KEYNOTE ADDRESS

The Ebola Epidemic and Lessons for the Global Health Security Agenda

RADM Jordan W. Tappero, MD, MPH

Background. In August and September 2014, Dr. Tappero was the first CDC Lead for Public Health and Medical Response sent to Liberia to help control the Ebola epidemic exploding in West Africa. Then as Deputy Incident Manager from late September to February 2015, he helped direct the daily international and domestic Ebola response activities out of CDC Atlanta’s Emergency Operations Center. Tappero, who had joined the CDC in 1992 through the Epidemic Intelligence Service, had set foot on this journey as a young dermatologist during the peak of the AIDS epidemic in the latter 1980s, with passionate interests in both infectious diseases and global public health. As a dermatology fellow, he studied HIV-associated opportunistic infections of the skin (eg, Kaposi’s sarcoma) and made seminal discoveries illuminating bacillary angiomatosis/cat scratch fever. Tappero, a Rear Admiral in the U.S. Public Health Service, is now CDC’s Senior Advisor for Global Health, and he continues to enjoy his monthly clinical day at Emory University’s Department of Dermatology.

The basics. Ebola—a filovirus (which includes the Marburg virus), causing severe hemorrhagic fevers with high morbidity and mortality—is not new. The CDC had been involved in 25 outbreaks over roughly 40 years, and “we thought we understood everything there was to know to control these outbreaks,” Tappero said. Human-to-human transmission begins with an accidentally infected human host, who—once symptoms appear (typically within 7–14 days of a 21-day incubation period)—becomes highly infectious to others. Until the outbreak is recognized, those with direct unprotected contact with the infected person are highly vulnerable, creating a secondary chain of transmission more often than not including healthcare workers. Slower identification and reporting of the outbreak results in additional transmission chains. Once recognized, immediately isolating and caring for infected patients in an Ebola Treatment Unit (ETU) prevents them from infecting others and improves their survival chances. At the same time, identifying and following all persons who had direct contact with

DF Clinical Symposia: Proceedings 2017–Part I

ADVANCES IN DERMATOLOGY

The Dermatology Foundation presented its annual 3-day symposia series in January. This highly esteemed cutting-edge CME program provides the most clinically relevant knowledge and guidance for making the newest research advances accessible and usable. A daily provocative keynote talk precedes topic-focused, peer-reviewed caliber presentations. (Informal Breakfast Roundtables and evening Therapeutics Forums amplify the take-home value.) This year’s topics were: Infectious Disease; Pediatric Dermatology; CPC Session; Inflammatory Diseases; Monitoring for Malignancy; Skin Cancer; Care Delivery, Practice Improvement, and Politics; and What’s New: Therapeutic Updates. The Proceedings appear in the Spring (Part I) and Summer (Part II) issues.

Janet A. Fairley, MD, and Jack S. Resneck, Jr., MD—Program Co-Chairs

CDC Ebola Response by the Numbers

<table>
<thead>
<tr>
<th>Category</th>
<th>Figure</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
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<tr>
<td>Total CDC deployments</td>
<td>3,522</td>
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<tr>
<td>CDC staff involved in the response</td>
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<tr>
<td>Domestic</td>
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<td>Travelers monitored by health departments</td>
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<tr>
<td>Domestic clinical inquiries</td>
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<tr>
<td>US hospitals designated as Ebola Treatment centers</td>
<td>55</td>
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<tr>
<td>US labs approved to test for Ebola</td>
<td>57</td>
</tr>
<tr>
<td>International</td>
<td></td>
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<tr>
<td>CDC staff have deployed to West Africa</td>
<td>1,448</td>
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<tr>
<td>CDC person work-days in West Africa</td>
<td>72,000</td>
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<tr>
<td>Health workers trained in West Africa</td>
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<td>Transfers leaving West Africa screened for Ebola</td>
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<td>Transfers leaving West Africa</td>
<td>600</td>
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<tr>
<td>Health and frontline workers enrolled in Ebola vaccine trial</td>
<td>8,680</td>
</tr>
</tbody>
</table>

Last updated March 29, 2016

Also In This Issue

$2.6 Million in Research Awards for 2017

Eugene J. Van Scott, MD, Gift Strengthens Endowment Fund

Mark J. Holzberg, MD, Honored
2014: The perfect storm. When humans became infected for the first time ever in West Africa—in the small contiguous triad of Guinea, Sierra Leone, and Liberia, and months later in sizeable Nigeria well east of them—the familiar pattern of successful control prevailed only in Nigeria. “Fortunately, Nigeria had advance warning, and the capacity to respond with rapid isolation and contact tracing.” But in the other three countries, the chaos from decades of civil unrest had severely eroded organizational structures, oversight, and services. Thus they lacked the public health infrastructure for quick detection, response, and sharing of information about new chains of transmission; spotty border control left high population mobility unchecked; and infection control in health care facilities was essentially nonexistent—no protective gloves, no soap, no running water. WHO had declared the outbreak in March 2014. By late July 2014, unrecognized cases of Ebola had reached each country’s poor, densely crowded capitals, the first widespread Ebola transmission in crowded metropolitan areas. And these cities had international airports. Case counts rose exponentially from July through November. “Previous epidemics were considered big if cases were in the hundreds. These countries experienced 28,652 cases and more than 11,325 deaths. The situation had escalated to what was truly an epic epidemic by any scale.”

CDC leadership. In response, “our disease detective experts were on the ground, doing what they do best”—surveillance and contact tracing; isolation, triage, and infection control procedures (including safe burials); recruiting and training healthcare workers in ETUs; educating leaders and the public; promoting behavioral change and overcoming survivor-stigma; laboratory diagnostic confirmation; improving border control; exit screening at airports and borders. Tappero detailed the nature, implementation, and impact

Dr. Van Scott, often called a pioneer and true visionary, recently contributed $1 million to the Dermatology Foundation with the explicit aim “to build the DF Endowment Fund for inventive research.” One of the 10 founders of the DF, Dr. Van Scott has once again demonstrated his unparalleled commitment to the advancement of the specialty. The DF Trustees are profoundly grateful for his unyielding devotion and generosity.

Dr. Van Scott has had a formative impact on the specialty for many decades. He established the Dermatology Service at the NIH’s National Cancer Institute in 1953, then orchestrated its growth over the next 15 years to the Dermatology Branch that we know today. While still there, Dr. Van Scott collaborated with Thomas B. Fitzpatrick, MD, PhD, and Irvin H. Blank, PhD, to transform their inspirational idea into the Dermatology Foundation, bringing it to life in 1964 along with seven other foresighted colleagues. Dr. Van Scott was on the DF Board of Trustees until 1973, and was a founding member of the Annenberg Circle in 1995.

When the DF turned 40, Dr. Van Scott reflected on its achievements with immense satisfaction. In addition to fulfilling its mission to provide vital early career research funding, the DF “has also taken on the role of leadership,” he had pointed out. “Without the Dermatology Foundation, dermatology would not be in the position of strength that it is today.” In 2004, Dr. Van Scott helped to establish the Fitzpatrick Legacy Fund with a personal contribution of $100,000. He noted that “the Foundation addresses the renewal of dermatology, and keeps it young by sponsoring creative career scientists. Those of us able to make this financial investment are nourishing the evolution of dermatology’s future.”

His words apply equally to his recent gift. Bruce U. Wintroub, MD, chairman of the DF Board of Trustees, agrees. “Gene continues to see a critical role for the Foundation now—and for years to come,” he says. “We could not be more thankful that he has chosen to help fortify the DF’s Endowment Fund so generously.”

an infected patient for 21 days (contact tracing), and immediately isolating and caring for those contacts who become ill, prevents ongoing transmission chains.
of each element, and the array of exceptional challenges they had to conquer. January 2015 saw the epidemic clearly responding to the CDC’s massive and creative efforts. Guinea and Sierra Leone were essentially clear by April–May, and Liberia by February 2016.

**Sexual transmission.** A woman who developed Ebola 8 months after the last reported cases in her community led investigators to discover that this virus can survive in semen well beyond the CDC’s massive and creative efforts. Male survivors actually remain an extended risk to their community, requiring education and monitoring (promoting safe sex and stigma eradication), periodic testing of semen until virus-free, and community support.

The **dermatologist’s value.** “Because cutaneous presentations are common with infectious diseases, dermatologists are an important disease detection asset. We need to ensure good dermatologic support in the global community to quickly recognize disease threats like viral hemorrhagic fevers or emerging infections, such as Zika and dengue viruses.”

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### What Did CDC Contribute to in West Africa?
- Surveillance and contact tracing
- Isolation, triage, and infection control procedures
- Train healthcare workers in Ebola Treatment Units
- Educate leaders and the public
- Overcome stigma and promote behavioral change
- Laboratory confirmation
- Strengthen preparedness in border countries
- Exit screening at airports and borders
- Entry screening at U.S. airports

### CDC’s Response in the United States
- Enhanced entry screening at 5 U.S. airports
- Travelers coming from Guinea, Liberia, and Sierra Leone—actively monitored by state or local health department, given kits with information on Ebola, tools to help check temperature and symptoms for 21 days, a cell phone and calling information if they develop symptoms
- Educating U.S. healthcare workers on isolating patients and preventing infection
- Tightened infection control guidance for those caring for Ebola patients
- 55 U.S. hospitals designated as Ebola Treatment Centers; their readiness for care of Ebola patients was assessed by Rapid Ebola Preparedness teams

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### “New” and “Old” Viral Eruptions in Kids
**Erin F. D. Mathes, MD**

**Introduction.** The “new” (not really new) and the “old” (not really old) present diagnostic challenges. Some “old” ones differ from the conventional clinical presentation or are no longer familiar, and the “new” ones lack a precedent. Dr. Mathes provided guidance for diagnosing these viral eruptions in children, including post-vaccine issues, and triaging and managing some rare and new viral eruptions in this age group.

**Coxsackievirus A6 (CVA6).** Mathes described 3 initially puzzling patients referred to her pediatric dermatology clinic at UCSF between November 2011 and March 2012. One toddler had impetigo-like lesions, another with a history of AD was covered in small round erosions that were worst in AD-affected areas, and an infant with a giant bulla on one sole also had many smaller lesions—puzzling patients referred to her pediatric dermatology clinic at UCSF between November 2011 and March 2012. One toddler had impetigo-like lesions, another with a history of AD was covered in small round erosions that were worst in AD-affected areas, and an infant with a giant bulla on one sole also had many smaller lesions—

It can mimic classic hand-foot-and-mouth disease (HFMD). Eczema coxsackium is typical with concomitant AD. The diagnosis can be a survivor, and requires new thinking in controlling this virus.”

**Coxsackievirus A6 (CVA6).** Mathes described 3 initially puzzling patients referred to her pediatric dermatology clinic at UCSF between November 2011 and March 2012. One toddler had impetigo-like lesions, another with a history of AD was covered in small round erosions that were worst in AD-affected areas, and an infant with a giant bulla on one sole also had many smaller lesions—puzzling patients referred to her pediatric dermatology clinic at UCSF between November 2011 and March 2012. One toddler had impetigo-like lesions, another with a history of AD was covered in small round erosions that were worst in AD-affected areas, and an infant with a giant bulla on one sole also had many smaller lesions—similar to the previous two. Partnering with the CDC and California Department of Public Health (DPH), she diagnosed and confirmed the enterovirus CVA6. Rare in the U.S. through 2005, it had begun increasing in Finland, Singapore, and Japan and first circulated in the U.S. in 2010. “Almost everyone has a vesiculobullous and erosive presentation that varies from tiny papulovesicles to large bullae.”

It can mimic classic hand-foot-and-mouth disease (HFMD). Eczema coxsackium is typical with concomitant AD. The diagnosis can (Continued on page 6)
DF Annual Meeting: 2016 Support Fuels Progress

Dermatology Foundation President Dr. Michael D. Tharp presided at the DF’s annual membership meeting this past March in Orlando, Florida. He expressed profound gratitude for the steadfast membership support that individual dermatologists have continued to provide over this past year.

Award Survey Measures Success

Dr. Tharp began his address with very good news—the DF’s most recent survey of career development award (CDA) recipients. Nearly 80% of CDA recipients have remained in academic medicine, and about 75% of this group have received highly sought after federal funds. “These survey responses confirm that the DF’s approach to ensuring a dynamic specialty is effective. They clearly validate the Foundation’s ability to identify and support tomorrow’s thought leaders,” Dr. Tharp affirmed.

Benevolent Gift Earmarked for Future Research

Dr. Tharp also shared that Eugene J. Van Scott, MD, one of the DF’s 10 founders, has donated $1 million to the Foundation’s Research Endowment Fund to help ensure a constant source of funding for future investigators. “We are exceptionally grateful for this remarkable gift and his generosity,” Dr. Tharp said. (See article on page 2.)

Individual Contributions: $2.7 Million

“Annual membership contributions are the lifeblood of the DF, directly impacting our ability to fund research awards every year,” Dr. Tharp told the full room. “I want to thank all of our colleagues who made it possible for the Foundation to accomplish its mission this year.” He personally recognized 23 new Annenberg Circle members, each pledging $25,000, 20 new AC Sustaining members who gave an additional $5,000 last year beyond their AC commitment, and the 29 who extended this $5,000 annual gift for years into the future. He welcomed 205 new Leaders Society members ($1,500 annually), with a special thank-you to the 46 Young Leaders who joined the DF within 5 years of completing their residency.

Industry and Society Supporters

Dr. Tharp noted the generosity of the nine companies comprising the Corporate Honor Society, which recognizes annual contributions of $50,000 or more. He expressed tremendous gratitude for Unilever’s 3-year renewal of sponsorship for 50 residents to attend the DF Clinical Symposia each year.

“The DF is extremely appreciative of contributions from 15 national and local societies,” Dr. Tharp said. “Our sincere thanks go to the American Academy of Dermatology and the Women’s Dermatologic Society for their individual contributions of $55,000 to the Research Awards Program.”

Physician Support—More Vital Than Ever

Dr. Tharp continued, thanking the many campaign volunteers who worked so diligently to expand Leaders Society and Annenberg Circle membership. He expressed special gratitude to his fellow officers and Trustees for their unwavering commitment to the DF. He then welcomed newly elected DF President Dr. Kim B. Yancey, chair of the Department of Dermatology at the University of Texas, Southwestern, to his tenure as DF president.

In closing, Dr. Tharp emphasized that “strengthening our specialty and advancing patient care still further requires us to increase our commitment to our specialty. It will only be as strong as the support we give it. Please consider joining the DF if you are not yet a member. And for those of you who are DF members, we hope you will consider increasing your contribution.”

Honorary Award Recipients

Practitioner of the Year: Dr. Mark J. Holzberg (left) with presenter Dr. S. Wright Caughman

Lifetime Career Educator: Dr. William D. James (left) with presenter Dr. Jeffrey J. Miller

Clark W. Finnerud recipient Dr. Phoebe Rich (left) with DF President Dr. Michael D. Tharp
$2.6 Million Invested in Research

“I am pleased to announce that $2.6 million in funding has been awarded to 52 promising individuals for 2017,” Dr. Bruce U. Wintroub, chairman of the DF Board of Trustees, told annual meeting attendees. A significant portion of this support is devoted to the highly effective career development awards—37 were funded this year in various areas of the specialty. The list rounds out with eight fellowships, five grants, and two Stiefel Scholar Awards. “This is a significant milestone in your respective careers,” Dr. Wintroub congratulated the 52 recipients. “We all look forward to watching you progress.”

New Stiefel Scholar Award Available. Dr. Wintroub also shared news of Charles and Daneen Stiefel’s most recent act of generosity, “a $1 million gift that will fund three new Stiefel Scholar Awards, beginning in 2018, for early- to mid-career investigators focused on skin cancer.”

2017 Research Awards

$2.6 million in research funding
52 individuals/projects
◆ 2 Stiefel Scholar Awards
◆ 37 Career Development Awards
◆ 8 Fellowships
◆ 5 Research Grants

2017 Leadership Gala

Each year, the eagerly awaited DF Annual Leadership Gala is a special way to thank those who have demonstrated their strong and ongoing commitment to the future of dermatology as members of the Leaders Society, Annenberg Circle, AC Sustaining, and Fitzpatrick Legacy Fund. This year’s celebration was held the evening of March 5, 2017 amid the inspirational beauty of Orlando’s Orchid Garden. The evening began with the Young Leaders Pre-Gala, demonstrating the DF’s special gratitude for the support of Leaders Society members joining within five years after completing their residency.

DF Honors Dr. James J. Leyden

James J. Leyden, MD, became only the fifth person in Foundation history to be honored with the prestigious Distinguished Service Medallion. It is bestowed in recognition of exemplary leadership and service to the Foundation and the specialty. This honor is a tribute to an individual whose guiding vision and commitment have had a profound impact on the work of the DF and on the specialty.

Dr. Leyden has been a DF member since 1973. During these 44 years he served in a variety of leadership roles, including as a member of the Executive Committee, as vice-president of the Foundation, and as chairman of the Board of Trustees. He was instrumental in growing industry support for the Foundation’s mission, and a powerful proponent of the Endowment Fund to ensure consistent research funding levels in the future. He is also a notably generous supporter at every level. Dr. Leyden was a founding member of the Leaders Society and then the Annenberg Circle. He was one of the first to join the Thomas B. Fitzpatrick Legacy Fund—and finally, the first to provide a 50th Anniversary gift.
usually be made clinically; confirmation requires PCR from skin or pharynx swab or serum, as it will not grow in culture.

**Varicella zoster.** A live attenuated vaccine—that has greatly reduced outbreaks and deaths—is given at 12–15 months, then at 4–5 years, with a 15% failure rate reflected in *breakthrough varicella* that is significantly milder than the *primary varicella* that occurs within the unvaccinated population or older children and adults whose immunity has waned. Mathes discussed *zoster*, seen in both immunosuppressed and immunocompetent children, which can occur without previous vaccination or infection. “We are not close to eliminating or eradicating varicella. Be aware of breakthrough varicella and zoster in children, and consider treatment with acyclovir within the first 42–78 hours.” Take precautions, as varicella is highly contagious.

**Measles (rubeola).** The live attenuated vaccine—given at 12–15 months, then at 4–6 years—has reduced mortality by ~80% and eliminated self-propagation in the U.S., but there is an occasional outbreak. Breakthrough disease is called *modified measles*. Because of its rarity and exceptionally infectious nature, know how to recognize it and take the following steps: do PCR from the throat, a nasal swab, or urine; check IgM titres; immediately initiate respiratory isolation; and call your DPH.

**Rubella.** Although normally a mild disease, avoiding the devastating impact of congenital rubella led to vaccination with a live attenuated vaccine given at 12 and 15 months. In a vaccinated immunocompromised infant, however, this virus risks triggering persistent cutaneous granulomas. Avoid live vaccines for patients who are immunodeficient or immunosuppressed.

### Zika Virus Outbreak: The Science and the Situation

**RADM Jordan W. Tappero, MD, MPH**

**Introduction.** Zika is an RNA flavivirus—related to dengue, yellow fever, West Nile, and Japanese B encephalitis—carried by the *Aedes aegypti* mosquito. Dr. Tappero, Senior Advisor for Global Health with CDC’s Center for Global Health and adjunct professor in Emory University’s Department of Dermatology, discussed Zika’s history and epidemiology, its appearance in the Americas, its transmission and clinical manifestations and diagnostic testing, and the public health impact and response. He emphasized the clinical dermatologist’s front-line value in identifying unrecognized infection, thereby preventing unintended sexual transmission that can lead to birth defects.

### Laboratory-confirmed Zika Virus Disease Cases Reported to ArboNET by States or Territories — United States: 2015–2017

<table>
<thead>
<tr>
<th>Case Type</th>
<th>States (N=5,282)</th>
<th>Territories (N=36,583)</th>
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<tr>
<td>Travel-associated*</td>
<td>5,010</td>
<td>143</td>
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<tr>
<td>Locally acquired</td>
<td>224</td>
<td>36,440</td>
</tr>
<tr>
<td>Laboratory acquired</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
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*Includes cases in travelers and their contacts with presumed sexual or in utero transmission, and one case with unknown route of person-to-person transmission.
The beginnings. Zika was discovered in 1947 (in the blood of a local rhesus monkey) at the Uganda Virus Research Institute. The next 60 years saw only sporadic human cases in Africa and Southeast Asia, with the first significant outbreak reported on Yap Island in the Western Pacific in 2007. Reported cases exploded in 2013–2015 as Zika progressed eastward from French Polynesia, Island in the Western Pacific in 2007. Reported cases exploded in intrapartum, transfusion, and sexual transmission.

Non-mosquito-borne Routes of Zika Virus Acquisition

- Documented
  - Sexual
  - Blood transfusion
  - Intrauterine resulting in congenital infection
  - Intrapartum from viremic mother to newborn
  - Laboratory exposure
- Possible
  - Organ or tissue transplantation
  - Breast milk
  - Other body fluids

Clinical manifestations. The classic presentation is a non-specific maculopapular rash seen in roughly 90% of patients, with or without low-grade fever and myalgia; most infections are otherwise asymptomatic. The greatest risks involve infection of women in the first trimester of pregnancy, which can result in intrapartum infection followed by fetal loss, microcephaly, and severe congenital anomalies.

Zika in the U.S. and U.S. territories. The majority (96%) of cases reported in the continental U.S. through January 11, 2017 were travel-associated, mostly in the states of Florida, New York, California, and Texas. In contrast, the majority of cases reported in the U.S. territories (>35,000; 97% from Puerto Rico) were locally acquired.

“Because patients will see a dermatologist about their rash, you are at the front lines, able to diagnose Zika* and make sure—especially with male patients—that they are aware of the risks of unintended sexual transmission and the need for protected sex,” Tappero said.


Red, Skin-Colored, and Blue: Vascular Anomalies Update

Erin F. D. Mathes, MD

Introduction. Dr. Mathes discussed the latest progress in understanding and treating vascular birthmarks and anomalies.

Red. One of the most exciting developments of the past several years is the discovery that port-wine stains (PWS) and Sturge-Weber syndrome (SWS) are caused by a somatic—ie, occurring only in affected areas—activating mutation in the skin/skin and brain of GNAQ (GEE-nack), a subunit of guanine nucleotide binding protein. This mutation increases blood vessel growth, proliferation, and survival, explaining clinical and treatment observations. It also points to possible therapeutic value from sirolimus (under study). Recent research shows PWSs to be mosaic

Who Gets a SWS Work-up?

- High risk:
  - Forehead and upper lid
  - Large surface area (bilateral, multiple segments)
- My practice:
  - Send to neuro if sx/exam +
  - Send to ophtho for any lid or sclera involvement
  - If glaucoma present  neuro
  - Neuro decides on imaging

(Continued on page 9)
DF Honors Excellence in Dermatology

The Dermatology Foundation pays yearly tribute to dermatologists whose exemplary capabilities and dedication have helped to make the specialty what it is today. Presentation of the 2016 awards was a highlight of the DF Annual Meeting on Saturday, March 4 in Orlando, FL. The leaders and role models honored by their peers were:

Clark W. Finnerud Award—Phoebe Rich, MD
Lifetime Career Educator Award—William D. James, MD
Practitioner of the Year—Mark J. Holzberg, MD

(Drs. James and Rich were highlighted in the Winter 2016/17 issue.)

2016 Practitioner of the Year:
Mark J. Holzberg, MD

This annual award recognizes dermatologists for exemplary service as a private practitioner combined with significant contributions to the specialty through leadership and teaching.

“Mark is the quintessential practitioner of dermatology,” says a colleague who has known Dr. Holzberg since medical school. “Simply put—he is outstanding.” This well-rounded Atlanta-based private practitioner, volunteer teacher, nail expert, and impassioned advocate for the specialty is highly regarded. Another colleague calls Dr. Holzberg “one of the finest, most intelligent dermatologists in the private practice of our specialty.” Yet another calls him “a key member of Emory’s outstanding volunteer clinical faculty and one of our most valued teachers, and the consummate community physician who gives constantly of his talent and enthusiasm for dermatology on a daily basis.”

Dr. Holzberg chose to stay in Atlanta after completing medical school and then his residency at Emory University School of Medicine 30 years ago. His clinical practice in the Atlanta metropolitan area remains the focus of his vibrant and multifaceted career because of the value he places on the relationships he builds with his patients. He is a volunteer teacher of medical students and residents at Emory, and an internationally recognized expert in nail disease who runs the Nail Clinic that he founded 30 years ago at Grady Hospital—a public hospital in the Emory system where he is also an attending dermatologist. Dr. Holzberg teaches at dermatology meetings and has co-authored a seminal textbook and chapters on nail diseases. He finds time to contribute to the dermatology community (including the presidency of local and regional organizations, and meetings with legislators and lobbyists). “The more I do, the more I get back in satisfaction and joy,” he says.

Dr. Holzberg had his first contact with the specialty when a dermatologist visited the medical school to talk to students. He was hooked. “I am visually oriented, and not only is pattern recognition such a neat feature of dermatology, but these patterns could potentially be a window to the health inside the body.” Dr. Holzberg also appreciated the variety that dermatology offers in content (medical dermatology, surgical dermatology, dermatopathology, etc.) and in the broad age range and treatment needs of patients.

Dr. Holzberg’s enduring focus on nails began during his Internal Medicine rotation at Grady Hospital in medical school. The attending physician asked everyone to choose a single feature to evaluate on every patient. Dr. Holzberg chose nails, which led to an observation and discovery about a condition called Terry’s nails and ultimately a paper in The Lancet. He pursued this fascination with nails during his residency, then started the nail clinic at Grady Hospital. There was little formal education about nails then, and Dr. Holzberg deeply appreciated the guidance of two mentors—Dr. Robert Baran in France and Dr. Richard Scher in the U.S.—with particularly challenging patients.

Dr. Holzberg delights in sharing the joys he finds in his practice, which includes children and grandchildren of many of his early patients. He works to maintain an environment that gives his patients and staff a sense of confidence and security. “When you give some, you get back so much more.”

“Dermatology gives me the opportunity to have these special relationships,” Dr. Holzberg asserts. “I don’t think I will ever retire from dermatology!”
rather than dermatomal, corresponding to embryologic segments called facial placodes and prominences. Mathes discussed the findings that should prompt workup for SWS.

Pyogenic granulomas (PG) arising in PWSs and sporadic PGs frequently reflect mutations in BRAF or RAS. Nodular lesions also contain the PWS-associated GNAQ mutation. Timolol is appropriate to try off-label. The gel-forming solution adheres best; apply it twice daily. Mathes finds moderate efficacy, but uses excision and curettage if symptoms are severe. Propranolol, FDA-approved 1 year ago for treating infantile hemangiomas (IH), is now first-line treatment. Timolol is frequently effective for smaller, more superficial lesions. Timing is critical for both, Mathes emphasized—the earlier the better, and optimally beginning at 4–8 weeks.

Skin-colored, Lymphatic malformations—cystic hygromas and lymphangiomas—are now known to be caused by a somatic mutation in the P63/KC gene, producing increased signaling and growth of lymphatic tissue. The mTOR growth-regulating pathway is downstream, making sirolimus a therapeutic option with topical application for more localized disease (but use cautiously in children). Mathes described benefits, and also noted appropriate laser use.

Blue, Congenital hemangiomas. These are fully formed at birth, then some involute. They were just discovered to be caused by somatic activating mutations in a version of the GNAQ gene called GNA11.

Take-home. This “explosive understanding of the pathogenesis of vascular anomalies” should translate to better therapies. For now, you can cautiously add topical timolol and sirolimus to your toolbox. Lasers are very powerful tools but carry significant limitations.

Most important is recognizing that multidisciplinary care is key: plastic surgeons, ENTs, neurologists, ophthalmologists, radiologists, interventional radiologists, cardiologists.

Pediatric Lumps and Bumps

Moise L. Levy, MD

Introduction. Neonatal lumps and bumps may represent the clinical signs of an underlying process that must be identified to enable an understanding of significance and management. The differential diagnosis is very broad—infec tious, developmental, inflammatory, hamartomatous, and benign or malignant tumor. Dr. Levy presented illustrative cases from this range and highlighted respective issues, challenges, and concerns.

Cases. Levy discussed identifying and treating subcutaneous fat necrosis of the newborn, and the need to monitor for potential hypercalcemia for 6 months. An asymptomatic papule over the midline of the posterior scalp, present since birth, was imaged and diagnosed as sinus pericranii. A hair collar sign—a congenital ring of dark hair often surrounding a midline scalp nodule—is suggestive of underlying cranial dysraphism, but the co-presence of another vascular anomaly can indicate the need for a higher level of concern for something deep. Levy presented other developmental anomalies as well: a 4-month-old male with a treatment-unresponsive rash surrounding an umbilical nodule that was actually a urachal remnant and thus draining urine; and a 3-year-old girl with an inflamed upper chest nodule (present since birth) identified as a branchial cleft remnant. Many “blue-berry muffin” infants with biopsy-diagnosed cutaneous Langerhans cell histiocytosis clear spontaneously, but some progress to fatal multisystem disease that suddenly appears several years later. An approach is needed for predicting ultimate outcome.

Summing up. “The ultimate decision is how to proceed.” If you don’t know what it is—biopsy it. But go no further. If it is in the midline or over a fusion line—which points to developmental pathology—image it first, then biopsy if necessary and appropriate. Levy noted that “it is our responsibility to distinguish between benign and malignant lesions,” listing the characteristics that should raise suspicions and concluding that “we are never faulted for biopsying a suspicious lesion.”

Newborn Lumps and Bumps

- Single or multiple; might not be helpful variable
- Regular or irregular; might not be helpful variable
- Be suspicious
- Midline or over fusion lines: developmental
  - Imaging: MRI, U/S
- Responsibility to distinguish benign from malignant
  - Rapid/progressive growth, ulceration, fixation, >3cm (firm)
- Biopsy

MINI-SYMPOSIUM: CPC SESSION

Medical Dermatology

Lindy P. Fox, MD

Case 1. A 45-year-old Chinese man presented with a 6-month history of painful nodules on his lower legs, fever, chills, and night sweats. His history included PPD positivity, and thrombophlebitis more recently. The pathology report had pointed to a medium-vessel infiltrate with neutrophils, with features suggestive of polyarteritis nodosa (PAN). “This case is a great example of how to approach the differential diagnosis of nodules on the legs when the pathology shows inflammation around a vessel.” Dr. Fox explained that it does show an arteritis, but due to nodular tuberculosis, not to PAN. (id describes a secondary immunologic reaction to circulating antibodies or activated T cells directed against microbial antigens derived from nonliving organisms.) She noted that nodular tuberculosis resembles PAN because they both result in vasculitis of medium-sized vessels at the dermal-subcutaneous interface, then explained how to identify the differences between them—critical for treatment. Cutaneous PAN requires immunosuppression or disease-modifying therapy while nodular tuberculosis requires 3–4 drug tuberculosis therapy (which produces rapid improvement).

<table>
<thead>
<tr>
<th>cPAN vs. Nodular Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papulonodules on the legs</td>
</tr>
<tr>
<td>Histopathology: dermohypodermal junction</td>
</tr>
<tr>
<td>- Muscular walled artery</td>
</tr>
<tr>
<td>Evaluate for associated infections/medications</td>
</tr>
<tr>
<td>Evaluate for APLA</td>
</tr>
<tr>
<td>Treat with immunosuppression</td>
</tr>
<tr>
<td>- ? Role for anticoagulation</td>
</tr>
<tr>
<td>Papulonodules on the legs</td>
</tr>
<tr>
<td>Histopathology: dermohypodermal junction</td>
</tr>
<tr>
<td>- Muscular walled artery OR vein</td>
</tr>
<tr>
<td>PPD or quantiFERON® Gold positive</td>
</tr>
<tr>
<td>Treat with 3–4 drug therapy (RIPE therapy)</td>
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</tbody>
</table>
Case 2. A 46-year-old woman with a history of metastatic anal SCC “in remission” came to the ER with palpable purpura, some coalescing and forming overlying hemorrhagic bullae and a lesion of palpable purpura—the primary lesion—on the lateral aspect of her foot. Biopsy showed findings consistent with leukocytoclastic vasculitis, and a direct immunofluorescence indicated deposition of perivascular IgA. Although the workup for systemic vasculitis was negative, the CT scan revealed new metastatic nodules (in lungs, liver, and lymph nodes). Fox discussed the prognostic significance of IgA in paraneoplastic vasculitis. In all-comers with paraneoplastic vasculitis, two-thirds of the malignancies are liquid, one-third are solid. But the presence of IgA in vasculitis reverses this ratio. Compared to Henoch-Schonlein purpura (HSP) in children, in adults with IgA vasculitis the lesions are more necrotic and hemorrhagic, a clear infectious trigger is less likely, joint symptoms are worse, renal sequelae are more common, and life-threatening sequelae are more likely. Thus with leukocytoclastic vasculitis, Fox always does a biopsy for direct immunofluorescence to look for IgA. Other than looking for recurrence if there was a previous cancer, how to search for malignancy is not clear-cut but Fox always includes an age-appropriate malignancy screen.

Paraneoplastic Vasculitis

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leukocytoclastic (45%)</td>
<td>• Hematologic (63%)</td>
</tr>
<tr>
<td>(36.7%)</td>
<td>– MDS (32.3%)</td>
</tr>
<tr>
<td>• Polyarteritis nodosa</td>
<td>– Lymphoid (29.2%)</td>
</tr>
<tr>
<td>(36.7%)</td>
<td>• Solid tumor (36.9%)</td>
</tr>
<tr>
<td>• Wegeners (6.7%)</td>
<td>– GU (13.8%)</td>
</tr>
<tr>
<td>• Microscopic polyangiiitis</td>
<td>– GI (10.8)</td>
</tr>
<tr>
<td>(5%)</td>
<td>• Lung (7.7%)</td>
</tr>
<tr>
<td>• HSP (5%)</td>
<td></td>
</tr>
</tbody>
</table>

IgA Vasculitis in Adults

vs HSP in Children

• Lesions more necrotic or hemorrhagic
• Less likely to have antecedent infection
• Increased joint symptoms
• Acute/life threatening
  – GI perf/bleeding, alveolar hemorrhage
• Renal sequelae more common
  – Acute renal disease (30–80%)
  – Moderate to severe chronic kidney disease (30%)
  – ESRD (11%)
• Requires more aggressive treatment
  – No evidence that immunosuppression improves outcome
• Relapse common (20%)

Association with Malignancy

• DIF with IgA (92%): 67% skin, 33% renal
• Solid tumors (61%): NSCLC (25%), prostate (16%), renal (6%)
• Hematologic malignancy (39%)
  – Myeloma (16%), non-Hodgkins lymphoma (9%), Hodgkins disease (6%)
• HSP presented within 1 month of cancer diagnosis in 55%

Conclusions

• With purpuric papules, perform a DIF
• If IgA is present, consider the diagnosis of IgA vasculitis
• Associated with worse renal involvement
• Malignancy screen
  – Base on history and physical
  – Age-appropriate malignancy screen
  – Suspect recurrence or metastases if a patient has a history of malignancy
  – Look for malignant transformation of indolent disease


Case 1. A 68-year-old man, otherwise healthy, came in 2 years ago with a very large squamous cell carcinoma (SCC) and indurated nonfunctional lower lip. He could close his teeth but not his mouth. Pathology showed a well-differentiated SCC with no perineural invasion, and no note of depth. Dr. Bordeaux decided to rebuild the patient’s lower lip with tissue from his cheeks, harvested via a full-thickness cut all the way through both sides. By 4 weeks after surgery, the patient had regained the ability to smile, eat, and pucker his mouth. Because there was no evidence of perineural invasion and Bordeaux was confident in his margins, observation—seen every 3 months—was chosen over radiation. He is doing okay.

Case 2. An older woman presented with “an unbelievably huge” disfiguring basal cell carcinoma (BCC) above her left eye, wanting to look well for her granddaughter’s relatively imminent wedding. Other than exceptional size, tumor histology was unremarkable. Bordeaux did no presurgical imaging for possible penetration of bone or muscle because results are highly unreliable and would not change his management. He began with a Mohs procedure, alerting his patient that if he discovered the need to enter the eye orbit, surgery would be completed in the OR. The inside of her eyelid turned out to be intact, simplifying reconstruction. For fixation, Bordeaux rejected granulation (the wedding was too soon) and skin flap (not enough skin to move over) options. A skin graft would die if placed over the bone. A galeal muscular flap was incised and rotated into place and a full thickness skin graft was placed over the muscle flap. The patient healed in time for the wedding, with excellent cosmetic results.

Case 1.

Case 2.
Pediatric Dermatology
Erin F. D. Mathes, MD

Case 1: Term 5-day-old girl with PHACE syndrome. Although completely flat, the larger caliber arborizing telangiectasias are tell-tale for IH. She was at risk for PHACE syndrome (Posterior fossa malformations, Hemangiomas, Arterial, Cardiac, and Eye abnormalities), which her work-up confirmed. Her MRA detailed the abnormal blood vessel feeding her brain. The echocardiogram documented aortic stenosis. She had hearing loss and micro-ophthalmia on the affected side.

Our concern with maintaining perfusion to her brain left us unsure about the safety of propranolol, the treatment of choice. Stenosis of a major cerebral vessel and aortic stenosis are both stroke risk factors. Propranolol would modify her mean arterial pressure, exacerbating this risk. Our cardiologists and neurologists believed her defects were not substantial enough to defer treatment, so we began with low-dose propranolol, increasing it very gradually with continuous blood pressure and heart rate monitoring. In several weeks her hemangioma looked better, her eye was more open, but her ear was ulcerated (losing 50% of the helical cartilage). Switching her to prednisone only impaired her healing, and ulceration progressed. In retrospect, I believe the distribution of her abnormal blood supply would have caused this damage in any case. In general we do treat patients with PHACE with propranolol, using added caution and care. Anyone lacking regular experience prescribing propranolol should refer a patient with PHACE syndrome to someone with experience.

Follow-up: Did Propranolol Do This?
Before Propranolol
After Propranolol

Case 2: Term 5-day-old girl with fat necrosis of the newborn. This afebrile infant had red fluctuant nodules on her arms after a prolonged labor with heart decelerations prior to a forceps delivery. Concern that the nodules were infectious kept her in the hospital. Blood and tissue cultures were negative. Histopathology showed some inflammation in the dermis, with fat globules off to the side showing a predominantly neutrophilic (rather than histiocytic) infiltrate, and needle-shaped calcium clefts. The largely neutrophilic infiltrate is somewhat atypical, but we have seen several similar cases. This might reflect very early timing of the biopsy, when the fat is still liquifying. This diagnosis can also be confirmed with a fine needle aspiration, an option for anyone hesitant to do a biopsy. As her calcium was slightly elevated, we monitored her calcium weekly, then monthly.

Subcutaneous Fat Necrosis of the Newborn
• PMH
  – Prolonged labor with decelerations prior to forceps delivery
  – No fever after delivery
• Work-up
  – Biopsy with fluctuant material
  – Culture of pus negative
• Histology
  – The calcium is 11.8 mg/dl (normal 7.9–10.7 mg/dl)
  – What monitoring and for how long?

Dermatopathology
Philip E. LeBoit, MD

Case 1. Morphology: Dr. LeBoit showed a woman with minute facial papules covering her face all the way to her hairline. They were extremely difficult to detect without careful lighting. Before showing the biopsy slides, he elicited thoughts from others based on the morphology. One attendee, noting the predominantly dermal nature of these tiny nodules, found herself thinking about infiltrative (eg, scleromyxedema) or neoplastic (eg, epithelial adnexal tumors) processes. Another mentioned trichodysplasia, seen in transplant patients due to polyomavirus infection. LeBoit added Burt-Hogg-Dubé syndrome. Biopsy: There was no obvious tumor. Scanning magnification showed a mostly lymphocytic

Term 5-day-old Girl With Segmental Infantile Hemangioma
• At high risk for PHACE: admit for PHACE work-up
• Propranolol is treatment of choice
• Diagnosis: Segmental infantile hemangioma \(\rightarrow\) PHACE syndrome
• Found to have intracranial hemangiomas and anomalous vasculature, coarctation of the aorta, hearing loss, micro-ophthalmia

Can you give her propranolol safely?
inflammatory infiltrate concentrated around the upper part of the hair follicle and obscuring the junctional zone. Thus the minute facial papules represent *frontal fibrosing alopecia with vellus hairs on the skin of the face*. When this scarring alopecia occurs in vellus follicles, it is not easily perceived as alopecia but instead appears to be tiny follicular papules. The histopathology of frontal fibrosing alopecia and lichen planopilaris are practically indistinguishable, and one giveaway here is the concurrent loss of eyebrow hair.

**Balance/imbalance and Tregs.** “We think that understanding this balance will be crucial to elucidating the pathogenesis of various autoimmune and inflammatory diseases that we see, and help us develop better treatment strategies.” Therapeutic strategies until now have all aimed to suppress proinflammatory conventional T cells. Those now entering the pipeline will focus on improving Treg function to enhance the body’s ability to suppress and regulate inflammation. Tregs are the current focus because they are by far and away the most well-accepted and well-characterized immune regulatory cell. The synthesis of mRNA from the gene for this CD4+ (helper) T cell is controlled by the transcription factor Foxp3. Tregs are normally derived in the thymus but can be derived elsewhere. Mice and humans born with defective Tregs die during infancy of fulminant autoimmunity—with the skin being one of the primary organs affected—unless this cell population is replaced via bone marrow transplant. Rosenblum has been studying Tregs in mice and in humanized mouse models, and discussed the basics of what he has learned so far.

Notably, the skin is “one of the largest homes” for these regulatory T cells. Their stable numbers account for ~10% overall of the body’s total CD4+ population, but are ~50–60% of the skin’s resident CD4+ population. Rosenblum described the technique he used to track down where in the skin these Tregs reside, discovering their home in the regenerative follicular epidermis in both mouse and human skin. His lab pioneered a novel technique, using a 2-photon microscope, that allows researchers to observe the normal activities of normal Tregs in real time. “They tend to be dynamically active, preferentially localizing around hair follicles (HFs).” Tregs are enriched in the head and neck region compared to the trunk and extremities. And they rarely migrate out of healthy noninflamed skin.

**Tregs and the hair follicle.** Rosenblum had learned that Tregs elsewhere have tissue-specific functions in addition to suppressing inflammation and maintaining immune homeostasis, and was intrigued by genetic data from Angela Christiano’s probing of alopecia areata. The combined results of her genetic analyses “were basically a Treg hit.” And after a small study in 2014 that treated 5 alopecia totalis patients with low-dose IL-2—which augments Treg numbers—induced partial hair growth in the 4 patients whose Treg counts had increased, Rosenblum and his group began exploring the role of Tregs in HF biology. They found that Tregs reside in the bulge region of the HF, where the HF stem cells (HFSs) also reside, presumably protecting the stem cell niche from inflammatory mediators. Then Rosenblum demonstrated the specialized local role of Tregs in maintaining normal stem cell behavior, and thus the hair cycle. His work made it clear that without Tregs, the HFSs cannot maintain their stemness and are unable to proliferate and differentiate to form the different layers of the HF and create the new anagen follicle. “So we think that deficient or dysfunctional Tregs may be one of the main things happening in alopecia areata and...”
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, opthalmic, 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.
Reference: 1. JUBLIA [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use JUBLIA safely and effectively. See full prescribing information for JUBLIA.

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, ophthalmic, 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 rabbits. 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).

JUBLIA is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.

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U.S. Patents 8,039,494; 7,214,506

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Manufactured by:
Valeant Pharmaceuticals International, Inc., Laval, Quebec H7L 4A8, Canada

Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA

Manufactured for:
Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA

Valeant Pharmaceuticals International, Inc., Laval, Quebec H7L 4A8, Canada
potentially the cicatricial alopecias. An immune cell population that lives in our skin, residing around hair follicles, plays a major role in the fundamental biology of the hair follicle and hair follicle cycling.” Rosenblum has now elucidated the molecular steps comprising this process, opening up potential therapeutic targets.

**Tregs: Summary**
- Tregs comprise a large percentage of CD4+ T cells in both mouse and human skin
- In the steady state, they are a relatively stable resident population in both mouse and human skin
- Tregs localize to hair follicles in both mice and humans
- Tregs are required for:
  - hair regeneration
  - anagen induction
  - bulge HF stem cell activation
  - HF stem cell differentiation

### Th2-targeting drugs
Experimental drugs target Th2 activity at various points in the pathway. One drug inhibits TSLP (thymic stromal lymphopoietin), a cytokine expressed by damaged epithelial cells that promotes transformation of naïve T cells to Th2 cells, and then their return to the skin. There are drugs inhibiting the signaling of Th2 cytokines (IL-4, IL-13, IL-31). Other targets are the prostaglandin D2 receptor on T cells enabling their recruitment to the skin, and even IgE. Beck summarized dupilumab trial results: rapid clinical improvement, including greatly reduced itch, with reductions in depression and anxiety. An anti-IL31 drug has been approved for canine AD, with “really revolutionary” impact. Beck spoke of PD4 inhibitors to counter the general inflammatory component, noting the recently approved (for 2 years old and up) topical PDE4 inhibitor crisaborole for the mild-to-moderate pediatric population. The current interest in tofacitinib—a JAK (Janus kinase) inhibitor used to treat psoriasis—reflects the increasing therapeutic relevance of JAK inhibitors in human disease.

### New Therapies for Atopic Dermatitis

**Lisa A. Beck, MD**

**Background.** AD is the most common inflammatory skin disease, affecting ~20% of children and at least 6–9% of adults, yet by early 2017 there was still no approved systemic treatment. Approval of the very first one—dupilumab—was anticipated by the end of March*, and new candidates (topical, oral, and injected) are in the pipeline. Dr. Beck sketched the current view of AD pathogenesis, then discussed “the finally exciting area of new therapies for AD.”

**Pathogenesis.** AD is not either immune- or barrier-mediated, but a complex disorder caused by the interaction of both components. The skin is leakier in both directions, more reactive to the inflammation. Beck characterized the cytokine profile that evolves from clinically normal-appearing skin (which is already affected), to acute lesions, to chronic lesions. It does not switch from Th2 to Th1 cytokines, but adds Th1 to the predominantly Th2 mix. AD is actually the atopic disease with the highest level of Th2-derived serum biomarkers.

**MINI-SYMPOSIUM: INFLAMMATORY DISEASES**

**Systemic Th2 Targeted Therapies (≥ Ph2)**

1. Anti-TSLP
2. Dual Anti-IL-4/IL-13
3. Anti-IL-13
4. Anti-IgE
5. Anti-IL-31 or IL-31R
6. PGD2 Receptor (CRTh2) Antagonists

**Conclusions**

- Last FDA-approved therapy for AD had been 15 yrs ago—until crisaborole approved 12/14/16 and dupilumab approved 3/28/17
- Many new topical and systemic Rx’s are in the pipeline. The only ones (now approved) that have reported Ph3 data are:
  - **Dupilumab**—biologic targeting IL-4 Receptor, alpha chain (moderate-severe AD)
  - **Crisaborole**—topical PDE4 inhibitor
- A major focus is on inhibiting components of the Type 2 (Th2) pathway
- Whether there are AD endotypes that might respond better to Th17 or Th22 antagonists is currently being explored
- A number of more general anti-inflammatory therapies show promise (PDE4 inhibitors, JAK inhibitors, H4R inhibitors)
- Whether a purely anti-itch approach will sufficiently improve the disease has yet to be tested
- Whether targeting skin barrier disruption or *S. aureus* colonization will be effective strategies has also not been tested

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www.dermatologyfoundation.org
Conclusion. With the development of new treatments approved for young children, investigators are hopeful that their use may decrease the progression to food allergy and airway disease. Starting even earlier, Beck stated that applying petrolatum daily to the skin of at-risk infants for the first 6 months of life reduces the appearance of AD by 62%. Dr. Guttman’s lab reported that petrolatum enhances antimicrobial peptide production and other innate immune genes, as well as the expression of key barrier proteins, suggesting this might be the mechanism by which early application of moisturizers may prevent AD development.

*Dupilumab was subsequently FDA-approved on March 28.

Vasculitis: What Have We Learned Recently?
Lindy P. Fox, MD

Introduction. Dr. Fox discussed the different diagnostic groupings of vasculitis, clarifying differences and overlaps both within and between them. She noted the important gains in recent knowledge (and any implications for diagnosis and treatment), and continuing puzzles. Throughout, Fox emphasized the greatly increased level of complexity that is clearly emerging, and characterized the focus her thoughts and questions have been taking on further understanding these inflammatory diseases.

PAN. Fox laid out the clinical and diagnostic basics of cutaneous and systemic disease, which both spare the lungs. She illustrated her clinical pearls with cases, and discussed both digital necrosis and the role of thrombosis in depth. She emphasized “the complex interplay between vascular inflammation and vascular thrombosis.” Fox also explored lymphocytic thrombophilic arteritis and macular lymphocytic arteritis. She discussed ADA2 deficiency (adenosine deaminase 2 is an enzyme involved in purine metabolism and maintenance of the immune system) at length, and her speculation that “ADA2 deficiency may be driving the variation in presentations of PAN.”

ANCA-associated vasculitides. The vasculitides involving ANCAs (anti-neutrophil cytoplasmic antibodies) are microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. They overlap, and all cause pulmonary and renal disease. ANCAs are identified through either indirect immunofluorescence or ELISA. Fox discussed the intricacies of what/how to test and what results indicate, including findings for anti-PR3 (proteinase-3) antibodies and anti-MPO (myeloperoxidase) antibodies, adding that atypical results may point to drug-induced disease. She discussed the growing

**Polyarteritis Nodosa**
- Critical to demonstrate inflammation around medium-sized vessels at the dermal/SQ interface
- Digital necrosis is due to vasculitis of medium-sized vessels feeding the digits
  - Probable role of thrombosis
  - Consider anticoagulation
- Related diseases
  - Lymphocytic thrombophilic arteritis
  - ADA2 deficiency

**ANCA-Associated Vasculitis Syndromes**
- Microscopic polyangiitis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis
- Features of these 3 diseases overlap, but pulmonary hemorrhage and necrotizing glomerulonephritis are characteristic of all 3
- Other ANCA+ diseases: SLE (20%), RA, cryoglobulinemia, Goodpasture’s (20%)

**Pearls**
- These are “pauci-inflammatory”
  - little to no complement or IC deposition around vessels with immunofluorescence
- Usually PR3+ or MPO+, but not both
  - If both are positive, think exogenously-induced vasculitis
- ANCA is false+ in ~5% population (does not increase with age)

**Implications for Therapy**
- Deplete B cells
  - Rituximab: approved in combination with corticosteroids
- BAFF inhibitors to target autoreactive B cells
  - Belimumab, blisibimod: in clinical trials
- C5a receptor blockade: in clinical trials

(Continued on page 18)

DF Research Award Recipients: Where Are They Now?

The Dermatology Foundation’s mission is providing the research support that helps develop and retain tomorrow’s teachers and researchers in dermatology, enabling advancements in patient care. A look at the faculty for this year’s **DF Clinical Symposia** is a clear indication of success. The faculty are all chosen for outstanding expertise in their respective areas. Of this year’s 14 speakers, nine (9) began their careers with DF funding.

Lisa A. Beck, MD Moise L. Levy, MD
Jean L. Bologna, MD Henry W. Lim, MD
Jeremy S. Bordeaux, MD, MPH Erin F. D. Mathes, MD
Lindy P. Fox, MD Michael D. Rosenblum, MD, PhD
Jordan W. Tappero, MD, MPH, RADM

The Foundation is deeply grateful to all of the specialty experts who contributed their time to the 2017 DF Clinical Symposia.
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.

**Platinum Benefactor**
($200,000 or more)

- Abbvie
- Galderma
- Unilever
- Valeant

**Gold Benefactor**
($100,000 or more)

- Sun Dermatology

**Silver Benefactor**
($50,000 or more)

- Amgen Inc.
- Lilly USA, LLC
- Merz North America, Inc.
- Novartis
awareness of B-cell participation in these diseases, noted significant co-morbidities (especially infection), and stressed here too “the complex interplay between vasculitis and thrombosis.”

### ADA2 Deficiency

- Think about it:
  - Early onset “PAN”
  - Familial “PAN”
- Screening
  - ADA2 levels
  - Immunodeficiency workup (B cells, Immunoglobulins)
  - Look for end organ damage (brain, PNS, kidney, GI)
- Treatment
  - TNF-alpha blockade, HSCT, tocilizumab, ? Fresh frozen plasma
- Are MALTA/PAN all versions of ADA2 deficiency or similar process?

### Vasculitis: Summary Thoughts

- PAN and related diseases
  - Illustrating the complex interplay between genetics, inflammation, and thrombosis
  - ADA2 deficiency may be a window into deeper understanding of vasculitic diseases
- ANCA-associated vasculitis
  - Neutrophils, B cells, and complement all play a role in pathogenesis
  - Be aware of comorbidities, especially vascular and infectious

### Phototherapy for Inflammatory Diseases in 2017

**Henry W. Lim, MD**

**Introduction.** Narrowband UVB (NB-UVB) is that subset of the ultraviolet B spectrum centered at roughly 311 nm. UVA1—a more recent addition to the phototherapy toolbox that penetrates the dermis more deeply than UVB can—involves the longer spectrum of ultraviolet A (340–400 nm). Dr. Lim provided a therapeutic overview and guidance for each of them, including existing support from clinical trials.

**NB-UVB.** Among the more common indications, NB-UVB for *psoriasis* is an important alternative to the biologics that is almost as effective as PUVA—but with far less side effects and much easier to administer. It is the first-line treatment for widespread *vitiligo*, commonly used for patch-stage *cutaneous T-cell lymphoma*, and helpful with *atopic dermatitis* and *generalized pruritus*.

### NB-UVB Protocol

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Initial UVB Dose (mJ/cm²)</th>
<th>Dose Increase per Treatment</th>
<th>Maximum Dose* (mJ/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>150</td>
<td>10–15%</td>
<td>3000</td>
</tr>
<tr>
<td>II</td>
<td>150</td>
<td>10–15%</td>
<td>3000</td>
</tr>
<tr>
<td>III</td>
<td>250</td>
<td>10–15%</td>
<td>3000</td>
</tr>
<tr>
<td>IV</td>
<td>250</td>
<td>10–15%</td>
<td>3000</td>
</tr>
<tr>
<td>V</td>
<td>400</td>
<td>10–15%</td>
<td>3000</td>
</tr>
<tr>
<td>VI</td>
<td>400</td>
<td>10–15%</td>
<td>3000</td>
</tr>
</tbody>
</table>

*maximum dose for face

### Other Indications

- Polymorphous light eruption
- Urticaria
- Morphea
- Lichen planus
- Pityriasis rosea
- Pityriasis lichenoides chronica

### Summary

- Can be considered as the first line treatment for sclerodermoid conditions
- Well tolerated
- Induces skin pigmentation
- No significant side effects have been reported
- Long-term side effects: unknown

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**2017 DF Clinical Symposia Faculty Disclosures (Part I)**


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Although less commonly used for *polymorphous light eruption*, Lim finds it particularly helpful for “hardening” patients’ skin (3 times weekly for 5 weeks) before seasonal exposure. “In our experience, roughly 80% of patients respond well,” a rate comparable to PUVA. Lim uses NB-UVB for *chronic idiopathic urticaria* that is insufficiently controlled with antihistamines, before moving to systemic immunosuppressants. It has been used for *morphea* if UVA1 is not available. Lim also noted use for *lichen planus, pityriasis rosea,* and *pityriasis lichenoides chronica.* Lim explained the protocol, based on the MED.
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“The DF Drives our Field Forward”

Anthony M. Rossi, MD

surgeon at Memorial Sloan Kettering Cancer Center and an Assistant Professor of Dermatology at Weill Cornell Medical Center in New York City.

He has been part of the Foundation’s Leaders Society (LS) since 2015, joining just after completing his Mohs fellowship at Sloan Kettering, and is recognized as one of the DF’s Young Leaders, LS members who joined within five years of their residency.

Taking his commitment one step further, Dr. Rossi volunteered to participate in the national LS campaign in downstate New York to recruit dermatologists who are not yet DF members. His fellowship mentor at Sloan Kettering taught him about the DF’s critical role in launching the academic careers of talented new teachers and investigators in all areas of dermatology, and the profound impact this has on scientific progress. Now he gives his time to share this information one-on-one with other dermatologists, and encourages them to support the DF.

Dr. Rossi gives to the DF because it effectively strengthens the specialty that gives him so much. Dermatology has enabled him to combine his interests in skin cancer, noninvasive imaging, and lasers and light applications. He enjoys being able to see a diverse range of patients at Memorial Sloan Kettering. His research activities—addressing noninvasive treatment and imaging for skin cancers—are stimulating. Dr. Rossi has also found volunteering to provide dermatologic care in remote areas of Ghana, Botswana, Kenya, and Tanzania to be uniquely rewarding.

“The DF supports and promotes scientific endeavors—that’s what really drives our field forward,” Dr. Rossi points out. “It’s a great cause to be part of.” As DF members “we are helping our colleagues become scientific leaders. They, in turn, are helping the field move forward and expand our ability to care for our patients.”

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