The History of Injectable Facial Fillers

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ABSTRACT

In an attempt to maintain a youthful appearance or to reconstruct facial deformities, physicians have greeted new technologies with excitement. In the late 1800s, shortly after the invention of the syringe, chemical agents were used for facial augmentation. Unfortunately, history has taught us that new technologies must be used with care, because complications can occur, sometimes many years after initial treatment. The first injectable filling agent was paraffin, whose use was abandoned after complications of migration, embolization, and granuloma formation were described. More recently, silicone use was banned by the U.S. Food and Drug Administration (FDA) because of similar complications. In 1981, bovine collagen was the first agent to be approved by the FDA for cosmetic injection. Since its approval, dozens of injectable filling agents have been developed, and many are already FDA approved for cosmetic use. This article will review the highlights of the evolution of facial filling agents.

KEYWORDS: Paraffin, silicone, collagen, hyaluronic acid

To understand where we are going; it is important to understand where we have been. Throughout history, mankind has used elaborate costumes, facial painting, jewelry, piercings, and tattooing to enhance appearance. In addition, the desire for eternal youth permeates the mythology of cultures throughout the world; it drove Ponce de Leon to the edge of the known world.

In considering the history of facial filling agents, the common theme is the desire to develop the perfect material to replace volume and fill lines in the face. Our dream filler would be safe and biocompatible. It would be nonteratogenic, noncarcinogenic, and would not be susceptible to infection. It would stimulate a minimal immune response (no skin test necessary), and it would not depend on that response for its clinical effect. The volume injected would be the volume of correction. It would not migrate from the spot where it was injected. It would last a long time—several years would be optimal. It would feel soft and look natural. It would also be inexpensive, easy to use, and be easily stored. Lastly, it would be fully reversible, disappearing without a trace.[1]

The road we travel in the quest to develop such a material makes for an interesting story. We learn from our mistakes, but we should always evaluate new devices and techniques with a skeptical historical eye, keeping in mind that these novelties have always been greeted with enthusiasm until complications arose.

THE SYRINGE

The prologue to this story must start with the development of the appropriate technology, namely, the syringe. For obvious reasons, injections could not have been performed until this was invented. The hollow needle was invented in 1844 by Irish physician Francis Rynd. He used the needle to treat neuralgias by subcutaneous injections. In 1853, French surgeon Charles Pravaz and Scottish physician Alexander Wood independently developed the medical hypodermic needle and syringe (Fig. 1 and Fig. 2). This syringe was a screw-type piston, which allowed small amounts of fluid to be accurately delivered.[2] Ironically, Wood's

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Figure 1 Charles Pravaz (1791–1853) invented the syringe for intra-arterial injections in the treatment of aneurysms.

wife died from a morphine overdose due to a self-administered injection.

PARAFFIN: THE FIRST FILLER

The filler saga begins in 1830, when a German chemist, Baron Karl Ludwig von Reichenbach (Fig. 3), discovered

Figure 2 Alexander Wood (1871–1884) simultaneously invented the syringe to administer morphine to treat neuralgic pain.

Figure 3 Baron Karl Ludwig von Reichenbach (1788–1869), a German chemist known for the discovery of paraffin, kerosene, and phenol.

a material created by the dry distillation of beech-wood tar.[3] He noted this substance to be very unreactive and named it *paraffin*, from the Latin *parum* (barely) and *affinis* (affinity). He believed this substance would likely replace beeswax for candles and could also be used as a lubricant. In the following years, the medical community found multiple uses for this new material. At the University of Vienna, Theodur Billroth (1825–1899) used paraffin to lubricate resected joints.[3] Dermatologists also used paraffin as a vehicle to inject heavy metal salts as a treatment for syphilis. The first reported use of a material injected into the body for "cosmetic" purposes was by Robert Gersuny (1844–1924), who studied under Billroth in Vienna (Fig. 4). In 1899, Gersuny injected mineral oil (liquid paraffin) to create a testicular prosthesis in a patient with tuberculous epididymitis who had been treated by castration.[4] In 1875, the Cheeseborough Company produced petrolatum, a combination of solid and liquid paraffin, with the trade name Vaseline. Gersuny experimented with different combinations of paraffin with Vaseline and olive oil.[3] Because of the 40°C melting point of Vaseline, it could be liquefied by heating, injected into the body, and would rapidly harden, even in a febrile patient. He cautioned other physicians to only inject sterile paraffin and to use small amounts with each injection. Paraffin was enthusiastically embraced by the medical community and became the treatment of choice for nasal augmentation. However, in 1901, a case was reported of a 39-year-old woman who underwent paraffin injection for urinary incontinence and developed pulmonary and cerebral paraffin emboli.[3] The sequelae associated with paraffin injections were outlined in 1911 by Kolle,[4] who described inflammation, infection,

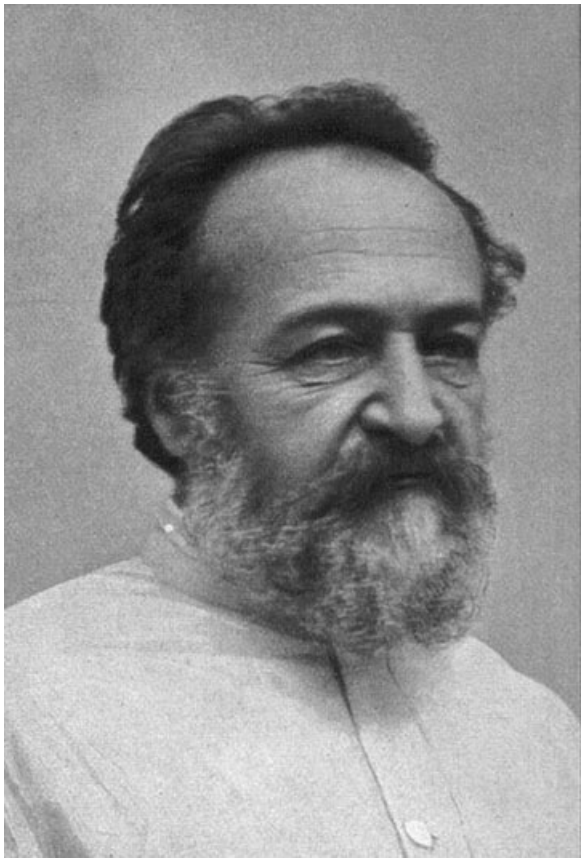

Figure 4 Robert Gersuny, an Austrian physician who was the first to inject paraffin for cosmetic purposes. [Permission requested]

Figure 5 Gladys Spencer-Churchill (1881–1977), second wife of the 9th Duke of Marlborough, became severely disfigured after paraffin injections to her nose.

embolism, and yellowish skin plaques at the site of the injection. In the following years, the term *paraffinoma* was used to describe the granulomatous foreign-body reaction that developed as a result of paraffin injection.[5] The most famous account of the complications of paraffin injection was that of the Duchess of Marlborough (Fig. 5). This American-born, dazzling beauty was preoccupied with the "kink" of her nose and underwent paraffin injections to her nasal dorsum. The paraffin subsequently migrated into her chin producing paraffinomas throughout her face. She became so disfigured she did not permit mirrors in her house, and she died a recluse in 1977. The biology of injected paraffin is now well understood. There is an initial inflammatory phase, followed by a latent phase that can last for decades.[6] Over time, the fatty tissue calcifies and develops hyaline sclerosis, producing yellowish skin nodules. These lesions can become infected or fistulize. Because the paraffin is inert, it remains completely unchanged in the body and can migrate through the fatty tissue, stopped only by fascial planes. Over the subsequent years, similar injectables such as vegetable oil, mineral oil, lanolin, and beeswax have been used for cosmetic injections were but abandoned due to undesirable complications including migration, granuloma formation, and scarring.[7] A tragic example of such injections was recently described in the London Daily Telegraph (November 11, 2008). A Korean woman received silicone injections from a physician who also gave her syringes to self-administer. After she ran out of silicone, she substituted cooking oil for self-injection and ultimately became severely disfigured (Fig. 6).

AUTOLOGOUS FAT

During the late 1800s, autologous fat injections were used for facial augmentation. Neuber[8] (1893) described the use of fat harvested from the upper arm to augment facial defects. Lexter[8] (1910) also described the use of autologous fat, but like modern-day fat-injection techniques, his results could not be reproduced by other surgeons. Autologous fat transfer was popularized again with the introduction of high vacuum suction with blunt cannulas (Illouz method) in 1982. Since that time, many different techniques have evolved for fat harvest and transfer to the face, often with inconsistent results and unpredictable longevity.

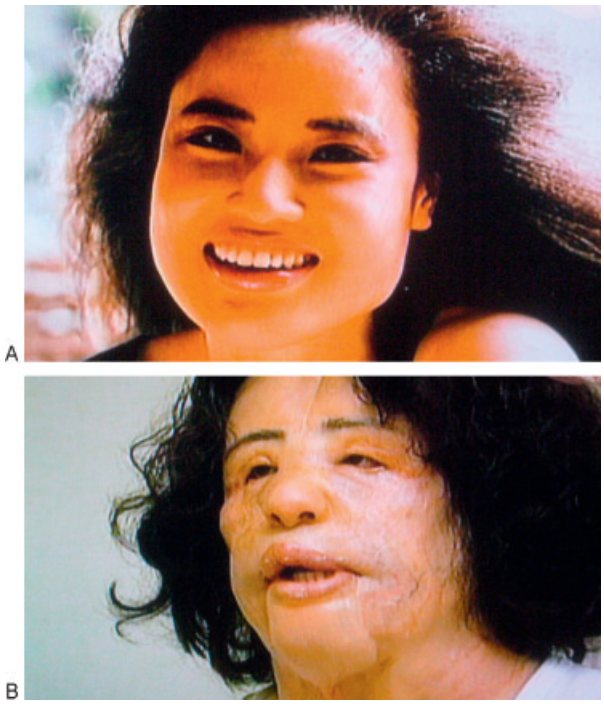

Figure 6 A Korean woman (A) injected silicone and cooking oil into her face, (B) which resulted in disfigurement. (Photographs by © Saigo-Sinopix/Rex Features.)

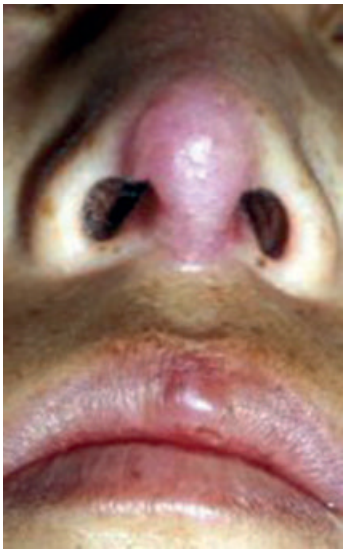

Figure 7 Inflammatory reaction of the nasal tip and columella due to injected silicone. (Photograph courtesy of Ira Papel, M.D.)

SILICONE

In the 1960s, liquid silicone injection became a popular cosmetic treatment. Like paraffin, silicone is an inert, clear, oily substance that is easily injected and, unfortunately, had similar disastrous sequelae. Silicone, a polymer of dimethylsiloxanes, was first used in Japan during the 1940s for breast augmentation.[9] This practice spread to the United States (California, Texas, and Nevada), particularly used to treat Las Vegas showgirls. In 1965, Dow Corning developed a purified silicone that could be used for injection, called MDX4–4011.[10] Over the following years, it was noted that the injected silicone would migrate and fistulize, and it had resulted in several deaths. Some patients with severe complications required mastectomies. Because of the complications encountered in the Las Vegas showgirls injected with silicone, Nevada was the first state to ban the use of injectable silicone. In 1964, Weiner coined the term *siliconoma*[11] to describe the soft tissue granuloma that developed from injected silicone. These disfiguring inflammatory responses could sometimes be seen decades after silicone had been injected (Fig. 7). Although medical-grade silicone was also used to treat facial wrinkles and augment the lips, the U.S. Food and Drug Administration (FDA) considered it an investigational device and never approved silicone for cosmetic use. In 1964, the FDA regulated the use of injectable silicone as a *drug*, and the Medical Device Amendments of 1976 restricted the use of silicone as a *device*. After reports of the sequelae of injected silicone, in 1979 the FDA and the American Medical Association condemned the use of injectable liquid silicone. Although today medical-grade silicone is available for ophthalmic use in the treatment of detached retinas, its cosmetic use is considered illegal in some states. In spite of the problems encountered with injectable liquid silicone, silicone injections are still performed in Europe, Canada, Mexico, and by some physicians in the United States. Since 1994, two medical-grade silicone products were available to treat detached retinas, and use of these products cosmetically is considered "off-label." Even though the use of injectable silicone for cosmetic purposes is federally banned and illegal in some states, some physicians feel that in the hands of experienced surgeons, injections can be extremely efficacious. They purport the "microdroplet" injection technique using a small needle and deep injection into the dermis and subcutaneous fat. These injections are performed in multiple treatments over 1- to 3-month intervals.[12] Celebrities often fall prey to unscrupulous physicians. In 2003, an unlicensed Argentine physician injected industrial-grade silicone into the faces of American celebrities, one of which developed large lip granulomas.

FDA REGULATION OF FILLING AGENTS

The Federal Food, Drug, and Cosmetic Act of 1938 gave the FDA the authority to oversee the safety of food,

cosmetics, drugs, and medical devices. The FDA[13] regards a "device" as

"an instrument, apparatus, implement, machine, contrivance, in vitro reagent or other similar article which is
1. recognized in the official *National Formulary*, or the *United States Pharmacopeia*,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

Medical devices are further classified by class[13]:

Class I: Devices that do not require premarket approval or clearance but must follow general controls. Examples of these devices are Band-Aids, dental floss, and crutches.

Class II: Devices that are cleared using the premarket approval process. Diagnostic tests, cardiac catheters, and amalgam alloys used to fill cavities and hearing aids are all class II devices.

Class III: Devices that are approved by the premarket approval (PMA) process. These tend to be devices that are permanently implanted into a human body or may be necessary to sustain life. The most commonly recognized class III device is an automated external defibrillator. Devices that do not meet either criterion are generally cleared as class II devices. Injectable filler agents are considered class III medical devices.

The Federal Food, Drug, and Cosmetic Act requires device manufacturers to notify the FDA at least 90 days in advance of their intent to market a medical device. This is known as premarket notification, or PMN. The PMN allows the FDA to adequately classify the category for the device by noting its similarity to currently approved devices. If the device is notably different than the approved devices, it must undergo a PMA. Not all devices undergo the PMA before they are marketed to the public. Devices that undergo the PMN are considered "cleared" devices.

Under the Federal Food, Drug, and Cosmetic Act, manufacturing companies may only promote uses of their product that have been deemed safe and effective by the FDA. A device used "off-label" refers to use of the product in a method not approved by the FDA, and it is illegal for the manufacturer to promote off-label use of the product.[14]

COLLAGEN

Clinical trials of bovine collagen were performed in 1977–1978 to improve age-related wrinkles. It underwent 6 years of development, testing, and clinical trials before its approval by the FDA in 1981.[15] Bovine collagen is produced by a closed herd of cattle to prevent the transmission of bovine encephalopathy virus. In addition, skin testing is required to diagnose bovine collagen allergy prior to facial injection of the product. Zyderm made history in 1981 when it became the first facial filler to be approved for cosmetic use. This was soon followed by the FDA approval of Zyderm II and Zyplast (Allergan, Inc., Irvine, CA) in 1985. (Zyderm is 96% type I collagen and 4% type III collagen. Zyderm II is 6.5% collagen by weight compared with 3.5% in Zyderm I. Zyplast is 3.5% collagen cross-linked with glutaraldehyde to increase duration of effect.)

Although not FDA approved for lip enhancement, collagen injections became the rage following the movie *Beaches* in 1988. Actress Barbara Hershey (then age 40) had to portray a woman who was 10 years younger. To appear more youthful, Hershey underwent collagen injection into her lips.[8] The publicity surrounding her collagen injections and the production of her "pouty lips" received almost as much attention as the movie itself!

THE FILLER PHENOMENON

We have become a society of fast food and fast results. There was a need for fillers that did not require a skin test and would last longer than collagen. Hyaluronic acid (HA) was the first material to satisfy these requirements. HA is a highly hydrophilic glycosaminoglycan that is part of the extracellular matrix of a large variety of tissues in all organisms. It remains the most widely used filler material today, combining safety, reliability, and a relatively long duration of action. Hyaluronic acid is structurally identical across species. Two techniques were developed for its manufacture: bacterial fermentation and extraction from rooster combs. The animal-derived fillers (Hylaform [INAMED Corporation, Santa Barbara, CA]) provided excellent cosmetic results but were seen to have a shorter duration of effect than that of their bacterial-fermented cousins (Restylane [Medicis Aesthetics, Inc., Scottsdale, AZ] Juvéderm [Allergan, Inc., Irvine, CA] Captique [Genzyme, Ridgefield, NJ] Elevess [Anika Therapeutics, Woburn, MA]).

Once HA was FDA approved in 2003 for cosmetic use, the floodgates were opened and new filling agents rapidly appeared. More than a dozen new filling agents have been FDA approved in the past 5 years:

2003: Restylane (Medicis Aesthetics, Inc., Scottsdale, AZ), CosmoDerm (Allergan, Inc., Irvine, CA), CosmoPlast (Allergan, Inc., Irvine, CA)

2004: Hylaform (INAMED Corporation, Santa Barbara, CA), Sculptra (Sanofi-aventis, Dermik Laboratories, Bridgewater, NJ), Captique (Genzyme, Ridgefield, NJ)
2006: Juvéderm (Allergan, Inc., Irvine, CA), Artefill (Artes Medical, San Diego, CA), Radiesse (Bioform Medical, San Mateo, CA), Elevess (Anika Therapeutics, Woburn, MA)
2007: Perlane (Medicis Aesthetics, Inc., Scottsdale, AZ)
2008: Evolence (ColBar Life Science, Ltd, Herzliya, Israel), Prevelle Silk (Genzyme, Ridgefield, NJ)

Although most of these products are approved for use only in the nasolabial folds, most are used to augment all areas of the face. This off-label use of medical devices was legalized by the FDA Modernization Act of 1997. Because of the rapid development of the filler market, the FDA convened a panel in November 2008 to discuss the postmarket experience of dermal fillers.[13] A total of 804 adverse events (AEs) were reported by the manufacturing companies of all the injectable dermal fillers. The majority of AEs occurred in patients aged 50 to 60 years at the nasolabial folds and lip sites. The most common AEs were swelling, inflammation, erythema, allergic reaction, infection, vascular events, and pain. As a result of this meeting, the FDA will create an advisory panel to amend product labeling requirements and change the safety-testing protocols of injectable cosmetic filling agents.

Predicting the future is a tricky game, but this industry seems headed for further rapid expansion. Many new fillers are currently going through the FDA process, as are modified versions of existing products. Examples of the former include Aquamid (Ferrsoan, Soeburg, Denmark) (a long-lasting polyacrylamide hydrogel) and Belotero (Anteis, Geneva, Switzerland) (a monophasic hyaluronic acid). Examples of the latter include Evolence Breeze (ColBar Life Science, Ltd, Herzliya, Israel) (a less dense version of Evolence) and Macrolane (Q-Med, Uppsala, Sweden) (a denser, larger particle version of Restylane).

The history of filler use and development has been a fascinating journey. As our technology improves, we come ever closer to developing the ideal filler. However, our lessons from the past warn us to proceed with caution and, above all else, "do no harm."

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