# Long-Lasting and Permanent Fillers: Biomaterial Influence over Host Tissue Response

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**Background:** The purpose of this study was to attempt to understand why some injectable fillers produce frequent ill effects and some do not, by reviewing the available agents and analyzing them through the knowledge of biomaterial studies, which show clearly what type of reactions can be expected according to the chemical used.
**Methods:** A study of long-lasting and permanent fillers was performed in an attempt to understand the specific reactions induced by each agent. Agents were then compared with manufacturers' allegations and published data on complications.
**Results:** All the available products have a potential for complications. However, the difference between the normal healing process and true inflammatory granuloma must be established. For a volume effect, the implant, although deep, should induce the smallest inflammatory reaction, to avoid any long-term side effects. Particulate implants with porous or irregular surfaces are potentially more reactive than spherical, smooth-surface particles. Gels and oils have a potential for fragmentation, and each droplet will start a new inflammatory phase. For a superficial treatment, is seems better to use a "passive" filler, which should have no inflammatory reaction. The problem remains for combined indications: volume and smoothing, deep and superficial. After hyaluronic acid injections in areas previously treated with a nonresorbable agent, severe inflammatory granulomas have appeared, and it is not possible to state whether they are attributable to the new product, even a resorbable one, or to reactivation of the sleeping reaction from the previous implant.
**Conclusion:** There is an obvious need for serious, precise, and objective studies on most of the available fillers, which have not been properly scientifically studied on human skin. (*Plast. Reconstr. Surg.* 119: 2271, 2007.)

Facing the multiplicity of available injectable fillers, the first question one should ask is "Do we have to fill?" Answering "yes" means both the physician and the patient must accept the risks and consequences of implanting a foreign body. The ideal filling agent should be well tolerated by the tissues, with no allergic reaction and no immediate or delayed inflammatory reaction, and should either give an immediate permanent or long-lasting filling effect, or induce the stimulation of the host's fibroblasts and fibrocytes, with a long-lasting effect (i.e., giving a result for no less than 18 months, but with no visibility or palpability, and be easy to use).

None of the available products complies with all of these requirements. Some have a very short duration of their effect, whereas others will induce unacceptable and sometimes dangerous reactions. Some of these reactions result following injection using improper technique, but some reactions are attributable to the filler substance itself. All filling agents are not equivalent, and it is in this field of long-lasting fillers that physicians have to be careful in their use and extremely demanding of the manufacturers. The purpose of this study was to review the available agents and to analyze them through the knowledge of biomaterial studies.

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Injecting a foreign body into the host's tissue prompts a series of reactions directed at its identification, its isolation from the host tissues, and, if recognized as dangerous, its removal. These reactions form the normal healing and scaring process.

## HOST TISSUES REACTIONS

### Normal Healing and Foreign Body Reactions

#### Normal Healing

Normal healing starts with the wound, although minimal, caused by the injection.[1] The released platelets, when in contact with the extracellular matrix, liberate hemostatic factors, chemotactic agents that attract neutrophils and monocytes from the bloodstream, and fibroblasts. The extracellular matrix is composed of fibers, elastin, collagen, and liaison or adhesion glycoproteins. Within 2 hours after the initial trauma, the inflammatory phase begins. Activated neutrophils start phagocytosis of the alien elements and secretion of cytokines and proteolytic enzymes. Edema appears, which facilitates cell migration. Monocytes transform into macrophages to eliminate those particles too large to be phagocytized by the neutrophils and also to eliminate apoptotic neutrophils. Apoptosis is a genetically programmed cell self-destruction. It differs from necrosis, as it results in a disappearance of the cell membranes, chromatin condensation, chromatin fragmentation in small corpuscles (apoptotic bodies) that can easily be phagocytosed.[2] This allows for elimination of cells without inflammation (i.e., without negative impact on local tissues). Macrophages also secrete growth factors, to regulate the change from the inflammatory phase, cellular and for cleaning, into the proliferative phase, for reconstruction. The fibroblasts secrete into the extracellular matrix, initially type I collagen, immature fluid gel, and then type III, mature collagen. This maturation phase starts with collagen reticulation, which then leads to collagen contraction that tightens the net and brings back strength to the tissues.

#### Foreign Body Reactions

The foreign body must be recognized by the host. This recognition is based on the monocytes, which circulate inactivated in the bloodstream. Once activated, they will adhere to the firm substrate. The adhesion is the most important aspect of the cellular interaction.[3,4] Through adhesion, cellular responses are activated for spreading, proliferation, and differentiation. It is a complex process, implying protein adsorption on the surface of the foreign body, glycoproteins from the plasma or the extracellular matrix. The more proteins that are deposited on the surface of the implant, the more efficient the resulting cellular adhesion, spreading, and proliferation.[5]

These proteins start a specific recognition by cell surface receptors, and then a nonspecific interaction between cell surface molecules (oligosaccharides), the adsorbed proteins, and the implanted material.[6] This recognition is determined by podosomal structures between giant cells and the foreign body, microfibrils, and microvesicles at the interface implant/cells.[5] It is possible that these cells will then produce and may deposit new proteins over the foreign body.

Macrophages fuse into giant cells to attempt to phagocytose large particles.[2,7] There are two types of multinucleated giant cells, according to the type of granuloma, inflamed or from a foreign body.

*Langerhans cells* are seen in inflamed granulomas or in autoimmune diseases such as sarcoidosis. They show only a small number of nuclei, less than 20, that are positioned in a circular fashion at the periphery of the cell. The nonphagocytic material is surrounded by a collar of mononucleated cells, which are mainly lymphocytes.

*Foreign body giant cells* are found within foreign body granulomas. They show a much greater number of nuclei, well over 20, which are irregularly placed within the cytoplasm. Nonphagocytosed tissue is surrounded by a thin layer of macrophages, derived from monocytes and foreign body giant cells, without the lymphocyte collar. Foreign body giant cells are found at the interface of the host and the implanted medical devices, and will stay there for the lifespan of the implant even if their lifespan is 2 days only. Some have even been observed after 50 years, with slow and gradual replacement by scar tissue.[8] Anderson[9] has called this phenomenon "frustrated phagocytosis," with formation of a compartment between the foreign body giant cells and foreign body into which degradation enzymes, oxidizing oxygen ions, and other products are secreted. Foreign body giant cells play a part in polymer degradation, as they concentrate phagocytosis and degradation capacities at the host/implant interface, thus giving a greater efficiency than isolated macrophages. Furthermore, this transformation in foreign body giant cells could be a way of survival for the cells adhering to biomaterials.[2]

Between 7 and 10 days after introduction of the foreign body, the level of macrophage fusion increases, with an associated decrease in the num-

ber of apoptotic cells. Therefore, it appears that this cellular fusion, and thus the formation of foreign body giant cells, is an adaptation to the difficulties of eliminating foreign bodies, and "inefficient" cells are going into self-destruction (apoptosis) in a first step. Apoptosis is proved by cell prints on that protein layer.[5]

Thus, the more the cells are adherent to the surface, the less apoptosis will take place. In contrast, the more cell apoptosis is induced by a foreign surface, the less the macrophages will adhere. In other words, macrophages either adhere, phagocytose, or fuse into foreign body giant cells, or there is no adhesion and no phagocytosis. In that case, there is destruction without remnants of the inefficient protective cells, and the foreign body will be isolated by a thin fibrillar membrane, which is relatively poor in cells.

The inflammatory response comes in two steps: first, an acute inflammatory reaction with neutrophil polynuclear cells; then, over 2 weeks, chronic inflammation with lymphocytes or monocytes, according to the type and location of the implant. Fibroblasts will then isolate the implant with a fibrous collagenous capsule and will gradually be replaced by fibrocytes. Each foreign particle will finally be encapsulated independently from the others.[10,11] This local foreign body reaction has been measured and quantified by Duranti in a field with 400× magnification,[12] as follows:

Grade 0: no visible reaction.
Grade I: light reaction with few inflammatory cells (neutrophils, monocytes).
Grade II: obvious inflammatory reaction with one or two giant cells in the 400× field.
Grade III: fibrous tissue with inflammatory cells, lymphocytes, and giant cells.
Grade IV: granuloma with encapsulated implant and obvious foreign body reaction. (It must be stated this is precisely the reaction anticipated for encapsulation of our cosmetic implants.)

## Factors Modifying This Reaction

The body does not always respond in the same way to implants, and numerous factors may be involved in its reactions.

### Implant Size and Volume

Particle sizes larger than 20 μm are not phagocytosed by macrophages, keratinocytes, or foreign body giant cells.[13] The smaller the particles, the faster they are phagocytosed[14] and the greater the local inflammatory reaction, which may lead to local necrosis.[7,15] Furthermore, small particles can be transported, sometimes to distant organs, and cause dramatic complications (see Borgatti and Al in Pannek et al.[16]). However, even large particles (251 to 300 μm) injected into veins around the urethra to treat urinary incontinence can be transported at a distance.[16]

For fluid implants, either liquid or gel, such as silicone, the reaction at the host/implant interface will diminish within 3 to 4 weeks, but will be reactivated in an acute manner for each droplet that becomes detached from the main mass.[17] Thus, the inflammatory reactions can last for years and follow the eventual displacement of the implant. The same can be seen with solid implants, such as Teflon paste.[8,18]

### Implant Morphology

Tumor necrosis factor levels are an excellent indicator of macrophage activation.[19] However, prostaglandin $E_2$ and tumor necrosis factor production is more important for particles of irregular shape when compared with round smooth particles of the same material.[15] This was described by Matlaga et al.,[20] in which triangular polymeric implants induced greater acid phosphatase enzymatic activity than round or pentagonal rods. The fibrous capsule around an implant is not always regular, showing thicker zones over flat surfaces and thinner zones at the edges.[21] Smooth surfaces induce the formation of a much thicker fibrous capsule than textured surfaces, with less cellular adhesion, and only one or two layers of macrophages and foreign body giant cells at their interface,[13,22,23] whereas irregularly shaped particles show a much longer lasting inflammatory reaction, with less mature collagen deposition.[24] The same can be seen with polylactic acid, where porous microspheres, with numerous recesses and channels, induce a severe foreign body reaction with local destruction and necrosis within the implant,[25] whereas smooth microspheres will induce only moderate reaction.[14]

### Surface Area

Gelb et al.[15] calculated a critical value for a particle area above which the inflammatory response increases spectacularly. This explains why, for a set volume of implant, induced reactions are less with round particles, as the round shape has the smallest surface for a given volume. The same applies for 100-μm-diameter microspheres which, for an equal mass, induce formation of 56 percent fibrous tissue, whereas 40-μm-diameter microspheres induce 78 percent fibrous tissue, because the total surface area for the same mass composed of the smaller microspheres is larger.[26] This concept of threshold surface area could also play a

part for particles of irregular or porous surface, which increase their total surface area.

**Chemical Composition**

The chemical composition of the implant also plays a part, as noticeable differences in local reactions appear according to the type of particle.[3,7,27] Indeed, the chemical characteristics of the implant induce adhesion of macrophages, then indirect induction of cellular apoptosis.[2] Hydrophobic compounds favor fibronectin adsorption and thus cellular adhesion and inflammatory reaction. In the same manner, carboxylic groups (hydroxyethylmethacrylate) are strong activators of the C3 fraction of the complement, making them easily recognizable by specific macrophages.[28] For example, sialic acid is present on the cell surface of vertebrates and therefore carboxylate anions are present. This does not exist in bacterial cells, except in some pathogenic strains. This is a simple and efficient way for the human body to quickly recognize alien elements. The higher the carboxylate anion concentration is, the less macrophage spreading and fusion into foreign body giant cells there is.[4] Cell adhesion is stronger on a silicone/hydroxyapatite composite film or a biodegradable polymer/hydroxyapatite composite than on a silicone film.[3,29] A nonresorbable composite, glass microbeads/polymethylmethacrylate allows for an osteointegration that does not exist with polymethylmethacrylate alone.[30] As macrophages also play a role in control of fibroblast activity, the resulting fibrous capsule will be different according to the chemical characteristics of the implant. This can affect repartition and transportation of particles within the body. Phagocytosed polymethylmethacrylate microparticles may be transported some distance with the macrophages, whereas polystyrene that has been phagocytosed will tend to stay within the fibroadipose local tissues.[7] Finally, if polymethylmethacrylate seems to have an important level of infectivity when polymerized in situ, polymethylmethacrylate-polyhydroxyethylmethacrylate association makes this material much more resistant to infection.[31]

**Electrical Charge**

The electrical charge of the implant plays a major role: positively charged microbeads within a wound attract and/or activate macrophages.[11,32] This helps formation of foreign body giant cells, then of fibroblasts, and increases the amount and the composition of the new connective tissue. In the same way, a negative surface charge could repel some negatively charged bacteria.[31]

**Implantation Site**

The implantation site clearly has a role in morbidity. The rate of complication is lower in the chin and malar areas and higher in the nose and ears, where cutaneous cover is thinner and often placed under tension by the implanted material. For the ear, a flexible implant seems to induce fewer complications than a rigid one.[33] Li et al.[21] have well described that the fibrous capsule surrounding hydroxyapatite disks was thicker over the subcutaneous face than over the lateral or deep faces of the disk.

## MATERIALS AND METHODS

**Products Available for Implantation by Injection**

Table 1 lists the available long-lasting and permanent injectable fillers, to date.

**Solid Acrylic Polymers**

**Dermalive and Dermadeep (Dermatech, Paris, France)**

Dermalive is made of fragments of two acrylic polymers, hydroxyethyl methacrylate and ethyl methacrylate, 45 to 65 μm in size, 2%, within 1.4% cross-linked hyaluronic acid in 96.6% saline. The CE mark is no. 0120, and it is sold in 0.8-ml syringes with a 27-gauge, ½-inch needle. It is kept refrigerated between 2° and 8°C and left to warm to room temperature 2 hours before injection. No allergy test is necessary. To be injected into the deep dermis, no overcorrection is required.

Dermadeep is made of fragments of the same two acrylic polymers, hydroxyethyl methacrylate and ethyl methacrylate, but 80 to 110 μm in size, 2%, within 1.4% cross-linked hyaluronic acid in 96.6% saline. The CE mark is no. 0120, and it is sold in boxes of two 1.2-ml syringes with a 26-gauge, ½-inch needle. It is kept refrigerated between 2° and 8°C and left to warm to room temperature 2 hours before injection. No allergy test is necessary. It should never be injected within the dermis, but only in a hypodermic or epiperiosteal position. No overcorrection is required.

**Polymethylmethacrylate: Artecoll (RMI, Breda, The Netherlands) and Artefill (Artes Medical, Inc., San Diego, Calif.)**

Artecoll is made of smooth, round polymethylmethacrylate microspheres, 30 to 42 μm in diameter, 20% as a suspension within a solution of partly denatured bovine collagen 3.5%, lidocaine hydrochloride 0.3%, saline 72.2%. CE-mark no. 0344, and it is sold in boxes of four syringes of 0.5 ml with 27-gauge needles, and is kept refrigerated above 4°C and left to warm to room temperature

## Table 1. The Available Long-Lasting and Permanent Injectable Fillers

| Composition | Commercial Name | Action | Location | Skin Test | Syringe, Needle | Duration | Manufacturer | Countries |
|---|---|---|---|---|---|---|---|---|
| Resorbable: moderate duration (12–18 mo) | | | | | | | | |
| 40/60-μm microspheres: dextran 2.5% in reticulated hyaluronic acid 2%, sterile water 95.5% | Beautysphere, Reviderm | Temporary volume, host stimulator | Intermediate/ deep dermis | No | 1 ml, 26 gauge | 12–18 mo | R.M.I., Breda, The Netherlands | Europe, Mexico, Argentina, Russia, Middle East |
| Reticulated polyvinylic alcohol 8% in sterile water 92% | Bioinblue | Temporary tissue substitute | Dermis, hypodermis, deep fat, mucosa | No | 2 × 0.7 ml, 24 gauge | 12–18 mo | Polymekon, Milan, Italy | Europe, Canada, Latin America, Israel, Turkey |
| Heterologous micronized acellular dermis in 0.5% lidocaine and 1:200,000 epinephrine | Cymetra | Temporary tissue substitute | Superficial/ intermediate dermis | No | | 12–18 mo | LifeCell Corp., The Woodlands, Texas | Europe, United States |
| Resorbable: long duration (2–4 yr) | | | | | | | | |
| Acrylic polymer gel, polyacrylamide 3%, sterile water 97% | Outline Fine, Outline Original, Outline Ultra | Temporary tissue substitute | Intermediate/ deep dermis | | 1 ml 27–30 gauge for Fine and Original; 1 ml, 27 gauge for Ultra | Fine, 50% 1 yr; Original, 50% 2 yr; Ultra: 50% 4 yr | Procytech, Marcillac, France | Europe, Canada, Southeast Asia, China, Lebanon, South Africa, Kuwait |
| 2/50-μm microspheres: polylactic acid 4.45% in carmellose 2.67%, mannitol 3.78%, sterile water 89% | New-Fill, Sculptra | Temporary volume, host stimulator | Intermediate/ deep dermis | No | Vial: 3–5 ml, 26 gauge | 36–48 mo | Dermik Laboratories, Berwyn, Pa. | Europe, U.S. FDA approval |
| Permanent | | | | | | | | |
| Microspheres: polyvinyl hydroxide in polyacrylamide gel | Evolution | Temporary volume, host stimulator | Intermediate/ deep dermis | No | | Permanent | Procytech, Marcillac, France | Europe, Canada, Southeast Asia, China, Lebanon, South Africa, Kuwait |
| 20/50-μm microspheres: calcium hydroxyapatite 30% in carboxymethyl cellulose gel 70% | Radiesse | Permanent volume, host stimulator | Hypodermis, intramuscularly, not epiperiosteal | No | 1 ml, 26 gauge | Permanent | Bioform, Inc., San Mateo, Calif. | Europe, United States |
| 30/41-μm microspheres: PMMA 25% in bovine collagen molecule solution 3.5%, lidocaine 0.3%, saline 72.2% | Artecoll, Artefill | Permanent volume, host stimulator | Deep dermis, hypodermis, epiperiosteal | Yes | 4 × 0.5 ml, 27 gauge, ½-inch | Permanent | R.M.I., Breda, The Netherlands; Artes Medical, Inc., San Diego, Calif. | Europe, China, Japan, Asia, South America, Canada, Russia, Turkey, Pakistan, Middle East, Europe, U.S. FDA |
| Fragments of acrylic polymer HEMA and EMA (45–65 μm) 2% in reticulated hyaluronic acid 4%, saline 96.6% | Dermalive | Permanent volume, host stimulator | Deep dermis | No | 0.8 ml, 27 gauge, ½-inch | Permanent | Dermatech, Paris, France | Europe, Canada, Africa, Latin America, Asia, Australia |
| Fragments of acrylic polymer HEMA and EMA (80–120 μm) 2% in reticulated hyaluronic acid 4%, saline 96.6% | Dermadeep | Permanent volume, host stimulator | Hypodermis, epiperiosteal | No | 0.8 ml, 26 gauge, ½-inch | Permanent | Dermatech, Paris, France | Europe, Canada, Africa, Latin America, Asia, Australia |
| Acrylic polymer gel alkyl-imide 4% in sterile water 96% | Bio-Alcamid Lips, Face, and Body | Tissue substitute | Lips: submucosal, intramuscular; Face and Body: superficial/ deep dermis, hypodermis | No | Lips: 2 × 1 ml, 21, 23, and 24 gauge; Face: 2 × 3 ml, 16,19, and 20 gauge; Body: 2 × 5 ml, 14-gauge cannula | Permanent | Polymekon, Milan, Italy | Europe, Canada, Latin America, Israel, Turkey |
| Acrylic polymer gel, polyacrylamide 2.5% in sterile water 97.5% | Aquamid | Tissue substitute | Hypodermis | No | 1 ml, 27 gauge | Permanent | Contura International S.A., Soeborg, Danemark | Europe |
| Autologous fibroblasts in specific medium | Isolagen | Host stimulator | Superficial/ intermediate dermis | No | 1.2 ml, 30 gauge | Permanent | Isolagen Laboratories, Paramus, N.J. | Europe, United States |

PMMA, polymethylmethacrylate; HEMA, hydroxyethylmethacrylate; EMA, ethylmethacrylate; FDA, Food and Drug Administration.

2 hours before injecting. No allergy test is required, but two allergy tests, at 4-week intervals, may be a precaution against potential allergies to bovine collagen. It is injected into deep dermis, hypodermis or epiperiosteally. No overcorrection is required, and 3 to 4 months should be allowed to elapse before a new injection.

Artefill is a made of smooth, round polymethylmethacrylate microspheres, 30 to 42 μm, and is highly purified, as the number of particles smaller than 20 μm in diameter is fewer than one in 100 microspheres. Microspheres are suspended 20% in a solution of highly purified collagen and lidocaine 0.3%. Artefill was recently tested in U.S. clinical trials[34] and received an approval letter from the U.S. Food and Drug Administration in 2004.

### Acrylic Polymer Gels

**Polyacrylamide Gels: Royamid, Formacryl, and Interfall (Contura S.A, Montreux, Switzerland, and Kiev, Ukraine)**

*Aquamid* (Contura International S.A., Soeborg, Denmark) is a cross-linked polyacrylamide gel 2.5% in 97.5% pyrogen-free water. The CE mark no. 0543, and it is sold in 1-ml syringes, kept at room temperature, to be injected with a 27-gauge needle. It should be injected deeply, not into the dermis. No allergy test is required, and no overcorrection or undercorrection is required.

*Outline* (Procytech SARL, Martillac, France) is also a cross-linked polyacrylamide gel 3% in 97% pyrogen-free water. The CE mark no. 0499, and it is sold in syringes of 1 ml with 27- or 30-gauge needles and delivered in three viscosities, to be kept at room temperature and to be injected into the mid or deep dermis. No allergy test is required and no overcorrection is required; an undercorrection is preferred, with touchup at 2 weeks.

**Polyvinyl Hydroxide Microspheres in Polyacrylamide Gel: Evolution (Procytech Sarl, Martillac, France)**

Evolution consists of porous polyvinyl hydroxide microspheres 40 μm in diameter, 6% in a cross-linked polyacrylamide gel 2.5% in 91.5% pyrogen-free water. It is sold in 0.5-ml syringes with 27-gauge needles. It should be injected into mid or deep dermis or hypodermis. No allergy test is required.

**Polyalkylimide Gel: Bioalcamid (Polymekon, Milan, Italy)**

Bioalcamid is an alkylimid polymer gel 4% in 96% pyrogen-free water. The CE mark is no. 0123, and it is sold under three presentations: lips, 2 × 1 ml syringes with 21-, 23-, and 24-gauge needles, not to be injected in muscle or mucosa; face, 1 × 3-ml syringe with 16-, 19-, and 20-gauge needles; and body, 2 × 5 ml syringes with a 14-gauge needle and cannula type tip. It is kept at room temperature. It must be injected subcutaneously and can be used deeply. No allergy test is required.

### Other Polymers

**Cross-Linked Polyvinylic Acid: Bioinblue (Polymekon, Milan, Italy)**

Bioinblue consists of polyvinylic alcohol 8% gel in 92% pyrogen-free water. The CE mark is no. 0123, and it is sold in boxes of two 0.7-ml syringes with 24-gauge needles. It can be injected into dermis, hypodermis or deep fat layers, and mucosa. It gradually disappears over 18 months. No allergy test is required.

**Polylactic Acid: New-Fill/Sculptra (Dermik Laboratories, Berwyn, Pa.)**

New-Fill/Sculptra is made of polylactic acid microspheres, 2 to 50 μm in diameter, 4.45% in sodium carmellose 2.67%; mannitol 3.87%, to be diluted in 3-ml pyrogen-free water 89%. The CE mark is no. 0459, and it is sold as a kit with two vials of lyophilized product with 26-gauge needles. It is kept at room temperature, reconstituted at least 30 to 60 minutes before injection, and injected into the dermis, intermediate or deep. No allergy test or overcorrection is required. At least 3 to 4 weeks should be allowed to elapse between two sessions.

**Silicone Particles: Bioplastique**

Bioplastique is composed of polymerized irregular-shaped silicone particles (polymethyl siloxane), 100 to 600 μm in size, suspended in polyvinylpyrrolidone as a carrier. No allergy test is required.

**Dextran Microspheres in Hyaluronic Acid: Reviderm, Philoderm, and Beautysphere (RMI, Breda, The Netherlands)**

Dextran microspheres 40 to 60 μm in diameter, 2.5%, mixed with cross-linked hyaluronic acid 2% in pyrogen-free water 95.5%. The CE mark is no. 0125, and it is sold in 1-ml syringes with 27-gauge needles. It is kept refrigerated between 2° and 8°C and injected into intermediate and deep dermis. No allergy test or overcorrection is required.

**Calcium-Hydroxyapatite Microspheres: Radiance/Radiesse (Bioform, Inc., San Mateo, Calif.)**

Calcium hydroxyapatite microspheres 25 to 40 μm in diameter, 30%, in a carboxymethylcellulose

gel 70%. The CE mark is no. 0086C, and it is sold in 1-ml syringes with 26-gauge needles. It must be injected subdermally or intramuscularly. Epiperiosteal injection must be avoided, to prevent stimulation of implant ossification. Overcorrection is to be avoided.

### Biological Products

#### Autologous Fibroblasts: Isolagen (Isolagen Laboratories, Houston, Texas)

This method uses tissue from a 3-mm punch biopsy specimen taken from the retroauricular skin, which is usually less exposed to ultraviolet radiation. Placed in a special medium and kept refrigerated, it must be sent to the laboratory by special transport on the same day; 1.2 ml is available after cellular growth over 8 weeks. It is injected within superficial or intermediate dermis with a 30-gauge needle.

#### Micronized AlloDerm: Cymetra (LifeCell Corporation, Branchburg, N.J.)

AlloDerm is an acellular dermal graft from cadaver or bank dermis. It provides extracellular matrix with collagen, elastin, and glycosaminoglycans. AlloDerm is sold as a sheet to be reconstituted in saline for surgical implantation. To simplify its use as an injectable, it has been micronized. Sold under the name Cymetra, it is a powder to be reconstituted with 0.5% lidocaine and epinephrine 1:200,000.

## DISCUSSION

### The Different Products

#### Dermalive and Dermadeep

Microparticles contained in these products combine a very hydrophobic element (ethyl methacrylate) that will strongly favor fibronectin adsorption and therefore cell adhesion, and a hydrophilic element that also bears carboxylic groups (hydroxyethyl methacrylate), a strong activator of the complement C3 fraction. These properties make the microparticles very recognizable by specific macrophages.[28] This association of hydroxyethyl methacrylate and ethyl methacrylate enhances particle recognition and isolation reactions. This gives a wanted neocollagenesis effect, but also provides the potential for a strong inflammatory reaction. This significant potential for clinical reaction is confirmed by up to 11 percent of patients presenting with complications including as much as 5.5 percent secondary granulomas with Dermalive.[35] These granulomas, grade IV on the Duranti scale,[12] are characterized by foreign bodies of different sizes and shapes, pink in color, extracellular, and with numerous foreign body giant cells showing many asteroid bodies, a proof of phagocytosis, some lymphocytes, and a thick and abundant layer of collagen.[36] Such products show us how difficult it can be to ascertain the risk of toxicity associated with the products offered to practitioners. A study on 455 patients who were followed up for 3 years has shown complications at a rate of less than 1.2 percent.[37] However, the amount of inflammatory granulomas observed after 1 to 3 years, and particularly following new injections of hyaluronic acid, has led many practitioners to choose not to use these implants and to contraindicate new injections in the same sites.[38] These granulomas present as very hard nodules, with often a very erythematous skin.

#### Artecoll and Artefill

The microsphere diameter, between 30 and 42 $\mu$m, prevents phagocytosis. Their smooth surface lessens cell adhesion and therefore foreign body reaction, and the collagen vehicle keeps them apart long enough to prevent a mass effect by agglutination.[14] From the ninth day after injection, all the empty spaces around the microspheres are filled with fibroblasts. After 2 weeks, the first capillary vessels are present, and by the third week, the first collagen fibers can be detected. The early reactions explain why there is no displacement of the product: the microspheres are first embedded in the injected collagen and then, while it is absorbed, by the fibrous reaction of the host tissues. The remaining new connective tissue volume is produced between 3 and 4 weeks.[39] After 2 months, the collagen fibers' density increases, with beginning of contraction of the free spaces and reduction of the spaces between the microspheres. At the fourth month, the active fibrosis phase is over, and the implant remains stable. After 7 months, there are very few differences between the collagen fibers around the implant and those of the surrounding connective tissue. Even on the histology slides of analyzed lesions, there are few foreign body giant cells, few lymphocytes, and a loose fibrous tissue, corresponding to Duranti's grade II. Microspheres are easily recognizable, appearing as extracellular, round, smooth, regular vacuoles.[40] However, for McClelland et al.[41] it could exist as a transepidermal migration of the particles. Lemperle and Kind[42] believe this to be highly improbable if the injection was correctly made at the deep dermal or subdermal level. It has also been seen, in a case of inflammatory granuloma of the forehead, that polymethylmethacrylate microspheres have been phagocytosed by macrophages and giant cells.[43]

Artecoll is one of the very few injectable implants for which proper scientific studies, and long-term follow-up of 200,000 cases over 10 years, have been performed. The alleged complication rate of 0.2 percent is probably close to reality.[39,44–48] It is more difficult to use it in the lips, as the injected strands could be compressed by muscle movement, giving unsightly nodules. These may be prevented by using the microdroplet injection technique or immobilization of the lip by adhesive tape for 2 to 3 days after injection, although some very good results have been achieved without tape.[49]

**Acrylic Polymer Gels: Polyacrylamide Gel**

When injected in small amounts, acrylamides break into small droplets, like silicone oil, whereas large injected volumes will stay as a mass. In fragmented implants, a thin collagen capsule forms around the droplet, which indicates good local tolerance, but the fragments also induce an important inflammatory reaction, with phagocytosis and foreign body giant cells. There is also microscopic infiltration of the surrounding tissues, with interdigitations within the connective and adipose tissues[50] or even the muscular tissue, although according to Christensen et al.,[51] "the secondary effects cannot be blamed on the characteristics of the gel itself." This displacement of the gel has been observed at long distance from the implant, notably from the submammary area, within the glandular tissue, and up to the clavicles, because of the absence of a thick capsule.[52] The reported complications range from simple indurations with palpable nodules to destruction of mammary or cutaneous tissue, with an invasive fibrosis that is impossible to distinguish clinically or radiologically from carcinomatous tissue.[53–57] An experimental study by Huo et al.[58] has shown that polyacrylamide gels are toxic for the kidneys, that the shape and location of the implant were not stable, and that it could not be entirely removed, in contrast to the manufacturer's assertions. In many countries, removal of the material has required a direct surgical approach. Use of polyacrylamide hydrogels is now forbidden in Russia and in Bulgaria.[57]

*Aquamid* has been studied by several authors,[50,51,59] some of whom are included in the laboratory presentation files. One currently submitted publication describes 68 patients receiving implants. However, on careful review, 20 of these patients were included in the study analysis who did not satisfy the inclusion criteria, and only 57 of the enrolled patients could be evaluated. It does not seem that these studies are scientifically irreproachable[60] and their analysis, when considering the numerous reports about their complications, brings one to conclude more toward caution than toward use of the implant.

Regarding *Outline*, according to the laboratory files, "porosity of the gel has been chosen to create a net so that only macromolecules can colonize it, so that cells, especially macrophages, remain outside the gel. It is slowly absorbed over 2 to 8 years, depending on the chosen viscosity, under the action, notably, of nonspecific esterases, which gradually shorten the molecular chains." Allegedly, there would not be any release of toxic acrylic monomers.

**Acryl-imides: Bio-Alcamid**

According to the manufacturer, this polymer is different from polyacrylamide as it contains imid-amid groups. In vitro, it does not interfere with fibroblast growth.[61] In vivo, it has the same type of reaction as the polyacrylamide gels, as it does not induce a thick capsule formation. It does not seem to induce an inflammatory cell reaction or foreign body giant cell formation.[62] It has been used in the treatment of human immunodeficiency virus–induced facial lipoatrophy in over 80 patients without apparent secondary effects.[63] For the authors and the manufacturer, this implant would be a true injectable endoprosthesis that could be removable by percutaneous puncture and manual pressure. For large volumes (some have injected up to 1600 ml), it is mandatory to divide the injection into several boluses with a maximum of 20 to 25 ml each. The manufacturer recommends a strict aseptic procedure and antibiotic prophylaxis. To date, follow-up is still short, and scientific clinical studies are lacking. It can also be said that Polimekon has sold the Russian acrylamide before it started manufacturing acrylamide. More scientific evidence of the differences between the two types seems mandatory.

**Cross-Linked Polyvinylic Alcohol: Bioinblue**

This polymer should not induce inflammatory reactions because it is metabolized into acetoacetic acid within the Krebs cycle. The implant shows a slow degradation and would be replaced in an isovolumetric fashion, by neocollagen. To our knowledge, there are no clinical or biological studies of its human intracutaneous use.

**Polylactic Acid: New-Fill/Sculptra**

New-Fill/Sculptra contains particles between 2 and 50 $\mu$m. Those larger than 30 $\mu$m should not be phagocytosed, but their enzymatic degradation makes them porous. Thus, after a first phase of moderate inflammation, when they become porous, there follows a secondary stronger inflammatory phase, with many foreign body giant cells,

to phagocytose and accelerate the degradation of the implant.[64] When polylactic acid screws and plates are used for craniofacial bone fixation, the absorption can last up to 2 to 3 years, and always shows, after 30 to 60 months, a strong sterile foreign body reaction.[33] At least one case of severe inflammatory granuloma has been described,[65] as has one case of diffuse probable infection, although the agent was not identified.[66] In my personal experience with New-Fill, no complications over a 4-year period were observed, despite repeated 3-ml injections in the cheeks for human immunodeficiency virus facial lipoatrophy.[67] I do not use it in the lips, as the microspheres can be displaced and can form unsightly nodules. I have removed several of these, injected by someone else deep into the muscles, fairly easily every time, as they always were well individualized into a strong capsule.

**Dextran Microspheres in Hyaluronic Acid: Reviderm, Philioderm, and Beautysphere**

The positive electrical charge of the dextran microspheres has a stimulating effect on macrophages, fibroblasts, and connective tissue formation.[11,32] Lemperle et al.[68] have shown that, despite this strong stimulation of the fibroblasts to produce collagen in human skin, no histologic evidence of its persistence could be seen after 9 months. This contradicts the results of Eppley et al.,[32] who found larger dextran microspheres, abundant collagen, and fibroblasts 1 year after their subcutaneous injection. It must be stated that they injected 1.5 ml of product under the skin of rats, which is a very large amount compared with Lemperle et al., who injected 0.1 ml subcutaneously into human skin. We did not find any clinical studies on these implants.

**Calcium Hydroxyapatite Microspheres: Radiance/Radiesse**

Calcium hydroxyapatite has been widely studied and used as a bone substitute, either as a filler or as a reconstitution matrix to support osteoblast attachment,[3,10,21] but also as a filler in other anatomical structures, such as the urethra and larynx.[18] The round microspheres induce less inflammatory reaction and disappear faster than irregularly shaped ones.[24] In the lips, as for any microsphere implant, it can be compressed by muscular action, which results in unsightly nodules. The first users seem satisfied despite a very high percentage (44 percent) of nodules in the lips.[69,70] Sometimes, the implant is visible in patients with thin skin as a white paste. There are yet no precise studies on its long-term durability in human skin.

**Silicone Particles: Bioplastique**

The size of the particles makes them nonphagocytable. However, their irregular shape will induce a strong foreign body reaction, as it does increase the total surface area of the implanted particles. The fluid carrier does not allow for keeping the particles apart, which favors cluster formation and increases the potential for foreign body reaction. Very active granulomas can be seen, with numerous foreign body giant cells, many phagocytes with asteroid bodies infiltrating all the spaces, even within the recesses of the particles themselves, and surrounded by very thick collagen bundles mixed with fibroblasts and a moderate lymphocytic infiltrate,[40] Duranti's grade IV. Despite the size of the particles, they have been transported to lymph nodes following urethral injection.

**Autologous Fibroblasts**

Isolagen is based on the hypothesis that the injection of collagen-producing cells should produce a longer lasting result than with injected collagen.[71,72] Supposedly, it is a permanent material. This seems to be confirmed by biopsies performed at 4 years.[73,74] Three injections are recommended at each site, and the result is achieved 6 months after the last injection. The patient's cell bank may be kept indefinitely in liquid nitrogen, so that additional injection syringes can be prepared without a new biopsy. Furthermore, adjunctive skin therapies, such as laser or peels, stimulate the fibroblasts and show enhanced results. The drawbacks to this approach include its cost, the stringent procedures required for biopsy, packaging and shipment under controlled cold temperature, use within 24 hours after delivery, and the time required to culture the fibroblasts before they can be shipped back to the clinic for the patient's injection.

**Cymetra (Micronized AlloDerm)**

The duration of the correction was hoped to be long lasting, but it does not seem to be any better than collagen or hyaluronic acid. Some authors have attempted to extemporaneously morselize AlloDerm sheets and inject the fragments with a 16- or 18-gauge catheter.[75]

## Clinical Indications

Obviously, it is difficult to choose which product will be the best to use in a given situation. Nevertheless, it is possible to make some recommendations.

**Lips**

The injection site is different according to the desired effect (Fig. 1). At the wet/dry border,

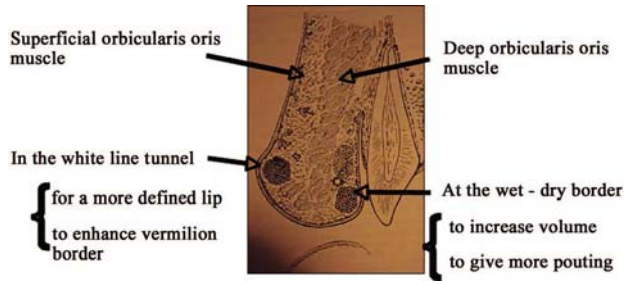


**Fig. 1.** Lip remodeling: where to inject.

injection will increase the volume and evert the lip. Within the white line, it will help define it, modify the cupid's bow, and increase pouting. However, muscular action will tend to displace the implant, especially those with microspheres. Should these be used in that location, very good training is needed. The lip has to be immobilized for several days. It is possible to use botulinum toxin in very small and diluted amounts to reduce movements temporarily. Radiesse is too white and will show through the mucosa, Sculptra will break into small fragments and form unsightly nodules, and dextran in Beautysphere will cause too much edema. My choice is Artecoll, provided the lip is properly immobilized (Fig. 2). Aquamid in very small amounts could be interesting, but long-term follow-up is yet to come.

**Superficial Wrinkles**

Regarding cheeks and crows' feet, no permanent filler should ever be used in these locations, as they will form nodules and ridges under this very thin skin. One has to be very cautious in the forehead, as the injection might seem deep but could still be within the thick superficial dermis. This will result in nodules and inflammatory reaction (Fig. 3).

**Deep Creases**

Regarding nasolabial folds and glabella, in these mobile areas, it is probably better to use a microparticle implant, as the gels (polyacrylamide) might be displaced. My preference goes to Artecoll or Sculptia, positioned in the deep dermis.

**Volume**

This is where acrylamide gels have been advocated the most, but I fear that they might migrate easily, as almost no capsule is formed around them. Also, the reports of serious complications following injection of large amounts do lead to caution in their use. New-Fill has been approved by the U.S. Food and Drug Administration for its use in human immunodeficiency virus–related facial atrophy and gives good lasting results. Several sessions at 4- to 6-month intervals are necessary for large amounts (Figs. 4 and 5). Artecoll also gives good results, even if its price could make it quite expensive for use in large volumes. It is nevertheless very efficient for facial bone augmentation (Fig. 6) or to repair subcutaneous defects (Fig. 7). I do not use, and will not recommend using Dermalive or Dermadeep, considering the number of late major inflammatory granulomas induced.

## Treatment of Complications

Treatment of complications almost exclusively concerns inflammatory granulomas. It is important to stress that all nodules encountered are not inflammatory.[48] It is especially so for most of those removed from the upper lip, which often are

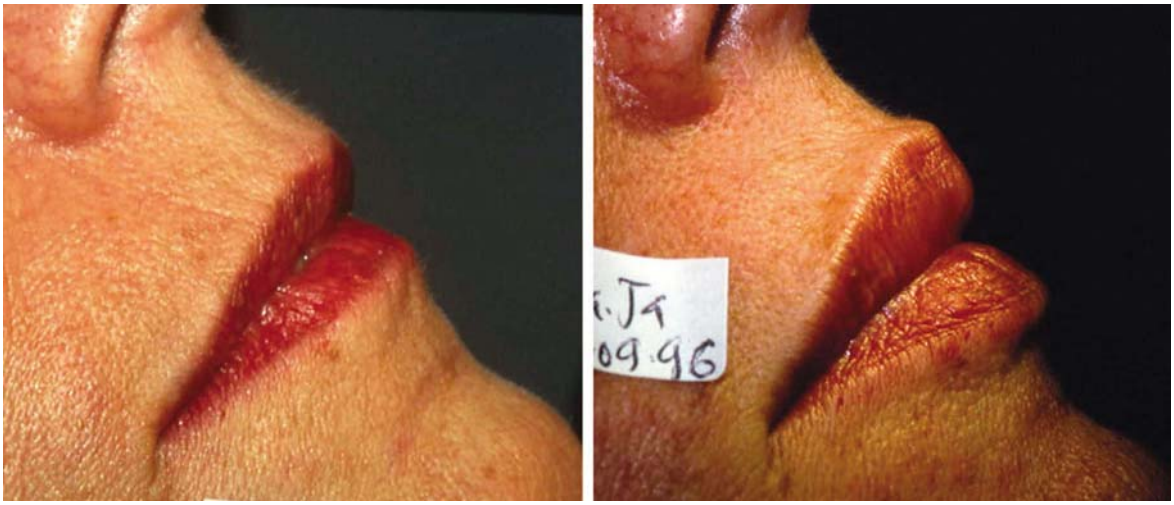

**Fig. 2.** Photographs of lips before injection (*left*) and after Artecoll injection, 0.5 ml, in two sessions at 6-month intervals (*right*).

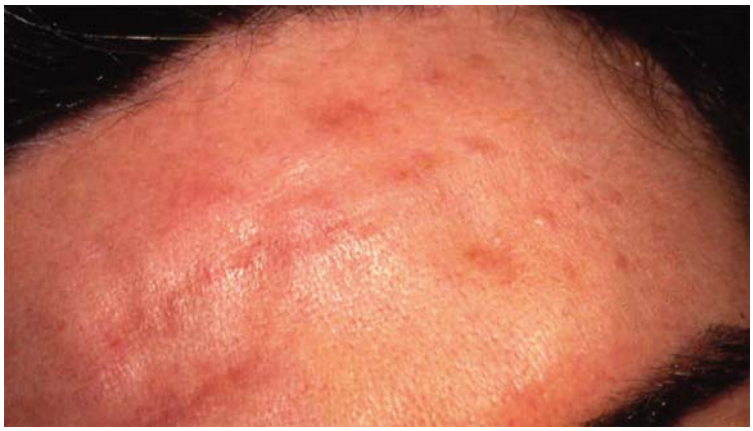

**Fig. 3.** Injection in the forehead that is too superficial.

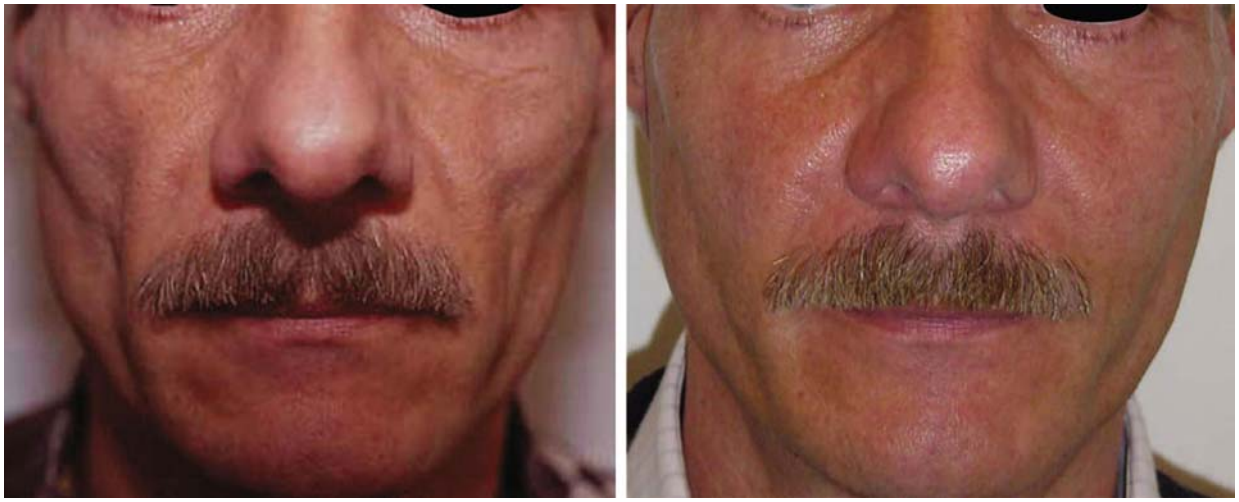

**Fig. 4.** (*Left*) Human immunodeficiency virus–related facial atrophy: New-Fill before injection. (*Right*) New-Fill, after three sessions of 3 ml on each side at 6-month intervals.

caused by compression of the implant along the white line or by intramuscular injection, and are mainly associated with implants consisting of microspheres (Artecoll, New-Fill, Radiesse, and Reviderm) (Fig. 8).

The etiologic diagnosis is mandatory. For medicolegal reasons (e.g., unauthorized silicone injections), it should be impossible that patients do not know what product has been used. Several granulomas were first attributed to Artecoll, but the implants were actually silicone oil.[36] For an appropriate treatment, the following should be considered:

- Corticosteroid therapy, which diminishes cellular activity and inflammatory response, is almost ineffective in Dermalive implants, forbidden in polyacrylamide gels (Aquamid, Bioalcamid), and disappointing in silicone oil nodules.
- 5-Fluorouracil, which should suppress macrophage and fibroblast activity, gives moderate results in Dermalive granulomas but causes the appearance of a perilesional violet discoloration.[38]
- Allopurinol, successfully used in the treatment of cutaneous lesions in sarcoidosis, has proven to be efficient in treating Arteplast granulomas.[43] I have successfully used it as a complement for local corticosteroid therapy in one case of recurrent Dermadeep granuloma.
- Surgical excision is indicated for unsightly lesions and/or for those with major psychological impact. Polyacrylamide gels, despite the manufacturer's claims, are not always removable, and have a rate of superinfections that is not acceptable.[53] It is important to keep the resulting scar as small and inconspicuous as possible. Deep nodules can sometimes be re-

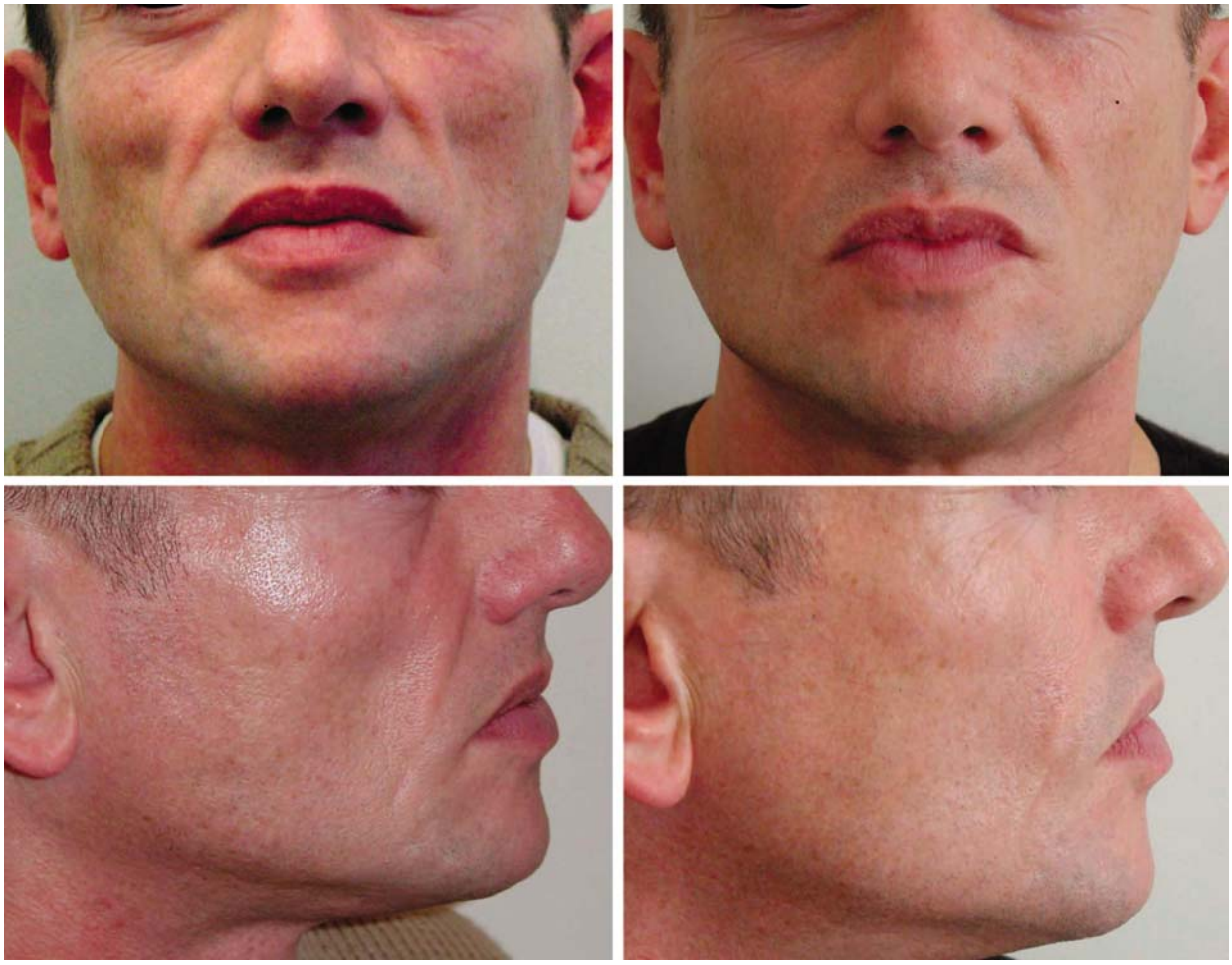

**Fig. 5.** (*Above*, *left*) Frontal view obtained before injection of New-Fill. (*Below*, *left*) Profile view obtained before injection of New-Fill. (*Above*, *right*) Frontal view obtained after injection of New-Fill, 6 months after one session of 3 ml on each side. (*Below*, *right*) Profile view obtained after injection of New-Fill, 6 months after one session of 3 ml on each side.

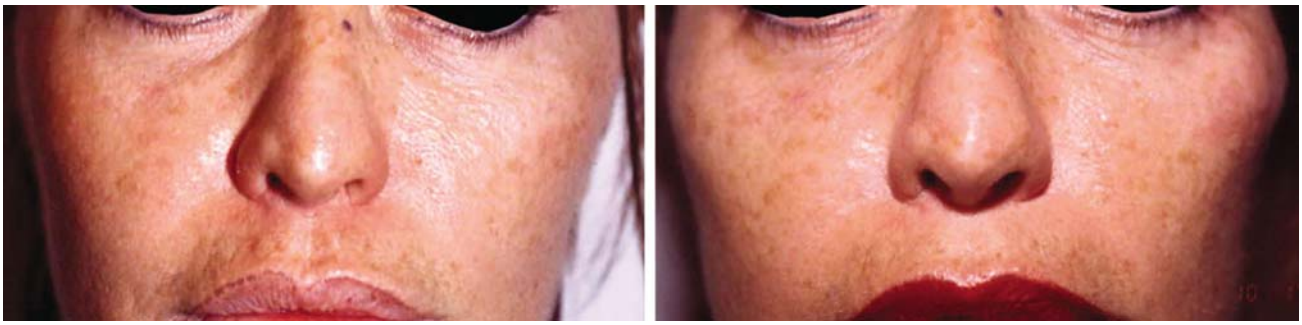

**Fig. 6.** (*Left*) Cheek bones before injection. (*Right*) Image obtained after injection of 1 ml of Artecoll on each side.

moved through distant skin incisions. In the lips, mucosal scars are easily hidden, but deformation can persist.

- Pulsed dye laser reduces angiogenesis and endothelial cell growth factors, and has been used with modest results on superficial lesions. It is contraindicated for silicone oil, as several cases of burns have been reported, especially with carbon dioxide lasers.[76,77]

## CONCLUSIONS

There are two types of injectable products: tissue substitutes and host tissue growth stimulators. Obviously, any injection, through the very

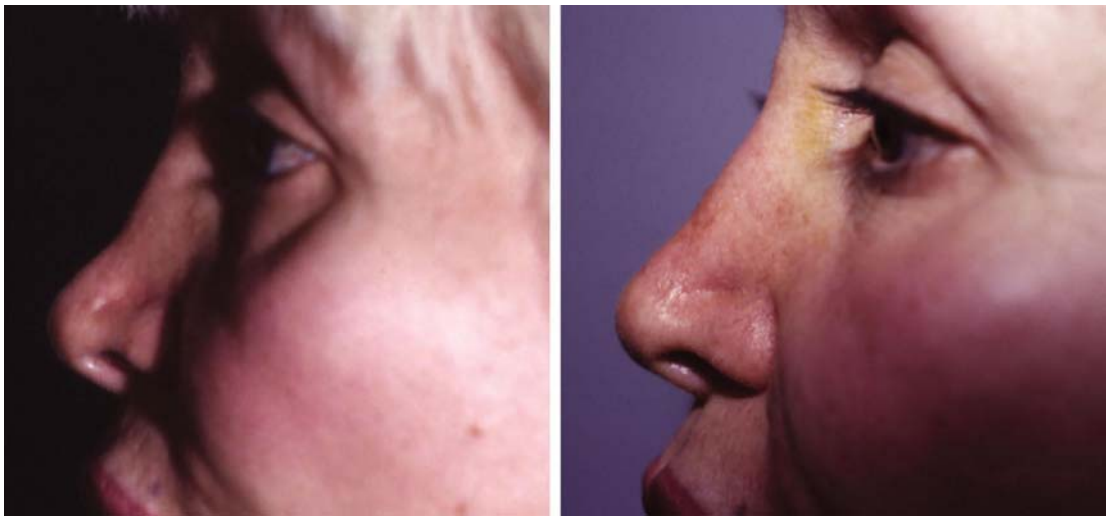

**Fig. 7.** (*Left*) Postsurgical nasal defect and (*right*) after two sessions using 1 ml of Artecoll and then 0.5 ml at 6-month intervals.

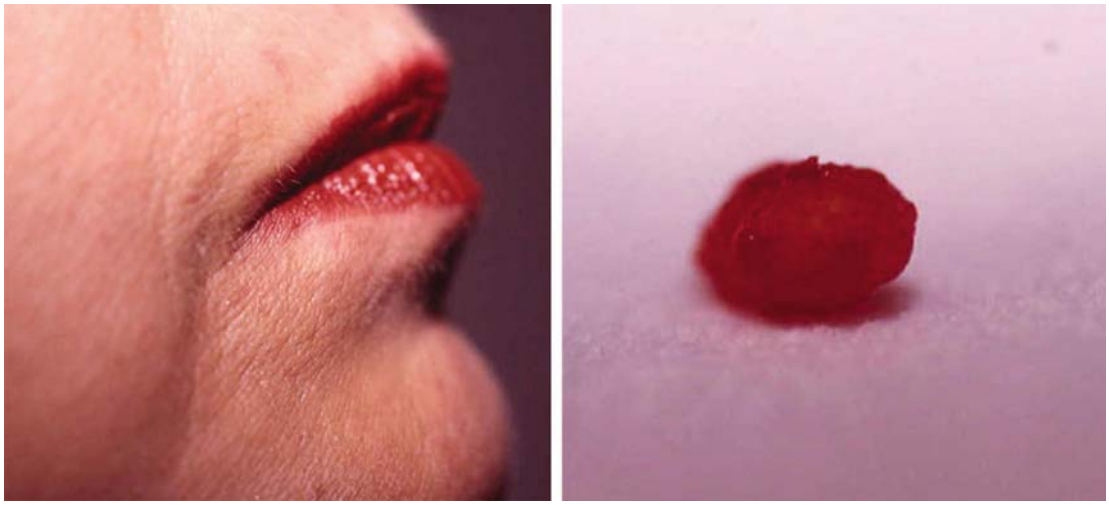

**Fig. 8.** (*Left*) An injection in the lip that is too superficial. (*Right*) The Artecoll nodule is easily removed.

process of healing, will induce some form of neocollagenesis. However, its effects do not last. This is well seen with resorbable implants such as collagen and hyaluronic acid.

It is therefore mandatory, before injecting a filler, to precisely define the aim or objective of the implant. Is it for a volume effect with filling of the soft tissues and smoothing of the skin by increasing superficial tension, such as in human immunodeficiency virus–induced lipoatrophy? Or is it for smoothing the superficial wrinkles, for instance, in photo-induced aging caused by sun exposure? How should these two goals—volume and smoothing—be coordinated, such as in the hollow zones with skin creases as in the glabella or in the nasolabial folds?

For a volume effect, the implant should induce the smallest inflammatory reaction to avoid any long-term side effects. This seems to be the case for the polyacrylamide gels, where there is minimal inflammatory reaction around the bulk of the implant. However, the displacement of the product, either by micromigration within the tissue and/or by distant macromigration facilitated by the absence of a fibrous capsule, does activate these reactions in a permanent way. Particulate implants with porous or irregular surfaces (Bioplastique, Dermalive, and Dermadeep) potentially cause more tissue reactions than smooth surface microspheres (Artecoll and Radiesse). The carrier medium for these particulate implants plays an important part: the longer it will keep the particles apart, the more it will prevent cluster formation and major inflammation. In this respect, the collagen in Artecoll/Artefill seems to be more efficient than the hyaluronic acid of Dermalive, the

methylcellulose gel of Radiesse, or the sodium carmellose of New-Fill.

For a superficial intradermal treatment, is it better to use a true filler, which should cause no inflammatory reaction, as it would be immediately visible within the skin. An agent inducing neocollagenesis, which implies fibroblast stimulation, might cause inflammatory reaction that would be too visible. In such indications, it is probably safer to use short- or moderate-lasting absorbable agents, bearing in mind that sebaceous glands and hair follicles, present in the dermal and subdermal planes, can expose the implant to external bacteria.

The problem remains for combined indications: volume and smoothing, deep and superficial. After hyaluronic acid injections in areas previously treated with a nonabsorbable agent, especially with Dermalive, severe inflammatory granulomas have appeared. In such cases, it is not possible to state whether they are attributable to the new product, even an absorbable one, or to the reactivation of the quiescent reaction from the previous implant.[38] Such difficulty in determining which element is the starter of these reactions, and to find an efficient treatment, has brought many authors and manufacturers to contraindicate the use of injectable fillers in previously treated areas, even though there is no proof that all permanent fillers would induce such a reaction. There is an obvious need for serious, precise, and objective studies on these associations.

No available product to date can be considered as perfect. They all have a potential for complications. However, the difference between a normal healing process and a true inflammatory granuloma must be established. Any biopsy specimen will be interpreted as a granuloma, but the presence of foreign body cells does not mean it is pathologic. Too often I have seen patients referred for granuloma treatment when these were simple nodules caused by muscular displacement or incorrect positioning of the implant. For most of the available products, more true scientific studies are needed.

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## DISCLOSURE

*The author has no financial interest in any of the cited companies and has received no help in any way from any of them for this work.*

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