

# An Overview of Permanent and Semipermanent Fillers

Kevin W. Broder, M.D.  
Steven R. Cohen, M.D.  
*San Diego, Calif.*

**Summary:** The demand for safe, effective, long-lasting, biocompatible dermal filler materials is increasing. Many products that include synthetic polymers and autologous tissue have emerged that attempt to meet these criteria. An overview of injectable permanent fillers, including ArteFill, Aquamid, and silicone, and semipermanent fillers, including Radiesse, Sculptra, and autologous fat, is presented. A discussion of their composition, histologic characteristics, antigenicity, U.S. Food and Drug Administration approval status, indications for use, efficacy, injection technique, and adverse effects is provided. (*Plast. Reconstr. Surg.* 118 (Suppl.): 7S, 2006.)

The aging of the face is often combined with a volume loss of the subcutaneous fat.<sup>1</sup> Therefore, fat would be the ideal filler substance if the present technique of fat grafting had a predictable outcome. Until now, all reports on successful fat grafting have been anecdotal, and no statistics on the “take” of fat have been published. Otherwise, there would be no need for artificial filler substances. Although subdermal fat disappears and the thickness of the dermis diminishes at the extremities, in the face, the dermis thickens and loosens with aging.<sup>2</sup> Most described face-lift techniques take care of the surplus of facial skin. Critical surgeons know, however, that even the stretching of the nasolabial folds during a face lift persists for only a few months. Although skin laxity accentuates the fold, the loss of dermal thickness beneath a wrinkle from repetitive mimetic muscle function often requires replacement with some type of dermal filler agent. The wrinkles in the perioral and glabellar region can be softened with Botox, which may permit some dermal regeneration; however, once the dermal fat is lost, generally, a filler is needed to diminish the wrinkle depth. Although superficial perioral and periorbital wrinkles can be treated effectively with laser and chemical peel and those around the mouth can be treated with dermabrasion, deeper wrinkles and folds may require soft-tissue fillers for dermal replacement.

Beginning in the 1970s, dermal filler substances consisting of highly viscous fluids<sup>3-5</sup> or polymer particle suspensions<sup>6,7</sup> were injected beneath wrinkles and acne scars.<sup>8,9</sup> These substances are useful for the correction of congenital or traumatic facial, bony, and soft-tissue defects<sup>10</sup> and in patients suffering from scleroderma, Romberg’s disease, facial wasting, or facial lipodystrophy following acquired immunodeficiency syndrome treatment.<sup>11</sup> Additional indications are unilateral paralysis of vocal cords,<sup>12-14</sup> augmentation of the lip and soft palate in cleft lip patients, anophthalmic orbits,<sup>10</sup> and enophthalmos. Other potential applications for fillers are as bulking agents for the lower esophageal sphincter in gastroesophageal reflux patients<sup>15,16</sup> and for the bladder neck or anal sphincter in patients suffering from urinary<sup>17</sup> or fecal incontinence.<sup>18</sup> The injection of a permanent filler substance into damaged vertebral disks with an intact annulus might even relieve the pain caused by narrowing of the disks.<sup>19</sup>

Animal studies and clinical trials<sup>20,21</sup> have shown good acceptance and short- and long-term efficacy in accordance with the chemical structure and surface characteristics of polymer microparticles. Resorbable materials such as collagen, hyaluronic

*From the Division of Plastic and Reconstructive Surgery, University of California.*

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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/news\\_room/press\\_releases/Injectables-at-a-Glance.cfm](http://www.plasticsurgery.org/news_room/press_releases/Injectables-at-a-Glance.cfm) or [www.surgery.org/press/news-release.php?iid=320&section=news-botox](http://www.surgery.org/press/news-release.php?iid=320&section=news-botox).

acid,<sup>21-23</sup> hydroxyethyl methacrylate,<sup>24</sup> dextran,<sup>25</sup> and polylactic acid<sup>22</sup> are removed by phagocytosis over a period of 3 to 24 months, depending on the amount and type of bulking agent implanted. Permanent fillers such as paraffin,<sup>3</sup> fluid silicone,<sup>11,26</sup> Teflon,<sup>27</sup> or silicone particles<sup>6</sup> have an irregular surface that cannot be phagocytized and may eventually form foreign body granulomas because of the memory of macrophages and giant cells (so-called frustrated macrophages).<sup>25</sup> Particles and microspheres smaller than 15  $\mu\text{m}$ <sup>28,29</sup> are generally phagocytized and can be transported to local lymph nodes. Larger microspheres from non-resorbable polymers with a smooth surface<sup>30</sup> are encapsulated with fibrous tissue and escape phagocytosis.

Clinically, all injected fluids<sup>31,32</sup> and particles<sup>33</sup> have been shown to cause foreign body granuloma in a small percentage of patients.<sup>34</sup> Until the mechanism of granuloma formation is fully understood, the chance of its late development is not predictable.

The ideal soft-tissue filler substance for wrinkles and skin defects should be safe, biocompatible, stable after implantation, nonmigratory, resistant to phagocytosis, and pliable, and should persist and maintain its volume without being absorbed or degraded. It should induce minimal foreign body reaction, including granuloma formation; be nonteratogenic, noncarcinogenic, noninfectious, and nonallergenic; not require pretesting; be U.S. Food and Drug Administration approved or autologous, painless, and inexpensive; and able to be stored at room temperature.<sup>22,35-38</sup>

Although the ideal filler has not yet emerged, there is an ever-increasing body of data demonstrating the search for a filler that meets these demanding criteria. This supplement concentrates on permanent and semipermanent fillers, namely, fillers that last longer than 1 to 2 years. A review of permanent and semipermanent fillers presented here includes a discussion of ArteFill, Aquamid, silicone, Sculptra, Radiesse, and autologous fat; a close look at complications associated with their use; and insight into the future role stem cells may play in the development of autologous fillers (Table 1).

Currently, there are four types of permanent and semipermanent fillers, three of which are synthetic. These include polymer gels (Silikon 1000 and Aquamid), nondegradable polymer microspheres suspended in resorbable liquid (ArteFill), slowly degradable polymer microspheres suspended in resorbable liquid (Sculp-

tra and Radiesse),<sup>39</sup> and autologous fat. Nonpermanent fillers, which are not being focused on in this discussion, include other natural fillers such as collagen and hyaluronic acids. These offer short-term effects and are eventually enzymatically metabolized or phagocytized slowly, with minimal histologic reaction.

## PERMANENT FILLERS

### ArteFill

ArteFill is manufactured by Artes Medical, Inc. (San Diego, Calif.). It is composed of 20 percent homogenous polymethylmethacrylate microspheres evenly suspended in a solution of partly denatured 3.5% bovine collagen (derived from calf skin of a closed herd in the United States) and 0.3% lidocaine. Each ArteFill kit contains three syringes of 0.8 ml and two syringes of 0.4 ml of ArteFill. It should be stored at 2° to 10°C and warmed to room temperature before use.<sup>20</sup>

All microspheres have a diameter of 30 to 50  $\mu\text{m}$ , are completely polymerized, and have a smooth, round surface. The size, smooth surface, and lack of electrical charge enables the microspheres to resist phagocytosis and dislocation, as they are encapsulated by the patient's own collagen. Without evidence of tumor necrosis factor- $\alpha$  production, an inflammatory response is less likely.<sup>31</sup> Histologic evaluation of human skin has demonstrated encapsulation of each individual microsphere by a thin layer of collagen, macrophages, and fibroblasts at 1 month after injection. At 1 month, there was one macrophage and a few multinucleated giant cells present for every 15 microspheres. There were no cells present within the centers of the lesions. At 3 and 6 months, macrophages and isolated giant cells extended deeper into the lesions. The bovine collagen is completely resorbed by 1 to 3 months and is replaced with human collagen. Rare inflammatory cells are evident, indicating a minimal immunogenic response induced by the bovine collagen component. At 9 months, the ArteFill injection is unchanged in size, which suggests a lack of microsphere dissipation, phagocytosis, or migration to lymph nodes.<sup>22</sup> Although longer histologic follow-up is not reported, some authors consider ArteFill a permanent filler.<sup>40</sup>

Patients must be skin tested for allergy to the bovine collagen component. Double skin testing for collagen may be recommended before use, as it has been shown to decrease both the severity and incidence of adverse reactions.<sup>41</sup>

**Table 1. Comparison of Permanent and Semipermanent Fillers**

| Filler   | Manufacturer   | Composition   | Particle Size  | Injection Technique  | Depth                         | Permanency      | Skin Testing       | Anatomical Sites  | Adverse Effects   | List Price/Syringe | Price/Syringe to Patient |
|----------|--|---|--|--|-------------------------------|-----------------|--------------------|---|---|--------------------|--------------------------|
| ArteFill | Artes Medical, Inc., San Diego, Calif.   | 20% homogeneous polymethylmethacrylate microspheres evenly suspended in a solution of partly denatured 3.5% bovine collagen (derived from calf skin of a closed herd in the United States) and 0.3% lidocaine | 30- to 50- $\mu$ m-diameter microspheres                     | 26-gauge needle; layered, tunneling technique  | Reticular dermis              | Permanent       | Collagen skin test | Glabellar frown lines, nasolabial folds, upper lip lines and mouth corners  | Allergy to collagen, hypertrophic scarring, and granuloma formation | \$750              | \$1200–\$1500            |
| Aquamid  | Ferrosan A/S, Copenhagen, Denmark; marketed and distributed by Contura International S.A., Soeborg, Denmark                      | Gel composed of 97.5% apyrogenic water bound to 2.5% cross-linked polyacrylamide  | 30- to 40- $\mu$ m-diameter microdroplets                    | 27-gauge needle, injected into subcutaneous tissue using fine multiline retrograde technique   | Subcutaneous                  | Permanent       | None               | Lip augmentation, nasolabial folds, mouth corners, perioral wrinkles, glabella; cheek, chin, nose and vermilion border contouring | Hematoma, edema, skin pigment changes, granuloma                    | \$350              | \$1000                   |
| Silicone | Bausch & Lomb Pharmaceuticals, Inc., Rochester, N.Y. (Adatosil 5000); Alcon Laboratories, Inc., Fort Worth, Texas (Silikon 1000) | Highly purified injectable long-chain polydimethylsiloxane silicone oil of 5000- or 1000-cS viscosity   | 20- to 100- $\mu$ m-diameter microdroplets (after injection) | 28- to 30-gauge needle; microdroplet technique with a tuberculin syringe through either a linear or fanning subdermal or a multiple-stab technique | Intradermal                   | Permanent       | None               | Facial rhytides and scars, augmentation of facial eminences, correction of facial asymmetries, lip augmentation                   | Hardness, nodules, granuloma  | \$50               | \$250                    |
| Radisse  | BioForm Medical, Inc., San Mateo, Calif.   | Suspension of 30% calcium hydroxylapatite microspheres in a 70% gel consisting of 1.3% sodium carboxymethyl cellulose, 6.4% glycerin, and 36.6% sterile water for injection                                   | 25- to 45- $\mu$ m-diameter microspheres                     | 26-gauge needle; without overcorrection  | Deep dermis                   | 9–18 mo         | None               | Soft-tissue filling of nasolabial folds, lipodystrophy of cheeks, acne scars, wrinkles and hand, and liposuction contour defects  | Ecchymosis, hematoma, nodules (lip augmentation), granuloma         | \$250              | \$500                    |
| Sculptra | Dermik Laboratories, Berwyn, Pa.   | Powder of poly-L-lactic acid microspheres, sodium carboxymethylcellulose, nonpyrogenic mannitol, and sterile water for injection  | 40- to 63- $\mu$ m-diameter microspheres                     | 26-gauge needle; tunneling or threading, depot injection (zygoma, temples), massage  | Deep dermis or subcutaneous   | 1–2 yr          | None               | Cheeks and temples of HIV patients on HAART   | Ecchymosis, edema, subcutaneous papules, granulomas                 | \$192              | \$300                    |
| Fat      | Autologous   | Autologous liposuctioned fat  | 0.1-cc aliquots  | 17- to 18-gauge needle or blunt cannulae; withdrawing technique  | Subcutaneous or intramuscular | Months to years | None               | Lips, nasolabial folds, postliposuction deformities, hands  | Resorption, fat cysts, edema  | N/A                | \$1500 per site          |

HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; N/A, not applicable.

On February 28, 2003, the U.S. Food and Drug Administration's General and Plastic Surgery Devices Advisory Panel recommended that ArteFill be approved, with conditions, for marketing in the United States. Full U.S. Food and Drug Administration approval is expected in July of 2006.<sup>42</sup>

ArteFill has demonstrated safety with respect to adverse events and is an efficacious filler for glabellar frown lines, nasolabial folds, upper lip lines, and mouth corners. Using a 26-gauge needle, ArteFill is injected into the reticular dermis, just above the dermal-subcutaneous fat interface, by means of a tunneling technique. As the needle is passed back and forth beneath the wrinkle, it is deposited in a layered fashion, providing a scaffold for tissue infiltration. This is followed by gentle digital massage to evenly distribute the material.<sup>20</sup>

Complications and adverse events include inaccurate depth of injection, allergy to the collagen component, hypertrophic scarring, and granuloma formation (<0.02 percent incidence).<sup>34</sup> An injection that is too deep can lead to ineffective treatment and may require repeat injection. An injection that is too superficial can lead to erythema and itching, which may require treatment with topical or intradermal steroids. Dermabrasion can be useful for intradermal granules, and intralesional corticosteroid injections are effective in treating granulomas.<sup>34</sup>

### Aquamid

Aquamid is manufactured by Ferrosan A/S in Copenhagen, Denmark, and marketed and distributed by Contura International S.A. (Soeberg, Denmark). Aquamid is composed of a homogenous transparent gel composed of 97.5 percent pyrogenic water bound to 2.5 percent cross-linked polyacrylamide, which is obtained by polymerization of acrylamide and *N,N*-methylenebisacrylamide monomers. The monomer concentration is below 2 ppm.<sup>37</sup> Each prefilled syringe contains 1.0 ml of product. Aquamid should be stored at room temperature and protected from direct sunlight.

Histologically, the acrylamide gel causes a fine fibrocellular capsule, without evidence of foreign body reaction. At 6 and 9 months, the fibrous capsule is more pronounced around millions of mini droplets of gel. The capsule is surrounded by fibroblasts and macrophages. The water component of the gel is bound to the polyacrylamide polymer and is not absorbed or biologically degraded. The implant is clinically still palpable at 9 months.<sup>22</sup> Reportedly, polyacrylamide has a half-life in the human body of longer than 20 years.

This may be true for large quantities; however, the injection of 0.1 cc of Aquamid was absorbed in human skin within 9 months.<sup>22</sup>

Aquamid is approved for use in Europe, Australia, South America, and the Middle East; however, it is not U.S. Food and Drug Administration approved. In recent investigations, Aquamid has demonstrated efficacy, with 93 percent of patients being satisfied or very satisfied with their aesthetic results at 1 year after injection. Indications for use include lip augmentation; smoothing of nasolabial folds; filling depressed mouth corners, perioral wrinkles, and glabellar frown lines; and for cheek, chin, nose, and vermilion border contouring.<sup>37</sup>

Using a 27-gauge needle in a fine multiline retrograde fashion, Aquamid is injected into the subcutaneous tissue. A 1:1 injection to augmentation effect is expected, as the product is nonabsorbable. Fifteen day intervals are recommended between injection sessions.

An adverse event rate of 20.7 percent was reported occurring in 52 of 228 treated patients.<sup>37</sup> Only 30 percent of adverse events were either probably or certainly related to hydrogel injection. Most of these cases were attributed to transient local tissue response that resolved spontaneously. These included hematomas, edema, alteration of skin pigment, itching, tingling, and moderate pain. Ten cases of gel accumulation or lumps occurred, eight of which resolved spontaneously and two of which required gel withdrawal. There were no reports of granulomatous proliferation, observed rigidity of tissues, or other serious adverse events.<sup>37</sup> Granuloma formation does occur, however, with the use of polyacrylamide gel. Lemperle et al. describe increasing evidence of palpable indurations described by the Russian and Chinese experience with hydrogel injection.<sup>34</sup>

### Silicone

Medical grade silicone is available in two forms in the United States. Bausch & Lomb Pharmaceuticals, Inc. (Rochester, N.Y.) manufactures Adatosil 5000, which has the chemical formula  $(\text{CH}_3)_3\text{SiO}-[(\text{CH}_3)_2\text{SiO}]_n-\text{Si}(\text{CH}_3)_3$ . Alcon Laboratories, Inc. (Fort Worth, Texas) manufactures Silikon 1000, which has the chemical formula  $(\text{CH}_3)_2\text{SiO}-x$ . Both products are highly purified, injectable, long-chain polydimethylsiloxane oils. The numbers 5000 and 1000 refer to centistokes (cS), which is a measure of viscosity (water has a viscosity of 100 cS). Silicone oil can be stored at room temperature (15° to 32°C).

After injection, silicone is dispersed into the tissues as millions of microdroplets (1 to 100  $\mu\text{m}$

in diameter). Lymphocytic infiltration is evidence of transient inflammation that occurs locally and subsides after 2 weeks.<sup>43</sup> At 1 month, the droplets are encapsulated by fibroblasts and collagen. At 3 to 6 months, foamy, translucent, birefringent material was found within macrophages and giant cells. At 9 months, granulomatous depots were found in the dermis and subcutaneous tissue surrounded by fibrous tissue.<sup>22</sup> At 14 months, an intense fibrosis can be present that clinically gives the impression of soft-tissue augmentation.<sup>43</sup>

No skin testing is required. Silicone does not induce tumor necrosis factor- $\alpha$  production by phagocytic cells.<sup>31</sup>

Medical grade silicone is U.S. Food and Drug Administration approved for intraocular injection as indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments and is used off-label as a soft-tissue filler. Clinical trials are underway in the United States for the use of silicone oil as a facial soft-tissue filler, and it may receive Food and Drug Administration approval in the future. Areas of injection include filling of facial rhytides and scars, augmentation of facial eminences, and correction of facial asymmetries. Lip augmentation is also an off-label use that has gained some popularity.

The microdroplet technique is used, as follows<sup>44,45</sup>: 0.01 to 0.02 ml of silicone is injected subdermally with a tuberculin syringe through a 28- to 30-gauge needle either by means of a linear fanning or a multiple-stab technique. In time, the implant can harden through ingrowth of connective tissue, and it may form a granuloma or "late siliconoma."<sup>5</sup> These can generally be treated with steroid injections<sup>46</sup> or antimitotic agents.<sup>47</sup>

## SEMI-PERMANENT FILLERS

### Radiesse

Radiesse is manufactured by BioForm Medical, Inc. (San Mateo, Calif.). It is composed of a suspension of 30 percent calcium hydroxylapatite microspheres (25 to 45  $\mu\text{m}$ ) in a 70 percent gel consisting of 1.3 percent sodium carboxymethyl cellulose, 6.4 percent glycerin, and 36.6 percent sterile water for injection. Each Radiesse package contains a prefilled syringe with 1.0 cc of material. It should be stored at room temperature (15° to 32°C) and expires 2 years from the date of manufacture.<sup>48</sup>

Histologically, Radiesse stimulates almost no foreign body reaction. At 1 month after injection, fibrin and scant cellular tissue surround the microspheres, which appear smooth and uniform, without evidence of inflammation. A fine outer

capsule consisting of fibrin, fibroblasts, and macrophages surrounds the microspheres at 3 months. The microspheres become deformed, appearing irregular, and start to adsorb at 9 months, likely because of enzymatic breakdown of the calcium hydroxylapatite; however, electron microscopy shows calcium particles extracellularly and microspheres within macrophages.<sup>22</sup> Granuloma formation and foreign body reactions were not present.<sup>49</sup> The effects of Radiesse have been reported to last from 2 to 7 years,<sup>40,49</sup> although clinical effects may disappear as early as 6 to 9 months. Presently, we tell our patients that Radiesse may last 9 to 18 months. No skin testing is required before use, as Radiesse is immunologically inert.

Radiesse is U.S. Food and Drug Administration approved for use in oromaxillofacial defects, which includes implantation on facial bones. Efficacy has been demonstrated, with 87 percent patient satisfaction within an 18-month follow-up period.<sup>50</sup> Radiesse has been used off-label for lip augmentation, soft-tissue filling of nasolabial folds, facial lipodystrophy, acne scars, wrinkles, and hand and liposuction contour defects. Its use for lip augmentation is controversial, however. The carrier methylcellulose dissipates soon after injection and leaves the microspheres clumped, appearing as white, hard calcium nodules in approximately 50 percent of the injected lips.<sup>51</sup> The concomitant movement of the orbicularis muscle during chewing compresses the injected strands into a lump. Based on this reported high rate of nodule formation in the lips, we do not inject Radiesse into the lips. This practice is supported by other experienced injectors of Radiesse.<sup>42</sup>

Using a 26-gauge needle or larger, Radiesse is injected into the deep dermis. Because the gel component offers a 1:1 implant-to-tissue defect correction, no overcorrection is required.<sup>49</sup>

Radiesse has demonstrated safety, with no evidence of systemic adverse effects or immunologic responses and a 5 percent incidence of hematoma and ecchymosis. Complications, including ecchymosis and hematoma, are temporary. When used for lip augmentation, nodules that occur can be surgically excised.<sup>50</sup> There have been three reports of nodule formation in the lips in over 150,000 patients treated with Radiesse.<sup>52</sup>

### Sculptra

Poly-lactic acids do not occur naturally, but were synthesized by French chemists in 1954. Poly-lactic acid and polyglycolic acid have been used safely in suture materials (Vicryl, Ethicon, Inc., Somerville, N.J.; and Dexon, Davis & Geck,

Manati, Puerto Rico); in resorbable plates and screws; in guided bone regeneration; in orthopedic, neurologic, and craniofacial surgery; and as drug delivery devices.<sup>53</sup>

Sculptra, also known as New-Fill in Europe, is manufactured in Italy and distributed by Dermik Laboratories (Berwyn, Pa.), a division of Sanofi-aventis (Bridgewater, N.J.). It consists of a powder of poly-L-lactic acid microspheres (1 to 63  $\mu\text{m}$  in diameter), sodium carboxymethylcellulose, non-pyrogenic mannitol, and sterile water for injection. Sculptra is supplied as a sterile freeze-dried preparation for injection in a clear glass vial. Each carton of Sculptra contains two vials (367.5 mg of powder each). Sculptra can be stored at room temperature up to 30°C during and after hydration. Seventy-two hours after reconstitution, any remaining material should be discarded.<sup>54</sup>

Poly-lactic acid is metabolized to carbon dioxide and water. Long-term tissue filling effects are caused by ingrowth of type I collagen into the areas of accumulated particles as the poly-lactic acid microspheres undergo dissolution, which takes place weeks to months after injection.<sup>55</sup> Nine months after implantation, no polymer or remnant cicatricial fibrosis could be detected histologically, demonstrating good biocompatibility of the poly-lactic acid microspheres.<sup>22</sup> Sculptra contains no animal proteins, so allergies are not expected; however, tumor necrosis factor- $\alpha$  is produced by phagocytes.<sup>31</sup>

Sculptra obtained U.S. Food and Drug Administration approval in 2004 for use as a soft-tissue filler into lipotrophy of cheeks and temples of human immunodeficiency virus patients who are under highly active antiretroviral therapy. Sculptra has demonstrated efficacy by increasing dermal thickness of up to three times baseline, which correlates with a clinically visible volume deficit correction.<sup>56</sup> Quality of life<sup>56</sup> and anxiety and depression<sup>57</sup> were also improved in human immunodeficiency virus-positive patients.

Reconstitution is accomplished by hydrating the powder with 5 ml of sterile water for injection. One milliliter of 2% lidocaine can be used with 4 ml of sterile water as an alternative.<sup>57</sup> The manufacturer recommends waiting 2 hours before agitating the vial and injecting the product. Some experienced physician injectors recommend waiting 24 hours after suspending the microspheres in sterile water to allow for full hydration.<sup>58</sup> Using a 26-gauge needle, 0.1 to 0.2 ml of material is injected into the deep dermis or subcutaneous space by means of a threading or tunneling technique with each pass. A depot or small bolus injection

can be used in the areas of the upper zygoma or temples. Massage of the product is performed at intervals during injection. No overcorrection is required. Most patients will require a series of three to four injections spaced 2 weeks apart.<sup>56,57</sup>

Sculptra has demonstrated safety in human immunodeficiency virus patients, with short-term adverse events consisting of localized ecchymosis and edema at the site of injection and long-term events that included nonvisible subcutaneous papules<sup>56</sup> occurring within up to 2 years after injection and granulomas at 9 to 14 months<sup>59</sup> after injection.

### Autologous Fat

In 1893, Neuber first used autologous fat harvested from the arms to augment facial depressions.<sup>60</sup> In the 1970s, Fischer and Fischer described suction extraction of fat.<sup>61</sup> This was followed by the modern technique of liposuction described by Illouz.<sup>62</sup> With the introduction of tumescent anesthesia by Klein<sup>63</sup> and the refinements of microcannula fat transfer by Fournier<sup>64</sup> and Asken,<sup>65</sup> modern autologous fat transfer as soft-tissue filler has evolved.<sup>35</sup> Unfortunately, the literature on fat grafting consists of the description and demonstration of anecdotal cases only. No statistics exist, however, that could demonstrate the overall survival of transplanted autologous fat.

Autologous fat requires no pretesting, is non-antigenic, and is readily available from common donor sites including the abdomen, thighs, suprapubic region, knees, and flanks.<sup>66</sup> Fat can be used as a filler in the lips, nasolabial folds, and hands and to fill and to correct postliposuction deformities. It can last from weeks to years,<sup>40</sup> depending on the technique of harvest and transplantation. Coleman developed a widely accepted technique of structural fat grafting.<sup>66</sup> Donor sites are injected with tumescent anesthetic and fat is harvested with syringe aspiration. Centrifugation is then performed followed by expulsion of the infranatant (i.e., cell debris, water, and lidocaine) and pouring off and wicking away the oily supernatant. The residual fat is then injected subcutaneously or intramuscularly using a withdrawing technique with a 17- or 18-gauge needle or a variety of blunt cannulae. Only 0.1 cc of fat is injected with each withdrawal to maximize the surface area of contact of the grafted fat, which should minimize postinjection resorption.<sup>66</sup> Overcorrection is avoided.

### Stem Cells

Autologous adipose tissue is readily harvested with liposuction and can provide a source of stem cells. Moseley et al. provide a review of the science of

stem cells and insight into the potential use of adipose derived stem cells as soft-tissue fillers and as supplements added to other fillers such as autologous fat and hyaluronic acid that may improve their longevity.<sup>67</sup>

## CONCLUSIONS

The clinical persistence of an injectable material and its effect on wrinkles depends in part on the amount, depth, and shape of the implant. A thin strand applied beneath a constantly moving wrinkle is absorbed faster than a round depot in the skin of the forearm or a rat's forehead. The carrier substance, whether fast or slowly resorbable, may play an important role on persistence as well. Host defense mechanisms react differently to the various filler materials, but all substances—resorbable or nonresorbable—appeared to be clinically and histologically safe, although all may exhibit undesirable rare clinical side effects. Because the mechanism of late inflammation or granuloma formation is still unknown, early histologic findings are not useful in predicting possible late reactions to filler substances. These can only be verified in exact clinical long-term studies and in an independent centralized European and/or U.S. independent implant registry.

Although trepidations about the use of permanent and semipermanent fillers with respect to reported risks and potential complications<sup>68</sup> may have some merit, expanding use of soft-tissue fillers is evident.<sup>69</sup> Temporary fillers may be used as a trial or prelude to a permanent or semipermanent filler. This will give the patient an idea of what can be accomplished and an estimate of how much material is needed. It will allow the patient to determine whether they would like a longer lasting filler, and it will give the surgeon a good idea of the amount of filler needed to accomplish the patient's goal.

**Steven R. Cohen, M.D.**  
 FACESplus Aesthetic Facility  
 8899 University Center Lane, Suite 350  
 La Jolla, Calif. 92122  
 scohen@facesplus.com

## DISCLOSURES

*Kevin W. Broder, M.D., has no financial interest in any of the products, devices, or drugs mentioned in this article. Steven R. Cohen, M.D., has served on the medical advisory board of Artes Medical, Inc., the manufacturer of ArteFill, and currently serves as a consultant to the company. He is also a shareholder in Artes.*

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