Aesth. Plast. Surg. 22:356–365, 1998

Aesthetic Plastic Surgery

PMMA-Microspheres (Artecoll) for Long-Lasting Correction of Wrinkles: Refinements and Statistical Results

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Abstract. The corium is diminished to about half of its thickness in skin defects and wrinkles. All biological materials that increase the thickness of the corium are resorbed within a certain time. Therefore, a lasting effect can be achieved only with nonresorbable synthetic substances. Artecoll consists of microspheres of 30–40 μm in diameter, of exceptional surface smoothness, purity, and homogeneity related to PMMA. These microspheres are suspended in atelocollagen which serves as a vehicle for *subdermal* implantation. Due to its smooth surface and consequential lack of electrical charges, each single microsphere is immediately encapsulated with the patient's own collagen fibers, thus preventing dislocation. Within 3 months, collagen (making up 75% of Artecoll) is replaced by the body's own connective tissue. The microspheres (25% of Artecoll) serve merely as a stimulus to the fibroblasts. Indications for Artecoll are all facial folds, lip- and philtrum augmentation, chin- and malar augmentation, dark-shadowed eyelids, enophthalmos, bony defects in face and hands, nipple reconstruction and augmentation, and urinary incontinence. Questionnaires were sent to all patients who had received Artecoll in 1993 and 1994. Of a total of 950 questionnaires sent, 515 were returned by September 1995. Satisfaction was rated ''very good'' in 29%, ''good'' in 38%, ''satisfactory'' in 23%, and ''no difference'' in 8% of the patients. The question, ''Would you repeat the treatment again?'' was answered by 91% of the patients with ''yes.'' The overall complication rate was 3%. Strictly subdermal implantation will prevent longer lasting redness or visibility of the Artecoll.

Key words: Nonresorbable synthetic fillants—(Artecoll) microspheres—Fibroblast growth stimulants

Presented at the New York City Biennial ISAPS Congress, September 1995.

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More types of therapy are available for facial wrinkles than for any other physiological aging process. Small wrinkles such as crow's feet, perioral lines, and wrinkled cheeks can be effectively treated with dermabrasion, chemical peel, or CO_2-laser resurfacing (15). Striking folds like glabellar frowns, nasolabial folds (Fig. 1) or depressed corners of the mouth have to be surgically stretched or lined with certain tissues. Since all biological tissues such as fat, dermis, collagen, and even bone, cartilage, or tendon will be resorbed at sites where they are not naturally formed, synthetic biomaterials have to be used for permanent leveling. Silicone granules (Bioplastique) are known to cause granulomas (1) because of their irregular surface and accumulation of electrical charges. Goretex (SAM-facial implant) has an excellent biocompatibility and seems good for lip augmentation (11). However, larger pieces placed under nasolabial folds will eventually show their margins and may need to be trimmed or removed. Silicone fluid, (6) although eas-

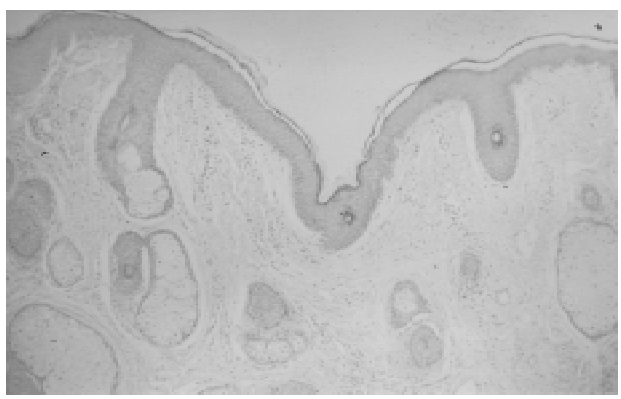


Fig. 1. Cross-section through a nasolabial fold showed normal thickness of epidermis, but diminished thickness of dermis to about ¼ of its normal thickness.

ily and effectively applied beneath wrinkles, may eventually cause chronic inflammation or migration (4).

Therefore, when collagen preparations were introduced in 1982, we envisioned a nonresorbable material in powder form which could be added to the collagen solution as a mean to be implanted (13). For more than 100 years collagen has been used in surgery in the form of catgut to be resorbed during the wound healing process. Implanted under wrinkles and folds, it resorbs within 4 weeks to 4 months depending on the single volume (2). Among the various injectable biomaterials in powder form which have been in use for many decades, Polymethyl-metacrylate- (PMMA) microspheres used as bone cement (Palacos) showed the least number of tissue reactions during animal experiments (13).

Artecoll (14) consists of 25% microspheres of 30–40 μm diameter (Fig. 2) suspended in 75% atelocollagen (Resoplast). The collagen is phagocytized by macrophages within 1–4 months. In the same period of time, each single microsphere is encapsulated with collagen fibers secreted by the body's own fibroblasts (Fig. 3). The microspheres serve merely as a stimulus for connective tissue formation. The amount of connective tissue depends on the individual's typical scar formation, but appears to be closely related to the prior content of bovine atelocollagen, e.g., 75% (Fig. 4).

Material

Artecoll (Rofil Medical International, Breda, The Netherlands) is a 1 in 3 suspension of Polymethyl-metacrylate (PMMA)-microspheres of 30–40 μm diameter in a 3.5% collagen solution. Atelocollagen (Resoplast, Rofil) is derived from the hide of calves from a pharmaceutical herd in southern Germany, fed solely with milk and grass. No feed additives such as animal meal are used, and no foreign cattle are brought into this herd. Therefore, this herd is absolutely free of Bovine Spongiforme Encephalopathy (BSE). Furthermore, during the manufacturing process, the collagen is subjected to a viral inactivation procedure by treatment with 1N-sodium hydroxide for 1 h at 20°C. This method is internationally recognized not only for the complete inactivation of BSE causative agents, but also for a multitude of other viruses, which cannot be detected by routine testing methods. Removal of the immunizing endings of the molecule guarantees low antigenicity of the atelocollagen. Filtration through 0.2-μm pores removes any possible bacteria.

German collagen has been tested in a controlled study on the left forearm of 200 patients. Except from short-lasting redness in six patients, no allergic reactions of the acute or late type were observed. One patient who had been allergic to Zyderm 10 years earlier showed an acute allergic reaction to Resoplast as well.

The uniformity of the microspheres is achieved by a complicated process of straining. An ultrasound-bath removes all dust and irregular particles from the microspheres. Washing in Tween 80 makes the microspheres suspendable in the watery collagen solution. Lidocaine 0.3% is added in order to diminish pain after implantation. The gel state of the PMMA-collagen suspension is stable at room temperature but, preferably, should be kept in the refrigerator. The collagen gel melts at 50°C as the microspheres sink to the bottom. Simple heating by turning the syringe several times under warm tap water brings the microspheres back into suspension. The gel state of the suspension is regained by lowering the temperature of the running tap water.

Technique of Artecoll Implantation

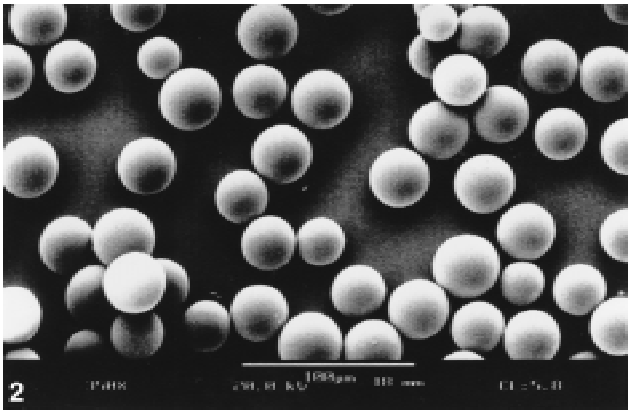
If a patient is not yet sure about Artecoll or whether she would like the effect of augmentation of the lip or the wrinkles, a trial implant with collagen should be recommended.

Artecoll should be implanted subdermally at the junction between the dermis and the subcutaneous fat (Fig. 5). The gray of the needle should never shine through the skin (Fig. 15). Should this occur, the needle should be withdrawn immediately and implantation restarted at ⅒ of a millimeter deeper. Should blanching be observed following a too superficial injection, the implant should be flattened by applying strong pressure using the finger nail. Younger patients, generally have a tendency toward more scar formation than elderly patients. Therefore, overcorrection in elderly patients is harmless, especially when Artecoll is distributed in a fanlike manner beneath the wrinkle. The best candidates are those between 40 and 50 years of age without surplus skin, i.e., without need for a frontal, facial, or midfacial lift.

Using a short 27G-needle Artecoll requires stronger pressure than pure collagen implants. The addition of 25% PMMA-microspheres increases greatly the viscosity. The best distribution beneath a wrinkle can be achieved by moving the needle back and forth several times while maintaining constant pressure throughout the injection procedure. The volume of Artecoll to be implanted depends on the extent and number of wrinkles. Overcorrection is almost impossible since the junction between dermis and subcutaneous fat allows only a limited amount of implanted material. The volume of the absorbable collagen (75%) in Artecoll is approximately proportional to the growth of connective tissue expected in patients with normal tissue reactions (Fig. 4). A second or even third implantation may become necessary after a few months. This technique results in the material being distributed under the fold and up to 3 mm into the neighboring areas in a partly parallel, partly fan-shaped manner.

Immediately following injection the implant should be spread and modeled by applying mild pressure with the finger tips. To keep an even distribution of Artecoll, the implant site should be firmly taped (Transpore, 3M) for about 3 days. Strong mimic muscle movement can form nodules from the flat implant, especially in the lips and corners of the mouth.

Artecoll can be dislodged from the subdermal area of implantation into deeper layers by pronounced facial mimicry within the first 3 days following implantation diminishing the expected result. For this reason, new



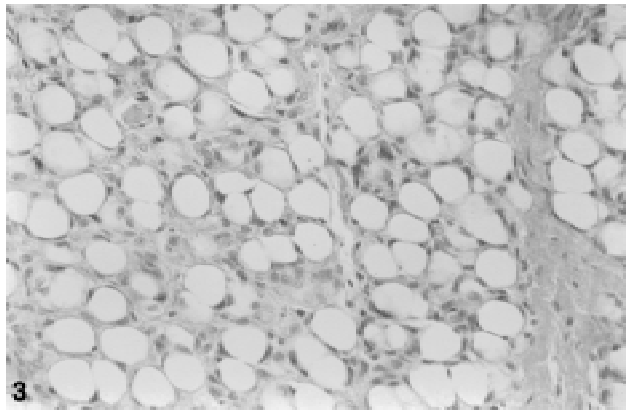


Fig. 2. PMMA-microspheres of 30–40 μm in diameter and absolute surface smoothness.
Fig. 3. Histology of Artecoll 3 months after implantation demonstrates encapsulation of all microspheres with body's own connective tissue. No foreign body reaction.

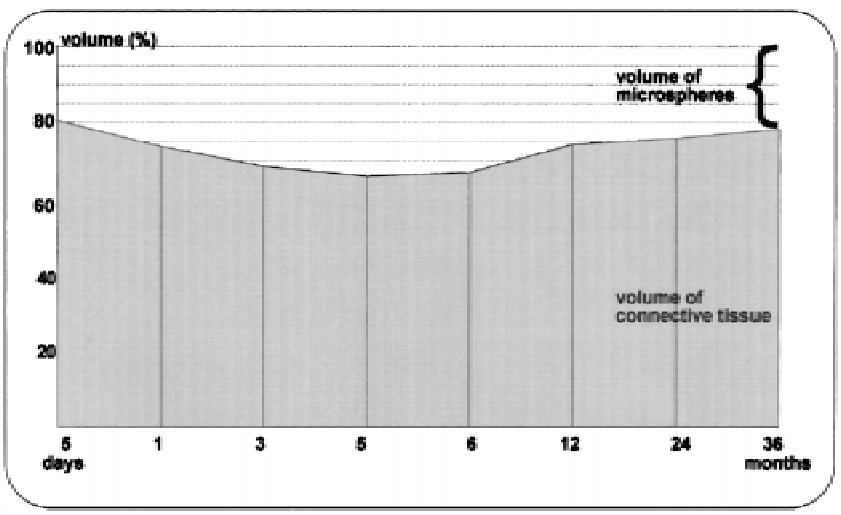


Fig. 4. Computer calculation of the relation of microspheres to connective tissue in eight histological pictures at different time intervals. The initial volume of 75% collagen is almost totally replaced by connective tissue.

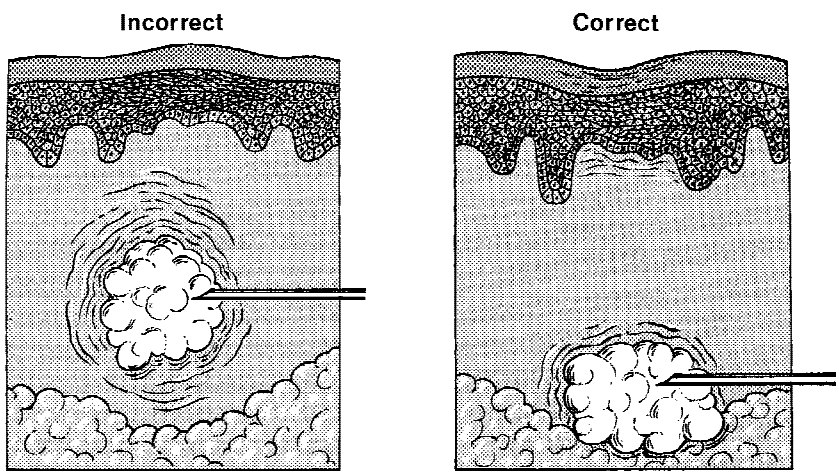


Fig. 5. Artecoll has to be implanted strictly subdermally. A blanching effect must be avoided, since this may cause visible granulations (see Fig. 14).

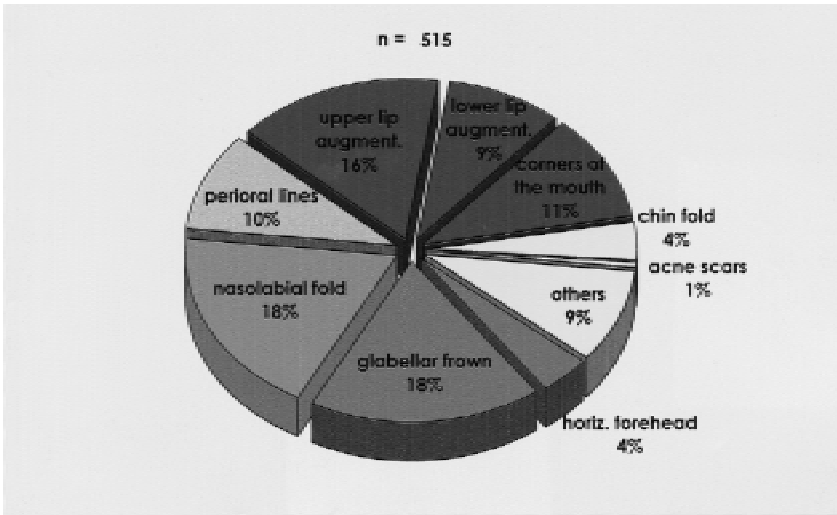


Fig. 6. Locations of Artecoll implantation in Study III.

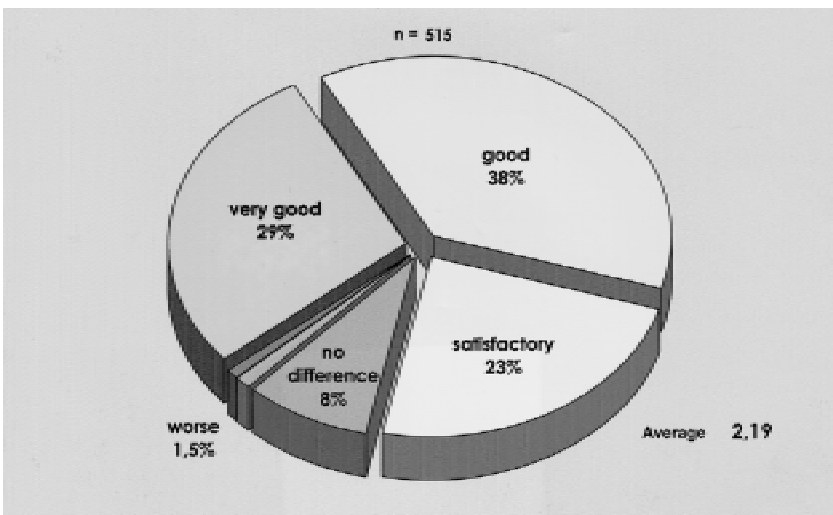


Fig. 7. Patients assessment on the effect of implantation after 1 year or more.

implantations should be supported with a transparent tape for about 3 days.

Local anesthetics are necessary only for implantation into the orbit or for augmentation of upper and lower lip. Here, 1 ml of 2% or 1% Lidocaine solution should be injected along the mucosa of the labiogingival folds to achieve a field block. Patients with low pain thresholds may receive a topical anesthetic (EMLA-creme), applied 30–60 min before implantation.

Patients who never had collagen treatment should receive a test injection of Artecoll or Resoplast in the forearm to exclude sensitivity 4 weeks prior to Artecoll treatment. Patients with atrophic skin (Fig. 16) and flaccid skin are poor candidates for Artecoll since the implant may shine through, may be palpable, or may even be visible as rubber-like nodules following implantation.

Patients

A third clinical study was designed to get subjective and objective data from 320 patients with a total of 950 subdermal Artecoll implants into different pairs of wrinkles during 1993 and 1994. By September 1995, 515 questionnaires had been returned from 290 patients. All data were computerized, and patient's assessments were statistically analyzed. Roughly 20% of all questions and answers referred to each of the following categories: glabellar frowns, nasolabial folds, depressed corners of the mouth, lip augmentation, and ''other'' wrinkles (Fig. 6). ''Other'' implantation sites included forehead wrinkles, dark-shadowed eyelids, perioral lines, horizontal chin folds, and acne scars. Of the 515 pairs of wrinkles, 61% had been treated once, 27% twice, 11% three times, and 1% four times.

Results

The questionnaire contained 27 questions concerning aesthetic result and acute side effects such as pain, swelling, and redness. Furthermore, the change of volume, dislocation, new folds, and side effects like nodules, itch-

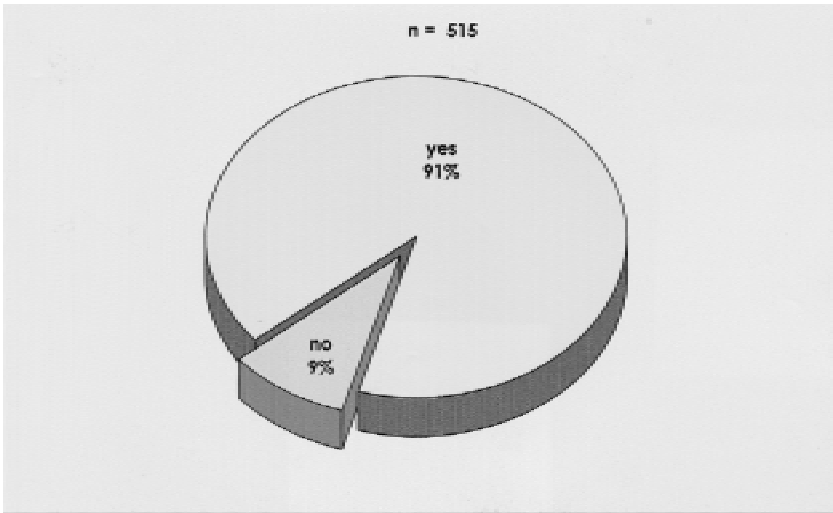


Fig. 8. 91% of the patients who were asked, ''Would you repeat the treatment with Artecoll again?'' answered with ''Yes.'' The cause for the negative answers of 9% of patients was ''lack of efficacy'' or ''visibility of the implant'' (3%).;

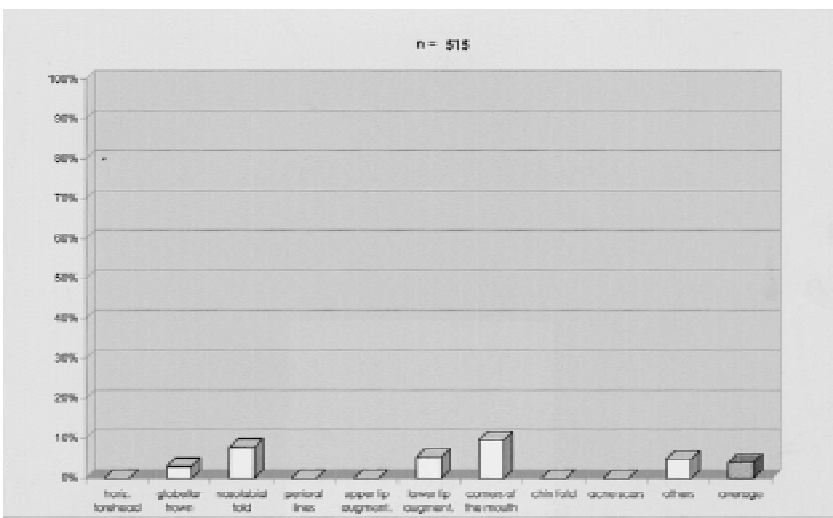


Fig. 9. Long-term side effects. Visible nodules or persistent redness were rated as long-term side effects in a total of 3% of the treated wrinkles.

ing, pain by pressure, discoloration, unevenness, and unpleasant feelings were ascertained. The last five answers referred to the subjective and objective judgment of the patient, which were then compared with the notes of the implantor and the ''before'' and ''after'' photographs.

A number of patients reported an improvement of the depth of the wrinkles in time. As it is observed in elderly patients with facial palsy or post CVA, most wrinkles disappeared on the paralyzed side of the face, meaning, that even in old age the dermis in a fold is able to recover up to its previous thickness. The same mechanism may be true for facial folds which cannot be moved to the same extent as before Artecoll implantation.

After at least 1 year following Artecoll implantation, 77% of the patients reported an ''optimal or clear improvement,'' 19% saw ''little improvement,'' and 4% ''no improvement'' in the treated wrinkles.

The overall *subjective judgment* of the patients regarding the effect of Artecoll implantation was ''very good'' in 29%, ''good'' in 38%, ''satisfactory'' in 23%, i.e., a total of 90% of the patients were pleased with the result (Fig. 7). ''No difference'' was noted by 8%; this was probably due to implantation of inadequate volume or due to excessive mimic movement of the patient following implantation. ''Worse'' was the judgment of 1.5% of the patients, mainly because of redness and unevenness of the implant. The question, ''Would you repeat the treatment again?'' was answered by 91% of the patients with ''Yes'' (Fig. 8).

A *lasting effect* of Artecoll implantation for at least 1–2 years was reported by 91% of the patients; 29% felt that the implants decreased in size, and 6% said that they increased in size over the years. New folds or deepening of the old fold occurred in about 20% of the implanted areas. A coworker whose deep glabella frowns were erraded by Artecoll implants 6 years ago developed a new glabellar frown in the midline after 5 years. As mimic muscles move new folds are created in elderly skin over the years.

Visible implants, mainly in nasolabial folds, horizontal frowns, and corners of the mouth, were reported by 3% of the patients. No transparency was reported, however, after lip augmentation or implantation beneath glabella frowns, perioral lines, chin folds, and acne scars (Fig. 9).

Palpable implants were reported by 64% of the patients, mainly after lip augmentation and implantation of glabellar frowns and corners of the mouth. Of the patients with lip augmentations, 40% complained about little *pain on pressure*, as did 15% after implantation of Artecoll beneath glabellar frowns and perioral lines as well as 8% after implantation beneath nasolabial folds. An overall satisfaction was reported by 100% of the patients after Artecoll implantation in horizontal chin folds and acne scars, by 91% for all other treated folds, and only by 80% for horizontal forehead furrows. Among the ''others'' were patients with depressed scars, acne scars, nipple augmentation, and nipple reconstruction, enophtalmos, and depressions after rhinoplasty.

Indications

The treatment of horizontal *frontal frowns* was judged ''insufficient'' by 35% of the patients. All had received only one treatment. This suggests, that a second, more superficial, implantation between the first base implant and the wrinkle is necessary after about 3 months.

The best results and least complications were seen in the treatment of *glabellar frowns.* A single intradermal and subdermal implantation of 0.5 ml of Artecoll gives a long-lasting and satisfying result. Overcorrection is necessary, even if the implant can always be palpated.

The treatment of *dark-shadowed eyelids* (Fig. 10A and B) provides a challenge since there is no other simple treatment available. The implantation has to be strictly *epiperiostally*, i.e., below the orbicularis muscle and just above the insertion of the septum orbitale. The bone can be felt with the tip of the needle. Moving the needle backward, the Artecoll can be spread along the lower orbital rim. Care has to be taken in withdrawing the needle, since implantation into the muscle will cause a nodule!

A preferred indication are *single crow's feet* in a thick skin just as crow's feet in a thin and flaccid skin are an absolute contraindication. A perfect indication for Artecoll are depressions of the dorsum of the *nose after rhinoplasty* or irregularities of the nostrils and a negative nasolabial angle. Here, the possibility of implanting a small dosis of Artecoll epiperiostally or into the nostril (Fig. 11A and B) easily satisfies the patient. An open roof or the visible border of a silicone implant can also be corrected easily so. So far, no infection after Artecoll implantation has been seen. Augmentation of a *saddle nose* or a rather flat dorsum in the Asian nose is possible in a two- or three-step procedure; during the first treatment 2 ml of Artecoll should be sufficient. The dorsum of the nose has to be modeled by the patient her/himself throughout the first 3 days after implantation. Artecoll has the advantage over other biomaterials of full ingrowth of connective tissue and the possibility of further augmentation or later correction.

Augmentation of malar bones or of a *receding chin* with Artecoll is possible, however, 5–10 ml of Artecoll may be required; therefore, prefabricated implants may be more economical. Still, Artecoll is ideal for correcting malpositioned or asymmetric implants.

The *nasolabial folds* (Fig. 12A and B) are best supported by criss-cross implantations like the armament of concrete building structures. Care must be taken not to implant too superficially, otherwise the implant is visible (Fig. 14), as this was the most common complaint in our survey. A second implantation is often necessary, especially in the corner of the mouth and in the upper part of the nasolabial fold. Here, a triangle of Artecoll must be implanted subdermally around the nostrils.

For most women *lip augmentation* was the most rewarding therapy (Fig. 13A and B). In the elderly, the filling of the white roll and cupids bow prevents further development of radial lip lines, and augmenting the lost *philtrum* may give the lip a more youthful look. Artecoll is not indicated in other lip defects because it may become hard. Under no circumstances should the ''droplet technique'' be applied in the lip.

Some patients complained of burning of the lips during the first few days. Hypersensitivity to pressure lasted for several months, even if kissing was not a problem. Other patients reported dry lips and increased scaling, some of them were forced to massage their lips over several months. Especially young patients had difficulty biting into an apple or opening their mouth at the dentist, because of tension or pain during the first 3 months. Herpes labialis developed in three patients who had been susceptible to it. Therefore, this problem should be discussed with the patient beforehand and prevented by Acyclovir.

In order to increase the pouting effect, a second row of Artecoll can be implanted under the mucosa close to the frontal teeth. Care has to be taken in long upper lips, since too much Artecoll may increase the volume of the red of the lip but hide the frontal teeth. Should this happen, an upper lip lift through a bullhorn excision is very effective.

Perioral lines are best treated by lip augmentation along the upper and lower white roll. Between the border of the red of the lip and the underlying muscle is a natural pocket, which can usually be filled easily under pressure with 0.5 ml of Artecoll. Thereafter, the remaining radial lines can be underlined with Artecoll from above made more even by the criss-cross method of implantation.

In order to treat depressed or *negative corners of the mouth*, one can start with a horizontal augmentation of the lower white roll, about 1 cm in length from the corners, and sometimes even of the upper white roll. Thereafter, 5–10 horizontal implantations should be added caudally and eventually combined with criss-cross implantations. There is a danger of implanting too superficially! If the implant is too close to or in the muscle, nodule formation may result! Therefore, Artecoll should be implanted in two sessions.

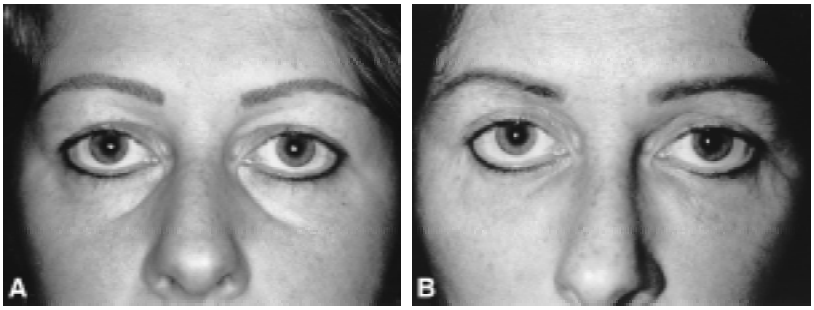


Fig. 10. (A) Dark-shadowed lower lids. **(B)** Two years after treatment with 0.5 ml Artecoll on each side. The implants are still palpable like soft rubber on the orbital rim.

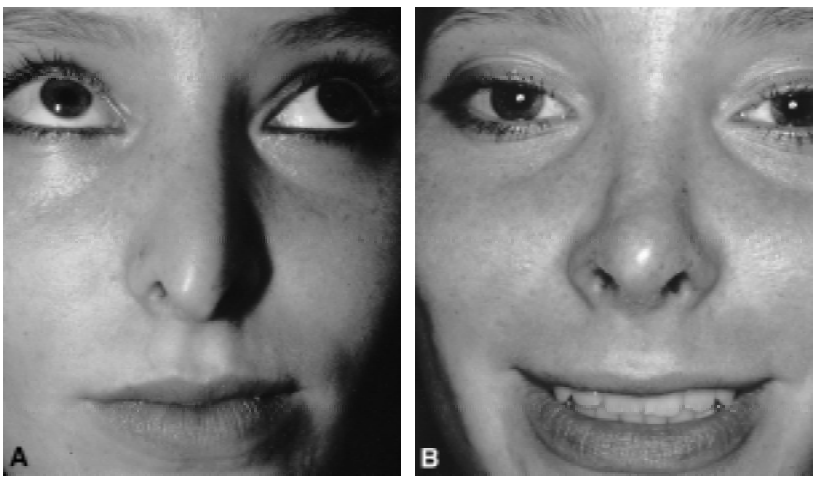


Fig. 11. (A) Collapsed nostrils after rhinoplasty. **(B)** After removal of the cartilaginous supra tip deformity and implantation of Artecoll (four times about 0.2 ml) into the nostrils.

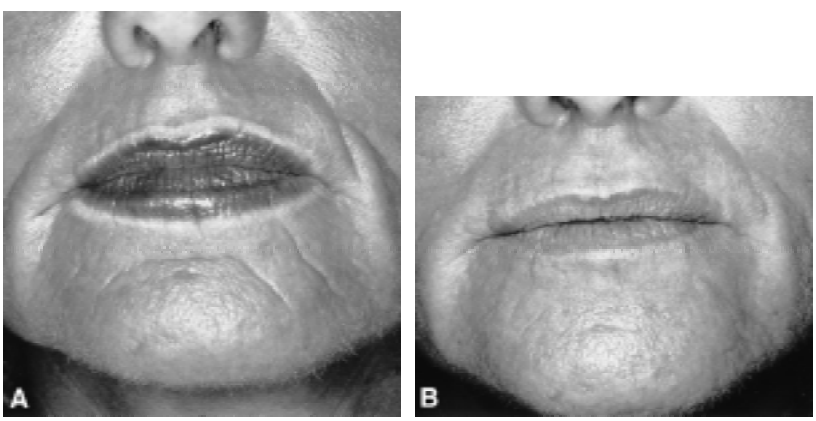


Fig. 12. (A) Nasolabial folds and deep perioral wrinkles. **(B)** Three years after implantation with 1.5 ml Artecoll.

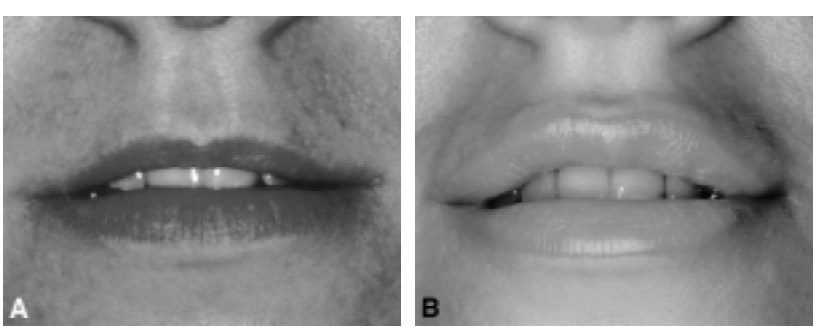


Fig. 13. (A) Small upper lip in a 30-year-old patient. **(B)** The same patient 3 years after implantation of 1.8-ml Artecoll in three sessions (augmentation of the cupids bow and implantation along the border of the red of the lip to mucosa).

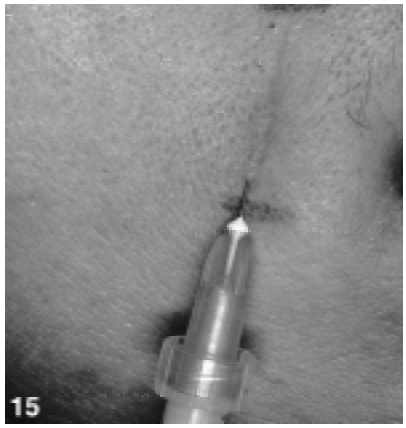


Fig. 14. Visibility of Artecoll after faulty intradermal implantation.
Fig. 15. The needle shines through the skin and is positioned intradermally. This would cause a blanching effect and should be avoided!

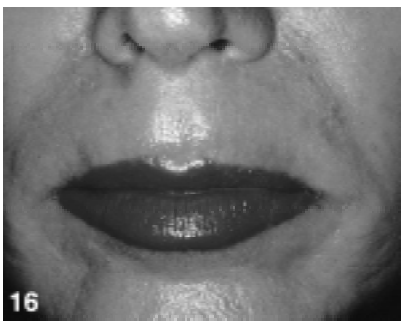


Fig. 16. A very thin skin with capillary injection is a contraindication for Artecoll treatment. Artecoll has to be implanted rather deep in order to avoid long-lasting redness.
Fig. 17. The movement of the M. orbicularis has caused two nodules from the pressed-down implant. An injection of triamcinolone (Kenalog) will diminish the hypertrophic scar formation around the single microspheres.

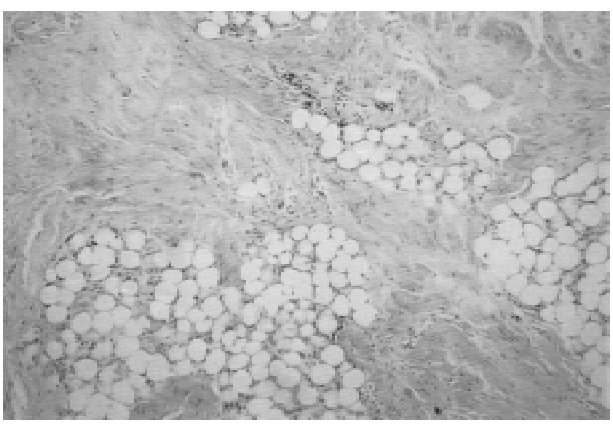


Fig. 18. Artecoll granuloma (less than 1%) in a 76-year-old woman which developed 1 year after the first implantation and 3 months after the second implantation—only at locations of the latter. No allergic reaction was noted at follow-up.

The horizontal *chin fold* and single oblique folds along the skin folding lines of the cheek do present a problem. Sometimes a second implantation is necessary. The same is true for the horizontal *folds of the neck.* They are to be implanted cautiously, preferably in two sessions. A flaccid neck is, of course, an absolute contraindication.

Complications

Acute side effects. Acute swelling after implantation generally subsided on the following day. Bruising was rare but lasted up to 1 week. Itching has been reported during the first months. The ''perfect result'' began to wane after 1–3 weeks because of resorption of the water content of the collagen. A long-term result, therefore, can only be expected from 3 months on, when all microspheres are covered with the body's own fibrocytes and collagen fibers (Fig. 3).

Late side effects. Longer lasting redness after Artecoll implantation was reported by 6.1% of the patients treated in 1993, however, by only 0.5% of those patients treated in 1994. Transparency of Artecoll, recorded for 9% of the wrinkle implants in 1993, was reduced to 2.5% in 1994 (Fig. 9). In five of these patients (1%), intralesional treatment with triamcinolone or surgical excision became necessary. The decrease in the complication rate within 1 year was due to the change to a strictly subdermal implantation technique in 1994.

The long-term side effects such as transparency, dislocation and unevenness occurred primarily in the nasolabial folds (Fig. 14) and depressed corners of the mouth (Fig. 9).

The overall complication rate of wrinkles treated with Artecoll in 1994 was 3.0% (six out of 201 wrinkles). An exclusively subdermal implantation in the future will lead to a further decrease of this rate. *A blanching effect* (Fig. 15) (as is desirable in collagen implantation) *should be avoided under all circumstances in order to prevent longer lasting redness* (Fig. 16). On the other hand, pure collagen or hyalurouic acid (12) preparations can be im-

planted intradermally above the Artecoll implant in order to improve the primary result—if the wrinkle is too superficial to be erased totally with Artecoll. Likewise, laser resurfacing of deep wrinkles can be applied directly after Artecoll implantation, since it will be located subdermally (15).

Allergic reactions. Among the 290 patients, an acute allergic reaction occurred in one women, who had received collagen (Zyderm) 2 years earlier. After a single intravenous injection of 1000 mg prednisolone, all symptoms subsided immediately. Another patient, on the other hand, who had had 4 years earlier a severe cellular allergic reaction of the late-type IV to Zyderm, tolerated Artecoll well following repeated testing for sensitivity.

Theoretically, an allergic reaction to PMMA is also possible. Millions of patients, however, have tolerated artificial dentistry, bone cement, ocular lenses, and pacemakers without any sign of sensitivity. We are aware of only one severe allergic reaction in a laboratory technician who had worked in PMMA dust containing monomers for years (7).

Tween 80 is used for washing the PMMA-microspheres and to make their hydrophobic surface suspendable in water (tixotropy). One out of a 1000 persons will be allergic to Tween 80. No histological specimen taken after Artecoll removal showed eosinophilic or lymphocytic cells typical for allergic reactions.

Granulomas may develop at a rate of 1 in 1000 patients. The manufacturer is aware of 10 out of over 8000 European patients (five in France, three in Germany, 1 in the Netherlands, 1 in Switzerland) who developed nodule formation (Fig. 17) 6 months to 2 years after Artecoll implantation. All of them except for one 76-year-old woman responded to intralesional triamcinolone (Kenalog) or betamethasone (Diprosone) injections. Histology revealed new fibroblast activity with thick bands of collagen fibers as in hypertrophic scarring dispersed with rare foreign body granulomas (Fig. 18). The cause for this late development of nodules is not yet understood.

Discussion

The secret of PMMA-microspheres, not to evoke a foreign body reaction, is due to their totally smooth surface. It is well documented that the sharp edges of polyurethane foam, the rough surface of silicone particles (Bioplastique) or porous hydroxylapatite stimulate macrophages and giant cells to remove this material (4). Eppley et al. (5) recently showed with dextran beads in rats that neutral or positively charged surfaces are chemotactic for macrophages and fibroblasts, a cellular response which is favorable to dermal and subcutaneous tissue repair and augmentation. No evidence of a foreign body or chronic inflammatory response was seen, as is typical for materials with rough surfaces. Surface charges accumulate on ridges and edges and, therefore, strongly stimulate giant cells, which are ''frustrated'' macrophages (4), i.e., macrophages, which cannot achieve a proper phagocytosis of the polymer. Positive surface charges are important for bone substitutes, since they enhance bone formation (7).

After implantation, all foreign materials are at once covered with proteins. In response to the structure and electrical charge of the surface, one or more protein layers are formed by the surrounding cells. If there are no shearing forces, then a stable electrical field will result (21), and the secreted proteoglycols will remain chemically and electrically inert.

The late development of granulomas in a few patients (10 in 8000) is not yet understood. For several reasons, Artecoll should not be implanted intramuscularly. The constant movement of the mimic muscles may cause hypertrophic scarring as has been shown in study II (14). On the other hand erythematous nodules occurring at the injection sites of pure collagen are well known and have been described (16). They subsided very slowly despite topical and systemic corticoid therapy and may last up to 3 years (3). Moscona (16) published a case of a severe delayed type hypersensitivity reaction to Zyderm I. Two years after the injection, the woman noted a sudden appearance of swelling and induration around the mouth and lips. Biopsy showed a dense inflammatory cell infiltrate composed mainly of sarcoid-like granulomas along with a focal collection of lymphocytes. The positive reaction of an erythematous nodule at the original skin test site was due to multinucleated histiocytes in a palisade-like array.

The Artecoll-granulomas do not show an allergic reaction of the late-type IV, but rather a simple foreign body reaction. Five of the eight tested patients did not have an early or late reaction at a second skin test site. The manufacturer prevents impurities in the PMMA microspheres through continuous electron microscopic control of all charges. Some people, however, react against even the smoothest surfaces like that of the microspheres (Fig. 7). Contact dermatitis on finger tips and palmar sites of nurses and surgeons following exposure to the monomer of acrylic cements has occasionally been reported (8).

Methylmetacrylate appears to be essentially inert, but capable of triggering macrophage activation due to the presence of phagocytable debris particles (18). Electron microscopic pictures of the sifted and washed PMMA-microspheres (14) showed not a single debris (Fig. 2) which might eventually stimulate phagocytosis. Fragmentation or erosion of the 40-μm microspheres in time can also be ruled out through the extensive data on bone cements available from orthopedists (19).

Intravenous injection of inert polystyrene microspheres demonstrated that 1- and 3-μm spheres could be found in monocytes and granulocytes while the 12-μm spheres were observed only outside the cells. The serum protein levels were unchanged indicating that the spheres did not stimulate the immune response (10). Peritoneal macrophages in the mouse showed much less phagocytosis for microspheres with nonionic hydrophilic surfaces than for microspheres with hydrophobic surfaces (20).

Phagocytosis of 40-μm PMMA-microspheres is an

extremely rare occurrence among all the histologic specimen taken after Artecoll implantation.

A longitudinal study (17) of human histologic specimen (Fig. 4) demonstrated that these microspheres are usually well tolerated by the cellular immune system, that they are nonantigenic, nonmigratory, and permanent.

The authors are grateful to Dr. Ulrich Charrier in Frankfurt/Main for independent review of the histological specimens, and Mrs. Lydia Kerr in Basel for a critical reading of the manuscript.

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