a registry for ichthyosis.** 2) Your child/ sister/ brother/ parent suffers with this condition. 3) Ichthyosis causes pain, discomfort, disfigurement, disability and dependency. 4) We would like the Appropriations Committee in charge of the NIAMS budget to increase the budget amount to $300 million for FY 1993. 5) You very much appreciate the research being done by Dr. Steinert and Dr. Bale but feel more could be done. Ichthyosis needs a registry to help with research.

Frances McHugh

Continued on page 3

Senator Mark O. Hatfield receiving award from Coalition of Patient Advocates for Skin DIsease Research

Representative Carl D. Pursell

From the Director's Desk . . .

The winter was busy here at the F.I.R.S.T. offices. Our intern, Carolyn Sullivan, a student at North Carolina State University, has been going through our donor files and entering relevant information onto our new database. She has done some research on pertinent published articles about ichthyosis and may be contacting you to chat and answer questions. She is currently studying to be a genetic counselor. In March I spent three days in Washington D.C. where I met with Dr. Lawrence Shulman, director of the National Institute of Arthritis, Musculoskeletal and Skin Disease (NIAMS), one of the National Institutes of Health. As you can see from the name of this institute, the umbrella of conditions it covers is tremendous. However, I feel confident that we have many advocates at NIAMS. I participated in the efforts of over 45 professional and voluntary patient groups to request additional funding for research. As members of the Coalition of Patient Advocates for Skin Disease Research, we made special visits to thank those congressmen who have helped us

Susan Snyder

tremendously in the past. Last year the Coalition gave an award to Senator Harkin, chairman of the Senate Subcommittee for Labor, Health and Human Services and Education. This year, an award was given to Rep. Carl D. Pursell of Michigan for his work on our behalf on the House Appropriations Subcommittee for Labor, Health and Human Services and Education. An award was also given to Sen. Mark O. Hatfield of Oregon for his efforts for skin research on the same committee on the Senate side.

While in Washington, I made two trips to Bethesda, MD to visit the National Institutes of Health and specifically the Skin Biology Laboratories where scientists under Dr. Peter Steinert and Dr. Sherri Bale are working on ichthyosis. I was impressed by the genuine caring of these researchers, their excitement, enthusiasm and dedication to finding the genetic causes of ichthyosis.

Over and over again they told me how appreciative they were to members of F.I.R.S.T. for they willingness to come to Bethesda and participate in this very promising work. Their successes are the direct result of F.I.R.S.T.'s efforts to advocate for research and to follow through with willing patients. Thanks so much to all of you!

May is also a busy month for us. I will attend the National Organization of Rare Diseases conference and will once again visit the Hill to advocate for an ichthyosis registry. We are also preparing to participate in the World Congress of Dermatology which will be held in New York this June.

The F.I.R.S.T. office is open Monday through Friday. If we aren't there, please leave a message and we will return your call. Our toll free number is 1-800-545-3286.

Welcome all new members!

Susan Snyder

Continued from page 2

6) Add a personal note of your own. Anything will be fine.

You can call the F.I.R.S.T. office to find out the names of your representatives. In addition to your own representatives, the following are the people on the Appropriations Committee in charge of the NIAMS budget who should also be contacted. If you cannot write to them all, the names with the * are the most important

House of Representatives: *William H. Natcher (D-KY); Neal Smith (D-IA); *David R. Obey (D-WI); Joseph Roybal (D-CA); Louis Stokes (D-OH); *Joseph D. Early (D-MA); Steny H. Hoyer (D-MD); *Carl D. Pursell (R-MI); Joseph E. Porter (R-IL); C.W. Bill Young (R-FL); Vin Weber (R-MN); and Robert Mrazek (D-NY).

Senate: *Thomas R. Harkin (D-IA); Robert C. Byrd (D-WV); Ernest F. Hollings (D-SC); Quentin N. Burdick (D-ND); Daniel K. Inouye (D-HI); Dale Bumpers (D-AR); Harry Reid (D-NV); Brock Adams (D-WA); *Arlen Specter (R-PA); *Mark O. Hatfield (R-OR); Ted Stevens (R-AR); Warren Rudman (R-NH); Thad Cochran (R-MS); Phil Gramm (R-TX); Slade Gorton (R-WA).

When we speak, our representatives in Washington DC listen; and the louder we speak - the better they listen. Ask your friends and relatives to also write.

Happy Writing !!!

Frances McHugh

Correspondence Corner

Donna Rice, 22714 Royal Arms Court, Katy, TX 77449 has a new baby, Haley, who was born with ichthyosis on Feb. 2. She would love to hear from other parents who can share helpful tips and friendly support. Please write to her. Congratulations on your new addition, Donna!

Patty Coppola, 5538 W. Golden Lane, Glendale, AZ 85302 wants to let folks know that Melrose Hand and Skin Cream has helped her husband and three children who all have ichthyosis. "I'm not saying that Melrose Cream might work for all forms of skin conditions, but it can help some and at least that's a start." says Patty. "Keep up the good work, F.I.R.S.T. Your newsletter is definitely newsworthy," she says. Patty gave us the address of the Melrose Company. It's 500 S. Alabama St., Amarillo, TX 79106. The phone number is 1-806-372-4691.

Mary Williams, of Franklin, LA says that her 16-year old daughter, Misty, has tried NuSkin products and has had great results, especially with the Intensive Eye Complex. You can contact Mary or Misty at (318) 828-4962.

Ryan Erickson, age 9, is looking for a pen pal who is around his age. He has Bullous Congenital Ichthyosis (EH). Any children who want to write to Ryan can send letters to: 4911 200th SW #B-5, Lynnwood, WA 98036.

Sidney Hastings, 91 years young, writes to tell us that he has had a recent experience with radiation for cancer and that these treatments aggravated his ichthyosis. Sidney uses LacHydrin and finds it helps a great deal. "In 1905, my father took me to a skin specialist in New York, and we were told there were only five reported cases in the world, so maybe this is one of the scarce types," says Sidney. We think there are quite a few more of us around these days! Sidney lives in Deltona, FL.

Gerald Woodward, (602) 461-5003 or (602) 831-2728, has also had good results with Melrose Cream. He has two brothers who also use this product. "One brother was never able to wear short sleeved shirts because of the brown dry scales on his arms, but now that is not a problem. I can honestly say that this cream is a miracle for me." Gerald says that he showers at least twice a day and uses the cream immediately after each shower.

Debbie Gullickson, says that her son Chad, age 10, has ichthyosis and that the winter months are the worst. "His skin has always looked dirty, or like a tweed coat and at school the children would ask what's wrong with you?" Thanks to Atrac-tain Cream, Whirl-Sol Bath Oil and Gentle Rain Soap, Chad is looking and feeling much better, "This winter has been a big change. He has normal colored skin for the very first time. I have waited to write this letter because I wanted to be sure that during the worst months the dry, black unshedding skin would not reappear. It has not!" These products are made by Sween Corporation. The company will send you a free sample if you call 1-800-533-0464.

Herald Pharmacal, makers of Aqua Glycolic Lotion, have extended their generous offer to sell this lotion to F.I.R.S.T. members at a price of $48 per case (12 bottles). This lotion can cost as much as $15 in some stores. Several F.I.R.S.T. members have had amazing results from using this product. You may need to use it for at least two weeks before you begin to notice results - As with any new product you use, F.I.R.S.T. encourages you to consult with your dermatologist.

News from NIAMS . . .

By Sherri J. Bale, Ph.D

Exciting things are happening in the field of skin and skin disease research. As you will read in other articles in this issue, both Dr. Ervin Epstein and Dr. Elaine Fuchs have each made a significant breakthrough in understanding the underlying problem in a subset of patients with epidermolysis bullosa (EB). The methods they have used, and the information they have gained, are directly helpful to those of us involved in ichthyosis research.

Our approach here at NIAMS (National Institute of Arthritis, Musculoskeletal and Skin Disease in Bethesda, MD) is to collect biological specimens (especially blood) from patients with ichthyosis and from their family members who do not have the skin problem. We then extract the DNA (the genetic material) from the blood and compare the genes of persons with ichthyosis to those without, in the same family.

In this way, we expect we will be able to identify a gene (or genes) which is passed from affected parent to affected child (in the case of EH, for example) but which is NOT passed from affected parent to unaffected offspring. Of course, we can't look at all the genes. We have about 100,000 of them! But we have certain genes in mind which we hypothesize are likely to be involved in ichthyosis.

Dr. Epstein's success in EB research, with a genetic approach similar to ours, gives us hope that these methods will yield results in ichthyosis research as well.

How is it helpful to ichthyosis patients to know what gene is causing their skin disorder? Initially, it may not be terribly helpful. However, knowing the CAUSE of a problem is the first step in learning how to fix it. While our ultimate goal is to be able to cure ichthyosis, and this is probably still some time off, the knowledge we gain from identifying the genetic cause of ichthyosis will immediately help us in diagnosis and, soon, in designing better treatment methods.

Our whole research group at NIAMS, including molecular biologists, protein chemists, dermatologists, nurses, and geneticists, are very grateful to the members of F.I.R.S.T. for their continued enthusiasm and support of our work. We could not even attempt to do what we do without the cooperation of all of the F.I.R.S.T. families who have come to Bethesda to participate in the research.

By the time you receive this newsletter, we hope to have seen at least 30 families. If you are an ichthyosis patient with either lamellar ichthyosis, congenital ichthyosiform erythroderma, epidermolytic hyperkeratosis, or severe ichthyosis vulgaris, AND you have at least one other person in your family who is affected, we'd love to hear from you. Please call collect at (301) 402-2679. And again, thanks so much to the board of directors and members of F.I.R.S.T.!

Michael Smith, MD, a dermatologist at East Carolina University in Greenville, NC recently sent a survey to the F.I.R.S.T. office which was mailed to several hundred families. If you received a survey asking you about the types of treatments that work and don't work for you, please be sure to return the questionnaire as soon as possible. "We hope that the results of the survey will provide us with a consensus regarding effective and ineffective treatment modalities for ichthyosis," says Dr. Smith. The results will be published in a later issue of FOCUS.

Ervin Epstein, MD, a member of our Medical Advisory Board, continues his research and is looking for patients who have EH. To volunteer for this exciting study, call Dr. Epstein collect at (510) 444-8282.

Julie Pregenezer, (201-305-0023) of New Jersey is looking for plastic sleeves to go over arms and legs after moisturizing before bedtime to keep skin lubricated. She says they worked wonders but can't find a pharmacy or hospital supplier that has them. Can you help her find these plastic sleeves? Please call.

If you would like a pen pal, have a comment to make, or would like to be in touch with others who have ichthyosis, write to: Ichthyosis Focus, P.O. Box 20921, Raleigh, NC 27619, and we will include your name and address in Correspondence Corner. We do not release names and addresses without permission.

A Very Special Thank You Note

F.I.R.S.T. wants to thank everyone who contributed to the Foundation in 1991. Some have given in the form of personal time and energy. Others have supported us with notes of encouragement and suggestions, and many have contributed financially to help keep our programs running. Thanks to all of you, the word is spreading about ichthyosis. We frequently get calls now from new parents and physicians who are interested in learning more about this condition. Perhaps someday ichthyosis will not be so unknown to the general public. Special appreciation goes to those who gave at least $100 or more during 1991. If we have overlooked you, please let us know. We want to thank each and every one of you for your continued support.

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Researchers Make an Important Discovery about Cause of Genetic Skin Disorder

By Nick Gattuccio

Introduction: The power of the ongoing revolution in human genetics has now touched individuals suffering from a genetic epidermal disease somewhat like ichthyosis in two significant studies of gene linkage. The first was from the laboratory of Dr. Ervin Epstein at the University of California Medical School in San Francisco (Science, Vol. 254, pp 1 202, 1991). Dr. Epstein is a member of the F.I.R.S.T. Medical Advisory Board and has been dedicated to skin research for many years. The second study came from Dr. Jouni Uitto's lab at Jefferson Medical College, Philadelphia (American Journal of Human Genetics, Vol. 49, pp 978, 1991). Both of these important studies implicated specific genes expressed in the epidermis, namely the keratins, as the probable defective genes in certain families suffering from epidermolysis bullosa simplex (EBS).

The keratins form a major part of the epidermal cell internal "skeleton." These genetic studies support the hypothesis that abnormal keratin proteins in these EBS patients are causing weakening of this "skeleton," localized rupture through the most internal epidermal cell layer, and blistering of the epidermis (a notion also supported by work from Dr. Elaine Fuchs' lab described in the article below).

Now, with identification of the abnormal protein, further research can be specifically directed at understanding the involvement of this protein in normal and abnormal epidermal function. In this way lies hope that new and improved specific therapies will be facilitated.

Three factors made possible the success of these, and indeed, of ongoing studies. First and most critical is the participation of families and individuals affected by genetic skin disease in the research programs of teams of geneticists, molecular biologists and dermatologists.

Secondly, gene mapping studies are progressing more rapidly due to the dramatic and continuing advances in the genetic tools available. And thirdly, the application of cell and molecular biology has created steady progress in our understanding of important proteins in the epidermis, insights into normal skin function, and new clues as to the possible causes and treatment of diseased skin.— John G. Compton, PhD, NIAMS, NIH.

1991 saw a remarkable advance in research into the cause of a major genetic skin disorder. Although it is well known that faulty genes cause many congenital skin disorders (including the ichthyosis), the precise nature of these gene mutations and their resulting effects on the body's structure and metabolism at the molecular level has never been well understood. We who live with these disorders naturally relate to them on the symptomatic level. We live with their effects on our skin, and every day we deal with their effects on our lives. However, research into genetic disorders focuses on a much different level - the biochemical and molecular level - because it is at this level that the symptoms we deal with every day actually occur.

Using a very original approach to genetic research, a team of scientists at the Howard Hughes Medical Institute at the University of Chicago (working with colleagues at institutions around the country and in Canada) successfully located the site of a specific genetic "point mutation" associated with symptoms of a rare genetic skin disorder. They demonstrated the mutation's effect on cellular development and showed how the resulting molecular defect may account for some of the primary symptoms of the Dowling-Meara subtype of epidermolysis bullosa simplex (EBS). Researchers around the country agree that these findings, as well as the innovative methods developed for achieving them, are extremely significant to genetic research in general, and for research into the ichthyoses as well.

EBS is an inherited disorder that shares some characteristics with the ichthyosis called epidermolytic hyperkeratosis (or EH). It is characterized by a tendency for the epidermis to separate from the dermis very easily. Events as insignificant as mild rubbing or simply bumping a leg against a chair will cause this epidermal separation, and the result is severe blistering and skin loss. As with the ichthyosis, however, EBS involves a complex array of interacting symptoms.

The discovery of the gene for symptoms of EBS, which is reported on in this article, is significant to the ichthyosis community, even though EBS is not classified as an ichthyosis. This is so because on a very important level these genetic disorders are related. This is the invisible (to us) level of molecules, genes and proteins. It is no coincidence, after all, that symptoms of EBS show parallels with some of the symptoms of the ichthyosis EH. Therefore, understanding the biochemical "error" that results in symptoms of EBS (which is the subject of this article) has a great deal to teach us about the ichthyosis themselves-about how our skin works on the molecular level (or fails to work, in the case of a genetic disorder), and about how researchers investigate the biological machinery that accounts for these disorders. The article is a long one because it is important, I think, that we understand more than just the symptoms of the disorders that occupy our lives - that we understand their underlying mechanisms as well. **Knowledge is power, after all, and in power lies strength.**

> "... it is important that we understand more than just the symptoms of the disorders that occupy our lives. We must understand their underlying mechanisms as well. Knowledge is power, after all, and in power lies strength."

The research reported on here is contained in two articles authored by nine scientists (most at the Howard Hughes Medical Institute of the University of Chicago- see full citations at the end of this article). For simplicity's sake, I will refer to the research team as the Chicago Group.

BACKGROUND: GENES, PROTEINS & THE KERATINS

To understand the Chicago Group's work, we must view the body's structure and metabolism on its most basic level - on the level of the cells and their building blocks. These basic building blocks are protein molecules. Our genes control these proteins, and do so in several ways. Some genes direct the production (or synthesis) of protein molecules, while others regulate the rate at which they are produced, or else turn off their production altogether. Still other genes modify the activity of given proteins, regulating their effect on our metabolism. Our genes contain genetic blueprints for all of these proteins which, in turn, control virtually every facet of the structure and function of our cells.

In a genetic disorder, one (or a few) of our genes is defective due to a mutation; the blueprint is wrong. Because of this, the mutant gene produces a defective protein (or protein regulator), and the result is an error in the structure or metabolism of the cell. The outcome of an error of this kind is what we see as symptoms of genetic diseases, and they are usually serious,

There are a great many types and subtypes of proteins (thousands of them), but *the Chicago Group* focused on a small family of protein molecules called the keratins. The keratins are found in all epithelial cells. (Epithelial cells are cells that form the surface layer of both internal and external body structures. The epidermis of the skin is composed of epithelial cells.) There exist about 30 different keratins in epithelial cells and scientists identify them by number (K5, K10, K14, etc.). The keratins work in specific pairs (K1 is paired with K10, K4 with K13, and K5 with K14, etc.), and these keratin pairs are specific for the type of epithelial cells in which they are found.

Significant to the research here, keratins are known to form cell structures known as intermediate filaments (or tonofilaments), which are critical to forming the cell's structure. These intermediate filaments, which are long strands of keratin, create the cell's skeletal system. In fact, biologists refer to these intermediate filaments as a "cytoskeletal network" (cyto is the Latin prefix meaning cell). In short, these intermediate filaments support the cell's physical structure in the same way that our own skeleton supports our body tissue.

In summary, then, genes control the production of the proteins (including keratin) which, in turn, regulate the structure and function of cells. The description greatly oversimplifies gene action, but the model is useful: one gene produces one specific protein which, in turn, promotes one specific metabolic function.

THE KERATINS & THE CELLS OF THE SKIN

So the Chicago Group set out to understand precisely how this small family of keratin proteins affects the structure and function of epithelial cells in the epidermis of the skin.

The Chicago Group knew certain things at the outset from other research. Dr. Ervin Epstein of our own medical advisory board had been working with EBS families, for example. Thus, the researchers knew that in some genetic skin disorders the structure of epidermal cells breaks down. Since they knew that keratins are the major structural proteins of epithelial cells, the connection between keratin and structural abnormalities in the epidermis was evident. They also knew that a specific pair of keratin proteins (the K5/K14 pair) is particularly abundant during a key stage of the skin's fetal development - at a time shortly before birth when very active basal cells (the lowest level of cells in the epidermis) are dividing and differentiating (that is, modifying their structure and function to become the various upper layers of the epidermis - the stratum granulosum, stratum corneum, etc.). Furthermore, they knew how to "target" the expression of human keratin genes in experimental animals - that is, they knew how to make human K14 behave like mouse K14 for the purpose of their research.

With this information in hand, the Chicago Group set out, "to explore the relationship between keratin gene mutations and genetic disease. "And they did so in a remarkably elegant and straightforward manner. In mice, they genetically engineered a mutation in the

K14 gene (i.e., the gene that encodes the keratin protein K14), They bred these "transgenic" mice and then observed the effects of this mutation in their offspring. Ultimately, they found that "the pathobiology and biochemistry of the transgenic mice ... bore a resemblance to a group of genetic disorders known as epidermolysis bullosa simplex." Specifically, they found abnormalities in the structure, or architecture, of cells in the lowermost basal layer of the epidermis. This resulted in what is termed "basal cell cytolysis" (a breakdown of the cells in the skin's basal layer upon incidental contact, such as mild rubbing of the skin). There was significant blistering at these sites.

Through sophisticated tests, the Chicago Group established "definitive evidence" that the structural abnormalities they observed resulted from the K14 mutation which they had engineered. To cross-check this finding, they examined epithelial cells from other parts of the body in which it is known that K14 is expressed (the tongue, cornea of the eye, esophagus, and trachea), and indeed, despite some variations in severity, the expression of the mutant K14 gene and the resulting cellular abnormalities were consistent with those observed in the epidermis.

To establish a picture of exactly what was happening to cause these gross abnormalities, they cultured cells expressing the mutant K14 gene and studied them by electron microscopy. They found that the mutant gene caused significant disruption of the keratin networks (i.e.., the structural network of intermediate filaments, or tonofilaments). In short, the defective keratin 14 proteins constructed a defective cellular skeleton. Instead of structurally useful strands of keratin filament, they found "large clumps of keratin ... throughout the cytoplasm of basal cells. " As stunted clumps in the cytoplasm they are useless to the cell's architecture. Significantly, these keratin clumps contained the mutant keratin which they had engineered. They also observed widespread evidence of cell breakdown (cytolysis) and noted that where cytolysis occurred there was usually an absence of those essential keratin filament networks.

Step-by-step the Chicago Group successfully tied a very specific gene mutation (occurring on the molecular level) to a set of generalized symptoms of a genetic disorder (which occur on the level of tissue-i.e.., the skin).

KERATIN K14 & EBS

But wait a minute, you might say. A mouse is not a man. Engineering gene mutations in the laboratory is a far cry from pinpointing the cause of a major genetic skin disorder in humans.

The point is well taken, and the Chicago Group addressed this question when they expanded their research to include humans with EBS. They reported findings from this phase of their study in the September 20, 1991 , issue of the periodical Cell (vol. 66, no. 6). It was this article whose findings were reported in most newspapers across the country.

In their own words: "We now demonstrate that two patients with spontaneous cases of Dowling-Meara EBS have point mutations in a critical region in one (K14) of two basal keratin genes." Through a complicated, yet experimentally elegant, six-phase analysis, the Chicago Group demonstrated that, in a manner analogous to their findings in the transgenic mouse studies, several of the symptoms of Dowling-Meara EBS in humans results from a point mutation on the human K14 gene. The mutant gene produces abnormal keratin - 14, and the outcome is a complex of symptoms associated with EBS in humans: basal cell cytolysis and epidermal blistering.

Having located the site of the genetic mutation, the Chicago Group then described the mutant K14 gene's precise biochemical "error." Although the bottom-line finding (that is, the biochemistry of this fundamental genetic error) is well over my head, and over the heads of most non-scientists, here it is for the record: At a location on the human K14 gene that molecular biologists label " residue 125," there is a very small (infinitesimally small) mistake. But regardless of how small it is, this mistake gets copied onto every K14 protein which the mutant gene produces, and this occurs in every single epidermal basal cell in the body. And the final result is symptoms of EBS.

The biochemical error on the keratin - 14 protein may be infinitesimally small, but its effects are so profound that it bears looking at. To understand this mistake, visualize the K14 protein molecule as a chain. In fact, the K14 molecule is not unlike a chain, since protein molecules are made up of a very long series of repeating links.

The links of protein chains are called amino acids. These amino acids are regularly shaped bundles of atoms. There are 20 different amino acids and they have the ability to bond end-to-end. Because of this they can form long chains. These long chains of amino acids are protein molecules.

There are thousands of different kinds of protein molecules in our bodies, all of them constructed of these same 20 amino acids, and they differ only in the length of their chain, and in the order, or sequence, in which these 20 amino acids are arranged along the chain. In fact, it is the sequence of the amino acids on the chain which distinguishes one protein from another (and hence, the biological function of one from another). In the case of the K14 protein molecule, the chain is 472 amino acids long. This is a very large molecule.

> "Genes control the production of the proteins (including keratin) which, in turn, regulate the structure and function of cells. The description greatly oversimplifies gene action, but the model is useful: one gene produces one specific protein which, in turn, promotes one specific metabolic function."

Our genes carry the blueprints for the order or sequence of these 20 amino acids along the enormously long protein chains. Because there are only 20 amino acid "links" available to form the protein chains, and because the order in which the amino acid links are arranged on the chain determines the protein's identity, it follows that getting their sequence on the chain correct is critical. Getting all of this right is the job of the gene, since the gene's blueprint controls the making of the protein molecule. Consequently, if the gene has a mutation (that is, if its blueprint for the amino acid sequence is even slightly incorrect), then the protein it manufactures will be defective.

To see it another way, think of the 20 amino acids as letters of an alphabet. Like our own alphabet, which contains just 26 letters, the amino acid alphabet can "spell" an astronomically large number of protein "words." Unlike our own language, however, where misspellings are annoying but hardly catastrophic, the spellings of words in this biochemical dictionary of genes and proteins is critical. The protein "words" must be spelled absolutely correctly. In fact, genetic mutations and all of the havoc they wreak in living organisms are in a sense nothing more than misspellings of these protein words.

Which is precisely what the Chicago Group discovered in the case of EBS-A single little misspelling. In the K14 protein "word," which is 472 "letters" long, they discovered just a single letter out of place. At a point on the K14 protein chain (the point called residue 125), they discovered that one amino acid "letter" (cysteine) was incorrectly placed where a different one (arginine) should be. The result is a simple misspelling of the keratin - 14 "word," and the outcome is catastrophic for the cell. The ultimate result, however, is a devastating complex of symptoms associated with EBS.

That's it. That's all it is. It's that small. Not even a molecule - just a tiny piece of a molecule. Just one little amino acid - just a tiny handful of atoms. Just one letter in a word that's 472 letters long. And the result is the stuff of novels.

IMPLICATIONS FOR RESEARCH ON ICHTHYOSIS

The Chicago Group's findings have no direct implications for research into the ichthyosis. However, that said, there do exist indirect implications. The authors themselves imply this:

Interestingly, the linkage of blistering, cytolysis, and tonofilament clumping to filament - disrupting mutations in keratin genes suggests a molecular basis for several additional types of human genetic skin disease. One such disease is bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis), in which basal cells are normal, but tonofilament clumping and blistering begin at the first suprabasal layer.

The authors speculate (and I emphasize speculate) that since the mutant K14 gene, which is particularly active in cells of the basal layer, accounts for the symptoms of EBS which occur in the basal layer, then perhaps the symptoms of the ichthyosis EH (epidermolytic hperkeratosis), which occur in the first layer above - the basal layer, may be produced by different keratin genes, ones that are particularly active during formation of that layer of the epidermis. It will take a great deal of research to find out if this is in fact the case.

In a general sense, though, the Chicago Group's breakthrough has methodological significance. That is, their research methods (specifically, to engineer a specific genetic mutation and then analyze the resulting molecular and metabolic outcomes) could very well lead to additional breakthroughs in the area of genetic disorders.

Vassar, Robert, Pierre A. Coulombe, Linda Degenstein, Kathryn Albers, and Elaine Fuchs. (1991) "Mutant Keratin Expression in Transgenic Mice Causes Marked Abnormalities Resembling a Human Genetic skin Disease." Cell, vol. 64,pp. 365-380.

Coulombe, Pierre A., M. Elizabeth Hutton, Anthony Letai, Adelaide Hebert, Amy S. Paller, & Elaine Fuchs. (1991) "Point Mutations in Human Keratin 14 Genes of Epidermolysis Bullosa Simplex Patients: Genetic and Functional Analyses." Cell, vol. 66, no. 6, pp. 1301 - 1311.

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Regional Support Network

The purpose of the Regional Support Network is to facilitate communication between families and people affected by ichthyosis. Parents can exchange practical tips and child care information. Adult can support each other in job hunting, making new friends, dealing with depression, and other social coping strategies. If you are interested in joining the support group in your area, please contact the representative for your region.

Region One: NY, PA, VT, NH, NJ, CT, RI, MA, ME
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Region Two: DE, MO, WV, VA, NC, SC
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Region Three: TN, GA, FL, AL, MS, LA, AR
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