KEYNOTE ADDRESS

Improving Outcomes in Atopic Dermatitis
Lawrence F. Eichenfield, MD

Introduction. Dr. Eichenfield reviewed this “extremely exciting time in the world of eczema,” where psoriasis stood a decade ago. There is significant evidence-based progress in using current treatment modalities, efforts are underway to fill important gaps affecting successful patient management, and breakthroughs in understanding the immunopathogenesis of AD are driving the development of innovative targeted therapies. In this review, Eichenfield also discussed what is currently most helpful in enabling patients to achieve effective disease control—ie, minimized rash, itch, allergies, comorbidities, drug side effects/toxicities. “So much of what we encounter in AD is inadequate care of patients who can in reality be appropriately managed, and we want to minimize the percentage of patients who are inadequately controlled.”

The treatment horizon. Eight years of insight on genetic barrier dysfunction has shifted now to rapid progress in dissecting the immune pathways that drive AD. After a decade with no new medications, “a very rich pipeline” involves drugs—primarily non-steroidal agents, including biologic agents—in all levels of clinical trials. A boron-based topical PDE-4 (phosphodiesterase 4) inhibitor, with anti-inflammatory benefit and excellent safety and efficacy profiles, is well along the way. Dupilumab—a monoclonal antibody blocking key drivers of the inflammatory pathway in AD—has shown impressive results. In discussing skin microbiome research, Eichenfield raised the possibility that modifying resident bacteria may change the course of this disease over time. Some studies have shown probiotics benefit, but the risk of contaminated products is a concern.

Inadequate disease control. The current potential for sustained remissions is too often not realized, with a significant percentage of untreated, undertreated, and improperly treated patients. “A lot of the problems we face in active practice—especially with steroid-phobia—are partially fueled by” our failure to establish best practices, which left us ill equipped to train pediatricians and primary care physicians to care effectively for AD, including the appropriate use of medications. Eichenfield is
a leader of the AAD’s newly minted answer to this need, the four-part Guidelines of Care for the Management of Atopic Dermatitis published in the 2014 JAAD: 70(2), 71(1), 71(2), 71(6). Patient adherence problems—of a degree unique to AD—also create problems. Many parents and adult patients, convinced that doctors do not understand AD, turn to unproven alternative treatments or ignore treatment altogether.

Recent evidence-based answers. Moisturizer prevention: Preventive emollient care halved the risk of developing AD in a recent study of neonates followed for 6 months after randomization to daily full-body emollient therapy or emollient-free control. Prediction: A study of 1900 infants published early this year demonstrated that leaky skin at birth—significant transepidermal water loss (TEWL) by day 2—is highly predictive of developing AD within the first year. “These two studies together make us ask: ‘Should we be intervening very early in life—before dermatologists would ever see infants—and taking measures to decrease the development of AD?’” Bleach bath value: The use of bleach-enriched baths has been controversial, but 2 recent studies weigh in positively. One shows the anti-inflammatory effect in skin of a sodium hypochlorite solution, which blocks NF-kB-dependent genes in keratinocytes. And a bleach bath added to standard AD treatment decreased disease severity scores by 35–45% after 6 weeks.

Pediatric Pearls
• To improve adherence with topicals—advise g/wk, wks/tube; assure of safety with this quantity and time (eg, 30–80 g triamcinolone 0.1% ointment per wk x 2 wks)
• Discuss steroid strengths and safety
• Educational and instructional materials
  – Written action plans, helpful websites, video training modules, text/email reinforcers, apps (www.eczemacenter.org)
• QUICK follow-up!
• Aggressive maintenance
  – Intermittent Cs and/or TCIs
  – Assess sleep and itching as endpoints
  – Consider anti-infectives, bleach baths/products
• TROUBLES??
  • Check growth, infection history, differential diagnosis
  • Consider allergy referral if persistent, frequent flaring, reactions to food

Emollient From Birth—AD Prevention
• 42% percent of families agreed to be randomized
• Statistically significant protective effect
• Relative risk reduction of AD = 50%
  (relative risk, 0.50; 95% CI, 0.28–0.9; P = 0.017)
• No emollient-related adverse events; no differences in adverse events between groups
• If confirmed in larger trials, emollient therapy would provide a simple and low-cost intervention that could reduce the global burden of allergic diseases

Topical steroids. Eichenfield discussed their proactive value in patients with persistent or frequently flaring disease, applied to normal skin 2–3 times/week. Proactive use of the steroid-sparing calcineurin inhibitor tacrolimus—applied to normal skin twice weekly—is approved in Europe and recommended in the recently published guidelines.

Eichenfield discussed patient steroid fears and the role of non-dermatologists and pharmacists in propagating them. He motivates compliance through education and his dosing approach. Instead of using as little as possible to bring the disease under control—like treating a strep throat with just a little bit of amoxicillin for only a few days—he typically gives the amount needed (eg, an 80-g tube) with instructions to use it entirely within a short time (eg, 2 weeks) and return at that point with the empty tube to review the results. Follow-up visits are frequent.

Guidelines Highlights: Pediatric AD
Topical Corticosteroids:
• Proactive, as maintenance therapy (1–2 x/wk) on areas that commonly flare to help prevent relapses Rating: B II
• Address fears with use Rating: B III
Topical Calcineurin Inhibitors:
• Use as steroid-sparing agents Rating: A I
• Off-label use in those age <2 y Rating: A I
• Proactive use for maintenance Rating: A I
• Blood monitoring of TCIs not needed Rating: A I

AAD Guidelines—Bathing
• Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for appropriate frequency or duration of baths
• Neither the addition of oils, emollients, and most other additives to bath water, nor the use of acidic spring water, are currently recommended

MINI-SYMPHOSUM: NEW PERSPECTIVES, OLD DISEASES

Sarcoidosis: Emerging Knowledge
Misha A. Rosenbach, MD

Introduction. Sarcoidosis, an uncommon but not rare disease, is a puzzling multiorgan illness of devastating impact, with the lungs a primary target. Because it affects the skin in roughly 1/3 of patients, it is not uncommon for pulmonologists to refer patients to a dermatologist for skin assessment. Although the typical patient is a young African-American woman with infiltrated violaceous-to-pink papules clustered around the nose, periorificial and periocular areas, this protean disease can appear elsewhere and has a predilection for scars and tattoos. (The lifetime incidence among African-Americans is 2.4%.) Dr. Rosenbach discussed recent insights, articulated critical questions to answer, and provided off-label treatment recommendations.
What we know. Patients are genetically susceptible, although some of the culprit genes vary between populations. There is some genetic colocalization with psoriasis and Crohn’s disease. Sarcoidosis has been characterized as a Th1-predominant disease, but current research increasingly implicates Th17 cytokines and also innate immunity. Distinguishing between active disease and residual scarring in the lungs is immensely challenging, and the relative ease of evaluating skin lesions creates an invaluable role for dermatologists. Rosenbach discussed the Cutaneous Sarcoidosis Activity and Morphology Instrument (CSAMI) he has developed for measuring skin activity. He also described the expanding prospective patient database his group established. An early emerging outcome is the potential association between sarcoidosis and thyroid disease. Other studies show that sarcoidosis patients have increased rates of lymphoma and both melanoma and nonmelanoma skin cancers. Thus sarcoidosis patients must be inspected for other skin diseases as well.

Central questions. “What sets off this disease in susceptible hosts?” Rosenbach discussed microbes and particulate matter, also

Initial Evaluation

• History (occupational, environmental exposure, symptoms)
• Physical exam
• Chest X-ray, PA and lateral
• Pulmonary function tests (including DLco)
• Routine ophthalmologic examination
• Complete blood count
• Comprehensive serum chemistries (Ca, LFTs, creatinine)
• EKG, and ask about palpitations
  – If history of palpitations, do additional testing; note; some advocate cardiac imaging for all patients (cardiac MRI, PET, ± 24h Holter monitor)
  – If history of kidney stones, check 24h urine calcium
• Tuberculin skin test or IFNγ-release assay
• Thyroid testing
• Vitamin D 25, and Vitamin D 1,25 levels

Cutaneous Sarcoidosis Treatment Algorithm

SEVERITY

Topicals
  • Intralesional
  • Antimalarials
  • Minocycline
  • Methotrexate
  • Thalidomide
  • Adalimumab
  • Infliximab

(Continued on page 6)
From Start-up to Essential Force

In the spirit of this very special occasion, Dr. Tharp highlighted the DF’s evolution from a vision shared by 10 dermatologists and scientists to its current position as the largest private funding source for dermatologic research. “Dermatology was a small specialty in 1964. Our 10 founders believed that if it was to prevail as a rigorous discipline, it required research support. They believed that the specialty needed a national entity solely devoted to supporting this growth—a foundation that would be sustained by dermatologists.”

Three years after the DF was established, it awarded its first five grants for a grand total of $30,000. Physician and industry support grew continuously over the following five decades, enabling the Foundation to invest nearly $70 million in the specialty. To date, 1,100 individuals have benefited from DF funding, including almost 350 career development awardees.

Focus on the Future

“Since the start, the DF mission has kept pace with the current needs of the specialty. Its focus today is clearly fixed on identifying and retaining emerging leaders who will develop new knowledge that will ultimately advance patient care,” Dr. Tharp shared.

As the DF embarks on its next 50 years, “its eyes will remain firmly on dermatology’s future—and the challenges ahead for the newest generation of teachers and investigators.” Dr. Tharp outlined his central concerns. “The purchase power of NIH funding continues to decline steadily, and talented new individuals are discouraged from entering investigative careers because of tight funding. DF support will be more important than ever—and just as the DF founders believed, the future development of dermatology will depend on physician support.”

Ongoing Support Is Essential

Dr. Tharp expressed his profound appreciation to the DF’s many physician members and industry supporters during these past 50 years. “Your commitment has helped to transform dermatology into the prominent specialty it is today. For my colleagues who are not yet members, join us. Our field needs your help—and as dermatologists, we can and should do all we can to support it.”

Furthering Dermatology for Five Decades

President Michael D. Tharp, MD presided over the DF’s historic 50th annual membership meeting in San Francisco earlier this year. Thanks to the generosity of its many physician members and its industry supporters this past year, Dr. Tharp reported that, in 2015, the DF awarded $3.1 million in essential research funding to 60 promising individuals.
"The DF’s Research Awards Program has grown from a single grant opportunity to a robust offering of 16 award categories supporting all areas of the specialty," remarked Dr. Bruce U. Wintroub, Chairman of the DF Board of Trustees. "This year the Trustees are pleased to bestow 60 awards, 80% of which are multi-year Career Development and Scholar Awards."

### Career Development Awards
($55,000 annual salary support/3 years)
- 6 Health Care Policy
- 6 Dermatologic Surgery
- 9 Physician Scientist
- 1 Science of Human Appearance
- 6 Medical Dermatology
- 5 Dermatopathology
- 2 Women’s Health
- 3 Pediatric Dermatology
- 7 Basic Science Research

### Fellowships
($30,000–$45,000 salary support)
- 5 Dermatologist Investigator
- 1 Pediatric Dermatology

### Grants
($20,000 project support)
- 2 Patient-directed Investigation
- 4 Basic Science Research

### Charles & Daneen Stiefel Scholar Award
($100,000 annual salary support/3 years)
- 3 Autoimmune &/or Connective Tissue Diseases

### Gala Celebrates 50 Years
Many of the DF’s most dedicated members came together for the 50th Anniversary Gala at San Francisco’s historic City Hall. Over 500 guests joined to celebrate this significant milestone—and the growth of the specialty over these five decades. The DF Board of Trustees extends deep appreciation to Amgen Inc. for the generosity that made this exceptional evening possible, and for their firm belief in the Foundation’s critical role in the advancement of dermatology.

**DF officers:** Drs. Stuart R. Lessin (Vice President), Michael D. Tharp (President), Elizabeth I. McBurney (Secretary-Treasurer), and Bruce U. Wintroub (Chairman, Board of Trustees).
raising the possibility of an endogenous autoantigen. Critical too is whether the notable clinical variety reflects separate diseases that should be evaluated and treated differently.

**Treat**ment. Treat limited skin disease with topicalis. With more widespread disease, treat with either antimalarials or minocycline alone or in combination. Greater severity is addressed with methotrexate and thalidomide. For the most severe disease, a growing and robust literature supports the TNF inhibitors infliximab and adalimumab. Rosenbach also noted encouraging data for the 4-drug antitubercular CLEAR regimen (possibly due to its anti-inflammatory effects) and for apremilast and pentoxifylline.

**New Psoriasis Therapies**

Mark G. Lebwohl, MD

**Introduction.** Dr. Lebwohl reported on clinical trials with a variety of new and emerging psoriasis therapies that provide "abilities to take care of patients we had trouble treating." He concluded with a few words on biosimilars and on the financial burden of biologic therapy in the U.S. imposed by the current regulatory climate.

**New and emerging drugs.** The **phosphodiesterase inhibitor apremilast** showed modest overall efficacy (33%) of patients achieved a score of PASI-75, but it showed benefit in particularly challenging areas (nails, scalp, palms, soles), it is oral rather than injected, and does not require laboratory monitoring. The **Janus kinase inhibitor tofacitinib**, impairing Th1 and Th17 signaling, rapidly eliminates itch in those who respond to this drug. Impact on laboratory values appears less worrisome than with many other biologics. The **TNF blocker certolizumab** is PEGylated, allowing peak efficacy—75% of patients achieving PASI-75—at a lower dose. The two anti-IL-17 drugs blocking the IL-17 molecule are **secukinumab**—approved in January by the FDA—and **ixekizumab**, with FDA application expected this year. Both show extremely impressive efficacy and sustained responses. The two new **anti-IL-23 drugs** are **tildrakizumab** and **guselkumab**, with a 3-injection regimen that targets IL-23 more precisely than ustekinumab does. A "very impressive" 75% of patients achieved PASI-75, with responders still clear by the study’s end at 240 days.

**Itch Severity Item (ISI) Score Showed Rapid Improvement With Tofacitinib**

- Rapid significant improvement in itch severity seen for both doses as early as Day 2
- From Week 2 among patients with baseline ISI >1, all active treatment groups had a significantly greater proportion of patients with ISI ≤1 (time to no itching) vs placebo

**Biosimilars.** These generic biologics—almost, but not quite, identical to the original molecule—may dramatically reduce cost and thus increase the number of patients able to afford treatment. The generic rituximab developed by Dr. Reddy’s Laboratory in India for lymphoma, the approved indication, is only one-third the price and the number of treated lymphoma patients increased 6-fold.

**Erasure Study Results: Secukinumab Rapidly Improved Plaque Psoriasis, and Sustained High Efficacy Up to 52 Weeks**

- The co-primary endpoints (PASI 75 and IGA 0/1 at Week 12) were met for both secukinumab doses
- Response differences to secukinumab vs placebo appeared early during therapy

**Lichen Sclerosis: A Treatment Update From the GYN Perspective**

Andrew T. Goldstein, MD

**Introduction.** Dr. Goldstein presented a current overview of etiology, sexual dysfunction, treatment—including surgery—and risk of carcinogenesis, after introducing the irony surrounding dermatologic diseases of the vulva. Gynecologists know vulvar anatomy and have the proper equipment for examining it, but they know “next to nothing about vulvar dermatoses.” Dermatologists know these diseases, but typically do not look for them. Goldstein encourages dermatologists to examine this area thoroughly—not just a fast peek below the underwear—and with magnification (colposcope, loupe, or magnifying glass).

**Background.** Lichen sclerosus (LS), a chronic inflammatory skin disease, involves significant scarring and architectural changes that predominantly affect the anogenital skin and mucosa. The clitoral hood fuses, causing phimosis of the clitoris, reducing sensation, and often leading to acutely painful smegmatic pseudocyst abscesses. Dyspareunia is a highly common complaint. Well-estrogenized women often lack symptoms despite very significant active disease requiring treatment. Patients have a monoclonal Lymphocytic infiltrate in the basement membrane, and >50% have circulating autoantibodies. >30% of patients develop other autoimmune diseases, with thyroid disease (Hashimoto’s and Graves) the most common. Thus an annual TSH is essential. Because clinical presentation ranges from substantial lichenification/no scarring to minimal lichenification/extensive scarring, Goldstein suspects that “most likely LS is a range of diseases with different antigens.”


**Treatment.** A pre-treatment punch biopsy establishes a baseline histology. Clobetasol remains the treatment gold standard. Goldstein described the superiority of clobetasol in head-to-head trials with pimecrolimus, tacrolimus, cutaneous lysate of human fetal fibroblasts, platelet-rich plasma, high-frequency ultrasound, and UVA phototherapy. Begin clobetasol daily (4–6 wks), then every other day (4–6 wks), then continue twice weekly. (See Treatment Pearls table.) Treatment must continue after remission to prevent further scarring and reduce the otherwise dramatically high risk of vulvar cancer. Do not fear thinning of the vulvar skin. This is a highly overemphasized risk. Goldstein documented the life-changing impact—for the overwhelming majority of patients—of surgery to correct impairing architectural changes. Clitoral phimosis repair is an easy 10-minute procedure with unremarkable healing. Narrowing of the posterior fourchette and/or anterior vestibule are quite easily corrected. Very deep scarring requires a perineoplasty.

- **Lichen Sclerosus—Treatment Pearls**
  - Give the patient a photo or diagram to show her specific areas of active LS, and thus where to apply clobetasol
  - Instruct to soak in warm water for 15–20 minutes before applying drug, which significantly increases its penetration
  - 0.5 grams of clobetasol 0.05% ointment must be rubbed in for at least 90 seconds to enhance drug penetration
  - Apply QD for 4–6 weeks, then QOD for 4–6 weeks, then BIW

**Conclusions**

- **Please look!**
- Treat with clobetasol 0.05% ointment until all active disease has resolved, then wean down—but not off—steroids. Do not treat “only when symptomatic”
- Address sexual dysfunction
- Counsel patients that LS:
  - is a lifelong disease requiring lifelong treatment
  - has a 3–5% risk of malignant transformation
  - requires monitoring for other autoimmune disorders

**What Do We Really Know About Rosacea?**

*David E. Cohen, MD*

**Introduction.** Rosacea—a disease known since ancient Roman times—is a complex chronic inflammatory disorder seen almost exclusively by dermatologists. Dr. Cohen’s rosacea focus grew from his decision years ago to specialize in contact dermatitis. Large numbers of rosacea patients—who are sensitive-skin patients—came to him saying they were allergic to everything applied to their faces. “We are homing in now on the key issues that go wrong in rosacea,” Cohen said, and provided “a clinician’s perspective” on this basic science. The hope is for better treatment in the future.

**Inflammatory underpinnings.** The neutrophil infiltrate, once considered the centerpiece, is now recognized as just one link in a chain of events. The upper dermis in rosacea contains highly proinflammatory cytokines that facilitate neutrophil entry, which in turn create an environment hostile to microbe growth and also release MMPs (matrix metalloproteinases) that are central to the redness, vasodilation, and homogenization of the dermis seen in phymatous skin. The three groups of MMPs—which digest either collagen, gelatin, or elastin—play important roles in both health and disease. MMPs also call in cathelicidins, a family of inflammatory endogenous antimicrobial peptides that are highly expressed in rosacea skin. Their activating enzymes are also highly expressed. Cathelicidins further increase the neutrophil presence, creating an endless recruiting loop. The high cathelicidin and activating enzyme levels trace to TLR2—one of the toll-like receptors in the innate immune system—which is also overexpressed in rosacea skin. Cohen also discussed the overexpression of TRPV (transient receptor potential vanilloids) receptors in rosacea skin, explaining their hyper-sensitivity to spicy food, hot temperatures, and temperature changes. He emphasized that the factors promoting the increased angiogenesis and lymphangiogenesis in these patients are ongoing in the background for years, well before any obvious clinical signs.

**Current treatment.** Cohen discussed the therapeutic effect of antibiotics despite the lack of infection in rosacea skin. He parsed the multiple anti-inflammatory effects of tetracyclines—including their ability to inhibit MMP production and interrupt the cathelicidin pathway—and the fact that both antimicrobial and nonantimicrobial doses decrease rosacea papules. Cohen also discussed the puzzling observation that killing demodex decreases papule number, and briefly reviewed the efficacy of isotretinoin (which may interfere with neutrophil function) and carvedilol (a hypochlorite scavenger).

**Vascular Changes in Rosacea**

• Skin biopsies of patients with rosacea demonstrate increased:
  - VEGF
  - CD31 (platelet-endothelial cell adhesion molecule)
  - D2-40 (lymphatic endothelium marker)
• Abnormal cathelicidins in rosacea have angiogenic properties

**Tetracyclines Have Multiple Anti-inflammatory Properties**

Managing Rosacea in 2015

Diane M. Thiboutot, MD

Introduction. Dr. Thiboutot covered issues and questions that have emerged concerning rosacea, presented her approaches to treatment as well as suggestions from others, and looked at the horizon.

Questions. Does rosacea progress in all patients? Many young patients with papular-pustular disease want to know if they risk developing rhinophyma. A recent Canadian study of 113 patients found that 40 had not progressed. Of those with 2 subtypes (1+2, 1+3, 2+3), the majority had progressed in the expected direction (ascending numerical order) but a small percentage either developed both simultaneously or progressed in the reverse order. Is there an association between rosacea and CVD? Several small but interesting studies suggest that the inflammatory process in rosacea may extend beyond the skin. One in Turkey with age- and gender-matched controls found rosacea patients to have significantly higher total cholesterol, LDL, and the inflammatory marker CRP. Among rosacea patients in the VA system, those treated with tetracycline (primarily doxycycline, varied dosage)—which has anti-inflammatory as well as antimicrobial effects—had a significantly lower risk for developing vascular disease.

Treatment options. For flushing and blushing disease, the latest are the adrenergic receptor agonists brimonidine (approved) and oxymetazoline (in trials). There are reports in a minority of patients of increased erythema as the medication wears off.
For papular-pustular rosacea, there are subantimicrobial and antimicrobial doxycycline (inhibiting cathelicidin by blocking MMP synthesis), and antimicrobial minocycline, and topical azelaic acid (which inhibits cathelicidin) and metronidazole. Some recommend oral isotretinoin, but Thiboutot finds recurrence after it is stopped. Demodex is not likely to be the sole pathophysiologic agent but may play a role via TLR activation, and ivermectin trials show reduction of inflammatory lesions. For phymatous rosacea Thiboutot uses oral antibiotics to reduce papules and pustules, and finds “pretty dramatic results” with use of a primary cauteterizing scalpel to sculpt out the nose contour (performed by a Mohs surgeon). Treatment for ocular disease involves artificial tears and lid hygiene if needed. Consider doxycycline (subantimicrobial or full-dose), or cyclosporine, or erythromycin opthalmologic eye drops. On the horizon are improved protocols for laser and light treatments, and oxymetazoline trial data.

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Does Rosacea Progress in All Patients?

- 113 rosacea patients were surveyed about the order of appearance of their rosacea symptoms
- 40 had just one type; 70 had 2 subtypes

A Principal Component Analysis (PCA), identifying and plotting strong patterns in a complex dataset, found that the molecular phenotype of some DN overlaps with melanoma. These DN contain small foci of highly melanoma-specific MAGEA3 cells. Are they more likely to become melanoma? Are these foci minute melanomas restrained by immunosurveillance? Can we develop molecular criteria allowing very early diagnosis of melanomas hidden within DN?

MINI-SYMPOSIUM: MELANOCYTIC LESIONS

Molecular Basis of Dysplastic Nevi
James G. Krueger, MD, PhD

Introduction. Dr. Krueger’s interest in dysplastic nevi (DN) grew from the “lore” that DN increase melanoma risk coupled with the clinical challenge of identifying DN and determining those requiring biopsy. His lab has been (1) developing objective technology-based methods for the macroscopic evaluation and discrimination of common melanocytic nevi (CMN), DN, and melanoma, and identification of lesions requiring biopsy, and (2) advancing the molecular characterization of DN.

Macroscopic evaluation. The goal of error-free computerized detection of melanoma begins with developing new imaging hardware. This hyperspectral imaging dermatoscope, created by optical engineer Dr. Dan Gareau, uses 18 wavelengths across the visible spectrum plus UV and infrared, rebuilding the formidably detailed final color image from the individual spectral images. He has worked with Rockefeller statisticians to develop an automated analysis program to help discriminate DN from melanomas. It aims to detect all melanomas while classifying as few DN as possible as “high risk” for melanoma. Another goal has been identification of those visual melanoma features enabling their precise discrimination from benign nevi. We now know that the conventional criterion of lesion asymmetry is not highly valuable for this.

Molecular characterization. Krueger’s team created a resource for cellular and molecular exploration by retaining half of the primary pigmented dysplastic lesions sent to pathology and diagnosed as common DN or melanoma. They learned that DN are immunologically active, which may influence their biology. Nevus nests in both normal nevi and DN are a chimera of nevus cells and activated dermal dendritic—antigen-sensing—cells (DCs). DN have significantly more DCs, and T cells—all activated—plus immune-regulatory molecules. The “real surprise”—the #1 molecular difference between DN and CMN—was the hair follicle-associated gene trichohyalin, followed by several hair follicle-associated keratins. This suggests an epithelial differentiation program gone awry. With a major component of epidermal keratinocyte dysplasia toward follicular differentiation, Krueger suspects that DN may actually reflect “a disease of the cross-talk interaction between dysplastic keratinocytes and melanization.”

Nevis Nests are Cellular Chimeras

- 35 patients had both Subtypes 1 and 2 over the follow-up period
- 23 patients had both Subtypes 1 and 3 over the follow-up period
- 12 patients had both Subtypes 2 and 3 over the follow-up period

A: MLANA/HLA-DR
B: MLANA/HLA-DR
C: MLANA/CD11-c

Biopsies of Pigmented Lesions

Dirk M. Elston, MD

Introduction. Dr. Elston discussed four pigmented lesions for which precise biopsy technique is critical to an accurate diagnosis.

Acrail nevii. Perform a complete removal with a narrow margin, and bisect it across the dermatoglyphs. Scaurization technique is often optimal in this location. Elston illustrated with a benign acral nevus, half bisected correctly and half bisected parallel to the dermatoglyphs. Pathologists correctly diagnosed this latter portion, but uniformly misdiagnosed the incorrectly bisected specimen as melanoma.

Spitz nevii. The lesion’s most predictive features—dispersion at the base, presence of deep mitosis, sharp lateral circumscription—are at the lesion’s very deepest part and most outer edge of the periphery, both missing “in the vast majority of specimens received in our lab.” Elston explained the stains that can be helpful in specimens that don’t demonstrate the lateral and deep margins.

Lentigo maligna. 48% of lentigo maligna occur in collision with a second pigmented lesion—usually a pigmented actinic (Continued on page 12)
The Dermatology Foundation Trustees extend their deep appreciation to the following members who have made a special contribution to the future of the specialty in honor of the DF’s 50th Anniversary. Each gift has been allocated to the DF’s Research Endowment Fund and is Board-restricted for future research funding.

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**From the Public**

- Sonny Bringol
keratinosis or solar lentigo—and almost 7% of lesions have areas of lichenoid regression, which closely resembles benign lichenoid keratosis. Thus these mottled lesions are highly vulnerable to sampling error with a punch biopsy, even if the darkest area is chosen. Some advocate a single broad, paper-thin slice. Elston takes a small shave of each different color within the lesion and places them in the same bottle.

**Dysplastic nevus.** Histologically, an atypical nevus extends about .05 mm beyond what the eye can see. Because “the greatest atypia and confluence are in that lateral bit of the shoulder,” an extra .05-mm margin when saucerizing the lesion ensures an accurate diagnosis without affecting wound appearance or healing.

### Lesions Likely to Pose a Problem
- Acral nevus
- Lentigo maligna
- Spitz nevus
- Dysplastic nevus

### My Advice
- Acral nevus—bisect across dermatoglyphs
- Spitz nevus—complete excisional bx
- Lentigo maligna—broad shave, multiple bx
- Dysplastic nevus—Mohs layer-like bx with 0.5 mm margin

### MINI-SYMPOSIUM:
PEDIATRIC DERMATOLOGY

#### The Evolving Pathogenesis of Atopic Dermatitis and the Translational Revolution
**Emma Guttman-Yassky, MD, PhD**

**Introduction.** AD affects up to 25% of children, but is also the most common inflammatory skin disease in adults. It affects 4–7% of adults in Western countries and 10% in Asia, while psoriasis—another inflammatory skin disease now with many novel treatments—affects ≤2% of adults. Existing treatments for moderate-to-severe AD—including phototherapy, cyclosporine A, and oral prednisone—are inadequate and carry safety concerns. After demonstrating fundamental similarities between AD and psoriasis regarding histology, markers of proliferation, and cellular infiltrates, Dr. Guttman-Yassky was confident that, as with psoriasis a decade ago, dissecting the immunopathogenesis and translating these discoveries to the therapeutic arena would galvanize progress. Her results are transforming the AD landscape.

#### Dupilumab Conclusions
- Dupilumab is the first targeted therapy in AD demonstrating dose-dependent clinical and molecular disease suppression
- A phase III efficacy trial is underway, as are larger, longer studies to evaluate long-term suppression

#### Pediatric Acne: What’s Erupting
**Lawrence F. Eichenfield, MD**

**Introduction.** "Pediatric acne has many faces." Before discussing them, Dr. Eichenfield quickly reviewed pathogenesis—with sebaceous gland activity the critical prerequisite, and inflammation

#### Mid-childhood Acne
- Onset: 1–7 years
- MOST WORRISOME!
  - Mid-childhood acne is very uncommon and should warrant an endocrinologic workup for causes of hyperandrogenism
  - May be associated with: premature adrenarche, Cushing’s syndrome, congenital adrenal hyperplasia, gonadal/adrenal tumors, precocious puberty
  - If persistent, severe or virilizing:
    - Growth chart evaluation including bone age, Tanner stage, total/free testosterone, DHEAS, androstenedione, LH, FSH, prolactin, 17OH-progesterone

---

*The immunopathology. When Guttman-Yassky began her research trajectory, AD was regarded as solely a Th2 T-cell-driven disease. The reality she documented also includes Th22 T cells, with Th1 and IL-23/Th17 components. She discussed the cytokine profiles for each T-cell subtype, and explained that “Th2 and Th22 cytokines basically link the barrier and immune defects that characterize AD.” Chronic lesions do not represent a switch from Th2 to Th1-driven disease, but add Th1 to intensified Th2 and Th22 activity. This holds therapeutic implications, as does her observation that intrinsic and extrinsic AD involve similar Th2 immunologic activity, but intrinsic AD shows significant increases in IL-17/IL-23 markers. Cyclosporine-induced disease reversal correlates with suppression of Th2- and Th22-driven inflammation, supporting Guttman-Yassky’s hypothesized immunologic model. But because cyclosporine also acts on keratinocyte proliferation, she went on to characterize the clinical/immunologic/transcriptome effects of the experimental anti-inflammatory dupilumab, the first targeted treatment in AD.*

*Targeted therapies for AD. Dupilumab is a fully human monoclonal antibody targeting the IL-4 receptor alfa, thus inhibiting the Th2 cytokines IL-4 and IL-13. A phase IB dose-escalating safety study of 4 weekly injections “showed surprising efficacy, both clinically and mechanistically.” Dramatic clinical improvement was accompanied by appropriate changes in markers, cytokine activity, gene activity, and the AD transcriptome (AD-related RNA in tissues). This dose-dependent efficacy was repeated with the recently published phase II trial results. Guttman-Yassky discussed possible contributions of other cytokines to AD, including IL-23, IL-22, and IL-17, and noted that the phase III trial with dupilumab trial is underway. She also articulated important questions still on her list.*

*A Paradigm Shift in the Pathogenesis of AD* (Continued on page 15)

INDICATION
JUBLIA (efinaconazole) topical solution, 10% is indicated for the topical treatment of onychomycosis (tinea unguium) of the toenail(s) due to Trichophyton rubrum and Trichophyton mentagrophytes.

IMPORTANT SAFETY INFORMATION
• JUBLIA is for topical use only and is not for oral, ophthalmic, or intravaginal use.
• Patients should be instructed to contact their health care professional if a reaction suggesting sensitivity or severe irritation occurs.
• The most common adverse reactions (incidence >1%) were (vs vehicle): ingrown toenail (2.3% vs 0.7%), application-site dermatitis (2.2% vs 0.2%), application-site vesicles (1.6% vs 0%), and application-site pain (1.1% vs 0.2%).
• JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and should be used with caution in nursing women. The safety and effectiveness in pediatric patients have not been established.

Please see Brief Summary of full Prescribing Information on the adjacent page.
JUBLIA® (efinaconazole) topical solution, 10%

For topical use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE
JUBLIA (efinaconazole) topical solution, 10% is an azole antifungal indicated for the topical treatment of onychomycosis of the toenail(s) due to Trichophyton rubrum and Trichophyton mentagrophytes.

DOSAGE AND ADMINISTRATION
Apply JUBLIA to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.

JUBLIA is for topical use only and not for oral, ocular, or intravaginal use.

CONTRAINDICATIONS
None.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two clinical trials, 1227 subjects were treated with JUBLIA, 1161 for at least 24 weeks and 780 for 48 weeks. Adverse reactions reported within 48 weeks of treatment and in at least 1% of subjects treated with JUBLIA and those reported in subjects treated with the vehicle are presented in Table 1.

Table 1: Adverse Reactions Reported by at Least 1% of Subjects Treated for up to 48 Weeks

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>JUBLIA N = 1227</th>
<th>Vehicle N = 413</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingrown toenail</td>
<td>28 (2.3%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Application site dermatitis</td>
<td>27 (2.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Application site vesicles</td>
<td>20 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>13 (1.1%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS
In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies with JUBLIA in pregnant women. JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons). In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

Nursing Mothers
It is not known whether efinaconazole is excreted in human milk. After repeated subcutaneous administration, efinaconazole was detected in milk of nursing rats. Because many drugs are excreted in human milk, caution should be exercised when JUBLIA is administered to nursing women.

Pediatric Use
Safety and effectiveness of JUBLIA in pediatric subjects have not been established.

Geriatric Use
Of the total number of subjects in clinical trials of JUBLIA, 11.3% were 65 and over, while none were 75 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and the younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
A 2-year dermal carcinogenicity study in mice was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded the interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons).

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).
prevalence. Over-reliance on topical therapy was described in both
patients with mild-to-moderate acne, scarring, and the acne lesions.

Recurrent topical treatment may also be beneficial in reducing
scarring. Topical therapy has been shown to be effective in reducing
scarring in patients with mild-to-moderate acne. However, the
effectiveness of topical therapy may be limited in patients with severe
scarring. In these cases, alternative treatment options may be
considered.

Acne Guidelines: Recommendation Highlights

- Topical antibiotics (clindamycin, erythromycin) are not
  recommended as monotherapy
- If topical antibiotic treatment is to be prolonged for
  more than a few weeks, topical benzoyl peroxide
  should be added, or utilized in combination products
- Topical retinoids (tretinoin, adapalene, tazarotene)
  may be used as single therapy or in combination products

Practice Changes—Where Are We in 2015? Marta J. Van Beek, MD, MPH

Introduction. Dr. Van Beek, Associate Clinical Professor of
Dermatology, discussed the imminent approach of alternative pay-
ment models and regulatory scrutiny of current global payments,
then addressed the concepts and early realities of big data. She en-
counters these issues as Chair of the AAD’s Council on Government
Affairs, Health Policy & Practice (which oversees the Academy’s
activities with government) and Chair of the Ad Hoc Task Force
on Data Collections & Platforms.

Alternative payment models. Because the current fee-for-
service model encourages volume rather than value, its elimin-
ation was bipartisanly built into the ACA. CMS (Center for Medicare
and Medicaid Services) recently announced that 80–90% of payments
will be based on an alternative model by 2016–18. The lack
of a consensus definition for “value,” however, fosters apprehen-
sion about models that could be an inverse incentive and discour-
se thorough patient care. “But if we remain engaged, we can be
masters of our own destiny.”

Bundled payments. These predetermined payments tie
fixed-dollar amounts to a specific patient and disease, calculated on
a yearly basis for long-term/chronic disease or tied to short-term
episodes (eg, 10 days for initial visit + excision + after-care visit). CMS
is looking for payment models that assemble payment into much
larger blocks, which will significantly affect our everyday practice.

Big data. Big data has exploded with respect to sources (includ-
ing cell phones and every aspect of on-line activity), volume, velocity,
and diversity. The 1.8 zettabytes (1 zetta = 1 trillion gigabytes) amassed
by 2011 surpassed the number of stars in the universe. The enormity
and velocity of data recorded now have overwhelmed traditional sys-
tems to structure and analyze it. The new organizational and analytic
approaches needed for deriving accurate, meaningful, useful results
are not easily apparent. In the medical world, recent CMS data release
aims at making better patient care decisions. The controversial value-
based modifier to determine payment basis in large practices is being
developed from big data. Van Beek described the challenges and

Practice Gaps

- Over-reliance on oral antibiotics
- Use of antibiotics without BP
- Use of antibiotics without retinoid
- Use of topical and oral antibiotics together
  without retinoid
- Under-appreciation of early significant acne
  as predictor of worse acne over time

Acne Guidelines: Neonatal—within the first 4 weeks of life: This is now
recognized as a pustular eruption often colonized by Malassezia, lipid-dependent
fungi that grow on the sebaceous areas of human skin. Renamed neonatal cephalic
pustulosis, it is self-limited. It typically does not require treatment, but topical keto-
conazole cream may be tried. Infantile—birth-1 yr: Mix of comedonal lesions and
deeper inflammatory lesions; treat with any topical agent alone or in combination;
oral antibiotics or isotretinoin can be used. Mid-childhood—1-7 yr: Persistent pimples
may indicate an endocrinopathy or gonadal/adrenal tumor, and requires pediatric
endocrinologic evaluation. Preadolescent—7-12 yr: “If it looks like acne, it’s acne.” Workup
is necessary only with signs of endocrinopathy, PCOS, or systemic abnormalities. General obser-
vations: Higher lesional counts when young are highly predictive of more severe acne later on. Scarring is not limited to nodular-cystic
acne. Comedonal lesions can leave scarring, so treat early. Isotretinoin—which should be used for severe scarring and refractory
acne in adolescents—is safe for use (off-label) in younger patients.

Treatment gaps. There is an underuse of topical retinoids, a
general over-reliance on oral antibiotics (especially clindamycin),
and a tendency to prescribe oral antibiotics for longer than 9
months. Also common are the use of oral antibiotics without ben-
zoyl peroxide (to minimize the emergence of bacterial resistance)
and without retinoids (to optimize efficacy). There is a significant
CDC initiative for the judicious use of antibiotics. When needed (for
moderate-to-severe inflammatory acne at any age), we typically
use them for 3 months—(occasionally 5)—then shift off.

Scarring: Not Just an Old Kids Process

- 22 patients with mild-to-moderate acne, scarring,
  and the acne lesions that preceded them

104 atrophic scars

- 30 were established scars
- 21 arose from acne lesions
- 53 arose from clinically normal skin
- 7 from papules
- 6 from erythematous macules
- 4 from pustules
- 4 from closed comedones

- Comedonal lesions as well as inflammatory lesions
  are capable of producing atrophic scars
- Atrophic scars may arise from clinically normal skin
- 12 weeks—for atrophic scars to develop
- Aggressive treatment of inflammatory and comedonal
  acne is warranted to minimize scarring

Patel MJ et al. SID Annual Meeting; May 5-8, 2010; Atlanta, GA. Abstract 344.
realities of this massive new landscape, cautioning that “big data affects you whether you want it to or not.” The AAD’s DataDerm™ will be a nationwide clinical database that will help dermatologists manage and benefit from big data in a variety of ways.

**MINI-SYMPOSIUM: SURGICAL AND AESTHETIC DERMATOLOGY**

Evidence-based Postoperative Wound Care

_Marta J. Van Beek, MD, MPH_

**Introduction.** Dr. Van Beek discussed what we do know as fact and what is simply opinion, as the elements that facilitate healing and remodeling are constantly discussed among dermatologists and plastic surgeons, yet “there is very little evidence to support what we do and why we do it, and wounds are managed very differently from one practice to the next.”

**What we know.** She discussed the main, partially overlapping, stages of cutaneous wound healing—hemostasis and inflammation, granulation and proliferation, remodeling and maturation—and the need to inform patients what to expect. They especially need to realize that inflammation at the start is normal and critical to healthy wound healing, that some early hemorrhage is necessary to trigger collagenesis, and that the surgical scar will continue to remodel for the first year. Van Beek also discussed the skin microbiome’s complex role in helping/impairing the innate immune response necessary for a healthy, rapid, and infection-free wound healing cascade, and the impact that stress of all kinds can have on the microbiome, and thus the immune response.

**Evidence also shows.** Moist occlusive dressings are beneficial, but no specific dressing is superior (guide choice by cost, plus patient preference and lifestyle). No benefit comes from keeping the bandage on beyond 48 hours. Keep the wound clean, but how or with what does not matter. Basic surgical technique makes a difference, and the smaller the wound the better. Inflaming the area widely can improve the scar. Avoid antibiotic ointment on surgical wounds because of its extremely high risk for contact dermatitis; vaseline is as effective. Hydrogen peroxide—inaccurately studied previously—actually does no harm and may in fact enhance early angiogenesis.

**Opinion.** Evidence is either nonexistent, inadequate, or contradictory for: hyperbaric oxygen, negative pressure wound therapy, skin substitutes, scar creams, type of antiseptic, type of suture, patient post-surgical activity.

**Bottom line.** Less is more. More costly is not better. Your nurses, MAs, and surgical techs are an informative interface with patients. Place the onus for ultimate surgical outcome on the patient, which typically produces the best result.

A Practical Approach to Soft Tissue Augmentation Based on Art, Science, and Economics

_Heidi A. Waldorf, MD_

**The art.** The artificial 2-dimensional facial rejuvenation—simply flattening wrinkled skin by deep abrasion or surgically pulling it taut—has been replaced by a 3-dimensional approach. Dr. Waldorf emphasized that this third dimension is what “makes us look normal.” She illustrated the 3-dimensional elements of the transition from the youthful to the aged face. Effective interventions address this dynamic reality of the full face, not just isolated features. Soft tissue augmentation requires an appreciaton of both anatomy and aesthetics. Waldorf explained that the patient’s face must be assessed from multiple angles to determine which procedural components will restore a more youthful and still natural-looking appearance. While each face is assessed individually, there are certain anatomic locations where injections will maximize lift per volume of injected filler.

**The science.** Waldorf discussed the individual characteristics—cross-linking, chain length, particle size, concentration, viscosity—and uses—filling, lifting, shaping, skin boosting—of different filling agents. Because no one product does it all, products are selected that dovetail to create a natural, blended look. Rather than relying on specific tools, Waldorf emphasizes injection technique plus product choice and placement to maximize results and minimize complications. For example, for glabellar lines she advised using only a very low viscosity hyaluronic acid gel injected superficially to reduce the risk of vascular occlusion.

**The economics.** The patient’s circumstances—finances, social and work calendar—determine how rapidly or slowly the work can be accomplished. Usually, the same result can be achieved with either

---

**The State of Knowledge**

**Irrefutable evidence**

- Moist or occlusive dressings
- Keeping it clean (nothing fancy)
- Basic surgical suture techniques
- The smaller the better, but diffuse inflammation obscures scarring
- Host factors are imperative
  - Smoking
  - Coagulation
  - Immunity

**A matter of opinion**

- Antiseptics
- Types of sutures
- Type of stitch
- Bandages
- Patient activity (within reason)

**Postoperative wound care recommendations**

- Less is more
- Listen to your MAs/nurses/surgical techs
- Put the onus on the patient for the surgical outcome

---

**Which Filler, Where, and When?**

<table>
<thead>
<tr>
<th>HA</th>
<th>CaHA, PLLA, HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lips</td>
<td>Temples</td>
</tr>
<tr>
<td>Glabella</td>
<td>Cheeks</td>
</tr>
<tr>
<td>Lateral brow/forehead</td>
<td>Jawline</td>
</tr>
<tr>
<td>Medial tear trough</td>
<td>Pre-jowel sulcus/chin</td>
</tr>
<tr>
<td>Fine lines (bello)</td>
<td>Panvolume (PLLA)</td>
</tr>
<tr>
<td>‘Skin booster’ (Resty silk)</td>
<td>Texture</td>
</tr>
<tr>
<td>Vascular danger zones</td>
<td>Structural/scaffolding’ (CaHA)</td>
</tr>
<tr>
<td>Anytime/anyplace you may want to remove it</td>
<td>Vascular danger zones (PLLA, HA yes; CaHA no)</td>
</tr>
</tbody>
</table>

HA = hyaluronic acid, CaHA = calcium hydroxyapatite, PLLA = poly lactic acid

(Continued on page 18)
The Dermatology Foundation is grateful to the following corporations for their generous contributions last year. Their support furthers the DF’s mission to develop and retain tomorrow’s leaders in the specialty, enabling advancements in patient care.

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one or two syringes of product at regular intervals over a year or two, or with multiple syringes in one or two sessions. Some conditions, like bound down scars or an extended scar-like commissure, require smaller successive treatments to achieve optimal results. Waldorf illustrated a diverse sequence of patients, discussing for each one the patient's presenting complaint, the respective solution (eg, where to treat, with what, how much and over what time course), and the results. She provided tips and pearls wherever appropriate.

How Fillers Really Work
Frank Wang, MD

Introduction. Cross-linked hyaluronic acid (CL-HA) is the most popular dermal filler. Dr. Wang and his colleagues noticed that patients receiving these injections seemed, over time, to need less filler for achieving the same cosmetic benefits. “We wondered if in addition to filling space, CL-HA actually stimulates the skin to produce new collagen,” Wang said. What they learned enhanced our understanding of skin biology.

Collagen and human skin. Wang summarized the structural importance of type I collagen, which is produced by dermal fibroblasts and gives youthful human skin strength, resiliency, and support. Type I collagen is the main component of the dermal extracellular matrix (ECM), and forms a scaffold that dermal fibroblasts attach to. The dermal ECM in young, photoprotected skin contains an abundance of long, intact, organized type I collagen fibrils. As these fibrils are reduced, disorganized, and fragmented by chronological aging or UV exposure, fibroblasts lose their attachment to the ECM. This causes them to collapse, which in turn reduces their synthetic behavior. Collapsed fibroblasts produce minimal collagen, and increase their synthesis of collagen-damaging matrix metalloproteinases (MMPs).

Conclusions and Implications

• ECM integrity, rather than “intrinsic” changes in dermal fibroblasts, is a primary determinant of age-associated decline of fibroblast function
• Thus, fibroblasts in aged/photoaged human skin retain their capacity for functional activation (cellular “rejuvenation”)

CL-HA’s impact. More than 50 subjects over 70 years old received CL-HA filler and control (physiologic saline) injections in chronologically aged buttock skin or photoaged forearm skin, then were biopsied at multiple time points. In filler-injected skin, pockets of injected CL-HA globules accumulated in the mid-to-deep dermis and lasted up to 1 year. Immunostaining of fibroblasts around these dermal pockets indicated active production of type I collagen as early as 2 weeks post-filler injection. Electron microscopy showed these fibroblasts to be mechanically stretched and highly synthetically active. Fibroblasts in control skin remained collapsed and synthetically dormant. Additional experiments revealed this mechanical stretching of filler-associated fibroblasts to be associated with activation of the collagen-stimulating TGF-signaling pathway. At 1 year post-injection, newly synthesized type I collagen fibrils had accumulated as highly organized thick bundles, similar to what is seen in youthful skin. These data suggested that “space filling by skin volumization is more important early on, then new type I collagen production becomes important to cosmetic improvement as the filler degrades.”

Implications. Fibroblasts in chronologically aged or photoaged skin retain their capacity for functional activation and can be rejuvenated at the cellular level. One way of doing this is by stretching them.

New Collagen

• Clinical improvement of injectable CL-HA is likely the result of two mechanisms:
  – Space filling (early)
  – Production of new collagen (later)
• Since type I collagen has a half-life of ~15 years, repeated CL-HA injections would be expected to produce long-lasting accumulation of collagen
  – Each treatment may reduce future need for retreatment

Imaging shows collagen bundles with a healthy rope-like structure, as in youthful skin.

Injected CL-HA Causes Fibroblast Stretching

Saline: Week 4 FBs remain relaxed
CL-HA: Week 4 FBs are stretched

2015 DF Clinical Symposia Faculty Disclosures (Part I)

Andrew T. Goldstein, MD: Strategic Science & Technologies, Emotional Brain. Emma Gutman-Yassky, MD, PhD: Amgen, Inc., AnaptyxBio, Celgene, Celsus Therapeutics, Dermira, Drais. James G. Krueger, MD, PhD: Abbvie, Amgen, Baxter, Biogen Idec, BMS, Boehringer, Delenex, Dermira, Immoderm, Janssen, Kadmon, Kineta Kyowa, Lilly, Merck, Novartis, Parexel, Pfizer, Serono, Sanofi, XenoPort. Mark G. Lebwohl, MD: AbGenomics, Actelion, Pharmaceuticals, Ltd., Amgen, Inc., Applied Biology, Can-Fite BioPharma, Ltd., Celgene, Celsus Therapeutics, Columbia Laboratories, Inc. (Bioscriptions), Centocor, Clinavel, Coroado Biosciences, Covagen, Dermispor, Dermira, Eli Lilly & Co., Fermdale, Forward Pharma, Genentech, GlaxoSmithKline, Janssen Biotech, LEO Pharmaceuticals, Galderma, Meda Pharmaceuticals, Merck Pharmaceuticals, Novartis, Pfizer, PharmAthene, Inc., Ranbaxy, Sandoz (Hexal AG), Taro Pharmaceutical, Thesan Pharmaceuticals, UCB Pharma, Valeant Pharmaceuticals, XOMA (US) LLC. (Dr. Lebwohl is a course director for the annual Fall and Winter Clinical Dermatology Conferences, the Real World Dermatology for Residents Conference sponsored by the National Society for Cutaneous Medicine, and the annual Mount Sinai Winter Symposium, which all receive support from numerous dermatology companies.) Mishra A. Rosenbach, MD: Celgene, Centocor/I&I. Diane M. Thiboutot, MD: Allergan, Dermira, Galderma, Stiefel/GSK, Sebacia, Mimetica, Novan, Xenon. Marta J. Van Beek, MD, MPH: None. Heidi A. Waldorf, MD: Allergan, Caudalie, Fermdale, Kythera, L’Oreal, Merz Aesthetics, Neobrida, Proctor & Gamble, Revance, Suneva, Unilever, Valeant. Frank Wang, MD: None.
CLINICAL SYMPOSIA 2015 FACULTY Proceedings—Part I

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DF CLINICAL SYMPOSIA
PROCEEDINGS 2015—PART II
Will Appear in the Summer
“Dermatology Focus”

Dermatology and Women
CPC With Masters of Dermatology
Keynote Talks

*DF Research Award Recipient
Giving Back—Profile of a DF Volunteer
“I Want to Make a Difference”

Dr. Carrie Kovarik has seen what the DF has done for many new investigators—and for the specialty. “There’s this hard transition between residency and becoming a faculty member. Some people can’t get the research funding they need to stay on the investigative path—especially in today’s difficult environment—and the DF gets them through it. There are so many promising individuals we just don’t want to lose. That’s the reason I got involved.”

Dr. Kovarik is a multifaceted dermatopathologist who is deeply committed to maintaining a strong specialty. She became a Leaders Society member in 2009, just four years after completing her residency, and then a DF Board member in 2012. Today she serves as a member of the national Leaders Society Committee and a volunteer for the LS Campaign in her state.

An Associate Professor of Dermatology at the Hospital of the University of Pennsylvania and Associate Professor of Medicine at Penn Medicine, Dr. Kovarik combines dermatopathology with an active clinical career that includes both local and international activities in Global Health Care. In addition to patient care at Penn Medicine and mentoring residents, she is the Head of Dermatology for the Botswana-UPenn Partnership. She is the primary dermatology consultant for the Baylor International Pediatrics AIDS Initiative in Africa, where she has established a network of teledermatology programs.

Many of the choices Dr. Kovarik has made in her career reflect her overriding conviction that life, for her, is about “making a difference.” This led her to choose medicine over engineering after college, then to work with medically underserved communities during medical school at Baylor, and to spend time working in the local Medical Examiner’s office there—in part “to gain justice for those who could not speak for themselves.” There she fell in love with pathology, and chose dermatopathology because she could continue working with patients.

Dr. Kovarik is a passionate, energetic volunteer. When she asks her colleagues to join her in leadership giving, she shares examples of research that began with DF funding and urges them to participate to secure the future of the specialty. “If we don’t continue to support our young people, the integrity of our field is at risk. We all need to ensure that dermatology continues to develop.”

The DF is exceptionally grateful to its many volunteers who give generously of their time and inspiration to keep dermatology at the forefront of medicine.