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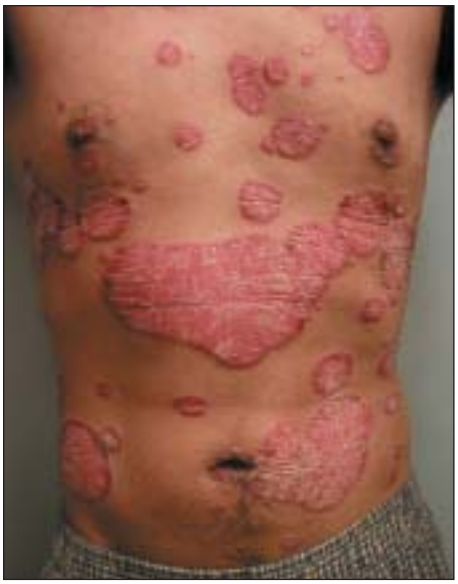
DERMATOLOGY FOCUS™

Epidemiology and Psoriasis– Eye-Opening Results That Impact Patient Care

Joel M. Gelfand, MD, MSCE (Assistant Professor of Dermatology, Medical Director of the Clinical Studies Unit, and Associate Scholar of the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania), brings his combined skills in dermatology, epidemiology, and biostatistics to bear on expanding our rudimentary understanding of psoriasis for the purpose of improving the dermatologist's ability to care for these patients. Gelfand has revolutionized the study of this common, chronic immune-mediated skin disease by conducting studies to develop an accurate estimate of prevalence within different groups, to begin the process of identifying risk factors for psoriasis, and to start understanding psoriasis itself within a larger pathologic context—including a role as an independent risk factor for other significant health issues (see photo at left).

Though Gelfand's initial answers raise a multitude of further questions, they also hold immediate and urgent implications for the medical care given to people with psoriasis.



The larger context. Psoriasis involves *antecedent risk factors* (genes; environment), *mediating factors* (pathophysiology: inflammation, hyperproliferation, angiogenesis;treatment; psychosocial impact), and *outcomes risks* for specific diseases (cancer; vascular disease; metabolic disease; arthritis) and excess mortality. (Photo courtesy of Dr. Joel M. Gelfand.)

Focusing In

Psoriasis affects 2% to 3% of the adult population, with incidence peaking during the 20s and then again during the 50s and 60s. It can also appear in children. The impact of psoriasis on quality of life can be substantial even with relatively limited disease. So although only 20% of patients with psoriasis have extensive skin involvement (>3% body surface area [BSA]) and 80% of patients are characterized by limited disease (<2% BSA), psoriasis involves significant morbidity and substantial economic costs to both patients and the health care system.

Gelfand has been "interested in psoriasis for a long time, in part," he says, "because it is a common disease that has a major impact on people's well being. And for a physician to be able to use therapy properly and make a difference in people's lives, he or she must be extremely knowledgeable. From a research perspective," he adds, "there is actually not very much known about psoriasis. There was a real lack of natural history studies attempting to identify

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Focus on Research

Filaggrin, Ichthyosis Vulgaris, and the Architecture of Atopic Dermatitis

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An intriguing phenomenon first noted in the literature back in 1966—the occurrence of both atopic dermatitis (AD) and ichthyosis vulgaris (IV) in many of the same patients—has finally been solved. Leading the successful detective team is geneticist Irwin McLean, who devotes himself to human genetic disorders affecting the structure, function, and differentiation of epithelial barrier tissues. The surprising answer opens new avenues for understanding and treating AD, a challenging condition that affects up to 20% of children—the most common skin disease among children in the developed world.

The Mystery

When R. S. Wells, MD, MRCP, surveyed the clinical features of patients with IV in a district of the U.K. in the early 1960s, he was puzzled to observe "manifestations of atopy" in many of them. Both IV and AD begin early

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and understand the factors directly and independently associated with psoriasis. So there is a lot of scientific opportunity for improving our understanding of this disease—and hopefully our ability to care for our patients with psoriasis."

Gelfand finds epidemiology to be a powerful research tool because "it provides the basic science that leads to our individual patient care decisions as well as to our public health decisions," he explains. "Epidemiologic methods also provide the basis for how we understand what diagnostic tests to use and how to interpret the results, and how we understand the safety and efficacy of a treatment and its risks and benefits." Very few dermatologists have been trained as epidemiologists, yet the dermatologist's knowledge base is essential for designing meaningful epidemiologic studies of skin disease. Thus dermatology has arrived much later than other disciplines at developing the kind of knowledge gained via epidemiologic research. Gelfand points to the example of cardiovascular medicine, which now benefits from awareness of a multitude of epidemiologically identified risk factors for heart attacks.


Joel M. Gelfand, MD, MSCE

"So if we are going to understand why people develop psoriasis and what risks psoriasis itself entails—which involves quantifying the relationship between an exposure and outcome—then we have to do epidemiologic studies."

It's All in the Database—Study the Population

Gelfand's evolving body of epidemiologic research represents a critical and fundamental departure from the small number of earlier studies. They had relied on patient groups that were easy to identify and access, ie, they collected data from patients in dermatology practices or specialty clinics, or from members of psoriasis lay organizations. Although the bulk of psoriasis patients—those who either are treated by their primary care provider, or not currently in treatment—were not represented, conclusions were extended to psoriasis patients in general.

Gelfand had learned that these skewed patient samples risked producing biased data, and thus distorted conclusions. The most unbiased way to gauge the variables under study is by collecting data on psoriasis patients and controls from the general population. His first three studies sampled the U.S. population. Then he gained access to the GPRD—the General Practice Research Database established in the United Kingdom in 1987 specifically to enable large—and valid—epidemiologic studies (see box on page 7).

Sampling the U.S. Population—The Whole, and Some of Its Parts

The Nuts and Bolts. Gelfand addressed three questions via a collaborative effort with the National Psoriasis Foundation to survey the epidemiologic characteristics of psoriasis in the continental U.S. population. Households to be contacted—ultimately providing 27,220 participants in all—were selected by random digit dialing and invited to complete a brief questionnaire. The 2.5% of respondents who identified themselves as having received a diagnosis of psoriasis from a physician were invited to complete the more detailed questionnaire during a follow-up phone call. Of the 328 who accepted, 81% completed this in-depth survey.

The comprehensive questionnaire—created by a committee of dermatologists—covered sociodemographic variables, treatment history, extent of disease (calculated using the palm of the respondent's hand), and quality of life. Palm coverage, documented as a reliable way to estimate extent of disease, provided the following range: none or very little; a few patches covered by 1–2 palms (~1%–2% BSA); scattered patches requiring 3–10 palms for coverage (~3%–10% BSA); and extensive psoriasis requiring more than 10 palms (≥10% BSA). A modified Psoriasis Disability Index (PDI) measured degree of impairment in quality of life.

The Overview. Respondents averaged 47 years of age, a disease duration of 18.47 years, and a PDI score of 4.88. The impact of psoriasis on health-related quality of life showed clear associations with extent of disease and with being female. "Even patients with 1 to 2 palms had statistically significant decrements in their quality of life compared to patients with no-to-minimal psoriasis," Gelfand notes. "And female patients had greater decrements than male patients with a similar self-report of extent of disease." A weaker inverse correlation emerged between younger age and greater impairment.

"Our finding that female patients and young patients suffer the greatest impairment from psoriasis has important treatment implications," Gelfand points out. "In particular, traditional systemic agents such as methotrexate and acitretin are associated with fetotoxic and teratogenic effects that limit their use in women of child-bearing potential. Viable treatment options for this group are particularly needed, and new biologic treatments may have an important role to play in this regard."

In 2003, Joel M. Gelfand received a career-enabling 3-year Dermatology Foundation Health Care Policy Clinical Career Development Award for *The Incidence of Cancer in Psoriasis Patients.*

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Gelfand and his group also found a negative association between income and both extent of disease and PDI score, "suggesting that patients most in need of aggressive psoriasis therapy—because of extensive disease and greater impairment in quality of life—may have limited access to care given the associated decrements in income."

African American Subgroup. This survey also enabled Gelfand to characterize the prevalence of psoriasis in African Americans. "Determining if prevalence varies between U.S. whites and African Americans is important to understanding genetic and environmental determinants," Gelfand explains. "And properly addressing health needs in a diverse population requires an understanding of the respective burden of an illness in various subpopulations." The 1965 study reporting psoriasis as rare (0.7%) in African Americans was based on patients seen in a private dermatology practice in Cleveland, Ohio. Gelfand found the actual prevalence to be 1.3%, "less common than in whites, but certainly not rare."

Again, more women than men were diagnosed with psoriasis. And though extent of disease in African Americans was more likely to be 3–10 palms and much less likely to be only 1–2 palms of involvement, treatment satisfaction and the daily impact of their disease were comparable to whites. Regarding these differences in disease severity, Gelfand emphasizes the need for additional studies to understand how psoriasis behaves in African Americans vs whites, and the extent to which this is driven by genetics vs environmental factors vs treatment differences.

Psoriatric Arthritis Subgroup. Gelfand was also able to learn that 11% of psoriasis patients in the U.S. have been diagnosed with psoriatic arthritis. Prior prevalence estimates—predominantly from referral populations that can introduce bias—of this potentially disabling inflammatory arthritis have found rates of up to 39%. The one population-based study was limited to residents of a single county in Minnesota, and found a similar prevalence to Gelfand's U.S. population-based study. Gelfand discovered that prevalence is actually tied to the extent of skin disease, increasing steadily from 6% of patients with little to no psoriasis to 14% with 1–2 palms, 18% of patients with 3–10 palms, and 56% of patients with more than 10 palms. The large variation in prevalence from clinic-based studies most likely reflects patient samples skewed toward those with more extensive skin disease.

Gelfand cautions that despite the lower prevalence of psoriatic arthritis in patients with milder skin disease, the joint disease can still be aggressive and physicians need to screen for it in this patient group. His studies, along with those from other populations, all indicate that severity of skin disease is a poor predictor for how aggressive psoriatic arthritis will be. "And when screening a psoriasis patient for systemic therapy," Gelfand adds, "we need to recognize that many patients with comorbid joint symptoms will benefit from treatments that target both skin and joints. Thus, identifying these symptoms is critical for optimum treatment selection."

Gelfand also found that 39% of patients with psoriatic arthritis rated it as a large problem in everyday life, compared to 12% of patients with only skin disease. This "significant impact on daily functioning emphasizes the need for accurate diagnosis and treatment."

GPRD—Testing the Fit

The U.K.'s *General Practice Research Database (GPRD)* (see box on page 7)—begun in 1987 to serve as a valuable tool for epidemiologic research—includes the diagnoses and medications of more than 9 million patients. It is relied on heavily for such things as making decisions about drug safety and effectiveness and has also enabled hundreds of published studies addressing a multitude of diseases.

Because Gelfand was the first to approach this vast database from the perspective of psoriasis, he needed to make sure that it accurately captures this disease. Gelfand and his research team looked for a prevalence of psoriasis similar to earlier studies in the U.K. with a similar methodology. The epidemiology of psoriasis in this huge database passed with flying colors—"similar to that of other epidemiologic studies performed in the U.K., as well as in the U.S. and other Western countries," Gelfand notes. In another series of careful validation surveys for diagnostic accuracy, he directly surveyed the GPs of 100 patients diagnosed with psoriasis and confirmed that three years after this diagnosis was entered into the record, it was still the diagnosis of record in 89% of patients.

In addition, this initial exploration of the more than 100,000 patients with psoriasis in the database identified intriguing patterns and questions for further study. In young (<20 years old) patients, prevalence increases more rapidly in females than in males, which may indicate some sort of hormonal interplay in the onset of psoriasis. At the other end of the age spectrum, prevalence unexplainedly declines dramatically in patients 70 years and older, regardless of sex. Compared to patients in their 60s, psoriasis prevalence falls by 28% during the 70s and by 60% during the 80s. This suggests that psoriasis may go into remission in the elderly or that it may be associated with excess mortality, thus leading to a declining prevalence. Prevalence in children <10 years is small in percentage (55/10,000), but translates across the population to approximately 40,000 pediatric patients. "And this emphasizes the need for safe and effective psoriasis treatments for children, who may be more susceptible to adverse effects," Gelfand says.

Psoriasis and Lymphoma

An association between psoriasis and risk of lymphoma has been hypothesized for several reasons. As a disease involving immune activation that is predicated on increased T-cell activity stimulated by antigen presentation, with some evidence of increased B-cell activity as well, psoriasis itself may present preconditions that facilitate the clonal reproduction of these lymphocytes. Therapeutic immunosuppressive medications may be an independent risk factor, or they may become a risk factor when taken in the context of psoriasis. Anecdotal evidence exists for both possibilities.

Gelfand points out that studying the risk of lymphoma in any patient group "is challenging because lymphoma is statistically rare, and therefore large sample sizes are needed to yield robust findings." These studies are important, though, because lymphoma, although rare, is of clinical and public health importance given that NHL (non-Hodgkin's lymphomas) is the fifth most common cancer in the U.S., affecting 19 per 100,000 individuals per year (an incidence similar to melanoma) and its incidence has increased approximately 3%–4% each year since 1973 while the overall 5-year survival is currently only 53%. Although cutaneous T-cell lymphoma (CTCL), the most common form of T-cell lymphoma, affects only roughly 0.5–1.0 person per year out of 100,000, "as a T-cell lymphoma of the skin it may be related to the pathophysiology of psoriasis," Gelfand says.

No clear picture had emerged from the body of studies attempting to explore lymphoma risk in psoriasis. Most important, previous patient samples were limited to those severe enough to be hospitalized or treated with psoralen. In addition, outcome varied from all lymphomas, to just NHL—which are primarily B cell in origin and represent 88% of lymphomas, to only Hodgkin's lymphoma (HL)—representing the remaining 12%.

Gelfand and his co-workers used the GPRD for two population studies that looked at lymphoma incidence in total and by major subtypes, with appropriate statistical treatment of resulting data.

(Continued on page 6)

Newest Fitzpatrick Legacy Fund Member Harley Haynes Urges, *"Join Me"*

"The Dermatology Foundation is doing the best of any organization I've ever contributed to," says Harley Haynes, MD, explaining why he has just substantially increased his personal commitment to support the DF's research award program. "I also discovered early on that giving more to the DF gives *me* more."

Dr. Haynes wears several prominent hats in the Harvard system: Vice Chair of the Department of Dermatology at Brigham and Women's Hospital, a member of of the Dana-Farber Cancer Institute's Cutaneous Cancer Oncology Center, Associate Chief of Dermatology at the Boston VA Health Care System, and professor and celebrated teacher at the Medical School. He joined the Dermatology Foundation shortly after arriving at Harvard, not long after the DF was founded in 1964 by Drs. Eugene Van Scott and Thomas B. Fitzpatrick, specialty leaders who became his first mentors and role models. His fellowship experience in Dr. Van Scott's NCI lab lured him to dermatology, then he trained under Dr. Fitzpatrick and joined the Harvard faculty.

After a colleague encouraged Dr. Haynes to increase his membership to the Leaders Society level, he discovered that giving more to the DF actually gave *him* more. "I found myself much more interested in attending the Annual Meeting and learning who received research awards and for which projects," he recalls. After a colleague convinced him to make a $25,000 commitment to the Annenberg Circle, "I enjoyed it even more!" Dr. Haynes remembers. He readily became a Sustaining Member, contributing an additional $5,000 each year.

The Thomas B. Fitzpatrick Legacy Fund was created in 2005 to provide an extraordinary level for individual support. When another colleague initially invited Dr. Haynes to join, he relished the opportunity to support the legacy of his mentor, revered colleague, and dear friend, but the $100,000 commitment gave him pause. Then a recent invitation inspired his realization that it *is* financially feasible, "and I began thinking of good things I could be doing with these funds."

Nothing comes close to the Dermatology Foundation for a meaningful and effective investment. "Funding the complete spectrum of dermatology research produces the progress in understanding diseases of the skin that evolves to better diagnostics and therapy. Dermatologists and our patients are the direct beneficiaries." With the stringent limitations on medical research funds, "if we aren't going to fund our own research, who else will! Also, other donors are more eager to give to an organization that attracts significant broad-based support from its own members."

Harley Haynes, MD

Dr. Haynes has accepted the invitation. Now he urges his colleagues to make the effort to identify $100,000 that they, too, can commit to the best in patient care and answer his call "to become part of the Fitzpatrick Legacy Fund. The pleasure will surprise you!"

Galderma Pledges Matching Funds for New LS Members

Galderma Laboratories, the DF's largest corporate supporter, is extending an opportunity to match new member pledges in 2008—raising its total contribution to $375,000 this year. The company has announced a challenge that will immediately result in a 50% increase in research funds generated by the first 100 new Leaders Society members. For the $1,500 provided by each of these new members, Galderma will invest an additional $750 in research that will ensure dermatology's continued progress. *To learn more about the Galderma challenge, contact the Foundation office at 847-328-2256 or via e-mail at dfgen@dermatologyfoundation.org.*

Their first effort was a cohort study of a socioeconomically diverse group of patients 65 years and older that followed (for a median of 46 months) 2,718 patients with psoriasis along with a 105,203-patient reference population and recorded 276 lymphomas. The incidence rate per 10,000 person-years was 6.1 without psoriasis and 18.3 in the psoriasis group, which was unchanged after controlling for sex and age. These results added psoriasis to the literature linking other chronic inflammatory diseases—such as rheumatoid arthritis and inflammatory bowel disease—to lymphoma.

Gelfand's second lymphoma study stratified 153,197 patients by disease severity. *Severe* psoriasis (n=3,994) reflected receiving systemic treatment consistent with extensive disease. *Mild* disease (n=149,203) patients did not receive such treatment. A varying picture of risk associations emerged after the analyses were adjusted for age, gender, and person-years.

The overall risk of lymphoma was significantly increased in the total patient group, although at a lower magnitude (1.35) than in the study looking only at patients ≥65 years. This translates to an annual excess risk of lymphoma of 7.9 cases per 100,000 psoriasis patients. This second psoriasis study, though, found relative risk of lymphoma similar across age groups, leaving open the question as to whether older patients are—or are not—at higher risk. NHL showed no increased risk in psoriasis patients. HL risk was 1.48 for all patients, with 1.42 in mild disease and 3.18 in severe disease. The lack of any association in earlier studies may have reflected their inadequate statistical power because Hodgkin's is such a rare form of lymphoma.

Psoriasis and CTCL in Particular

"The strongest association of lymphoma and psoriasis occurred for CTCL," Gelfand says, which supports earlier studies. It was 4.34 overall, 4.10 in mild disease, and 10.75 for severely affected psoriasis patients. "There seems to be a very strong relationship between having a diagnosis of and treatment for severe psoriasis," he adds, "and in the future the disease ultimately being called 'skin lymphoma.'" One possibility is that, early on, CTCL risks being misdiagnosed as severe psoriasis. Another is that this might be the natural history of the disease, or possibly a treatment effect.

But whatever the cause, Gelfand says, "this is an extremely valuable piece of clinical information. These cases do appear every so often, and they can be challenging to diagnose. Yet if a patient with undiagnosed CTCL is treated with immunosuppressive therapy, this lymphoma can progress dramatically," he warns. "So when a diagnosis of psoriasis presents any uncertainty, a biopsy is essential before placing the patient on immunosuppressive therapy." In this same context, "it has been our clinical experience," Gelfand points out, "that in some patients with well-documented psoriasis, the disease has evolved into CTCL, and we have had patients who exhibit clinical and histological features of both diseases." Immunosuppressive therapies are contraindicated in these cases.

Psoriasis, Cardiovascular Risk Factors, and Metabolic Syndrome

Previous research had suggested that psoriasis patients experience an increased frequency of a variety of cardiovascular comorbidities, but the typical study involved only patients hospitalized for their skin disease and precluded generalized conclusions. These studies also lacked any statistical treatment to identify those cardiovascular risk factors independently associated with psoriasis and those brought along only through their association with these direct risk factors.

Gelfand and his team turned to the GPRD "for a broadly representative population-based study to determine whether prevalence of the major cardiovascular risk factors identified by the Framingham studies—diabetes, hypertension, hyperlipidemia, obesity, and smoking—is higher in patients with mild and severe psoriasis than in patients without this skin disease. We also aimed to determine whether these risk factors are independently associated with psoriasis," he adds. Gelfand added BMI to the Framingham list as an additional index of obesity.

At the time of their studies, Gelfand and his research team identified 127,706 patients with mild psoriasis and 3,854 with severe disease, and randomly selected matched control subjects. A risk factor was considered present if its diagnostic code had appeared in the patient's electronic medical record at registration in the practice or at any time thereafter. Calculated prevalence rates were adjusted for age, sex, and person-years of observation to yield prevalence odds ratios (ORs) expressing the presence of a risk factor among psoriasis patients relative to the control group. Multivariable regression modeling identified risk factors tied directly to psoriasis. (Gelfand also regularly uses sensitivity analyses—altering the ways in which he defines his parameters and then recalculating risk—to make sure any significant findings are not artificial results pinned to one particular way of grouping his subjects or defining risk factors.)

The final results suggest that all of the major cardiovascular risk factors identified by the Framingham studies, plus increased BMI, are associated with both mild and severe psoriasis (see table at left). After controlling for traditional cardiovascular risk factors, they were all independently associated with mild disease but only obesity and smoking showed associations strong enough to be of clinical significance. Severe psoriasis appears to have an even stronger association with obesity and diabetes than mild psoriasis does, suggesting a possible dose–response relationship between severity and the odds of having diabetes or obesity. Gelfand also demonstrated that this increased prevalence of diabetes is independent of major risk factors for insulin resistance (eg, obesity), which suggests that psoriasis itself—or possibly its treatments—may directly predispose to diabetes.

"All of these results suggest that psoriasis is associated with the complex disorder of metabolic syndrome," Gelfand observes, which incorporates hypertension, dyslipidemia, obesity, and impaired glucose tolerance. He points out that "this association is stronger for severe psoriasis," but more research must be done before he and his colleagues can determine whether this is simply a dose-response relationship or whether mild and severe psoriasis may, in fact, be different diseases. It is also too early to know which comes first—psoriasis or metabolic syndrome—or whether they both manifest the same underlying process.

Logic points to an association based on a common underlying inflammatory pathology. Gelfand points out that "similar to psoriasis, the metabolic syndrome is characterized by increases in the immunological activity of type 1 helper T cells (T_H1), which suggests that psoriasis may be associated with the metabolic syndrome because of shared inflammatory

Prevalence Odds Ratios of Individual Cardiovascular Risk Factors in Patients With Mild and Severe Psoriasis vs Controls

Variable	Mild Psoriasis Model (95% CI)*	Severe Psoriasis Model (95% CI)*
Diabetes	1.13 (1.08-1.18)	1.62 (1.3-2.01)
Hypertension	1.03 (1.01-1.06)	1.00 (0.87-1.14) NS
Lipids	1.16 (1.12-1.21)	1.04 (0.84-1.28) NS
Smoking	1.31 (1.29-1.34)	1.31 (1.17-1.47)
BMI (25-30)†	1.12 (1.1-1.14)	1.27 (1.14-1.42)
BMI (>30)†	1.27 (1.24-1.31)	1.79 (1.55-2.05)

BMI, Body mass index; CI, confidence interval; NS, not statistically significant.
*Model adjusted for age, sex, person-years, diabetes, hypertension, hyperlipidemia, smoking, and BMI.
†BMI data were available in 61% of patients.

(Reprinted with permission from AL Neimann et al, *J Am Acad Dermatol*, 2006; see *Suggested Readings*.)

pathways." Dysregulation of the pro-inflammatory T_H1 cytokine TNF-α—the target of several biologic therapies for severe psoriasis and psoriatic arthritis—is a likely candidate. Another hypothesis is that psoriasis patients may be predisposed to develop metabolic syndrome due to conducive lifestyle behaviors—such as poor eating habits, alcohol consumption, stress, decreased exercise due to symptoms or fear of stigmatization—resulting from the psychological impact of this skin disease. And approaching from the other direction, metabolic syndrome itself might predispose an individual to developing psoriasis. Supportive data recently appeared from the Nurses' Health Study II, which tracked a variety of obesity and weight gain measures along with incident psoriasis in more than 78,000 women from 1991 to 2005. The investigators—finding that weight gain, greater waist circumference, greater hip circumference, and waist-hip ratio were all significantly associated with a higher risk of developing psoriasis—suggest that increased adiposity and weight gain are strong risk factors in women.

Although establishing an ironclad association between psoriasis and metabolic syndrome is still in progress, Gelfand's study started the ball rolling. Two subsequently published studies—one in Kiel, Germany and the other in Verona, Italy—evaluated patients hospitalized with plaque psoriasis and found a strong association. A population-based study just appeared that evaluated a database of the southern district of Israel's largest healthcare organization and identified a pronounced association between psoriasis and metabolic syndrome after age 50.

Psoriasis and Risk of Myocardial Infarction

The evidence linking T_H1 diseases to atherosclerosis and coronary artery disease continues to accumulate. Gelfand points out that very recently, inflammatory T_H1 diseases such as rheumatoid arthritis "have also been shown to be an independent risk factor for acute MI and multivessel coronary artery disease, after adjusting for coronary risk factors that include diabetes, hyperlipidemia, hypertension, and smoking," and he points to psoriasis as the most common T_H1 autoimmune disease. "Profound immune abnormalities lead to an estimated 20 billion T cells infiltrating the skin of a patient with severe disease, as well as dramatic increases in dendritic cells, T_H1 cytokines such as TNF-α and interferon, and chemokines," Gelfand explains. Psoriasis is also associated with increased C-reactive protein levels and other markers of systemic inflammation that are regarded as important to the development of atherosclerosis and, ultimately, MI.

These observations support the hypothesis that psoriasis predisposes patients to MI. Although the data from several hospital-based studies over the years tentatively pointed in this direction, they had not included controls to see if the risk factor was psoriasis iteself, or comorbidities—such as metabolic syndrome—and predisposing behaviors associated with psoriasis.

Gelfand and his colleagues used data from the GPRD to explore psoriasis as an independent source of risk for MI. Their study population consisted of all patients with psoriasis aged 20 to 90 years who had at least one day of observation time, providing 127,139 patients with mild psoriasis and 3,837 patients with severe disease. Each psoriasis patient was matched to a maximum of 5 control patients, totaling 556,995 controls. A history of MI reflected a code for MI on or before the start date. For all patients, follow-up ended when they either developed an MI, died, or transferred out of the practice. The mean follow-up time was 5.4 years. The rates of MI in the mild and severe psoriasis groups were statistically compared with the rate in the control population, and adjusted for hypertension, diabetes, history of MI, hyperlipidemia, age, sex, smoking, and BMI.

The crude incidence of MIs per 1,000 person-years for patients in the control, mild psoriasis and severe psoriasis groups were 3.58, 4.04, and 5.13. In addition, the increased adjusted relative risk (RR) of MI for psoriasis patients varied inversely with age (see graph on page 10). A 30-year-old patient with mild or severe disease, for example, had an adjusted RR of 1.29 or 3.10, respectively. For a 60-year-old patient these respective RRs were 1.08 and 1.36. Gelfand points out that the risk statistics observed in patients with severe psoriasis are likely to be underestimated because "most of the therapies—such as methotrexate, which is the major therapy we use—are actually cardioprotective."

Gelfand concludes that "the relative risk of MI associated with psoriasis is greatest in young patients with severe psoriasis, is attenuated with age, and remains higher even after controlling for traditional cardiovascular risk factors." The reason for this higher risk ratio in younger patients is not yet clear, but Gelfand speculates that "it may relate to the observation that psoriasis is a heterogeneous disease that is thought to have two subtypes. Type 1 occurs before age 40, has a stronger assocation with HLA-Cw6, and tends to be more severe, with Type 2 occuring after age 40 and typically less severe."

(Continued on page 10)

A Virtual Gold Mine—The General Practice Research Database

The General Practice Research Database, or GPRD, is an epidemiologist's dream. It contains electronic medical record information—including more than 40 million person-years of follow-up—from 1987 on the diagnoses and medications of more than 9 million patients, representing roughly 5% of the U.K. population and is broadly representative of this population across age, sex, and geographic distribution. The GPRD—maintained by the U.K. National Health Service, with data entered by GPs, who coordinate virtually all of their patients' care in the U.K.—contains each patient's complete medical record.

The medical record includes the documented diagnosis from any specialty referral, with most long-term therapies typically prescribed and monitored by the GP. "The validity of specialists' information and its capture by GPs has been well documented," Gelfand says. "And the validity of using this database to study a wide range of medical conditions had been demonstrated in numerous studies."

Gelfand is able to collect appropriate data on every psoriasis patient in this database. Patients are classified as having psoriasis if they ever received a diagnostic code consistent with this disease. *Severe disease* reflects an appropriate treatment code (psoralen or phototherapy, methotrexate, azatioprine, cyclosporine, etretinate, acitretin, hydroxyurea, or mycophenolate). Patients without these treatment codes are defined as having *mild disease*. (Because systemic therapies are often not used even when skin disease is severe, there is likely a subset of patients classified as "mild" who actually have more severe skin disease.) The GPRD enables identifying an extensive group of matched controls based on criteria that even include treatment and follow-up by the same medical practice during the same time period.

DF's Highest Awards Honor Outstanding Dermatologists

Continuing the honored tradition that began over 30 years ago, the Dermatology Foundation will pay tribute to five specialty leaders and role models at its Annual Meeting on February 2 in San Antonio, Texas. The following 2007 honorary award recipients will be recognized for their exemplary contributions to dermatology:

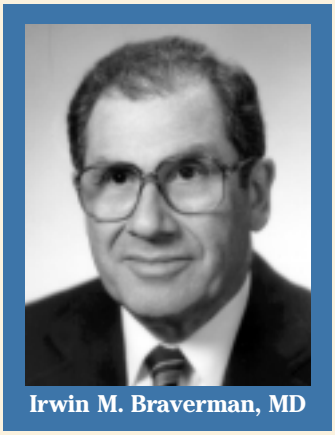
Irwin M. Braverman, MD—Lifetime Career Educator Award
R. Rox Anderson, MD and John A. Parrish, MD—Discovery Award
Robert Katz, MD—Clark W. Finnerud Award
Anne W. Lucky, MD—Practitioner of the Year

Three recipients are profiled in this issue—Drs. Braverman, Anderson, and Parrish. Drs. Katz and Lucky will be highlighted in the spring issue.

2007 Lifetime Career Educator Award: Irwin M. Braverman, MD

This award honors academic dermatologists who have been inspirational teachers and mentors to many generations of medical students and young dermatologists.

Few have served as a role model for more contemporary American dermatologists than Dr. Irwin Braverman, Professor of Dermatology at the Yale University School of Medicine. This gifted teacher of medical students and residents since 1962 has been formally recognized by Yale, the American Skin Association, and the NIH. His teaching reach extends through the classic text he authored, *Skin Signs of Systemic Disease,* currently in its third edition.


Irwin M. Braverman, MD

Dr. Braverman almost did not enter dermatology. His medical training at The Johns Hopkins School of Medicine predated inclusion of a dermatology component. During his post-internship work as a General Medical Officer in the Army, he had to refer his dermatology patients to a consultant. "I was very unhappy that I could not diagnose and treat them," he recalls. So when an opportunity arose to devote Wednesday afternoons to medical study, Dr. Braverman opted to spend this six-month period with his consulting dermatologist, Dr. John Reisner. This apprenticeship inspired his switch to dermatology and awakened his kindred spirit as teacher and consultation specialist. Dr. Braverman trained at Yale and then joined the faculty there, quickly making his mark as a consultative dermatologist and teacher. *Skin Signs of Systemic Disease* appeared in 1970, written to teach "what I have done for my entire career—to diagnose systemic diseases by *carefully looking* at the skin," he says.

Dr. Braverman is equally known for the revolutionary course he developed using paintings in the Yale Center for British Art. The course teaches medical students and residents the art and skills of *thorough observation and pattern recognition* to sharpen their diagnostic abilities. The idea grew from his realization that he taught what he observed, but "it had never occurred to me how to teach others to see these patterns on their own." Dr. Braverman sensed that the key involved training with objects that are unfamiliar and thus preconception-free, and recognized detailed paintings as ideal. A controlled trial of a single two-hour training session showed a 10% improvement in diagnostic capabilities. This class is now a model for other schools.

Presenting this award is Richard L. Edelson, MD, Chairman of the Yale Department of Dermatology and Director of the Yale Cancer Center, who finds it "especially poignant" that Dr. Braverman is receiving this Award. **"Irwin was my mentor and role model during my formative medical school days, when he was fathering the incipient field of Consultative Dermatology. He has shaped the careers and enhanced the clinical and correlative skills of many of our leading dermatologists. The course he teaches in the art museum to medical students is one of our school's most popular, and has been a transforming experience in their evolution to superb clinicians in all specialties."**

2007 Discovery Award: John A. Parrish, MD and R. Rox Anderson, MD

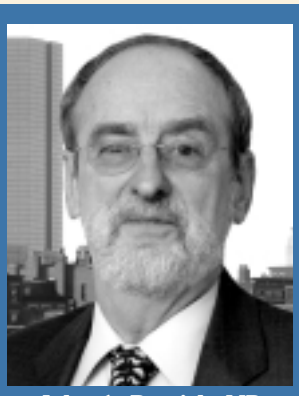
This prestigious career award recognizes research accomplishments with enormous impact on the specialty. It is jointly awarded this year for the landmark collaborative discovery of selective photothermolysis.

"Drs. Parrish and Anderson's concept of selective photothermolysis revolutionized the way physicians treat myriad skin conditions and was primary in ushering in the modern era of

cutaneous laser surgery," says a colleague. "Using precise microsurgery by selective absorption of *pulsed* radiation, it is the seminal event that led to using the medical laser to target specific chromophores in tissue."

Their new approach, first explained in their landmark 1983 article, minimized or eliminated the unwanted tissue damage and significant scarring severely impeding prior therapeutic use of laser energy for port-wine stains. It also opened a virtual treasure chest of therapeutic potential, including a range of vascular lesions, scar revision, tattoo removal, skin resurfacing, hair removal, acne treatment, and glaucoma in the eye—most of which Dr. Anderson developed.

It all began after Dr. Parrish, a young physician, fell in love with dermatology during his Navy clinic experience. He joined Dr. Thomas Fitzpatrick's department at Harvard and became deeply involved with photobiology research. He also played a critical role in the large multidisciplinary team that made PUVA feasible and safe—realizing PUVA's potential for severe psoriasis, thus revolutionizing its treatment. Through this project Dr. Parrish also introduced the laser to dermatology and, eventually, brought Rox Anderson to the laser.



John A. Parrish, MD

When Dr. Parrish introduced lasers into the lab as "ideal light sources to help us understand the reaction of psoralens on skin," he recognized their therapeutic potential and established a program to explore laser–tissue interactions. This is when Dr. Parrish and Mr. Anderson—a recent MIT graduate—met socially and discovered a shared passion for light and biology. Parrish immediately offered him a job as a technician "in a very small lab that he and Dr. Fitzpatrick ran exploring light and biology," Dr. Anderson recalls. He accepted on the spot. When work with them eventually moved him into a medical setting, it changed his plan to earn a PhD in physics. Observing his mentors successfully combine the clinic, research, and teaching "and connect it all to solve problems of people in need, I realized that my greatest pleasure is helping people, and that I really wanted to be an MD!"

Dr. Anderson entered Harvard Medical School in 1980, at age 30. That first year, at a discussion of argon laser treatment for port-wine stains, he learned of its high rate of scarring—especially in children, in whom the laser basically substituted one facial deformity for another. "I started thinking—how could we use a laser to remove the tiny, abnormal blood vessels *without* the risk of scarring. By the time I arrived home that evening, I had the basic idea underlying pulsed lasers for selective surgery." It was a *eureka* moment. Dr. Anderson brought his new concept to Dr. Parrish, which they discussed and refined, then worked out the treatment parameters. The rest is history.

R. Rox Anderson, MD

For many years afterward Anderson and Parrish were a synergistic team, teaching each other and exploring new ways that light can solve medical problems. Dr. Anderson became director of the legendary multidisciplinary Wellman Center for Photomedicine at MGH, which Dr. Parrish founded and built, has a clinical practice at MGH, and teaches at Harvard and MIT. His innovative light-based research and insights continue. Dr. Parrish followed Dr. Fitzpatrick as department chair, was founding director of the MGH–Harvard Cutaneous Biology Research Center, and then CIMIT—the Center for Integration of Medicine & Innovative Technology. "My romance came to be with multidisciplinary research," he says, which is the heart and soul of both Centers. He recently relinquished his other responsibilities to devote himself to CIMIT.

Dr. Parrish calls his longtime collaborator "a very, very special person, who went from being my technician to being my student to being my teacher—all in about two years!" Dr. Anderson insists that "I would never have thought of doing any of this work with light and pulses and treating kids with port-wine stains if not for the years of getting educated and discussing really interesting questions with John about what light does in there."

Ilona J. Frieden, MD, Professor of Clinical Dermatology and Pediatrics and Director of the Birthmarks and Vascular Anomalies Center, University of California, San Francisco, who is presenting their award, works closely with the profound therapeutic benefits these collaborators made possible. **"John Parrish and Rox Anderson richly deserve the Dermatology Foundation Discovery Award," she says. "Their concept of selective photothermolysis shifted the paradigm for how lasers and other light sources are designed for skin diseases, leading to a whole new generation of lasers for birthmarks and other skin conditions. Their insights have led to better treatments and improved lives for our patients, and the hope for more to come in the future."**

Severe Psoriasis and Increased Risk of Death

Psoriasis now presents a portrait of association with multiple comorbidities—including obesity, cardiovascular disease, internal malignancies (eg, lymphoma), smoking, and alcohol use—all of which could increase the risk of mortality in patients with this chronic inflammatory disease. Added to this are certain systemic therapies that, on rare occasion, have led to mortality due to chronic cumulative toxicity or idiosyncratic reactions, and rare instances in which psoriasis itself may lead to death. The few studies attempting to assess mortality risk in psoriasis patients have focused primarily on patients hospitalized for treatment. Those data are mixed, although they suggest a possible risk of mortality related to disease severity.

The GPRD provided Gelfand and his research team with 133,568 patients with mild psoriasis, 3,951 with severe disease, 560,358 control patients matched to those with mild psoriasis and 15,075 matched to patients with severe psoriasis.

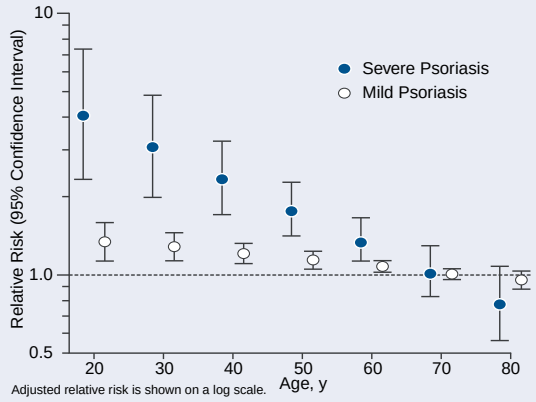
During the 1987–2002 study period, Gelfand and his research team found an overall hazard ratio (HR) of 1.5 for patients with severe psoriasis, ie, a 50% increased risk of death compared to patients with mild or no psoriasis (HR=1.0) (see table at right). The younger age groups showed the highest relative risk. Patients in their 30s had an HR of 2.5, gradually diminishing to 1.6 in patients in their 60s. This impact of severe disease on mortality persisted after adjusting for secondary mortality-associated risk factors and after excluding patients with inflammatory joint disease. Men with severe psoriasis died an average of 3.5 years younger than their counterparts in the control group, and for women with severe psoriasis, death averaged 4.4 years earlier. This translates to 1 excess death per 166 severe psoriasis patients per year overall. This frequency increased with age, from 1 excess death per 856 patients annually in the 30–39 year age group up to 1 excess death per 38 patients annually in the 80–89 year age group of severe psoriasis patients.

Gelfand notes that the decreased life expectancy he oberved in patients with severe psoriasis is similar in magnitude to the impact of severe hypertension. Future studies will determine the cause of this excess mortality, how it is affected by the extent of skin disease, and whether this risk of mortality in severe disease is modified in any way by various systemic therapies. In the meantime, these results underscore the tremendous burden that decades of severe psoriasis place on a patient's health, leading ultimately to a shortened lifespan.

Profound Implications for Clinical Care

Although each area illuminated by Gelfand's research spotlight has a list of additional questions to pursue, his accumulated observations hold immediate and urgent clinical relevance. They alter our understanding of the pathologic context in which psoriasis exists, and remodel our concept of standard of care—especially for patients with severe disease.

Adjusted Relative Risk of Myocardial Infarction in Patients With Psoriasis Based on Patient Age



(Reprinted with permission from JM Gelfand et al, *JAMA*, 2006; see *Suggested Readings*.)

Ratio of Mortality in Patients With Psoriasis

	Hazard Ratio (95% Confidence Interval)*		
Age, y	All Patients With Psoriasis	Patients With Mild Psoriasis	Patients With Severe Psoriasis
All ages (≥18)	1.0 (0.99-1.04)	1.0 (0.97-1.02)	1.5 (1.3-1.7)
35			2.5 (1.7-3.7)
45			2.2 (1.6-2.9)
55			1.9 (1.5-2.3)
65			1.6 (1.4-1.9)
75			1.4 (1.3-1.6)
85			1.3 (1.0-1.5)
95			1.1 (0.8-1.5)

*Data are adjusted for age and sex.

(Reprinted with permission from JM Gelfand et al, *Arch Dermatol*, 2007; see *Suggested Readings*.)

The tandem studies documenting a significant association for psoriasis with metabolic syndrome (a risk factor for cardiovascular disease) and with an independent risk for MI, "are suggesting that we have been thinking about psoriasis wrongly," Gelfand states. "For years we have regarded it as a skin disease in which the epidermis turns over too rapidly. But it is actually a dynamic disease, with a lot going on biologically," he explains. "It includes local inflammation in the skin, elevated markers of inflammation in the blood, inflammation in the joints in some patients, and excess angiogenesis. And as a consequence of all of this," Gelfand continues, "there may be other health effects—such as diabetes or MI—that are related to this disease due to common pathways."

Gelfand believes that "these patients have a significant degree of cardiovascular risk factors at baseline. And independently of this, there may be an extra risk of heart attack due directly to psoriasis itself." He strongly urges that "this is an appropriate population of patients to screen for cardiovascular risk factors—checking blood pressure, cholesterol levels, and diabetes—and then to treat risk factors in patients who have them." Gelfand adds that "these risk factors for cardiovascular disease tend to be undertreated," and he cautions appropriate interaction between dermatologist and primary care physician to ensure that these risk-related medical issues do not fall between the cracks. The large group of specialists who recently convened to discuss this emerging association between psoriasis, obesity, and subsequent cardiovascular comorbidity concluded that it makes psoriasis an important health care issue and concur that this requires an updated standard of care (*Br J Dermatol.* 2007;157:649–5).

Gelfand's documentation of increased mortality in patients with severe disease that persists after controlling for other major mortality risk factors intensifies this urgency. These patients "should receive comprehensive health assessments to enhance preventive health practices, improve overall health, and decrease their risk of mortality." And careful epidemiologic and experimental studies will be necessary to determine how treatment of psoriasis alters the risk of such health outcomes as diabetes, MI, and death.

Suggested Readings

Gelfand JM, Troxel AB, Lewis JD, et al. "The risk of mortality in patients with psoriasis: Results from a population-based study." *Arch Dermatol.* 2007;143:1493–9.

Gelfand JM, Neimann AL, Shin DB, et al. "Risk of myocardial infarction in patients with psoriasis." *JAMA.* 2006;296:1735–41.

Neimann AL, Shin DB, Wang X, et al. "Prevalence of cardiovascular risk factors in patients with psoriasis." *J Am Acad Dermatol.* 2006;55:829–35.

Gelfand JM, Shin DB, Neimann AL, et al. "The risk of lymphoma in patients with psoriasis." *J Invest Dermatol.* 2006; 126:2194–201. ■

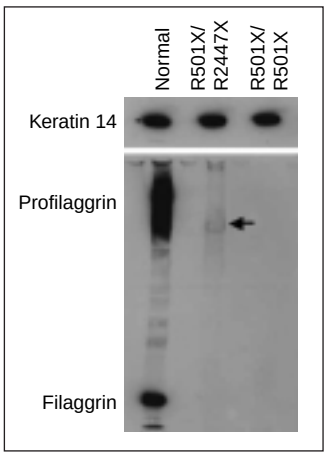
(Continued from cover)

in life and include disruption of the epidermal barrier and palmar hyperlinearity. IV—the most common inherited disease of keratinization—also involves fine scale on the limbs and keratosis pilaris. More severe cases include prominent scaling. AD, associated with substantial morbidity, is a chronically relapsing skin disorder with an immunologic basis that is typified by pruritus, eczematous lesions, xerosis, and lichenification. Did this frequent overlap reflect a mechanistic link, or simply the random joint presence of two extremely common skin diseases? Wells' clinical and histologic comparisons failed to provide any clue, and those who repeated this observation over succeeding years made little progress.

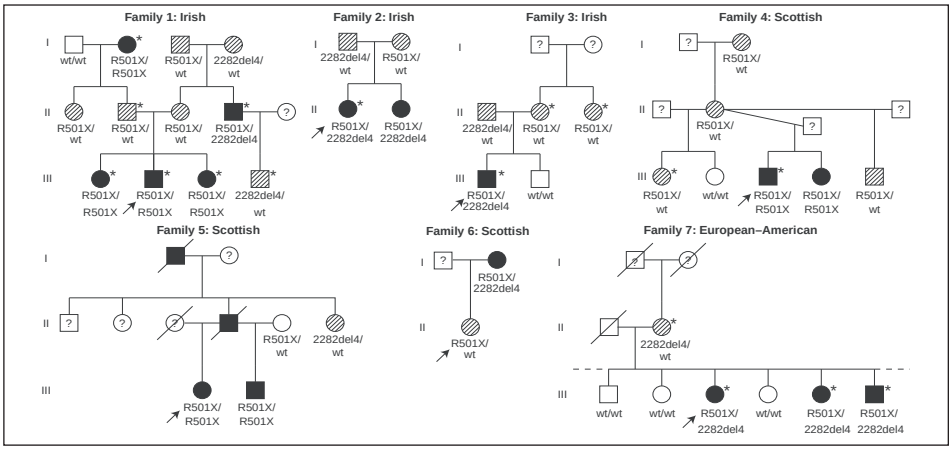
It would be 40 years before the evolution of technology enabled scientists with the right focus, experience, and insights to explain this mystery. The key lay in their ability to tame the enormously challenging filaggrin gene and make it accessible to analysis, and then in gradually identifying the variety and combinations of mutations—still in progress—that underlie IV and powerfully predispose to AD.

From Muscular Dystrophy to Defects of Keratinization

McLean's doctoral research at Queens University in Belfast had involved muscular dystrophy. In addition to muscle cells he studied fibroblasts, for which the skin is the best source. Thus began his relationship with dermatologists, which led to a collaboration in 1990 on the genetics of inherited blistering diseases and ultimately to the University of Dundee to work with a scientist whose lab focused on understanding keratinizing disorders. "Keratinizing disorders are caused by an interconnected collection of molecules," McLean explains. "We quickly identified the first mutations in several keratin genes, and that led us to *many* more genes associated with keratins and parts of the cytoskeleton—and eventually to the keratin-associated protein filaggrin." McLean developed an abiding fascination with the genes and proteins involved in keratinization and the production of epidermal or epithelial biotissues, including the diseases caused when these genes dysfunction.



FLG mutations eliminate filaggrin. Immunoblot analysis shows minimal truncated profilaggrin expressed in the compound heterozygote (*arrow*), none in the homozygote, and no filaggrin in either. (Reprinted with permission from A. Sandilands et al, *Nat Genet,* 2007;39:650–4.)



Pedigrees of IV Families Studied. *Roman numerals* = generations; *filled symbols* = severe IV; *cross-hatched symbols* = very mild IV; * = dermatologist-diagnosed AD; *wt* = wild-type. (Reprinted with permission from FJD Smith et al, *Nat Genet,* 2006; see *Suggested Readings.*)

Filaggrin: Early Hints and Confusions

Filaggrin—***fil***ament ***aggr***egating pro***tein***—is critical to formation of the stratum corneum, essential for epidermal barrier formation and hydration. Profilaggrin, its precursor, is the predominant component of keratohyalin granules in the granular layer of interfollicular epidermis. With terminal differentiation of these granular cells, profilaggrin is proteolytically cleaved into filaggrin peptides and a calcium-binding domain. The filaggrin rapidly aggregates the keratin cytoskeleton, causing the granular cells to collapse into flattened anuclear squames that are cross-linked by transglutaminases to form the cornified cell envelope, the outermost barrier layer of the skin that both prevents water loss and impedes entry of allergens and infectious agents. Thus filaggrin is a key protein in facilitating epidermal differentiation and maintaining barrier function. *FLG*—the gene encoding profilaggrin—resides within the EDC (the epidermal differentiation complex) on chromosome 1q21, a dense cluster of ~70 genes encoding epidermal structural proteins that include loricrin, involucrin, trichohyalin, small proline-rich proteins, and S100 proteins.

As early as 1972, evidence from diverse areas began to suggest a link between IV and a genetic defect in filaggrin. The flaky tail mouse—a mutant with the histologic and ultrastructural hallmarks of human IV—appeared, and eventually showed strong genetic linkage to the mouse filaggrin locus as well as revealing the absence of profilaggrin and filaggrin. Immunoblotting studies showed little to no filaggrin protein in patient skin and keratinocytes, and reduced filaggrin mRNA was documented in some patients. "But the evidence was not consistent between patients," McLean says, "which was confusing."

The inheritance pattern of IV was a further source of confusion. In some studies it behaved like a recessive disease, and in others it acted as a dominant model. This apparent contradiction continued even after John G. Compton, PhD of the NIH and Philip Fleckman, MD, at the University of Washington, published convincing gene modeling studies in 2002 using a large American family with IV whose skin had no granular layer. "They showed that IV really mapped right into the region of chromosome 1 containing the filaggrin gene," McLean notes. "The problem was that analyzing their genetic linkage data based on a recessive inheritance model produced significant results—but so did analyzing the data as a dominant disease!"

Then in 2003 a report on two Chinese families also suggested that IV maps to 1q21–q22, but tended to exclude a possible filaggrin mutation (which eventually turned out to be a misinterpretation of the data).

Annenberg Circle Support for the Future Grows by 38 New Members in 2007

The DF welcomes 38 dermatologists who have substantially increased their support of progress in the specialty as members of the Annenberg Circle. These new members each made a commitment of $25,000 to augment research support for tomorrow's specialty leaders, teachers, and scientists responsible for continued progress and the best in patient care.

Evan G. Bauer, MD
Louis Bauman, MD
Jean B. Braun, MD
David G. Brodland, MD
Marc R. Carruth, MD
Holly H. Clark, MD
David J. Clemons, MD
Raymond L. Cornelison, Jr., MD
Peggy S. Crawford, MD
Tony Sio-Ta Fu, MD
Richard D. Granstein, MD
Katherine R. Hamlet, MD
Bhushan D. Hardas, MD, PhD
Charles L. Heaton, MD
John D. Huber, MD
Kay S. Kane, MD
Grace F. Kao, MD
Robert S. Kirsner, MD
Susana M. Leal-Khouri, MD
Leslie S. Ledbetter, MD
Fu-Tong Liu, MD, PhD
Thomas W. McGovern, MD
Suzanne Olbricht, MD
Diamondis Papadopoulos, MD
Maritza I. Perez, MD
Peter A. Pollat, MD
Donald I. Posner, MD
Rudolf R. Roth, MD
James T. Sandwich, MD
Joseph F. Seber, MD
Stephen C. Somach, MD
Vera Y. Soong, MD
Kurt S. Stenn, MD
John Strasswimmer, MD, PhD
John R. Vydareny, MD
Mark L. Welch, MD
Patricia P. Westmoreland, MD
Jeffrey M. Wolff, MD

Parsing the *FLG* Gene—A Monumental Challenge

With the accumulating weight of evidence pointing increasingly to the filaggrin gene (*FLG*) despite persistent confusions, McLean and his co-workers decided to undertake a molecular analysis of the gene itself. They took genetic material from seven unrelated families with IV and eight additional sporadic cases in Ireland, Scotland, and the U.S.

Their challenge , though, was formidable. Exon 3 of the *FLG* gene—ie, one of the protein-coding sequences—is absolutely enormous. The exons of most genes contain 150 to 200 base pairs. *FLG* 's exon 3 not only contains 12,753 base pairs, it is made up primarily of 10 to 12 filaggrin repeats that share almost 100% homology. Conventional PCR-based sequencing was useless.

Fortunately, an earlier and ultimately successful effort undertaken with colleague Frances Smith, PhD, to explore the plectin gene—with a huge exon right at the end that is roughly half the length of *FLG* 's exon 3—provided essential insights. "We had learned a lot about long-range PCR and how to go after these genes by repeated trial and error, piece by piece, until you finally break them down," McLean says. "Filaggrin was bigger and badder," he comments, "and it took us a lot longer to get all the way through the exon, but we eventually got there." McLean developed long-range PCR conditions permitting him to amplify a 12,000-base pair segment of exon 3 that encompassed all of the repeat domains. Ironically, the extreme degree of homology was beyond the sensitivity of the newest labor- and time-saving technology. McLean and his team had to do it the old-fashioned way, manually aligning the gene with computer assistance and relying on visual inspection and acuity for spotting the ultrafine differences distinguishing the individual filaggrin repeats. Initially, they were unable to progress beyond the first of these repeats.

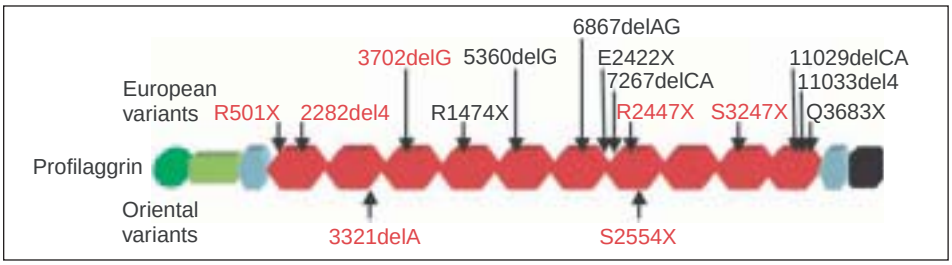
The First Mutations: R501X and 2282del4

The intense time and effort paid off with their first mutation—R501X—in this very first filaggrin repeat. "Although we were unable to sequence this exon fragment fully, we confirmed segregation of mutation R501X in family 1," McLean says, "and then we identified it in our other IV kindreds." With a mutation at the beginning of this exon, no processed filaggrin was produced.

In three of these families "the genetics finally made sense." IV patients who were heterozygous for R501X and thus produced too little filaggrin had a mild phenotype. Patients with a very pronounced phenotype were homozygous for the mutation, with no processed filaggrin at all—"essentially a knock-out situation," McLean indicates. Now he understood why IV had seemed to be both dominant and recessive. It acted as a dominant disease in patients with a mild phenotype, and thus a single mutant gene. It appeared as a recessive disease in patients with a severe phenotype, because they are homozygous. So IV actually involves a *semi-dominant inheritance pattern*—seen often in mice and other animals but infrequently in humans—in which one copy of the defective gene produces a mild phenotype that is often subclinical (and sometimes not expressed at all), and two copies of the mutation produce the full phenotype.

But McLean still faced a problem. Among the remaining four families and isolated cases, "we found individuals with the marked IV phenotype who were heterozygous for the mutation," he says (see family pedigrees on page 11). The only logical explanation was a second—as yet undiscovered—mutation and that these puzzling patients were actually compound heterozygotes, with a different mutation on each

(Continued on page 15)



Profilaggrin molecule with mutations. Schematic with positions of known loss-of-function *FLG* mutations. *Red* = common; *black* = rare or family specific. *Domain structure (from N terminus): green* = S100 domain; *lt. green* = B domain; *lt. blue* = partial filaggrin repeats; *red* = filaggrin repeats; *black* = unique C terminus. (Reprinted with permission from A. Sandilands et al, *Nat Genet,* 2007;39:650–4.)

CLINDAMYCIN & TRETINOIN

COME TOGETHER TO CREATE...

ZIANA™

(clindamycin phosphate 1.2% and tretinoin 0.025%) Gel

See reverse side for brief summary of Full Prescribing Information.

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The Dermatology Company®

BRIEF SUMMARY
(see package insert for Full Prescribing Information)

ZIANA™
(clindamycin phosphate 1.2% and tretinoin 0.025%) Gel

Rx only
For topical use only

INDICATIONS AND USAGE
ZIANA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

CONTRAINDICATIONS
ZIANA Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS
Colitis
Systemic absorption of clindamycin has been demonstrated following topical use of this product. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. When significant diarrhea occurs, ZIANA Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure
Exposure to sunlight, including sunlamps, should be avoided during the use of ZIANA Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., a hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with ZIANA Gel.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use for approximating rates.

The safety data presented in Table 1 (below) reflects exposure to ZIANA Gel in 1,853 patients with acne vulgaris. Patients were 12 years and older and were treated once daily for 12 weeks. Adverse reactions that were reported in ≥ 1% of patients treated with ZIANA Gel were compared to adverse reactions in patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the vehicle gel alone:

Table 1: Adverse Reactions Reported in at Least 1% of Patients Treated with ZIANA Gel: 12-Week Studies

	ZIANA Gel N=1853 N (%)	Clindamycin N=1428 N (%)	Tretinoin N=846 N (%)	Vehicle N=423 N (%)
PATIENTS WITH AT LEAST ONE AR	497 (27)	342 (24)	225 (27)	91 (22)
Nasopharyngitis	65 (4)	64 (5)	16 (2)	5 (1)
Pharyngolaryngeal pain	29 (2)	18 (1)	5 (1)	7 (2)
Dry skin	23 (1)	7 (1)	3 (<1)	0 (0)
Cough	19 (1)	21 (2)	9 (1)	2 (1)
Sinusitis	19 (1)	19 (1)	15 (2)	4 (1)

Note: Formulations used in all treatment arms were in the ZIANA vehicle gel.

Cutaneous safety and tolerance evaluations were conducted at each study visit in all of the clinical trials by assessment of erythema, scaling, itching, burning, and stinging:

Table 2: ZIANA Gel-Treated Patients with Local Skin Reactions

Local Reaction	Baseline N=1835 N (%)	End of Treatment N=1614 N (%)
Erythema	636 (35)	416 (26)
Scaling	237 (13)	280 (17)
Itching	189 (10)	70 (4)
Burning	38 (2)	56 (4)
Stinging	33 (2)	27 (2)

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and 2, 1277 subjects enrolled with moderate to severe acne, 854 subjects treated with ZIANA Gel and 423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were slightly higher for the ZIANA-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA Gel showed a similar adverse reaction profile as seen in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

DRUG INTERACTIONS
Concomitant Topical Medication
Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution. When used with ZIANA Gel, there may be increased skin irritation.

Erythromycin
ZIANA Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Neuromuscular Blocking Agents
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ZIANA Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA Gel. ZIANA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ZIANA Gel was tested for maternal and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA Gel at 600 mg/kg/day (approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA Gel for two weeks prior to artificial insemination and continuing until gestation day 18, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA Gel applied daily to a 60 kg person.

Clindamycin
Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin up to 180 mg/kg/day (175 and 88 times the amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin
In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (~ 78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on a body surface area comparison.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of ZIANA Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIANA Gel is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of ZIANA Gel in pediatric patients under the age of 12 have not been established.

Clinical trials of ZIANA Gel included patients 12–17 years of age.

Geriatric Use
Clinical studies of ZIANA Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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filaggrin gene. This initiated their second laborious exploration of that first filaggrin repeat, resulting in their second mutation—2282del4. And this explained all of the remaining severely affected IV patients. Each one carried a single copy of each mutation. They were indeed compound heterozygotes. The complete absence of filaggrin in their granular layer was clearly documented.

Once these genetics were pinned down and clarified, McLean and his group did population screening with these two filaggrin mutations and found each one carried by ~5% of the Irish, Scottish, and European-American populations—"kind of shocking" at the time. The expectation was that prevalence would reflect the prevalence of IV itself, but they were substantially higher. At the time, McLean had wondered "why in the world that percentage of people did not have IV?" Now he knows that they do. "Their symptoms are subclinical, and you really have to look closely to see them," he says.

IV and AD—What *Is* Going On?

McLean also noted that "consistent with the previously reported high incidence of atopic disease in association with IV, atopy was prevalent in all seven families." Of 36 IV patients—mild and severe phenotypes—44% had dermatologist-diagnosed AD (see pedigrees on page 11). Five also had asthma (2 R501X heterozygotes, 2 R501X homozygotes, and one compound heterozygote). A previous study had shown ~8% of AD patients to have classic features of IV. Recent twin and family studies had shown that predisposition to atopic disease is highly heritable, and although most genetic studies focused on immunologic mechanisms, awareness was growing that a primary epithelial barrier defect is a significant component. McLean speculated that filaggrin may be a factor, and addressed this in his next study.

Two families were added to his original group of seven, providing 50 individuals with IV—29 had mild disease and were heterozygous for a *FLG* null allele; 21 had severe IV and were homozygous or compound heterozygous for *FLG* null alleles. AD was present in 44% of mildly affected IV patients and in 76% of those with severe IV. No one without a *FLG* null allele had AD. "AD is also inherited as a semidominant trait in these families," McLean points out, "with high penetrance in *FLG* null homogyzotes or compound heterozygotes, and reduced penetrance in heterozygotes." Asthma was minimally present among IV patients, with a nonsignificant lod score.

But the lod score between AD and IV was highly significant, and there was no evidence of recombination. "These data strongly implied that *FLG* null alleles are a frequent transmissible predisposing factor in common AD," McLean explains. To pursue this, he and his research group studied a small cohort of 52 Irish pediatric patients with dermatologist-diagnosed AD, plus population controls. The combined frequency of the two filaggrin mutations in their control group matched population prevalence data. But they were almost eight times more prevalent in the AD cohort, "demonstrating a highly significant dominant risk for AD," McLean states.

Nearly half of these AD patients also had documented asthma, slightly more among those with severe AD (48% vs 41% with mild disease). McLean and his team replicated this association in a larger cohort by approaching from the opposite direction. In a cohort of 604 Scottish school children and adolescents with physician-diagnosed asthma, ~50% also had a history of AD. The combined frequency of the two *FLG* variants was extremely high (15.7%). AD was also present in 72% of children with a filaggrin mutation, and in all seven children who were homozygous or compound heterozygous. The association of these filaggrin mutations with asthma occured *only* in children with concurrent AD, indicating that *FLG* variants are only a predisposing factor for the clinical subtype of asthma that occurs in the context of existing atopic skin disease.

"Our data provide robust evidence of a heritable genetic defect common to AD and associated asthma," McLean concludes. "The exact contribution to the overall prevalence of AD and asthma is complicated—with temporal and disease severity issues in addition to environmental effects—and further longitudinal studies of individuals carrying these *FLG* null alleles will help define the lifetime health risks associated with this specific barrier function deficit," he says.

Looking for More

Because the prevalence of atopic disease varies significantly throughout the world, McLean and his co-workers wanted to explore the distribution of these two *FLG* mutations across a broad swath of ethnic groups. Step one was examining the Human Genome Diversity panel plus additional samples from the Centre d'Étude du Polymorphisme Humain, which showed that R501X and 2282del4 are not present in non-European populations. McLean believed it "likely that other *FLG* mutations will be identified in Western European populations, and that other populations will have specific mutation profiles, some of which may also lead to the complete loss of filaggrin peptide production."

Another Irish family with IV provided the third, and very uncommon, *FLG* mutation—3702delG, located in the third filaggrin repeat. The two individuals with the new mutation each had AD as well.

To prepare for a comprehensive analysis, McLean and his colleagues worked to extend their long-range PCR capabilities still further and finally succeeded in sequencing the entire filaggrin gene, including those with 11 and 12 filaggrin repeats. Analyzing 23 individuals originating from Ireland, Scotland, the Netherlands, and Austria—all with severe IV and thus most likely to have a *FLG* mutation—produced seven more mutations (see illustration on page 12). Two prevalent variants—3321delA and S2554X—were identified in Japanese individuals with concurrent IV and AD, and 3321delA was also prevalent in China. *FLG* variants now totaled 12, with seven of them prevalent. The mutations in later repeats are either nonsense or frameshift mutations that also eliminate filaggrin production in the epidermis.

An Irish case-control study showed the five most common European mutations to be strongly associated with moderate-to-severe childhood AD, with an odds ratio of 7.44 for heterozygotes climbing to 151 for homozygotes. Three new rare null mutations emerged from this case series, also with AD associations. McLean and his team have developed rapid tests to screen for the four or five most common mutations so far identified in the European white population, and are still working on rapid tests for the others.

And their progress continues. Two more mutations in Japan increased the percentage of AD-predisposing mutations there from 5.6%—for the first two mutations—up to 21%. "Although there are fewer filaggrin variants than in the white population," McLean points out, "we expect this number to creep up as we continue to do more work." A mutation has since turned up in the Chinese Singaporean population. "We are a little further behind in analyzing the other ethnic groups," he comments. "But we are beginning to find mutations in all races now—African, Indian, Middle Eastern, as well as Indian and Chinese."

Refining the Predisposition to AD Via the Original Mutations

A large German cohort of 476 well-characterized German families was ascertained through probands receiving treatment for AD at hospital dermatology departments. In this group, screening for the two original *FLG* mutations identified revealed significant associations with high total serum IgE levels and concomitant allergic sensitizations, and overall the data from this sizable German cohort was fully in line with all of McLean's previous evaluations. "Taken together," he

(Continued on page 18)

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asserts, "these data implicate *FLG* as the first really strong genetic factor identified in this common and complex disease. A genetically determined disruption of the epidermal skin barrier should be regarded as a key event in the pathogenesis of AD," he continues, "and as a considerable risk factor for the development of subsequent sensitizations and respiratory diseases in a subgroup of patients, possibly paving the way for a severe and long-lasting atopic career."

McLean also looked at susceptibility to early-onset AD persisting into adulthood. Onset of AD after adolescence is the exception, recorded in only 16.8% of adults with this disease. At least 85% of children with AD are affected before their fifth birthday, with onset by 12 months of age for 60% of children. Of those children with onset before age 2, 20% will have persistent disease. McLean's cohort consisted of 163 adults with persistent AD that began in childhood—all attending hospital dermatology departments—plus 1,463 ethnically matched population controls. "Specifically and strikingly," he says, "8.8% of the general population carried one or more *FLG* null alleles, whereas 42% of the AD cohort carried one or more."

Glimpsing the Genetic Architecture of AD

McLean and his research team have clearly and consistently demonstrated, across a variety of cohorts and populations, that filaggrin is a major susceptibility gene for AD, and that at least two highly prevalent null mutations in the first repeat of this gene—R501X and 2282del4—significantly predispose European individuals to early-onset, severe, and persistent AD, and also to the form of asthma associated with it. Their results have firmly established the importance of skin barrier dysfunction in

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the development of AD and associated atopic disease.

Improving their gene sequencing strategy has enabled them to uncover a broader spectrum of mutations that contribute to AD. More distal mutations allow a truncated profilaggrin that forms a minimal granular layer within the epidermis but still cannot be processed into functional filaggrin subunits (see photo on page 11)—explaining why some AD patients produce profilaggrin RNA. "The stage is now set," McLean says, "for the identification of *FLG* mutations in different ancestral groups worldwide, so the cumulative global contribution of these different variants to AD can be measured." Filaggrin will also be studied as a therapeutic target.

"What other genes confer susceptibility to AD?" McLean asks, addressing those AD patients with normal filaggrin in their epidermis. The EDC on chromosome 1q21, where the filaggrin gene resides, contains a dense cluster of genes with roles in the terminal differentiation of the epidermis. By genotyping carefully characterized AD case series and population-based cohorts, McLean will be able to remove carriers of *FLG* null mutations and create residual "non-filaggrin" data sets—which may be of profound value for finding still more AD susceptibility genes.

Suggested Readings

Smith FJD, Irvine AD, Terron-Kwiatkowski A, et al. "Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris." *Nat Genet.* 2006;38:337–42.

Palmer CNA, Irvine AD, Terron-Kwiatkowski A, et al. "Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis." *Nat Genet.* 2006;38:441–6.

Sandilands A, Smith FJD, Irvine AD, et al. "Filaggrin's fuller figure: A glimpse into the genetic architecture of atopic dermatitis." *J Invest Dermatol.* 2007;127:1281–4. ■

Stiefel Strengthens Support for the Future of Medical Dermatology

"The advancement of skin care is what Stiefel Laboratories is all about," says Charles W. Stiefel, Chairman and CEO. "This is why we continue to increase our support of the Dermatology Foundation."

In 2007, Stiefel Laboratories, Inc. increased their contribution to fund three medical dermatology career development awards in memory of Werner K. Stiefel—Charles' father and the architect of their company. Stiefel announced they will, once again, step up their support of the specialty by funding a fourth career development award in 2008.

The medical dermatology CDA is an important part of the DF's spectrum of research awards. It provides $55,000 yearly for up to three years to exceptional physicians beginning their careers in medical dermatology and researching ways to address complex dermatologic diseases. For Stiefel, these awards reflect the company's strong commitment to the specialty and their devotion to its continued development.

This new commitment raises their annual support to a new high of $320,000 in 2008. The company's ultimate goal, according to Bill Humphries, Chief Commercial Officer, "is to fund a total of six CDAs to launch the careers of dermatologists dedicated to progress in understanding and treating severe diseases of the skin."

Stiefel Laboratories has been a valued corporate partner of the Dermatology Foundation since 1993, contributing nearly $1,000,000 overall. This includes a pledge in 2003 to endow the Werner K. Stiefel Keynote Address at the DF Clinical Symposia for ten years. "He spent his entire career devoting himself to dermatology, and the mission of the Dermatology Foundation struck a particularly responsive chord in him," Charles Stiefel observed at the time.

Charles W. Stiefel

Father and son have also been strong personal supporters of the DF's mission. They were both Annenberg Circle members. When the AC Sustaining membership appeared in 2004, Charles Stiefel was one of the first to commit to this new opportunity. Now, as a member of the Fitzpatrick Legacy Fund, he has pledged $100,000 to further the specialty he and his father have long supported and respected.

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