The History of Injectable Silicone Fluids for Soft-Tissue Augmentation

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Background: The debate over the legitimacy of silicone as a safe tool for soft-tissue augmentation has spanned well over half a century. Proponents concede that injections of questionable purity and/or of massive quantities have produced unfavorable outcomes. They assert that in experienced hands with "injectable-grade" silicone, there are very few problems. Despite these claims, the literature is replete with disastrous outcomes following silicone fluid injection, often many years after the initial treatment.
Methods: An extensive review of the English-language literature was conducted using MEDLINE.
Results: A comprehensive review of injectable silicones was completed, revealing the origins, misuses, early clinical trials, and support for and against the injection of silicone fluids for the augmentation of soft tissues.
Conclusions: A better understanding of the history of injectable silicone fluids for soft-tissue augmentation can give insight into the pitfalls and complications surrounding its use. There has been an evolution in the technique and type of products used for soft-tissue augmentation. In its current use, silicone oil for permanent soft-tissue augmentation could be a very powerful tool. There is some literature that supports the use of a small amount of purified, high-viscosity silicone oil; however, there has not been a single longitudinal study to date with appropriate follow-up data. The unanswered question remains: Are the risks worth the potential benefits of silicone oil as a permanent filler? (*Plast. Reconstr. Surg.* 120: 2034, 2007.)

BEGINNINGS OF SILICONE

The Swedish chemist Johann Berzelius was the first to isolate elemental silicon in 1824. F. S. Kipping at Nottingham University first synthesized silicone in the late 1800s using the new Grignard reagent. This method of producing organosilicones is still in use today. He was primarily interested in the pure chemistry of silicones, not their applications. He described the silicone polymers as sticky messes that had no uses and called them "uninviting glues." From 1899 to 1944, he published 54 articles on the subject of silicon-carbon chemistry. The first polydimethylsiloxanes were first made in the late 1930s by Frank Hyde, an organic chemist working with Corning Glass Works at the Mellon Institute for Industrial Research. By 1939, it appeared that silicones would make excellent lubricants. Hyman Rickover, then head of the electrical section of the Bureau of Ships for the Navy, was impressed with the use of fiberglass tape covered with silicone resin, known as 990A resin. His comment after examining the tape was "now you've got something, I want it tomorrow."[1] As the demand for larger volumes of silicone increased, based on Rickover's demand and its potential as an industrial product, Corning Glass sought the assistance of Dow Chemical to further its product development and produce large volumes of silicones. The Dow Corning Corporation was founded in 1943. The first product was used by the United States Air Force to prevent ignition failure at high altitude, allowing an aircraft to remain at 35,000 feet for up to 8 hours; without the aid of this compound, aircraft could remain at that altitude for just a few minutes. It made possible the flight of airplanes, such as the B-17, to England and North Africa at a time when the United States was beginning to lose many aircraft through submarine attacks on the shipping convoys that carried our airplanes across the sea. Subsequent products that followed included those used for dampening vibrations in instruments, nonmelting grease for spark plugs, and antifoam-

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ing agents that prevented bubbles from forming in motor oil at high altitudes. Dow Corning explored nondefense applications of silicone, eventually creating more than 5000 products. One of the first products to reach wide usage was a silicone liquid used to insulate electrical transformers. Silicone was then tested on rats and monkeys and found to be chemically inert. John Holter, an engineer whose baby had hydrocephalus, developed the silicone hydrocephalic shunt in the early 1950s. The first shunt was placed in 1955, and by 1962, 4000 shunts had been placed. In 1959 Dow Corning established the Center for Aid to Medical Research as a source for in-house and independent medical research. Dow Corning supplied the silicone implants for Gerow and Cronin in the early 1960s, eventually leading to the introduction of their product in 1964.

CHEMISTRY OF SILICONE

Silicone describes a large family of silicon containing synthetics. Siloxane is a mnemonic acronym derived from the names of its chemical constituents: *sil*icon, *ox*ygen, and meth*ane*. The variety used for medical applications are polydimethylsiloxanes. The relative polymerization and chain length of the compound determines its viscosity, as measured by centistokes (100 cS equals the viscosity of water). By their nature, silicones are heavily contaminated with heavy metals, short-length volatile polymers, and other impurities that require an extensive purification process, depending on the specifications. For example, some of the specifications of Silikon 1000 are an average molecular weight of 38,000 to 48,000, less than 50 particles per milliliter (at <10 μm) and less than five particles per milliliter (at <25 μm), and less than 0.001% heavy metals. Some of the techniques used to purify silicone include fractionization with solvents, baking, a wet film still, and filtration. Typically, silicones are sterilized by a dry heat terminal sterilization process. Several silicones are described, as follows:

Dow Corning 200 Fluids: Polydimethylsiloxanes of different viscosities. Generally used for industrial purposes. Available in 20-kg pails and 200-kg drums. The product is not tested or represented as suitable for medical or pharmaceutical uses.

Dow Corning 360 Medical Fluids: Polydimethylsiloxanes available in five standard viscosities: 20, 100, 350, 1000, and 12,500 cS. It is the same as the Dow Corning 200 fluid, except that more rigid quality control procedures were established to remove heavy metals, low-chain-length polymers, and other impurities. It is supplied in 1-, 40-, and 440-pound containers.

Dow Corning MDX 4-4011: The designation of the Dow Corning 360 Medical Fluid, 350 cS, which was further purified and sterilized and used for U.S. Food and Drug Administration study new drug 2702 in 1965 to evaluate injectable polydimethylsiloxanes for soft-tissue augmentation. It was packaged by Philadelphia Laboratories in 1- and 50-cc ampules and certified as sterile by the packager.

THE MISUSE OF SILICONE

When World War II was over, American Army quartermasters noticed drums of the transformer insulating fluid (Dow Corning 200 fluid) disappearing from the docks of Yokohama Harbor in Japan. The silicone was being injected into prostitutes who sought a more "Western" appearance for the American servicemen. This practice spread to the United States, primarily in California, Las Vegas, Nevada, and Texas. A *Newsweek* article in 1963 quotes a Las Vegas physician as injecting over 200 patients' breasts. Carol Doda became famous for her large breasts after being injected with silicone in 1964. There were obvious problems with migration; therefore, attempts were made to improve success by mixing the silicone with "scarring agents" or "adulterants." This caused a significant inflammatory response, and this practice was quickly abandoned. The most popular was the Sakurai formula, which included the addition of vegetable oils (primarily olive oil).[2] Dr. Sakurai was a Japanese physician who then moved to Beverly Hills to "perfect" his technique. Thousands of women underwent injection of massive amounts of silicone oil in their breasts. This practice was often performed by lay people and never regulated. This silicone product (Dow Corning 200 fluid) that was used was made for industrial purposes and never intended for injection.

In 1962, Dow Corning 360 Medical Fluid was introduced with specifications of higher purity, but was not designed for injection. It was intended for medical use in coating needles, oral drug delivery systems, and immersion therapy for burn patients, but was never intended for injection. Dow Corning 360 Medical Fluid was readily available. Injection of silicone into the breasts of entertainers in Nevada was rampant and had disastrous results. By 1975, the Nevada legislature passed a law criminalizing the use of injectable silicone.

THE EARLY CLINICAL TRIALS

In 1964, The U.S. Food and Drug Administration stated that a silicone, when injected into the tissues, is a "new drug." Therefore, in 1965, Dow Corning filed a "notice of claimed investigational exemption for a new drug" no. 2702.[3,4] This was a nonblinded, single-treatment, prospective study. The Dow Corning 360 Medical Fluid specifically designated for this U.S. Food and Drug Administration–approved study for soft-tissue augmentation was designated MDX 4-4011. This 350-cS fluid had even higher purification specifications and was sterilized. The principal investigators included Thomas Rees (New York University), Franklin Ashley (University of California, Los Angeles), Reed Dingman (University of Michigan), Milton Edgerton (Johns Hopkins), Dicran Goulian (Cornell), and Norman Orentreich. Of the 1333 patients treated, 709 were treated for such conditions as wrinkles and acne scars, and only 408 were followed sufficiently to allow any data to be collected. There was only one reported complication: migration of the silicone in the leg of a polio patient that received a large quantity of silicone. In 1973, Rees, Ashley, and Delgado published an article describing their 10-year experience with MDX 4-4011 used on 73 patients with hemifacial or bilateral facial atrophy.[5] They showed good to excellent results in 68 patients, with a total of five complications that occurred from 2½ to 3 years after the procedure. The complications involved a cheek nodule in one patient that resolved with a Kenalog injection, firmness in three patients, and extreme hardness in one patient. It is interesting to note that the authors cautioned that individual doses should be kept small, but the total amount injected ranged from 3.5 to 55.5 ml. The average was 24.2 ml. The passage of the 1976 Medical Device Amendment to the Food, Drug, and Cosmetic Act charged the U.S. Food and Drug Administration with identifying certain drugs that would be classified as devices. That same year, the U.S. Food and Drug Administration suspended new drug 2702, citing inadequate follow-up, lack of case reports, and numerous patients who left the protocol. In 1977, Dow Corning submitted an amended new drug 2702 that received U.S. Food and Drug Administration approval: a 3-year clinical study of up to 300 patients to evaluate the safety and effectiveness of liquid silicone on the most severe facial deformities such as Romberg's disease and Weber-Christian disease. Weber-Christian disease is an idiopathic lobular panniculitis characterized by recurrent inflammatory subcutaneous nodules. The acute process is self-limiting, and resolution results in atrophy of the surrounding subcutaneous fat, leaving a depression. In 1979, new drug 2702 had been transferred to the Bureau of Devices and redesignated investigational device exemption L0002702. Between 1979 and 1981, 600 patients were enrolled. Only 144 patients had any documented follow-up. The only documented complications from this study were in three patients; two had a diagnosis of Weber-Christian disease. A 66-year-old woman with a diagnosis of Weber-Christian disease received a total of 12 cc of MDX 4-4011 in her cheeks over a 4-year period. She also had rheumatoid arthritis, and atypical mycobacteria were cultured from her facial lesions 1 year before her silicone injections. Inflammatory episodes began 11 years after her last injection. She required debridement and a latissimus musculocutaneous free flap reconstruction. According to the treating physician, "it was impossible to be certain if this was a reactivation of Weber-Christian disease or a reaction to the silicone."[6] The two other complications occurred 5 months and 16 months after the last injection, but there is little clinical information regarding either. In each case, the lack of chemical proof that the injected substance was indeed pure silicone further confounds analysis of these data. Before the application for premarket approval was submitted, the U.S. Food and Drug Administration requested an interim report on the status of the protocol, which Dow Corning filed in 1990. The U.S. Food and Drug Administration reviewed the report and found that there was no follow-up greater than 4 years, no objective measurements of improvement, and insufficient preoperative and postoperative photographs. By November of 1991, the hearings on the safety of breast implants had begun. The much larger breast implant issue had eclipsed Dow Corning's interest in injectable silicone. No attempt was made to correct these deficiencies, and Dow Corning elected not to pursue a formal premarket approval application. By 1992, the investigational device exemption became invalid. The company's position according to Arthur Rathjen, director of medical research for Dow Corning, was: "it was not for any reason of safety nor effectiveness of the product for facial treatments. The primary influence behind the decision was derived from Dow Corning's inability to devise a workable system of controls that would preclude misuse of the product."

CONCERNS ABOUT THE USE OF SILICONES

In 1977, Wilke published his results on the treatment of 92 patients for a total of 230 treatments with injectable grade silicone [MDX 4-4011 (1966 to 1970)/Koken Co., Tokyo, Japan (1970 to

1976)] over a 10-year period.[7] He reported 13 granulomas and noted that eight of these occurred within the first year after treatment, with a very high incidence in the glabella (20 percent). Five of the granulomas resolved spontaneously. He also reported a "worthwhile improvement in many patients." In 1978, Pearl reported five complications associated with silicone injections that resulted in significant inflammatory reactions in the face.[8] Only one of the patients was injected with injectable-grade silicone. The main focus of the article was a treatment regimen using systemic steroids starting with 60 mg/day of prednisone. They stated that "all of our patients who have been treated with this regimen are now improved and in acceptable condition, both functionally and cosmetically, though they continue to suffer mild symptoms from the low dose prednisone therapy and from the residual silicone." Another case of facial swelling 6 months after injection of an unknown grade of silicone originating from Italy was reported in Switzerland in 1993.[9] It is interesting to note that the patient had received injections to the nose, glabella, and cheeks, but developed only left cheek swelling 1 week after her last injection. In 1996, Rappaport et al. presented an extensive literature review and reported 54 patients over a 26-year period with problems associated with silicone injections occurring 0.5 to 28 years after injection.[10] Notable is the preponderance of complications occurring in the glabella and cheeks, and there were only three in the lips (two thickened upper lips and one nodule). They summarize with the following statement: "While the incidence of complications may be low, when they do occur, they are devastating and cannot be resolved satisfactorily." A recent article (October of 2005) describes the salvage of 23 patients treated with either injected silicone oil or silicone prosthetic blocks over the past 15 years.[11] Nineteen of the patients were treated with presumed silicone injections and 13 were treated for larger cheek deficiencies. These would have required larger doses of silicone. One of the most impressive deformities was a case report of a 60-year-old woman with hemifacial atrophy that had silicone injections as a child, putting her in the pre–MDX 4-4011 period.

SUPPORT FOR THE USE OF SILICONES

In the 1950s, Norman Orentreich, a dermatologist in New York City, pioneered the use of tiny droplets of silicone oil, coining the term "microdroplet technique." He performed further purification of the Dow Corning 360 medical-grade silicone, calling it "injectable-grade" silicone. He has claimed thousands of treatments without problems. Specifically, he contends that there are "1400 patients without serious flaw under continuous study."[2,12] In 1971, Ashley et al. presented hundreds of animal studies and followed 90 patients for 3 months, with excellent results.[13] They did mention that it was important to use small volumes at each session. Their average volume per injection was 4 cc, which was considered a small volume in the early 1970s. They also were the first to use higher viscosity silicones up to 1000 cS, noting that large volumes of low-viscosity silicones tended to migrate where the higher viscosity silicones did not migrate. In 1972, Rees and Ashley presented their findings of a 10-year study treating 73 patients with facial deformities using MDX 4-4011 with universally good results. Their treatment volumes ranged from 3.5 to 55.5 ml, with an average of 24.2 ml. In another report, Rees and Coburn demonstrated spectacular results in the treatment of facial lipodystrophies in nine patients without complications; again, these patients were followed for an unspecified amount of time.[14] Berger reported his 10-year experience with injectable silicone having favorable results in 1975, but does not mention how many patients were treated or how long they were followed.[15] Edgerton and Wells reported using MDX 4-4011 in 200 patients over a 10-year period in 1974; again, there are insufficient follow-up data.[16] Their only complication was a subcutaneous nodule in a patient with calf augmentation. They concluded that by carefully controlling patient selection, indications, and the technique of injection, most of the dangers of liquid silicone injection may be circumvented. In 1982, Milojevic reported on 1677 facial injections performed in Yugoslavia, but there is no mention of the number of patients treated or the length of follow-up.[17] They had only two granulomas, 4 and 5 weeks after injection, respectively. Both resolved with evacuation. In 1984, Aronsohn described his treatment of 4862 patients over a 22-year period and concludes that "There is absolutely no evidence to date that shows that the subcutaneous injection of minute amounts of pure silicone into suitable areas spaced over a long interval of time leads to any systemic physiologic problems."[18] It is interesting to note that Aronsohn used both 100- and 350-cS silicone oils and sterilized them himself by autoclaving 250-cc bottles at 250°F for 20 minutes. Also, for the first 538 patients, he added an adulterant, either oleic acid or sesame oil, as a 1% solution. He abandoned the use of the adulterant as he saw

erythema and/or skin nodules. Early in his series, he noted silicone migration, which disappeared when he began using the microdroplet technique. No follow-up data were included in this study. Webster et al. reported extremely favorable results in 2811 facial treatments in 235 patients over a 20-year period.[19] In another article, they reported favorable outcomes in 347 patients for a total of 1937 treatments used in postrhinoplasty deformities over a period of 20 years.[20] Of those patients, 100 were followed for an average of 76 months to assess erythema over the injection site, which developed in 10 percent compared with 3 percent in the control group. In 1986, Webster et al. reported on 17,000 treatments since 1962 but provide no data on how many patients were followed or the length of time they were followed.[21] Clark et al. in 1989 reviewed the safety of silicone injections and concluded that "past problems associated with silicone soft tissue augmentation are related primarily to the use of impure product, excess volumes, or inappropriate location."[22] In 1990, Duffy performed an extensive review of injectable silicone and reported on 2000 results using the microdroplet technique, much like Orentreich, over a 6-year period with only minor or transient problems noted. In 1997, Maas reported on seven patients with complications from injectable materials.[23] Six of the seven patients in which the materials tested were found *not* to have been injected with silicone; the substances recovered were paraffin, methacrylate, and Teflon paste.

THE NEWER SILICONES

In 1994, purified and sterilized high-viscosity silicone oil made by Adatomed of Germany was introduced for ophthalmologic use. More recently, Alcon and Bausch and Laumb introduced a high-viscosity, sterile, purified form of injectable-grade silicone under the brand names Silikon 1000 and Adato-Sil-Ol 5000, respectively. These have been approved by the U.S. Food and Drug Administration for ophthalmologic use.

The Richard James Corporation, manufacturer of Silikon-1000, which licenses to Alcon, introduced a new silicone fluid, Silskin, with even higher purification specifications than Silikon 1000 and is intended for use as a soft tissue filler. A U.S. Food and Drug Administration–approved trial involving Silskin started in January of 2002 with 26 patients enrolled. The patients were injected on one-half of the face with collagen and the other half with Silikon 1000 and followed for 1 year. The lead investigators are David Orentriech, Daniel Baker, and a dermatology group, Skin Care Physicians at Chestnut Hill (Drs. Dover, Arndt, and Kaminer). Alister Carruthers recently studied 24 patients with lipoatrophy of the face, assessing their quality of life after Silikon injection. The results of both studies have not yet been published as of the writing of this article.

DISCUSSION

An extensive review of the literature on the complications of silicone injections for soft-tissue augmentation of the face revealed several features: there can be impressive results and significant disasters associated with injectable silicone of the face. The majority of complications involved the cheeks, nasolabial folds, and glabella. The average time to first complication is 8 to 10 years, with a range of 6 months to 36 years. This extensive lag time makes the problem difficult to study because information regarding the history of the technique used and the amount and composition of the material injected is often not available. A "material" was injected in the past and is often presumed to be silicone. The majority of complications include granulomas, nodularity, migration, and chronic cellulites. It is interesting to note that there are only a few complications involving the lips, and none reported were severe. The fact that the MDX 4-4011 silicone was limited only to the initial seven "authorized' investigators (an additional investigator was added later) and never made available for widespread use indicates that nearly all of the injected silicone was of an industrial or medical grade that never was produced or intended for injection. Even MDX 4-4011 is contaminated by low-molecular-weight impurities by today's standards. Unfortunately, the majority of the larger trials are no more than anecdotal reviews; there are virtually no follow-up data. Generally, the only follow-up endpoint becomes a complication. It does seem unlikely that the six authors above that published the largest series that included over 9000 patients followed for an average of 15 years would extol the benefits of soft-tissue augmentation with injectable silicone if the complications were excessively high or the results were not acceptable. It can be assumed that litigation alone would have stopped their practices if there had been a large number of significant complications. A reasonable explanation would be that they did not see any of their own complications for many years; nevertheless, these same individuals were in practice for over 20 years and would presumably have been contacted by patients who did have complications. There is no question that pure injectable-grade silicone fluids that have been injected by competent practitioners have resulted in

adverse outcomes, but such cases appear to be rare. Using a conservative estimate, there are well over 100,000 patients who have had silicone injected for facial soft-tissue augmentation. However, the number of serious complications reported is significantly less than 200, many of which include the use of questionable silicones or nonsilicone products, large quantities injected, unknown technique, and/or poor treatment sites. Even if there is a larger underreporting bias, there are tens of thousands—the vast majority—of patients who have benefited from silicone injections. Because of the long latency before complications, there is a "ticking time-bomb" attitude toward silicone injections that casts a cloud over the treatment. In such cases, objective research should take precedence over subjective dogma. The U.S. Food and Drug Administration studies initially showed excellent results with few complications despite large volumes of silicone being injected and MDX 4-4011 having a relatively low viscosity. In fact, all studies involving MDX 4-4011 showed a low rate of complications. However, there is still a lack of long-term follow-up data.

There is a significant difference between the technique of silicone injection today and 20 years ago. The silicone is purified and sterilized and intended for injection which, in theory, would decrease the possibility of granuloma formation and infection. It is also much more viscous, which has minimized or even eliminated the issues with migration. The use of small-volume injections spaced at least 1 month a part should reduce migration, granuloma formation, and scarring. Lastly, there are certain areas that have had large numbers of complications, such as the breast, cheeks, and glabella. It is unclear whether these specific areas are actually prone to complications or are areas that typically require large amounts of silicone oil for correction.

Currently, silicone oil is used clinically for soft-tissue augmentation of the lips and nasolabial folds and to correct lipodystrophy of the cheeks and mild postrhinoplasty irregularities. Silikon-1000 appears to be the agent of choice. It can be administered with a 25-gauge needle or a modified 27-gauge needle. It is administered with the microdroplet technique, in which very small amounts (0.01 to 0.03 ml) are injected with a serial puncture technique. Alternately, a slightly larger volume of silicone is injected by a tunneling or fanning technique in which up to 1 ml is given in a treatment area. Most patients will require multiple treatment sessions, with a month between treatments.

CONCLUSIONS

The use of injectable silicone as a soft-tissue filler is a very controversial topic. Both the lay and scientific literature is replete with stories of disastrous results and disfigurement, often occurring many years after the initial injection. Anecdotal negative outcomes can be overpowering in just about every procedure that we perform as plastic surgeons, such as breast augmentation, free flap surgery, facial peels, and so forth. There are also reports of thousands of patients treated with spectacular results over long periods of time. It is probable that some of the successes that are claimed eventually had a complication if followed long enough or that they just were not reported. It is just as likely that poor technique and impure, low-viscosity silicones contributed to many of the complications. Some of the conflicting facts are that, before 1965, there was no silicone fluid available that was made for injection. The majority of injections were performed with Dow Corning 360 medical-grade silicone that was never intended for soft-tissue injection or augmentation. Often, silicone was not even the substance that was injected; "something" was injected in years past and was presumed to be silicone. It was not until 1965, when MDX 4-4011 was introduced, that a silicone intended for injection was produced, and this was given to only a few investigators involved with the U.S. Food and Drug Administration studies. Therefore, the overwhelming majority of silicone injections performed over the past 50 years have consisted of a grade of silicone that was never intended for injection. Furthermore, silicone at 350 cS is less viscous than currently available silicones. The volumes of currently injected silicones are much lower than those previously reported, especially when using the microdroplet technique. Lastly, there are clearly areas of the face and body that tend to have a higher percentage of complications than others (i.e., breasts and glabella).

Given that there are significant potential benefits to purified, high-viscosity, injectable silicone oil if used correctly, it would be important to elucidate those factors contributing to complications. Impure or adulterated silicone and large volumes of a low-viscosity silicone would clearly be implicated in significantly increasing the rate of complications. The question is, Will small amounts of a purified, high-viscosity silicone, injected correctly, cause the same problems of delayed and often disfiguring granuloma as previously reported? The only way to know is to conduct a

longitudinal study with appropriate follow-up data—this has not been performed to date. Before we discard the potential benefits of a material as powerful as injectable silicone oil, it would be prudent to determine the specific factors leading to its complications.

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DISCLOSURE

The author has no affiliation or financial interest in any of the products discussed in this article.

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