Roundup on Cosmetic Dermatology
WINTER 2006

TOPIC HIGHLIGHTS:
- Evolving Clinical Roles for LED, Fillers, Botulinum Toxin
- Combining New and Traditional Techniques Provide Maximal Benefits to Patients
- Laser Technique Zaps Focal Areas of Excess Fat
- Is a Cosmetic Practice for You? Consider These Tips
- Ferulic Acid
- Examine Patient Motivation For Cosmetic Surgery
- Fillers: Beyond the Mythic ‘Ideal’
- Injectable Silicone Called a Safe, Elegant Filler
- Pain-Relief Options Available For Cosmetic Procedures

GUEST EDITORS:
David J. Goldberg, M.D., J.D.
Clinical Professor of Dermatology
Director, Laser Research and Mohs Surgery
Mount Sinai School of Medicine
Adjunct Professor of Law
Fordham Law School
New York, N.Y.
Director, Skin Laser & Surgery Specialists of New York/New Jersey
Hackensack, N.J.

Christopher B. Zachary, F.R.C.P.
Chair and Clinical Professor
Department of Dermatology
Co-Director, Dermatologic Surgery and Laser Center
University of California at Irvine

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Please see brief summary of full Prescribing Information on adjacent page.

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University of California at Irvine

President, Elsevier/IMNG
Alan J. Imhoff

Vice President, Medical Education & Business Development
Sylvia H. Reitman, M.B.A.

Contributing Writer
Charles Bankhead

Program Manager, Medical Education
Malika Wicks

National Account Manager
Cheryl J. Gromann

Art Director
Elizabeth Lobdell

Production Manager
Yvonne Evans

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Evolving Clinical Roles for LED, Fillers, Botulinum Toxin

The field of cosmetic dermatology continues to explore, expand, and define the clinical utility of many commonly used tools, including light-emitting diode (LED) therapy, fillers, and botulinum toxin.

In the United States, LED therapy traditionally has consisted entirely of yellow light. The light has been used as an adjunct to laser therapy and light therapy for treatment of a variety of conditions. Recently, other colors of LED therapy have become available, including blue, red, and near-infrared.

“The impact of LED therapy on the skin is related to its effect on basic cellular structures,” said David J. Goldberg, M.D., J.D., Clinical Professor of Dermatology and Director of Laser Research and Mohs Surgery at Mount Sinai School of Medicine in New York City. “Each color of LED light penetrates to a different depth in the skin and has a potentially different effect on different portions of the cell structure. Thus, it should come as no surprise that different LED therapies are optimally used for different applications. Sometimes, the best approach is to use more than one LED therapy for the same patient.”

The role of LED therapy has yet to be fully defined, Dr. Goldberg added, but the modality’s popularity results from its ease of use, the ability to use it on people with all ethnic skin colors, and the lack of pain resulting from treatment.

Recently Dr. Goldberg spearheaded a multicenter United States/United Kingdom study that explored the roles of combining 633-nm and 830-nm LED therapy for the treatment of early photaged skin: “The combined treatment led to overall improvement in the quality of skin, with electron microscopic ultrastructural changes suggesting the formation of new collagen after treatment.” Traditionally, collagen fillers have been the treatment of choice, but over the past few years newer fillers have entered the market to expand treatment options. The newer fillers consist of hyaluronic acid, poly (L-lactic acids), and calcium hydroxyapatite. Each of the fillers has advantages and disadvantages, and the scope of application for individual products has yet to be defined. In some cases, different types of fillers are used together to achieve desired results.

“The era of fillers is just beginning in the United States,” said Dr. Goldberg. “If you look at Europe, many more short-acting, intermediate-acting, and long-acting fillers are available than in the United States.” Over the next several years, the United States can expect to see a variety of hyaluronic fillers. Some will be shorter-acting and others will last longer than currently available agents.

Development of new fillers continues, and clinical options in the United States should continue to evolve in the future, added Dr. Goldberg.

The role of botulinum toxin in cosmetic dermatology in the United States continues to expand. At present, the material is used to soften wrinkles around the forehead, eyes (crow’s feet), lower eyelids, lip, chin, and neck. Both botulinum toxin A and botulinum toxin B have been used in the United States, but botulinum toxin B is no longer readily available for cosmetic purposes, leaving cosmetic dermatologists with the Botox brand of botulinum toxin type A (Allergan Inc.). That could change in the future.

“Currently, US Food and Drug Administration sponsored studies are ongoing, involving the use of two newer types of botulinum toxin A,” said Dr. Goldberg. “These studies will lead to newer and potentially different botulinum toxins that can be offered to our patients.”

Dr. Goldberg has received funding for clinical grants from Photo Therapeutics, Cynosure, Inc., Neocutis Swiss Technology, Inamed Corporation, Thermage, Inc., and Cutera Inc. He is also a consultant to BioForm Medical Inc., Lumenis Ltd., and Juva Medical Inc. He discusses the off-label use of Mentor Corporation, Inamed, and Juva products.
SCULPTRA® is contraindicated in those individuals who have shown a hypersensitivity to any of its components. SCULPTRA® should not be injected in areas with active skin infection or inflammation. Avoid injection into the blood vessels.

The most commonly observed adverse event was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. Visible nodules, with or without inflammation or dyspigmentation, have also been reported. Other adverse events include immediate and transient injection-related events such as bleeding from the injection site, discomfort, erythema or inflammation, ecchymosis, and edema.

Please see brief summary on following page.
PRECAUTIONS

• No studies of interactions of SCULPTRA with drugs or other substances or implants have been made.
• The safety and effectiveness of SCULPTRA from clinical trials of SCULPTRA in non-Caucasians and women with human immunodeficiency virus are limited. Dermis® will conduct a post approval study in non-Caucasian and women with human immunodeficiency virus.
• The safety of using SCULPTRA in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied. Dermis® will conduct a post approval study to determine the likelihood of keloid formation and hypertrophic scars in patients with human immunodeficiency virus receiving SCULPTRA injections.
• The patient should be informed that he or she should minimize exposure of the treatment area to excessive sun and UV lamp exposure until any initial swelling and redness has resolved.

ADVERSE EVENTS

Adverse event data from four clinical studies that included 277 patients are summarized in Tables 1 & 2 below.

<table>
<thead>
<tr>
<th>INJECTION PROCEDURE</th>
<th>RELATED ADVERSE EVENTS</th>
<th>VEGA STUDY</th>
<th>AVERAGE DURATION (DAYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site</td>
<td>subcutaneous papule*</td>
<td>26(52%)</td>
<td>9(31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Subcutaneous papules refer to lesions of 5 mm or less, typically palpable, asymptomatic and non-visible. **Device-related adverse effect was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic and non-visible. Refer to ADVERSE EVENTS for details.

<table>
<thead>
<tr>
<th>PATIENT TREATMENT</th>
</tr>
</thead>
</table>
| For patients with an injection site reaction or bruising, injection site induration, injection site infection and delayed correction is needed. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of SCULPTRA occurs. The patient should be advised of the potential need for additional injection sessions at the first consultation.

STORAGE

SCULPTRA can be stored at room temperature, up to 30ºC (86ºF), DO NOT FREEZE. Refrigeration is not required.

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Bridgewater, NJ USA

1-800-633-1610

Pat. No. US 6,716,251

Prescribing Information as of August 2004.

Manufactured for: Dermis Laboratories A Division of Aventis Pharmaceuticals Inc.

1500 Westtake Drive

Bryan, TX 77801

USA

1-800-633-1610

Produced by: Gruppo Lepetit S.p.A. 20020 Lainate, Italy 02004 Dermis Laboratories

DERMIS®

The duration of the adverse events in Table 2 was not collected. The most common device related adverse effect was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. The study protocols did not include evaluation of treatment for subcutaneous papules, therefore, no information is available on how the papules were treated. In the VEGA study, the average onset of subcutaneous papules was 7 months after initial injection (range 0.3 – 25 months). Subcutaneous papules resolved spontaneously in 626 patients (24%) during the study. No information of onset and duration of papules is available from the Chelsea & Westminster study.

Treatment related adverse events, not included in Table 1 & 2, observed in clinical studies with a frequency of less than 5% were injection site bruising, injection site lesion, injection site bleeding, injection site induration, injection site infection and fever.

While looking ahead in anticipation of continued technologic advancement, cosmetic dermatologists should continue to make good use of the capabilities of older technologies, which still have much to offer.

“If people have extensive photodamage, they can see dramatic improvements with both traditional and current techniques,” said Christopher B. Zachary, M.D., Chair of Dermatology at the University of California, Irvine. “We should not forget about the real benefits of chemical peels, nor the significant benefits people might derive from dermabrasion. We should certainly not forget the excitement created about 10 years ago with the high-energy, short-pulsed CO₂ laser, typified by the UltraPulse (Lumenis Ltd.).”

Older technologies can still provide good cosmetic results, and Dr. Zachary continues to rely on some of the older technologies on a regular basis. However, he notes that “anything that causes dramatic improvement also has the potential to cause dramatic side effects, such as prolonged healing, persistent redness, delayed onset permanent hypopigmentation, and scarring.” Typical cosmetic dermatology patients today are unwilling to take time off from work or otherwise alter their normal routines and schedules to accommodate potential side effects of rejuvenation procedures.

Many of the newer devices that have become available in recent years combine modest cosmetic improvement with minimal downtime related to after-effects of treatment. That trend will likely continue in the future.

“I don’t know where we will be in 5 years, but I can guarantee that things will look very different,” said Dr. Zachary. “We are living in very exciting times. While the perfect device for facial rejuvenation does not exist at this point in time, there will indeed be new devices available to us in the near future.”

Current technology has much to offer in the way of nonablative rejuvenation. Devices such as the SmoothBeam (Candela Corp.), CoolTouch (CoolTouch Inc.), and ThermaCool (Thermage, Inc.) can tighten and rejuvenate the skin with considerably less downtime compared to older technologies, said Dr. Zachary.

Fractionated therapy with the Fraxel device (Reliant Technologies, Inc.) also has made inroads by providing the ability to rejuvenate skin with minimal surface damage. The 1550-nm device creates a myriad of three-dimensional areas of cylindrical damage affecting 5% to 10% of the skin surface. The cylinders of damage penetrate the skin to a depth of 200 to 400 microns, creating microthermal zones that rejuvenate the epidermal component of photodamaged skin, tighten the dermis, and induce significant improvement in acne scarring with a minimal amount of erythema and swelling and no exudate.

“We’re still in the early days with fractionated therapy, but I believe that fractionated therapy (treating only part of the surface of the skin with multiple microthermal zones), is as important to laser surgery as was the development of the selective photothermolysis and dynamic cooling, the latter protecting the skin during laser surgery,” said Dr. Zachary.

The intense pulsed light also has brought substantive benefits to cosmetic dermatology. The device selectively filters out light with a wavelength below that specified. The end result is the delivery of light that is well absorbed by pigment and blood vessels, leading to improved color, vascularity, and general tone of the skin.

The reduced skin damage associated with newer technologies does not mean that rejuvenation procedures have become trouble-free, Dr. Zachary cautions.

“It would be a mistake to think that these procedures can be performed without discomfort, without swelling, without redness,” he said. “Pret-
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• Aging Skin: Can we stop it? Can we repair it? What’s realistic?

• State of the Art Lecture: “How will the politics of cosmetic dermatology affect your practice in 2006?”

• Fillers and Botulinum Toxin Type A: A pragmatic look at the evidence for synergism in cosmetic dermatology.

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Combining Techniques
Continued from page 7

try much anything that’s going to give you any benefit is going to have some side effects, albeit on a temporary basis.”

Though cosmetic dermatologists have a leadership role in the use of rejuvenation techniques that are both safe and effective, they also have a responsibility to educate the public about the need to protect children from the potentially harmful effects of ultraviolet (UV) light (UVA and UVB). Dermatologists should lead the way in educating parents, teachers, and government officials about the need to provide children with adequate protection from UV light.

“Given what we know today, it is disturbing that approximately 90% of the population in the United States has had excessive sun exposure,” said Dr. Zachary. Besides the ultimate effects on patient health and quality of life, he points out that this “leads to millions of dollars in treatment costs annually for skin cancers and other conditions directly related to excessive sun exposure. It is imperative that our children get adequate protection. During childhood, we receive about 50% of our entire lifetime sun exposure.”

Continuing with the theme of responsibility, Dr. Zachary urged laser manufacturers to develop and distribute product information that is both accurate and well considered. Unsupported claims regarding technologic capabilities should be avoided in every case. When those claims get widespread distribution, physicians in general, and dermatologists in particular, are left with the responsibility for responding to unrealistic patient expectations created by misleading or inaccurate information.

“We can do very good work these days, and we can do it in a safe manner,” said Dr. Zachary. “But our expectations need to be carefully controlled, and that includes the expectations of physicians, of manufacturers, and particularly of the public.”

Dr. Zachary has nothing to disclose.

Laser Technique Zaps Focal Areas of Excess Fat

Laser lipolysis without fat suction appears safe and effective for the removal of small volumes of focal fat, according to data presented at the annual meeting of the American Society for Laser Medicine and Surgery.

Based on MRI, patients who underwent laser lipolysis alone showed an average of 17% reduction in fat, said Karen H. Kim, M.D., a dermatologist in New York. Those treated under the chin showed the greatest average loss (25%); other areas averaged a 13% reduction.

In this study, 10 patients were treated with laser lipolysis using a Nd-YAG laser (Cynosure Inc.), and 12 were treated with laser lipolysis and the Tri-Active therapeutic laser massage device (12 treatments). There were also 10 control volunteers. The patients had unwanted fat less than 120 cc in volume. Cynosure provided equipment and funding for the study.

Treatment involves the use of a 1,064-nm Nd:YAG laser with a 100-mm optic fiber and 1-mm microcannula. The low-power laser produces a photothermal effect when in contact with fat, Dr. Kim said. Treated fat was allowed to drain naturally in the patients. The Tri-Active device was used on 10 patients to facilitate drainage.

Of the 30 patients enrolled, 29 completed treatment. The area under the chin was the most commonly treated area. Total energy ranged from 758 J to more than 7,000 J. Greater energy was used at larger treatment sites, Dr. Kim said.

At 3 months, patients who received treatment considered the treated area to have improved 37% on average, based on observation. For those treated with the Tri-Active device and for the laser lipolysis only group, the figures were 47% and 33%, respectively. The most common side effects were bruising, swelling, and tenderness. The technique seems to be well suited for the treatment of focal areas of excess fat, Dr. Kim said. She and her colleagues are planning a larger multicenter trial using the technique.

This technique has been used in South America, Europe, and Japan. Previous studies have shown that it destroys more adipocytes than cannulation alone.

Is a Cosmetic Practice for You? Consider These Tips

Cosmetic dermatology is a rapidly moving and rewarding area of dermatology for those with the right mind set, Gerald N. Bock, M.D., said at the American Academy of Dermatology’s Academy 2005 meeting.

An elective procedures practice offers the gratification of learning new procedures, recognition as having specific expertise, and less stress as a result of upfront payments and fewer insurance hassles. Staff can be used to amplify income, and fewer patients can generate the same or greater income, he said.

“We’re in the golden age of minimally invasive procedures,” reported Dr. Bock.

That being said, a cosmetic practice is not for everyone.

“If you don’t enjoy working with these patients, who can sometimes be more demanding, don’t do it,” he said. “If your sole motivation is financial gain, don’t do it. This will lead you to make bad decisions. And if you just don’t have the flexibility or want to learn new things or take risks, this is not for you.”

Dr. Bock acknowledged that his views are colored by the fact that he established a private elective procedures practice in the unlikely Central Valley location of Stockton, Calif., a conservative agricultural community far from the aesthetically obsessed hills of Hollywood. He offered the following tips from his experiences:

• **Set realistic expectations.** It’s best to underpromise and overdeliver on your services. Have a humble attitude and offer great service. “You really want to be Wal-Mart with Nordstrom practices,” Dr. Bock said. Put everything in writing to avoid misunderstandings. Explain that retreatment may be necessary and failures can occur. Consent forms should list the worst-case scenario for each procedure. Dr. Bock’s Botox disclosures note that death can occur.

• **Follow-up and photographs are essential.** New patients should be seen 2-3 weeks after their first treatment to make sure they’re satisfied or to offer them additional treatments if the result is less than satisfactory.

• **Proper positioning is key.** Pricing your services below what people expect is one way to exceed their expectations. Start out with very reasonable pricing. You can always raise your prices later. At lower prices, patients will want more frequent and extensive treatments, leading to better results and earlier retreatment. You’ll get bigger and better faster, and this may intimidate potential competitors. “Just because you’re better doesn’t mean people will pay more for your services,” he explained.

• **Little details are important.** Dr. Bock strongly recommends using Air-Tite SteriJect 31-gauge needles for Botox injections. “Everybody tells us that our Botox injections are significantly less painful than injections they get elsewhere, and that’s because of these needles,” he said. Consider using vibration anesthesia, a technique developed by dermatologist Kevin Smith (Dermatol. Online J. Oct 15, 2004;10:1) to reduce discomfort during dermatologic procedures, particularly for needle-phobic patients.

• **Consider used equipment.** There are a lot of good machines available if you’re willing to do the research. One source is the Aesthetic Buyers Guide (www.miinews.com), which offers direct product comparisons and product roundtables. One exception may be microdermabrasion machines; Dr. Bock recommends buying a new, nonparticle system. These machines get a fair amount of wear and tear, but “once you’ve got a noncrystal machine, nobody will go back to using a crystal machine; that’s been our experience,” he said.

• **Keep up your training.** Botox, microdermabrasion, and hair removal generate the greatest revenue in Dr. Bock’s practice. But patients will demand what they can’t get elsewhere. Dr. Bock gained an edge, albeit temporary, by becoming the only practice in his area to offer soft tissue augmentation with Sculptra.
BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in patients 18 to 65 years of age.

Important Safety Information: BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation. Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft-tissue edema, and dyspnea. Patients with neurological disorders such as ALS, myasthenia gravis, or Lambert-Eaton syndrome may be at increased risk of serious side effects. The most common side effects following injection include headache, respiratory infection, flu syndrome, temporary eyelid droop, and nausea.

Please see brief summary of full prescribing information on following page.
BOTOX® COSMETIC (Botulinum Toxin Type A) Purified Neurotoxin Complex

INDICATIONS AND USAGE
BOTOX® COSMETIC is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients 45 years of age or older.

CONTRAINdications
BOTOX® COSMETIC is contraindicated in the presence of infection or inflammation at the proposed injection site, and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS
BOTOX® and BOTOX® COSMETIC contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of BOTOX® also have the potential to be associated with the use of BOTOX® COSMETIC.

Dust Exposure and Frequency of Administration of BOTOX® COSMETIC

Hypersensitivity Reactions
Following injection, hypersensitivity reactions have rarely been reported. These reactions include anaphylaxis, urticaria, skin tissue edema, and dyspnea. One fatal case of anaphylaxis has been reported in which laboratory data used as the basis for the diagnosis of anaphylaxis cannot be reliably determined. It is unclear whether or not injection of BOTOX® COSMETIC should be discontinued and appropriate medical therapy immediately instigated.

Pre-Existing Neuro muscular Disorders
Caution should be exercised when administering BOTOX® COSMETIC to individuals with peripheral motor neuropathic disorders (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic side effects including severe dysphagia and respiratory compromise from typical doses of BOTOX® COSMETIC. Published medical literature has reported rare case reports of administration of a botulinum toxin to patients with known or unreported neuromuscular disorders where the patients have shown severe toxicity to the systemic effects of typical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Dysphagia
Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with BOTOX® COSMETIC. In these patients, there have been reports of new cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed aspiration pneumonitis and died subsequent to the finding of dysphagia.

Cardiovascular System
There have also been rare reports following administration of BOTOX® of adverse events including chest pain, cardiac arrhythmia, chest discomfort, or myocardial infarction. These events were not considered to be representative of the expected pharmacological action of botulinum toxin, weakness of adjacent musculature, or as a result of the specific spread of the toxin. The injection of BOTOX® COSMETIC was being considered to be the cause and occurred within the first week. The events were generally transient but may last several months or longer.

Human Albumin
The albumin used in BOTOX® COSMETIC is derived from human plasma. Based on effective donor screening and product manufacturing processes, it is highly unlikely that any virus transmission would occur.

PRECAUTIONS
General:
The safety and effectiveness of BOTOX® COSMETIC depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX® COSMETIC must understand the relevant neuromuscular anatomy and physiology and be skilled in the injection techniques required to achieve local muscular paralysis. It is also important that procedures are performed in a manner consistent with the practice of medicine in the patient's area.

Drug Interactions:
No specific drug interactions with BOTOX® COSMETIC have been seen. It is recommended that BOTOX® COSMETIC be used with caution for patients taking medications that cause muscle weakness or sensory changes in the face, such as anticholinergic agents.

Informed Consent
Patients or caregivers should be advised to seek immediate medical attention if swelling, rash, sensation of tightness, or pain develops.

Infusion Reactions
Co-administration of BOTOX® COSMETIC and antihistamines or other agents interfering with histamine metabolism, such as sympathomimetics, tricyclic antidepressants, polyethylene glycol (PEG), quinidine, magnesium sulfate, anticholinesterase drugs, and others that block muscarinic receptors should be avoided.

Effects of Prior Botulinum Toxin Treatment
The effect of administering different botulinum neurotoxin serotypes at the same time or within one treatment area is not known. In general, all available evidence suggests that the effects of one botulinum neurotoxin type may persist for several months after the administration of another type of botulinum neurotoxin (presumably due to the presence of antibodies to the administered toxin).

IMMUNOGENICITY
Administration of BOTOX® COSMETIC is not recommended during pregnancy. There are no adequate and well-controlled studies in pregnant women. Treatment should be avoided in breastfeeding women until the infant is at least 6 months old. Breastfeeding should be avoided for at least 4 months after treatment of BOTOX® COSMETIC. When pregnant mice and rats were injected intramuscularly during the organogenesis period, the developmental toxicity of the observed lowest effective dose of BOTOX® COSMETIC was less than 1/1000 of its human dose (8 doses of 16 U/kg) was associated with reducts in fetal body weights and delayed embryonic survival. In a range finding study in rabbits, daily injection of 0.15 U/kg (equivalent to 8 to 16 mg/kg of BOTOX® COSMETIC) associated with reductions in fetal body weights and delayed embryonic survival. These findings were confirmed in rabbits. The rabbit is a species that may respond differently to the administration of the drug, this patient should be advised to report the potential risks, including abortion or fetal malformations that have been observed in rabbits.

Carcinogenesis, Mutagenesis, Impairment of fertility
Long-term observational animal studies have not been performed to evaluate carcinogenic potential of BOTOX® COSMETIC.

The reproducible NOEL following intramuscular injection of 0.4, 16, and 64 U/kg in mice, 16 U/kg in rats, and 2 U/kg in rabbits did not result in any change in survival or evidence of malformations. These doses were associated with decreases in fertility in female rats (where brl weak result was not observed in the inability to mate), and

Percent of Patients Reporting Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events by Body System</th>
<th>BOTOX® COSMETIC (N=605)</th>
<th>Placebo (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Body as a Whole</td>
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<tr>
<td>Pain in Face</td>
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<tr>
<td>Skin and Appendages</td>
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<tr>
<td>Skin Tightness</td>
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<td>Nausea</td>
<td>1</td>
<td>1</td>
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<td>Dyspepsia</td>
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<td>Hypertension</td>
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Immunogenicity

Treatment with BOTOX® COSMETIC may result in the formation of neutralizing antibodies that are detected in human serum. The formation of neutralizing antibodies to BOTOX® COSMETIC is correlated with a reduction in the biological activity of the toxin. The rate of formation of neutralizing antibodies in BOTOX® COSMETIC is low and the antibodies do not appear to be associated with loss of efficacy of BOTOX® COSMETIC.

It is important that patients are screened for the presence of anti-BOTOX® COSMETIC antibodies before treatment. The critical factors for neutralizing antibody formation have not been well characterized. The development of neutralizing antibodies to BOTOX® COcMETIC is not associated with loss of efficacy of the toxin. The formation of neutralizing antibodies may be minimized by injecting the lowest effective dose given at the longest feasible interval between treatments.

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Reference:
Ferulic Acid


Ferulic acid belongs to the polyphenolic compounds known as hydroxycinnamic acids, which also includes caffeic acid, p-coumaric acid, and cinnamic acid. These molecules are known to confer cutaneous benefits (J. Comest. Sci. 2002;53:321-35). Hydroxycinnamic acids are typically included in sunscreen formulations. In terms of direct benefit to the skin, ferulic acid is one of the more promising botanical ingredients. It is a potent antioxidant, protecting skin from UVB-induced erythema (Biomed. Pap. Med. Fac. Univ. Palacky Olomoue Czech Repub. 2003;147:137-45). It also strongly absorbs UV, like its related compounds (Int. J. Pharm. 2000;199:39-47). And phospholipid membranes are protected by ferulic acid from UV-induced peroxidation as the lipid peroxidative chain reaction is interrupted (Biomed. Pap. Med. Fac. Univ. Palacky Olomoue Czech Repub. 2003;147:137-45; J. Sci. Food Agric. 1999;79:476-80).

Antineoplastic Action

In a study of the inhibitory effects of three phenolic compounds on benz[a]pyrene- and 7,12-dimethylbenz[a]anthracene-induced neoplasia in mice, ferulic acid and chlorogenic acid were active—although less so than ellagic acid—against lung carcinogenesis, but were ineffective against skin tumor formation (Carcinogenesis 1993;4:1651-3). Since that study, the literature has added strong evidence of ferulic acid’s oral and topical benefits, particularly its protective effects against cancer.

The inhibitory effects of the topical application and oral administration of Ixora javanica flower extract on the growth and delayed onset of various kinds of tumors in mice were attributed, in a study nearly 15 years ago, to the active compound in the extract, namely ferulic acid (Cancer Lett. 1991;60:253-8). The phenolic nucleus and extended side chain conjugation of ferulic acid account for the compound’s facility in forming a resonance-stabilized phenoxy radical, to which its antioxidant activity is attributed (Free Radic. Biol. Med. 1992;13:435-48).

Previously, the topical application of ferulic acid was found to inhibit by 46% the induction of ornithine decarboxylase activity by 12-O-tetradecanoylphorbol-13-acetate (TPA) in female CD-1 mice. Similar treatment of mice with ferulic acid together with TPA also inhibited the number of TPA-induced tumors per mouse in a dose-dependent manner (Cancer Res. 1988;48:5941-6). And in a study a decade ago, the topical application of a dehydrogenation polymer of ferulic acid inhibited TPA-induced tumor promotion, although a monomeric ferulic acid failed to exhibit the same inhibitory effect in female ICR mice (Carcinogenesis 1994;15:2069-71).

Phenolic antioxidants, including ferulic acid, fed to male F344 rats significantly lowered the incidence of tongue neoplasms (squamous cell papilloma and carcinoma) and preneoplastic lesions (hyperplasia and dysplasia). The researchers concluded these compounds show promise as chemopreventive agents in the tongue, skin, and other organs (Carcinogenesis 1993;14:1321-5).

In a study evaluating the potential of dietary polyphenols as anticarcinogenic agents, ellagic acid, tannic acid, caffeic acid, and ferulic acid were combined with phorbol-12-myristate-13-acetate or mezerein and were topically applied to mice. The results showed significant protection against skin tumors induced by 7,12-dimethylbenz[a]anthracene under in vivo and in vitro conditions (Nutr. Cancer 1998;32:81-5).

Sun Protection

The vitamin E/ferulic acid compound alpha-tocopheryl ferulate (alpha-TF) has the capacity to absorb UV radiation, thereby maintaining tocopherol in a stable state. Thus, researchers investigated whether alpha-TF can act as a depigmenting agent and antioxidant to improve and prevent UV-induced facial hyperpigmentation.

The researchers studied the effects of alpha-TF on cultured human melanoma cells and normal human melanocytes in vitro, and found that alpha-TF inhibited melanization significantly better than arbutin, kojic acid, ascorbic acid, and tranexamic acid. The investigators suggested that alpha-TF has potential as a whitening agent, and hypothesized that it acted by indirectly inhibiting tyrosine hydroxylase activity (Anticancer Res. 1999;19:3769-74).

In related studies, most of the same researchers determined alpha-TF inhibits the biologic responses prompted by reactive oxygen species (Br. J. Dermatol. 1999;141:20-9) and may mitigate damage induced by active oxygen species, thus helping to suppress or decelerate skin carcinogenesis (Anticancer Res. 1999;19:3769-74).

Based on in vitro tests of the capacity of ferulic and caffeic acids to permeate excised human skin, researchers evaluated the capacity of the same organic acids to reduce UVB-induced Continued on page 14
**Ferulic Acid**

*Continued from page 13*

erythema in healthy human volunteers. Dissolved in saturated aqueous solution (pH 7.2), both compounds conferred significant cutaneous protection. Ferulic acid—which is more lipophilic and thus better able to penetrate the stratum corneum—and caffeic acid were assessed as worthy photoprotective agents in topical formulations and judged to be unaffected by the pH of the product into which they might be incorporated (Int. J. Pharm. 2000;199:39-47). In a recent study of the free-radical scavenging abilities of ferulic acid and eugenol that may summarize current thinking on this potent phenolic compound, ferulic acid was deemed an effective antioxidant (Anticancer Res. 2002;22:2711-7). The investigators concluded it may be useful in preventing cell damage by free radicals.

Buttressing such claims is a just-published study showing the addition of 0.5% ferulic acid to a solution of 15% L-ascorbic acid (vitamin C) and 1% alpha-tocopherol (vitamin E) stabilized the formulation and, more significantly, rendered the topically applied formulation a much better skin-protective agent, doubling photoprotection to skin from fourfold to eightfold (J. Invest. Dermatol. 2005;125:826-33).

The authors of this study found the addition of ferulic acid conferred a synergistic effect, greatly enhancing the existing synergistic effects seen in the combination of vitamins C and E, and further supporting research published by other investigators last year, which highlighted synergistic relationships between ferulic acid, vitamins C and E, and b-carotene (J. Agric. Food Chem. 2004;52:2411-20).

Authors of the more recent study speculate that a topical antioxidant formulation combining vitamins C and E with ferulic acid in a broad-spectrum sunscreen would be an optimal way to protect skin from sun damage via a topically applied product (J. Invest. Dermatol. 2005;125:826-33).

Ferulic acid is found in SkinCeuticals C E Ferulic and in small amounts in Murad Raspberry Face Wash.

**Conclusion**

Significant antioxidant, photoprotective, and anticarcinogenic properties have been seen with ferulic acid. The cutaneous benefits associated with this phenolic compound continue to be borne out by research. Given advances in combining antioxidant ingredients for optimal effects, I am optimistic ferulic acid will be a significant component in the armamentarium against photocarcinogenesis and skin cancer.

Dr. Leslie S. Baumann is director of cosmetic dermatology at the University of Miami. Reprinted from SKIN & ALLERGY NEWS, October 2005.

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**Examine Patient Motivation For Cosmetic Surgery**

Six simple words stop Rona Z. Silkiss, M.D., in her tracks after she greets a cosmetic surgery patient by asking, “What can I do for you?” Those words are the response: “I don’t know, you’re the doctor.” Within this seemingly innocuous exchange lies a warning that the balance of power between doctor and patient is already skewed, setting the scene for an unhappy outcome.

In cosmetic procedures, the doctor-patient relationship must be bilateral, with each person coming to the table with a defined role and measurable expectations, Dr. Silkiss said at a facial cosmetic surgery symposium.

Don’t bite when a patient says, “Take a look at me and tell me what you can do,” Dr. Silkiss advised. The patient is not taking responsibility for the initial objectives of his or her cosmetic surgery, she explained. “The environment is wide open and ill defined. As a result, it is impossible for the surgeon to meet the patient’s expectations” because they have not been clearly established, she said.

Maintaining a balance of power was just one of a series of tips offered by Dr. Silkiss, chief of the division of ophthalmic plastic, reconstructive, and orbital surgery at California Pacific Medical Center in Oakland.

Another patient to watch out for is one who presents at a young age with a very minor problem, saying she has read articles advocating early cosmetic surgery. “This is what I call surgery in search of a problem,” Dr. Silkiss said at the meeting, which was sponsored by the Multi-Speciality Foundation for Facial Aesthetic Surgical Excellence. Such a patient may be giving in to media pressure fueled by fashion magazines and reality TV shows such as “Nip and Tuck” and “Extreme Makeover.”

Reassuring such a patient that she does not need surgery exemplifies surgical integrity that will be rewarded later, she said.

Patients who arrive in the traumatic aftermath of a divorce or job loss might be well advised to come back in a few months, when life has stabilized for them. “The patient is at a stressful juncture in his or her life. What you do not want to do is give the patient the opportunity to transfer his or her unhappiness to the recent surgery and surgeon,” she said.

Dr. Silkiss described a scenario in which a 50-year-old man, recently divorced, came to her because his new girlfriend told him he needed blepharoplasty. “Actually, he didn’t notice he had a problem.” This patient, she said, had insufficient motivation to undergo an elective surgical procedure. “The patient is not personally committed to the surgery. This is his body and he has to want the surgery himself.” Such patients often come to a consultation hoping that the surgeon will agree that surgical correction for such an issue is purely optional. “They are trying to reestablish their self-esteem. Reassurance alone may be the best medicine,” she said.

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* British Journal of Dermatology

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Fillers: Beyond the Mythic ‘Ideal’

Any speakers include a slide on “the Ideal Filler” in their talks at cosmetic dermatology seminars. I don’t have such a slide for my presentations, because there is no ideal filler. There is not now; there never will be. Every time you consider using a filler, you are in a unique clinical situation. The face is going to be different, and the person attached to that face is going to be different.

Let’s say a woman who is concerned about her aging appearance comes to see you. Are you going to use the same filler in areas that need a little stiffening as you would use to fill out deep lines around her mouth? What if she doesn’t want to come back every 3-6 months for a retouch?

What we have today—and what I predict will increasingly become the norm—is an array of fillers, each with its own advantages, drawbacks, and, once in a while, a special niche in the cosmetic armamentarium. In Canada and certainly in the United States, a host of new fillers will soon be available. Some that currently sit on your shelf may not survive in this competitive market.

In my personal view, cadaveric facial fillers are as dead as the donors. Furthermore, I would not invest money in Isolagen, which uses a patient’s own cultured fibroblasts to produce a filler substance. I’m unconvinced that something that involves this much of a procedure, this much expense, and this much time is something that my patients will buy into.

On the other hand, I didn’t see the rationale for Sculptra (poly-L-lactic acid), and yet Sculptra clearly works. I was wrong about that and I could be wrong about Isolagen, too.

Artecoll, which may be approved by the Food and Drug Administration by the end of the year, will offer less potential for allergenicity than do collagen products we use now, as well as permanence. This and other future permanent fillers that are injected subdermally work by fibroblast proliferation. There are definite risks associated with this. Lumps are common and are technique related. Granulomas can and do occur, and they may be very difficult to treat effectively (SKIN & ALLERGY NEWS, August 2005, p.1).

I expect to see remarkably similar problems in other permanent-type fillers that are on the horizon, including Dermafill and probably Silskin as well. In addition, I am concerned that we do not yet know the true complication potential in normal individuals of fillers that are tested on and approved for HIV-associated lipoatrophy. My suspicion is that HIV patients, because of their altered immune systems, may be protected from many problems, such as infection.

My impression is, you can throw anything at patients with HIV-associated lipoatrophy; I have yet to see a significant complication. I would be very cautious about applying findings in these patients to patients in the general population seeking cosmetic improvement through the use of fillers. This is especially true for permanent fillers.

I think most cosmetic dermatology patients are satisfied with long-term temporary correction. People accept the concept of maintenance. They know they have to keep going to the gym, maintaining a healthy diet, and returning to the hairdresser. They will accept maintenance visits for filler touch-ups as long as the correction is “long-term.”

So how long is long-term? We’re pushing the envelope here. Certainly the longer-term the correction, the longer the risk of complications will last. For example, with Restylane, the complications are reduced because the product is immunologically simple. The duration of action is at least as long as that of Zyplast and CosmoPlast, but this and products like it aren’t dermal fillers; they’re volume replacers. They’re easy to inject and tolerant of mistakes.

Can these be made safer and longer lasting by changing the particle size? I am unimpressed that there is a difference in duration. Will there be fewer adverse events with smaller or larger particles? We have no evidence of that yet.

Sculptra seems destined to have a place in the future of fillers. I’m convinced it works. Designed for the subcutaneous space, it’s all about volume. Obviously, the injection technique is crucial to avoid nodules. There is a problem with the number of injection sessions required, and also with its inconsistency in terms of longevity. In some people, the correction lasts years; others lose the volume in 1-2 years. I like things that are very predictable, but I must say I am impressed with the results achieved with Sculptra. It’s not approved yet in Canada, but I look forward to the day when it will be.

Radiesse also works, but it is also unpredictable, albeit to a lesser extent. Some people get long-lasting correction, but the results can be more variable in others. Another problem with Radiesse is the cost. I am currently involved in a study of Radiesse for HIV-associated lipoatrophy, and the volumes I am using would be extremely expensive.

So what is my concept of an ideal filler? I look for long-term temporary correction, which I define as something that achieves good filling of the lips for 6-12 months. Something that induces fibroplasia is okay, but not if it produces individual results so varied that the filler becomes unpredictable. I think an acceptable filler is one that can be used with a 30-gauge needle.

Beyond these basic criteria, I think we need an array of fillers, to be mastered one at a time for the many varied types of volume correction sought by many different types of patients.
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JSJ Pharmaceuticals

If the condition worsens, consult your doctor immediately. The long-term use of the product may give rise to sensitization. Should this happen, discontinue the treatment and call your doctor. Do not administer to patients with known hypersensitivity to this product. Each tube of Bionect® should be used by one person only to reduce the risk of cross infection.


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Storage: Store BIONECT® at room temperature. BIONECT® Cream may be stored for up to 24 months. BIONECT® Gel may be stored for up to 12 months. BIONECT® Spray may be stored for up to 12 months under controlled conditions.

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U.S. Pat. No.: 5,905,826
Liquid injectable silicone can be a highly effective means of tissue augmentation, especially for acne scarring and HIV-related lipoatrophy, Derek Jones, M.D., said at a cosmetic dermatology seminar sponsored by the Skin Disease Education Foundation. “This can be an ideal filler that is long lasting and cosmetically elegant,” said Dr. Jones of the department of dermatology at the University of California, Los Angeles.

A “wealth of anecdotal data” indicates that liquid injectable silicone is safe and effective, but the following critical rules are key to its safe usage, he said:

- Use only pure, Food and Drug Administration–approved, injectable-grade liquid silicone; in the United States that means only Silikon-1000, made by Alcon Laboratories. The product has FDA approval for intraocular injection to treat retinal detachment, but it may be legally used off label, under the 1997 FDA modernization act that allowed medical devices to be used off label.

It’s important to note, however, that the law prohibits advertisement of off-label uses, and malpractice insurance carriers have different policies regarding such uses.

- Adhere to a strict serial puncture microdroplet technique, defined as 0.01 cc injected into the immediate subdermal plane or deeper at 2- to 4-mm intervals, with no double pass in the same plane. Intradermal injection should be strongly avoided except among the most skilled practitioners.

The technique is necessary to allow a fibroproliferative response that develops around each microdroplet between treatments, not only causing each droplet to become anchored and less likely to drift but contributing to further augmentation, Dr. Jones said.

“This is an oil, and if you inject a lot all at once, it’s like throwing olive oil on the floor—it’s going to spread out and track tissue planes along the path of least resistance,” he said. “But the microdroplet technique addresses this problem.”

- Inject only small volumes—2 cc or less for lipoatrophy, or 0.5 cc or less for other indications. “Avoid the temptation to use larger volumes,” Dr. Jones said, adding that injections should be spread out at intervals of at least 4 weeks.

In addition to these three critical rules, important considerations for silicone use include informing patients that liquid injectable silicone is permanent, and that its use is still investigational and likely to remain so for years. And, while patients can resume a normal routine immediately, they are advised to avoid activities that could predispose them to blunt trauma.

Dr. Jones demonstrated the injection technique on a patient with HIV-related facial lipoatrophy at the conference and said that most patients are highly pleased with the results.

Liquid silicone injections “really give an extraordinarily natural-appearing correction,” he said. “When you touch the cheeks of these individuals, they feel nice, soft, and supple, and the injections really can restore subtle and refined facial contours.”

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By Nancy Melville, IMNG News Service. Reprinted from SKIN & ALLERGY NEWS, August 2005. Based on a presentation at a cosmetic dermatology seminar sponsored by the Skin Disease Education Foundation.

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Pain-Relief Options Available For Cosmetic Procedures

Ice, vibrators, “talk-esthesia,” and sundry topical anesthetic creams and gels were advocated as safe and effective options for relieving pain during a mini-symposium at the annual Hawaii Dermatology Seminar sponsored by the Skin Disease Education Foundation.

“How much is a happy patient worth? If you hurt them, they won’t come back,” said Kevin C. Smith, M.D., a dermatologist practicing in Niagara Falls, Ont.

The discussion focused on patients undergoing cosmetic procedures, but the techniques, listed here, can be used on medical dermatology patients as well:

• Ice. It’s effective and about as cheap as pain relief gets. “We use it a lot,” said Alastair Carruthers, M.B., a dermatologist in practice in Vancouver, B.C.

• Vibrators. Snickers aside, the Hitachi Magic Wand with a Wonder Wand attachment provides excellent pain relief when applied under a patient’s chin during facial procedures by blocking pain signals to the brain, said Dr. Smith. The devices can be found at the Web site www.drugstore.com.

• Talk therapy. “It’s not enough to put some cream on a patient,” Dr. Smith said. From the time a patient first calls the office, the staff and the physician should convey calm reassurance. Patients will have less pain if they feel “confident of your skill and your care.” He said he always uses “talk-esthesia” to talk patients through procedures, even when other forms of pain relief are used.

• Analgesics. Some procedures call for up-front pain relief. Dr. Smith sometimes advises patients to take an NSAID in combination with acetaminophen for an additive effect. Patients who do not have asthma may be prescribed propranolol, which provides analgesia but does not interfere with a patient’s ability to drive.

• L.M.X. 4. This 4% lidocaine cream (formerly ELA-Max 4%) is sold over the counter, does not require occlusion, and provides anesthesia 30 minutes after application, Dr. Carruthers explained. He tested it against a vehicle cream in 24 patients receiving Botox (botulinum toxin type A) injections for crow’s feet.

“I like to think this is not a very painful procedure, so in order to reduce the discomfort, this stuff has to work very well,” he said.

The study showed a significant difference in patient visual analogue scale scores and observer ratings of discomfort when L.M.X. 4 was used, with \( P \) values in the range of .005.

• L.M.X. 5. This anorectal anesthetic cream is more appropriate for use in the mouth than alcohol-containing topical gels, which can cause sloughing of mucous membranes and irritation and stinging if they get in the eyes, Dr. Smith said.

For lip procedures, optimal anesthesia can be obtained by numbing the mucosal surface of the lips, including the anterior mucosa of the anterior labial alveolar sulci down to the gingival sulcus as well as the vermilion and a 1-cm margin around the vermilion border.

To achieve this without getting anesthetic all over the inside of the patient’s mouth, he cuts a Telfa pad to mimic a plastic laser shield designed to protect the teeth from laser work performed around the mouth. He cuts a 3-by-4-inch Telfa pad in half, lengthwise, then folds it over and cuts a slit in the middle (to allow the patient to breathe) and slits at the top and bottom to accommodate the frenula.

He inserts the pad into the patient’s mouth, against the teeth. He then uses a tongue depressor to apply L.M.X. 5 thickly over the lips and gums and attends to other patients for 30–45 minutes, until his watch alarm sounds to remind him to return to perform the procedure.

At that time, he can inject lidocaine painlessly or, for simple filler procedures, move directly to injections of Restylane (nonanimal stabilized hyaluronic acid gel).

Dr. Smith noted that previous research has determined that the anesthetic mixture in L.M.X. 5 does not produce toxic blood levels, even when applied to mucous membranes.

Dr. Carruthers disclosed that he has financial ties to Allergan Inc., which distributes Botox. Dr. Smith received L.M.X. 5 samples from Ferndale Laboratories Inc. for his research.

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