A Brief Overview and History of Temporary Fillers: Evolution, Advantages, and Limitations

Steven Fagien, M.D.
Arnold W. Klein, M.D.

Boca Raton, Fla.; and Los Angeles, Calif.

Summary: Facial soft-tissue augmentation by injection has become increasingly popular as a minimally invasive option for patients seeking cosmetic facial enhancement. Surgical rejuvenation procedures of the face often relate to a less than comprehensive solution to many of the changes that occur with age. Indeed, the surgical "lift," while providing the opportunity for soft-tissue repositioning, often fails to provide volumetric restoration to the face that is lost with aging. Appreciating the necessity of replacing depleted soft tissue has allowed for a more comprehensive approach to total facial rejuvenation. Hundreds of filling agents are available worldwide, and the enormity of options has led to confusion about which agents work best, where, and why. The vast array of available soft-tissue filling agents can be distilled into two simple categories: nonpermanent and permanent. In this article, the authors mostly limit their discussion, consistent with the mission of this supplement, to the evolution of nonpermanent filling agents, providing a rationale for their emergence and their individual use. (*Plast. Reconstr. Surg.* 120 (Suppl.): 8S, 2007.)

We have come to understand facial aging much better in recent years through a combination of revelations, including the actual anatomic and physical changes that occur with time and the failure of traditional surgical methods to address changes. In addition, photographic comparative imaging and morphing techniques, as described and demonstrated by Lambros,[1] have shed more light on the reality of facial change. As has been the case in aesthetic medicine, historically, the cure has related more to available options and the often ill-conceived concepts of causation. Although facial aging has been attributed primarily to soft-tissue descent, we now realize that qualitative and quantitative influences, including a depletion of components present in youth and volume loss, may have comparable relevance. Soft-tissue loss is now better understood and acknowledged as a necessary component that must be addressed in a comprehensive reversal of facial aging. Moreover, the causes of facial volume loss and shifts are many and include contributions from chronic facial animation that were previously less appreciated.[1] The ability now both to address volume depletion and to modify its cause (for instance, with chemodenervation) has yielded a more powerful approach to nonsurgical facial rejuvenation.

From private practice and Aesthetic Eyelid Plastic Surgery, and Department of Medicine and Dermatology, University of California, Los Angeles.
Received for publication March 3, 2006; accepted August 31, 2006.

DOI: 10.1097/01.prs.0000248788.97350.18

HISTORY AND EVOLUTION

One of the earliest agents used for soft-tissue augmentation was autologous fat, which was first used more than 100 years ago.[2] Interest in autologous fat transfer has been renewed by improved applications and techniques, but unlike most of the agents discussed in this article, autologous fat transfer is used primarily for subcutaneous volume augmentation.[3,4] Of historical interest, most of the early dermal-filling materials were potentially long-lasting (even "permanent") and were not necessarily native to the intended site. Paraffin, for instance, was used at the turn of the nineteenth century, but it fell into disfavor by the 1920s be-

FDA Status and Approved Uses: For a complete list of the FDA status and approved uses for the fillers mentioned in this article, please see the information throughout the article or visit the following Web sites: www.plasticsurgery.org/media/press_releases/Injectables-at-a-Glance.cfm or www.surgery.org/download/injectablechart.pdf.

cause of the appearance of severe granulomas. Nevertheless, its use continued in Asia throughout the 1960s. Pure injectable silicone was utilized by a relatively small group of physicians with markedly mixed reviews.[5–8] Others, albeit intuitively and anecdotally, without a strong scientific basis for their claims, felt that permanent agents such as these could cause severe facial distortion over time, hence their personal preferences for nonpermanent filling substances. Due in part to concerns about its use, the U.S. Food and Drug Administration eventually banned silicone for cosmetic procedures.[9] Ultimately, we have come to a greater understanding of the benefits and limitations of a host of filling agents, including the appropriate application and what factors, such as technique, might contribute to untoward events. This is also true for silicone, with experienced injectors showing good results while minimizing complications.[10–12] Recently, ophthalmologic 1000 centistokes of silicone was used in an off-label manner as a filling substance.[13]

"COLLAGEN" PRODUCTS

In 1958, Gross and Kirk at Harvard Medical School showed the potential for collagen extracted from calf skin to produce a solid gel by gentle warming.[14] In the early 1970s, a group of investigators at Stanford began work on a potentially useful injectable bovine collagen implant. This ultimately led to the development and approval of the Zyderm (Allergan, Irvine, Calif.) bovine collagen implant in 1977.[15] The early claims were that this filler could result in "collagen replacement" and more long-lasting results. Experience indicated otherwise. This led to the development of a more robust (cross-linked) form of the product called Zyplast, followed by the formulation of Zyderm 2, a more viscous form of the original Zyderm formulation that is used to treat moderate fine lines, wrinkles, and scars. These (pioneer) products paved the way for a better appreciation of what could be accomplished with filling agents in an outpatient setting by injection alone, with minimal downtime. Improved injection methods, including serial puncture for implantation and lip augmentation, also contributed to the success (better results and improved persistence) of these products. The lack of satisfactory persistent correction with bovine collagen was more often technique-related than product-related, although the reality was still that these agents, in most individuals, would last for only several months at best. The bovine collagen products, which were really the first widely used, commercially available, injectable soft-tissue augmentation agents, suffered many of the casualties of being "first generation." Physicians also often used ancillary (staff) help to implant these products, and little attention was paid to the details of implantation, which often yielded suboptimal results. In addition, the rare occurrence of severe localized allergic reactions also raised many questions regarding their usage. Satisfactory results could be obtained with these injectable collagen agents, however, and complaints were related mostly to the lack of persistence and the inability to substantially improve facial volume. There was also the requirement for skin testing, which evolved into double skin testing as physicians' understanding of collagen reactions became more sophisticated. Complications due to allergenicity were also most disconcerting, and these occurrences were sometimes quite difficult to manage (Fig. 1). Many of these problems were related to the lack of physician appreciation of the most applicable facial regions and injection techniques associated with these products. The theoretic biocompatibility of bovine collagen rested on the fact that the ultrastructure of type I collagen is quite similar among animal species. The risk of allergenicity due to different species specifications was said to be addressed by modifications of the "exposed" protein segments through a variety of processing techniques. Processing of bovine collagen involves conceptual removal of the nonhelical amino and carboxyl telopeptides in an attempt to reduce the immunogenicity to make the bovine collagen more compatible with human tissue. Cross-linking was also considered to render the collagen fragments more resistant to enzymatic degradation and to seclude other heterogeneous segments. Although severe allergic reactions were, fortunately, relatively rare, there has been inconsistent reporting, and best estimates of a severe reaction place it in the 5 percent range. Satisfactory results could be achieved, and the era of injectable bovine collagen facilitated an awakening of the field of soft-tissue augmentation. Other animal protein collagen-like products were introduced into the market, including porcine-derived collagen (Fibrel) and other bovine products available outside of the United States. The requirement for in-office formulation (Fibrel) and the lack of superiority over the then-available bovine products led to the continued use of the latter.

Concerns regarding the allergenicity of the bovine products led to the concept of creating a nonallergenic human collagen. The first agent commercially available in the United States was

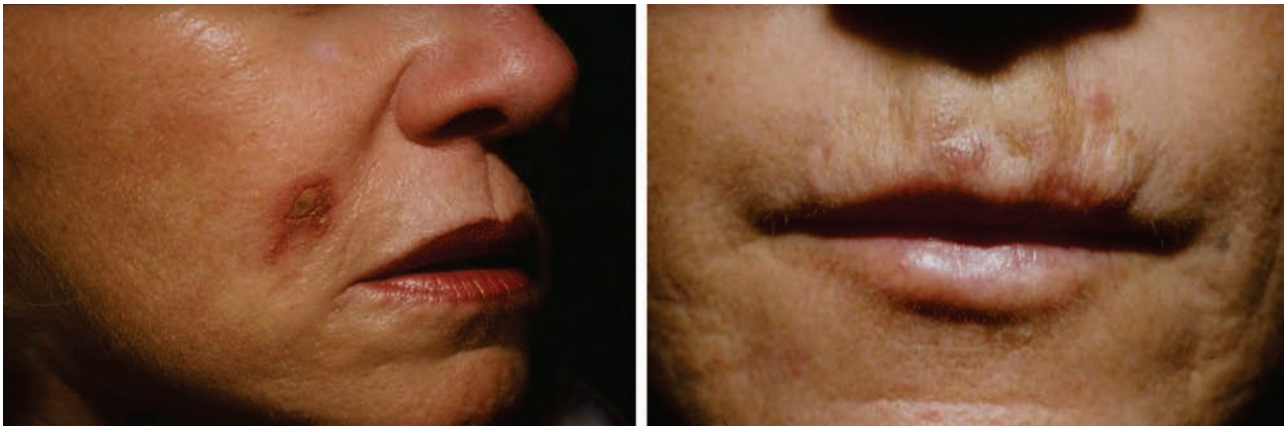

Fig. 1. Collagen reactions. (*Left*) Acute ulcerative reaction to Zyplast placed into the nasolabial fold. This resolved spontaneously without intervention in 5 months. (*Right*) Chronic granulomatous reaction reportedly to Zyderm placed into the upper lip rhytides 2 years earlier. The patient denied that any other product had ever been injected into the lip for augmentation. Intervention included intralesional injection of corticosteroids to cause focal dermal atrophy. Both patients had negative single skin tests to bovine collagen.

Autologen (Autogenesis Technologies, Acton, Mass.). Research and development culminated in the ability to extract human dermis with intact collagen fibers for injection from skin obtained during any surgical procedure. With autologous dermal tissue matrix, there was no need for skin testing and concerns about allergic inflammation and potential communicable diseases were eliminated. However, a relatively laborious process was required for skin harvest and procurement of the injectable Autologen (autologous human tissue dermal matrix). The skin was sent in sterile containers for processing, which involved sterilization with a proprietary technology that extracted decellularized dermal components, including collagen fibers, in a viable injectable form.[16–20] The required process of custom production for each individual patient was rather costly and heralded the typical inconsistencies of products that lacked mass production. Furthermore, the product did not contain the lidocaine found in the bovine agents; many physicians found it painful to inject, and it lacked the ease of use compared with the familiar bovine collagen. The viscosity of the early prototypes of this product also varied, and good results required a level of precision that at the time was not commonly practiced.

The interest in a readily available injectable human tissue matrix spawned the idea for a cadaver-based allogeneic agent. Dermalogen (Collagenesis, Inc., Beverly, Mass.), identical to Autologen in structure and substance, was created, but the source, rather than being autologous, was skin obtained from approved tissue banks.[21,22] One advantage was mass production, which allowed for greater quality assurance, mostly with regard to consistency, and lower costs. In contrast, the source of Autologen was limited, and turnaround of the product to the physician occurred despite slight variations in specifications.

The earlier prototypes of Dermalogen and Autologen were not fibrillar-purified agents but rather dermal extracts with distinctly different flow characteristics compared with the bovine products.[23] Dermalogen was refined in several ways. It was available in a 4% (40 mg/dl) range of concentration and could be injected through 27-gauge needles into the dermis. When a precision technique was used to administer the product, the results were highly satisfactory (Fig. 2).

As with the introduction of most injectable products, rare reactions were seen early in the evolution that were related to product impurities; these problems were eventually rectified. Although the many obstacles of the first human collagen injectable product were eventually overcome, its widespread use was limited as many awaited the introduction of newer agents that could both eradicate dermal defects and restore facial volume loss. In many ways, however, Dermalogen paved the way for other agents that could also satisfy the requirements of safety and efficacy with negligible adverse events and avoidance of skin testing.

To address the concerns about allergenicity, CosmoDerm and CosmoPlast (Inamed Division of Allergan, Santa Barbara, Calif.), human tissue analogs to Zyderm and Zyplast, were introduced. In March of 2003, the U.S. Food and Drug Admin-

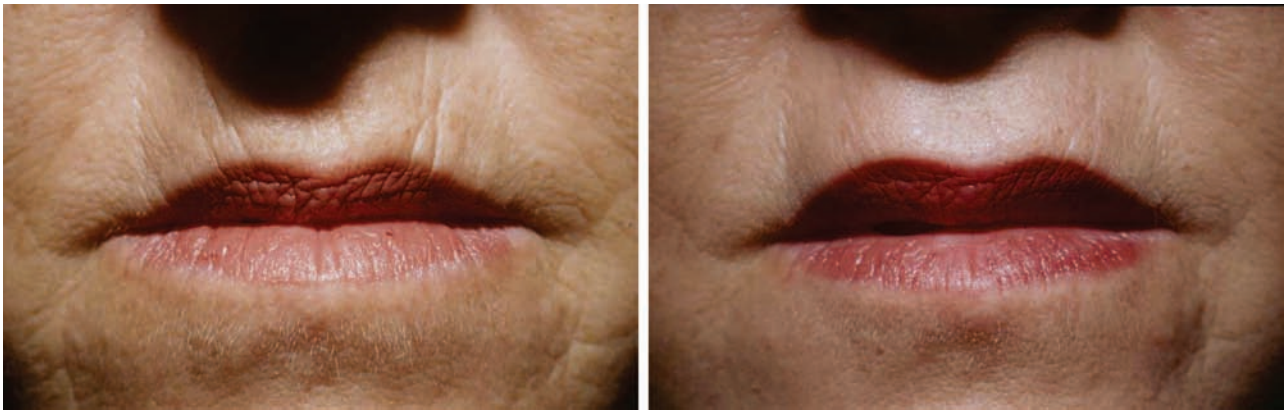

Fig. 2. (*Left*) This patient presented for treatment of (mostly) upper lip rhytides and lip augmentation. (*Right*) Two months after final treatment with Dermalogen, with 1 ml administered in three sessions. The result lasted approximately 6 months.

istration approved the CosmoDerm family of injectable dermal fillers (Allergan). CosmoDerm 1, CosmoDerm 2, and CosmoPlast were the first approved bioengineered human collagen dermal fillers and the first approved fillers, according to the manufacturer, that were nonallergenic and did not require skin testing before use. CosmoDerm 1 has a collagen concentration of 3.5 percent and CosmoDerm 2 has a collagen concentration of 6.5 percent. Both are used to correct fine to moderate lines, wrinkles, and scars. CosmoPlast, which is cross-linked, is a more robust formulation and is indicated to treat deeper lines and folds.

Another collagen-based product is Cymetra (micronized human cadaveric dermis; AlloDerm; LifeCell Corporation, Palo Alto, Calif.). The manufacturer claims a longevity of 3 to 9 months, but this injectable agent is costly. It costs about twice as much as collagen and typically requires multiple office visits. Fascian is an injectable human cadaveric fascia made by Biosystems (Beverly Hills, Calif.). First introduced in 1999, the manufacturer claimed that it lasted from 6 to 8 months. Most physicians, however, feel that its persistence is more comparable to the longevity of bovine collagen. In addition, both Cymetra and Fascian are relatively more difficult to use. In our experience, syringes are easily clogged by the product and the result can be irregular and "lumpy." In addition, Cymetra and Fascian have not enjoyed popularity similar to that of other "collagen" agents for many reasons, including larger particle size, which requires larger needles that make precise intradermal injection difficult. Ultimately, they have not proven superior with regard to persistence. A new cross-linked porcine collagen, Evolence (Colbar LifeScience, Herzliya, Israel, acquired in July of 2006 by Johnson & Johnson, Inc.), has shown promise, as there appears to be a renewed interest in collagen-based products with greater persistence due to cross-linking and other methods. In its first U.S. clinical trials, Evolence was matched against Zyplast for the treatment of nasolabial folds and showed equal efficacy in the short term and superiority to Zyplast beyond 6 months. Isolagen (Isologen Technologies, Inc., Paramus, N.J.), consisting of cultured autologous fibroblasts, has also been reintroduced. With this filler, a dermal specimen is harvested from behind the ear and sent to the Isologen laboratory, where the fibroblasts are cultured and packaged for injection into the patient. A test dose is required and it is reportedly quite expensive. There is no consensus regarding the validity of many anecdotal claims relating to both the real science and persistence. One study, however, reported that after two to three treatments the effects may last for up to 22 months.[24]

HYALURONIC ACID PRODUCTS

The concept of using hyaluronic acid for tissue augmentation was the result of years of research by Balazs and coworkers.[25] Its use was justified because it is a structural and elastic component of skin as well as partly responsible for maintaining skin hydration. Native hyaluronic acid, however, has a short residence time in the skin and likely lasts for only several days after injection. Clinically, hyaluronic acid had been used as a viscoelastic injectable material during intraocular surgery, to protect delicate structures such as the cornea during instrumentation of the anterior segment. Several derivatives of hyaluronic acid, including animal and bacteria fermented products, had been introduced in both the ophthalmology and ortho-

Fig. 3. (*Left*) This young woman desired lip augmentation. (*Right*) Postoperative view, after 1 ml of Restylane was applied to the upper and lower lips. This result lasted 4 months. Reproduced with permission from Steven Fagien, M.D.

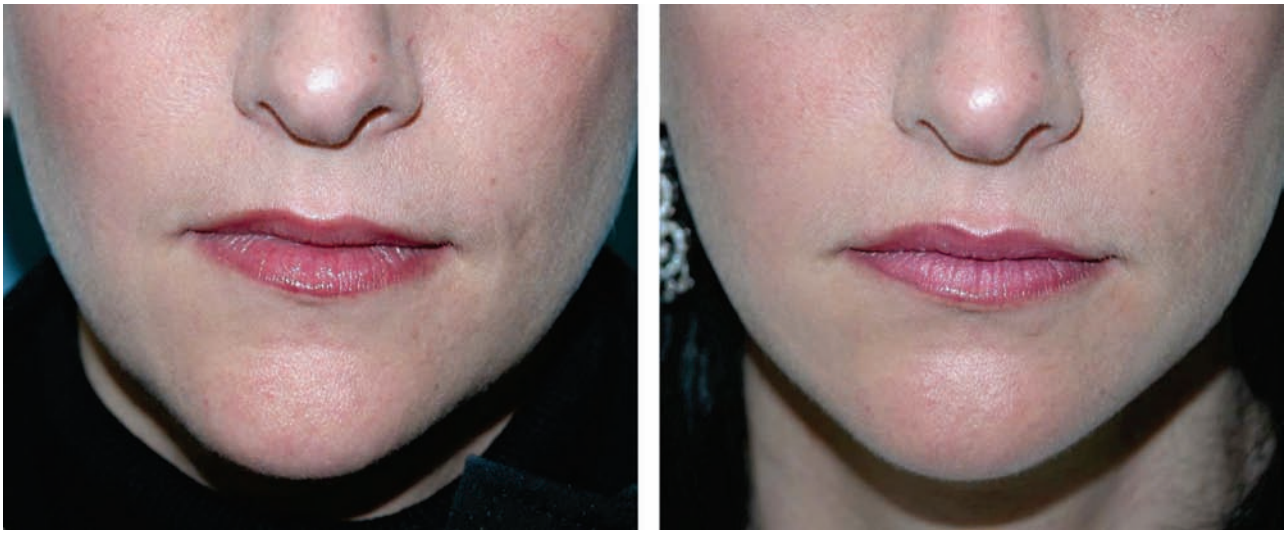

Fig. 4. (*Left*) This patient presented for treatment of early lower facial volume loss manifesting as extended marionette lines, perimental hollows, and reduced lip volume and definition. (*Right*) Postoperative view, after 2 ml (total) of Restylane was applied to these regions. Reproduced with permission from Steven Fagien, M.D.

pedic fields, with no obvious concerns about allergenicity in lieu of the transient residence time. The concept of cross-linking, which was well known in the collagen industry, was then applied to the hyaluronic acid products in an attempt to improve persistence by fortifying the molecule against enzymatic degradation. In the late 1980s, investigators reported the potential for injectable cross-linked hyaluronan to have a prolonged residence time in tissue and yet have the same biocompatibility as hyaluronan. In 1991, Piacquadio initiated a study of cross-linked hyaluronic acid (hylan B) for tissue augmentation.[26]

The Food and Drug Administration's approval of Restylane (nonanimal stabilized hyaluronic acid; Medicis, Scottsdale, Ariz.) in December of 2003 began a new era of injectable soft-tissue agents in the United States. This product proved to have several advantages over the existing "collagen" products, mostly due to its greater persistence and because it was an off-the-shelf agent that could be used for volume augmentation. "Nonanimal stabilized hyaluronic acid" simply indicates that the product is derived from a nonanimal source and is essentially "stabilized" by cross-linking. Several independent manufacturers of hyal-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.