Plexiglas (polymethylmethacrylate) implantation:
technique, pre-clinical and clinical experience

Christos Feretis, MD[a], Paul Benakis, MD[a],
Christos Dimopoulos, MD[a], Apostolos Dailianas, MD[a],
Konstantinos M. Stamou, MD[b],*, Andreas Manouras, MD[b],
Nickolaos Apostolidis, MD, FACS[b],
George Androulakis, MD, FACS[b]

[a]*Department of Therapeutic Endoscopy, "HYGEIA" Hospital, Erythrou Stavrou 4 & Kifissias Avenue,
115 23, Athens, Greece*
[b]*1st Department of Propaedeutic Surgery, Hippokrateion Hospital,
114 Vas. Sofias Ave., 115 27 Athens, Greece*

Over the past few decades, a great scientific effort has been made and many resources have been committed to treat the benign, nonlethal disease of gastroesophageal reflux. This reflects a trend in modern medicine toward optimizing quality of life, reducing health-related lost working hours, and minimizing costs of chronic treatments. It also reflects a revived interest in diseases that can be studied using novel equipment and that can be cured using minimally invasive techniques.

It is not surprising how much gastroesophageal reflux disease (GERD) relates to these trends. First, the disease has long been recognized as a significant public health concern. Nearly 44% of Americans experience "heartburn" and 18% of these individuals use nonprescription medication for this problem [1,2]. Approximately 2% of these cases progress to severe esophagitis. As a consequence, although the costs of treating GERD itself are low, the overall cost of treating people for the relief of symptoms that are generally attributed to GERD is considerably high [3]. It has also been suggested that the impact of GERD on quality of life is comparable to that of coronary artery disease when assessed with symptom severity scales [4].

Recently, specially designed catheters and transducers have been used because they permit an in-depth anatomic and physiologic study of the few-centimeters-

* Corresponding author. MD 20, Potamianou Street, 115 28 Athens, Greece.
E-mail address: cstamou@hotmail.com (K.M. Stamou).

long section of the gastrointestinal tract that forms the lower esophageal sphincter (LES) [5]. The LES constitutes the intrinsic component of a complex mechanism of competence at the gastroesophageal junction, an area of remarkable structure and function. In particular, prolonged transient LES relaxations not triggered by swallowing are considered responsible for GERD-related symptoms in the majority of patients [6–8]. Medical treatment relieves symptoms by altering the composition of the refluxing gastric juice, but it does not address the condition's mechanical etiology; thus symptoms recur in more than 80% of cases within 1 year of drug withdrawal [9].

The evolution of minimally invasive surgery has renewed interest in the surgical treatment of GERD. In an effort to further minimize surgical trauma, novel endoscopic techniques are beginning to challenge the standard therapeutic approach to GERD.

The use of implantable materials in medicine

Biocompatible materials have been used extensively as tissue augmenting factors in aesthetic surgery. Most interestingly, they were used as promoters of the remodeling of sphincteric mechanisms in urology. So far, polydimethylsiloxane (Macroplastique) and polytetrafluoroethylene (Teflon) implantable particles have been successfully used to treat intrinsic urethral sphincter deficiency [10,11], incontinence [12], and vesico-ureteric reflux [13,14]. Ideally, an implant should be biologically and chemically inert, nonmigrating, and long-lasting. Nevertheless, the induced foreign object reaction is not completely undesirable, because the formatting connective tissue may play a key role in satisfactory long-term results.

Polymethylmethacrylate (PMMA) was originally patented as Plexiglas by O. Rohm in 1928 and was initially used in human applications in 1936 as a dental prosthesis. As an implantable material, PMMA undergoes continuous manufacturing improvements to correspond to the desired properties of the implant. When produced in the form of microspheres of varying size, it can be used in aesthetic surgery for augmenting the diminished thickness of chorium in cases of skin defects and wrinkles. The microspheres have a smooth and completely round surface, and, when produced in the size of 100 μ, rarely migrate or dislocate from the implantation site. In addition, their phagocytosis is hindered, and they evoke a negligible foreign body reaction [15]. The relatively large size of the microspheres makes their injection through a needle catheter difficult though feasible.

PMMA's biocompatibility has been well enough justified that additional animal studies are not needed [16]; however, animal studies may be required if the material is to be injected in an anatomic site for the first time. Concerns about granulomatous reaction are related to the site of the injection and the possible complications that could arise [17,18].

The substance used as a PMMA carrier is a heated 3.5% bovine, spongious, encephalitis-free gelatin solution with the gelatin's allergizing ends removed. The final form of the implant is a 1 to 3 suspension of PMMA in gelatin solution.

Following implantation, the gelatin (75% of total volume) is phagocytized by macrophages within 3 months and replaced by the body's own fibroblasts and collagen fibers, a reaction that is stimulated by PMMA spheres (25% of total volume) [19,20]. These are encapsulated with connective tissue replacing 50% of the gelatin volume as proved by histological slides [21]. Finally, at least two thirds of the total volume of the implant remains in place.

The above-mentioned properties of the PMMA implant have rendered it an attractive tissue-bulking factor. This, together with the success of treating sphincter deficiencies in urology, has led to the hypothesis that the augmenting effect of submucosal implantation of PMMA into the lower esophageal folds could minimize the consequences of transient LES relaxation and reduce the severity of GERD.

Preclinical experience

To study the feasibility of injecting PMMA microspheres in the submucosal layer of the lower esophagus, an initial animal study was undertaken. Six domestic white pigs weighing 12 to 15 kg were used for the PMMA injection to the lower esophagus through an open gastrotomy. A volume of 5 to 10 mL of implant was injected into each animal under direct vision with the use of refillable syringes. PMMA was implanted circumferentially just proximal to the gastroesophageal junction. Each implantation session was completed when the esophageal folds were macroscopically approximated. All animals recovered from the operation and were fed on the fourth postoperative day. No eating disorders were observed; all animals gained weight and grew normally during the follow-up period. Specimens were retrieved in month-long periods and included the site of implantation, surrounding lymph tissue, and samples of liver tissue. A pathologist examined all specimens macroscopically and microscopically.

For the examined periods of time (1–6 months of implantation), no ulceration of the mucosa or formation of granulomatous tissue was evident at the site of injection. On the first postinjection month the microspheres were found in place, grouped into clusters that were surrounded by connective tissue strands. In the specimens that were retrieved on the fourth, fifth, and sixth month postinjection, the density of the collagen fibers had increased and the amount of foreign body cells remained stable. Perigastric lymph nodes were enlarged in three animals, and histology revealed signs of inflammatory reaction. It was not clear whether PMMA promoted a nonspecific inflammation or if local contamination due to the gastrotomy was responsible. No PMMA particles were identified in the examined lymph nodes, and liver specimens were normal.

The animal study was undertaken to examine the feasibility of the implantation and to investigate the stability of the implant when larger than usual volumes are injected into an area of the gastrointestinal tract with relatively high mobility. For the examined period, it was evident that no major complications should be anticipated from the injection of PMMA in the lower esophagus.

To evaluate the effect of implantation in GERD, an adequate porcine model of the disease had to be available. Similar animal models are based on the surgical disruption of the LES [22]. We considered that PMMA implantation would be efficient in treating GERD in cases of a noncompetent rather than a nonexisting sphincter. Therefore, an animal study that would require myotomy of the LES to provoke GERD may not correspond to the pathophysiology of GERD as related to transient sphincter relaxations.

Technique

A detailed description of the implantation technique has been recently published [23]. In brief, the patient needs to be still; therefore, a standard sedation protocol is required. Intravenous diazepam is usually sufficient and pulse oxymetry monitoring should be available. The PMMA solution is prepared in 3-mL syringes and warmed to 32° C with the use of a water bath. Warming of the material results in a technically easier procedure since the otherwise high viscosity would compromise proper injection. A short, wide-channel, flexible sigmoidoscope (Olympus CF 140, America Corp, Melville, NY) and a shortened, 90-cm long needle catheter are used to inject the viscous preparation. The needle is advanced into the submucosa layer 1 to 2 cm above the z-line, and the implant is injected (Fig. 1). Multiple injections in different sites are needed to induce thickening of the esophageal folds and cause their close approximation. A second or even third session with the same treatment end point should be performed 2 weeks later if reflux symptoms (heartburn, regurgitation) are not under control by then. Incremental treatments using less than 20 mL of implant employed in each session can also prevent minor and transient complications as dysphagia and gas-bloat syndrome. The end point of each implantation session is to create enough bulks in the submucosa so that the esophageal lumen appears almost sealed.

Clinical experience

Patients and methods

The pilot study was undertaken at the "Hygeia Diagnostic and Therapeutic Center" after approval by the institute's Scientific and Ethical Committee. All patients were informed about the experimental nature of the method and the possible hazards of the procedure, and all gave written informed consent. Ten patients (seven females, three males) of a mean age of 52.6 years (range: 23–73) with medically dependent or refractory GERD participated and were treated with submucosal PMMA implantation. All patients had already been on continuous omeprazole treatment for at least 6 months (40 mg daily for the first 2 months and 20 mg daily for the following 4 months). Nine patients had a symptomatic

Fig. 1. Injection of PMMA microspheres to the submucosa of the lower esophagus. (See also Color Plate 7.)

(heartburn, acid regurgitation) relapse 1 week after discontinuation of the treatment, and one patient had symptom recurrence at least twice a month during the treatment. Relapse of symptoms was verified to all 10 patients by an abnormal 24-hour pH monitoring study 2 weeks after the discontinuation of their 6-month medical treatment.

Patients who (1) were pregnant or lactating, (2) had a hiatal hernia larger than 3 cm, (3) had an immune deficiency or used corticoids, or (4) had a peptic stricture or Barrett's esophagus were not considered eligible for the study.

Evaluation

The primary outcome variable assessed was the severity of symptom score before and after the treatment. The assessment was performed by using a Likert unidimensional scale that provides a way for respondents to quantify varying degrees of agreement or disagreement with a given statement. Patients were trained in using a modified symptom scale in which heartburn, regurgitation, pain, and dysphagia were scored from 1 to 5, indicating respectively absence of symptom to intolerable symptoms [24]. The assessment was carried out 1 week before treatment from both patient and physician in face-to-face visits. In the follow-up period, the patients were asked to keep a monthly diary of their Likert scale and of their need for medication. All diaries were reviewed and the final

score was assessed from two face-to-face interviews approximately 6 and 12 months posttreatment. Further pre- and postimplantation investigation included: 24-hour esophageal pH monitoring (Digitrapper MK III, Synectics-Medical, Stockholm, Sweden), upper gastrointestinal endoscopy, and endoscopic ultrasound of the lower esophagus.

Statistical analysis included paired Wilcoxon's signed ranks test analyzed on SPSS 8.0 (SPSS, Inc., Chicago, IL) statistical software ($P \leq 0.05$).

Results

Each treatment session was performed as an outpatient procedure and was completed within 10 to 30 minutes. Patients received a mean volume of 31.77 mL (range: 24–39 mL). An initial follow-up visit was appointed at approximately 6 months posttreatment and a later one at a median period of 14.5 months (range: 5–24 months). All patients participated in the initial follow-up examination and only one refused to complete the long-term follow-up because of symptom relapse. Submucosal implantation of PMMA brought about an initial decreased in severity of the GERD symptom score in 9 of 10 patients; 2 additional patients had symptoms relapse when their follow-up exceeded 12 months. Finally, 7 out of 10 patients were completely off medication.

The mean symptom severity score in the 10 patients was 12.2 (range: 9–16) before and 7.7 (range: 5–11; $P = 0.005$) after the implantation. The decrease in the severity symptom score was associated with a fall in the mean fraction of total time with a pH less than 4 in the lower esophagus as recorded in 24-hour pHmetry. The mean pretreatment value in the 10 patients was 24.51 (range: 9.8–32) and the mean posttreatment value was 10.45 (range: 6.8–19.6; $P = 0.007$).
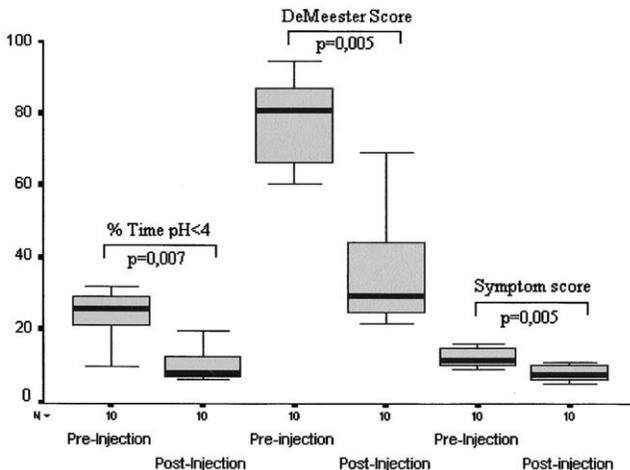

Fig. 2. Comparison of 24-hour pHmetry data and symptom scores before and after endoscopic treatment of GERD with PMMA injections.

Mean DeMeester score was 74.6 (range: 27–94.5) before and 36.3 (range: 21.6–69.3) after implantation. The difference also proved statistically significant ($P = 0.005$; Fig. 2). Complete discontinuation of medical treatment was recorded in 7 out of 10 patients. Of the 3 patients that relapsed, one continued the regular use of PPIs after the treatment and his relapse is attributed to a technical failure. The other 2 patients continued taking antireflux medication on demand.

Using the L.A. Classification system [25], in initial endoscopy, five patients proved to have GERD associated esophagitis (one patient had grade A, three patients had grade B, and one patient had a grade a C esophagitis). In a follow-up period of 7.2 months (range: 5–11), healing of esophageal lesions was noticed in three of five patients having prior GERD-associated esophagitis (two grade B, one grade C). Improvement of picture from grade B to grade A esophagitis was detected in one patient, while the lesions remained unchanged after treatment in one grade A esophagitis patient. All findings were similar on the latest follow-up.

Endoscopic ultrasound performed immediately postinjection was used to verify the submucosal position of the implant. At the initial follow-up examination, endoscopic ultrasound verified the continuing presence of PMMA particles in all sites of implantation in all 10 patients. During the later ultrasound examination, PMMA particles were identified scattered around the submucosal layer and small amounts were found in sites of the muscular layer.

Posttreatment, 9 of 10 patients were able to resume eating the same evening and to repeat their normal activities on the next day. Two patients experienced chest pain that required 2 days of oral analgesic treatment. In the follow-up, no granulomas formation or mucosal ulcerations were detected. Serious complications were not met.

Discussion

Mechanisms of action of antireflux treatments

When treating a patient with GERD-related symptoms, it is important to consider the variety of pathophysiologic mechanisms that could be responsible. The existence of hiatal hernia, abnormalities in the gastric emptying pattern, pregnancy, or the use of certain medications may be the cause of reflux through a normally functioning LES [26]. In these cases, treating the primary disorder or prescribing proper medical therapy have a high possibility of success.

Medical therapy, mainly with the use of proton pump inhibitors (PPI), aims to alter the composition of the refluxing gastric juice and to reduce the exposure of esophageal mucosa to acid. Especially following the withdrawal of certain prokinetic agents, the medical therapy of GERD is strictly symptomatic and does not address any of the proposed mechanisms that promote reflux. In addition, it is doubtful if antacid therapy affects the reflux of duodenal content into the esophagus, which is considered a cause of severe esophagitis. Experience from reflux esophagitis in patients that underwent proximal gastrectomy for cancer

indicates the devastating effect of the exposure of esophageal mucosa to alkaline duodenal content [27]. PPIs have excellent results in relieving GERD symptoms in most patients but require continuous prescription and highly motivated patients in altering their lifestyle and following doctors' orders. A new and interesting approach to the pharmacological treatment of GERD is to incorporate drugs that affect transient lower esophageal sphincter relaxations [28].

Interest in the surgical therapy of GERD was renewed with the advent of laparoscopic antireflux procedures. The excellent postoperative course of the patients possibly made surgeons much more willing to perform laparoscopic modifications of the Nissen fundoplication, not to treat a hiatal hernia but to relieve GERD symptoms. Efforts were concentrated on designing a fundoplication that would provide an extrinsic support to the LES rather than just secure the lower esophagus in the abdomen [29]. Manometric studies generally reveal the effect of fundoplication in increasing LES basal tone, reducing the frequency of transient LES relaxations, and altering swallowing-induced LES relaxations [18,30,31]. A concern arises from the tendency to overcorrect the deficient LES that frequently results to dysphagia or gas-bloat syndrome [32]. In addition, long-term results of the superiority of the laparoscopic versus the open approach are still questionable [33].

The few proposed endoscopic techniques for treating GERD focus on remodeling the intrinsic LES as a single factor accounting for the competence of the gastroesophageal junction. Therefore, to accomplish a satisfactory result,
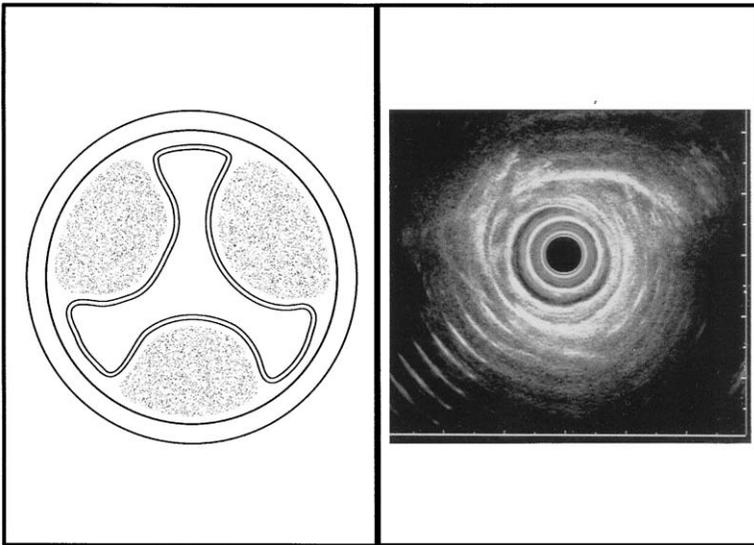

Fig. 3. (*Left panel*) Schematic appearance of PMMA distribution in the submucosa immediately postinjection. (*Right panel*) Endoscopic ultrasound of the lower esophagus 6 months following the injection. PMMA appears concentrated into large groups in the submucosa.

all other possible causes inducing GERD should be eliminated. The endoscopically guided delivery of radiofrequency energy to the LES is supposed to prevent reflux by ablating intramural vagal afferent nerve pathways or by tightening the gastroesophageal junction through collagen contraction [34]. Injection of collagen or polytetrafluorethylene in the lower esophagus has been reported to achieve only short-term benefits through a temporary bulk effect on the lower esophagus [35,36]. Endoscopic gastroplasty's antireflux action probably results from lesser gastric curvature plication that buffers the muscularis of the LES zone and alters regional anatomy [37].

Interpretation of the results of PMMA implantation

In the initial interpretation of our findings, we supposed that the increase of the thickness of the lower esophageal folds by the submucosal injection of PMMA was responsible for the success (Fig. 3) [23]. Later findings with the use of endoscopic ultrasounds directed us in revising the proposed explanation for the mechanism of action of the technique. In the long-term follow-up, clusters of PMMA microspheres were found scattered circumferentially in the submucosa, no longer forming bulky concentrations. In addition, small PMMA clusters were identified in the muscular layer (Fig. 4). This corresponds to the findings of biocompatibility studies in which several months are required for the process of connective tissue formation to be completed. The identification of PMMA in the muscular layer could be attributed to accidental injection that was not identified in
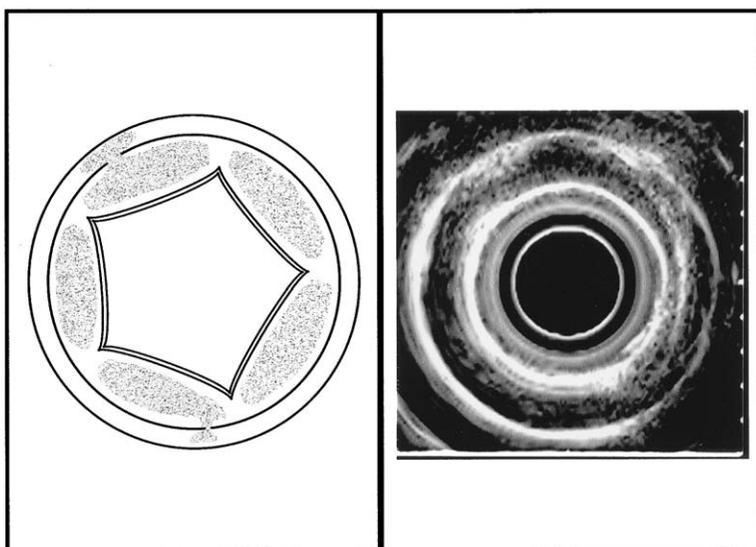

Fig. 4. (*Left panel*) Schematic appearance of PMMA distribution in the submucosa 14 months postinjection. (*Right panel*) Endoscopic ultrasound of the lower esophagus 6 months following the injection. PMMA appears grouped into clusters.

the initial United States study. In contrast, dislodgement of the material into deeper layers is not expected after the first 3 days following implantation. A varying amount of connective tissue not easily quantified in both the submucosa and the muscular layer is responsible for the tightening of the whole structure of the LES. This probably results in a reduction of the compliance of the lower esophagus, alteration of the manometric findings, and, eventually, a diminished reflux.

The technique was initially successful in 9 of 10 patients. In the patient that never responded to treatment, we suspect a technical failure or the existence of an additional reflux-promoting factor that was not identified in the pretreatment evaluation. The patient refused a second follow-up visit. Two more patients that initially responded to treatment relapsed when follow-up exceeded 12 months. Relapse of symptoms was accompanied with return of the 24-hour pHmetry and manometric findings to baseline levels. No valid explanation of the initial success can be offered. Apart from the possible placebo effect, we could suppose that these patients reacted hypoplastically to the stimulus for connective tissue formation. This could not be quantified in the follow-up United States studies. Similarly, we could suppose that the amount of implant used was not sufficient to promote granulation tissue formation.

Considerations on the technique

The implantation of PMMA above the z-line is a procedure of moderate feasibility because of the high viscosity of the compound. To overcome this, the endoscopist has to use the shortest possible length of endoscope that is capable of both reaching the z-line and accommodating a wide lumen needle-catheter. Nevertheless, the technique is less demanding than endoscopic valvuloplasty and less time-consuming than radiofrequency energy delivery.

In the posttreatment evaluation, although decreased in a statistically significant degree, the percentage of total time of pH values less than 4 were not normalized posttreatment in any patient. Accordingly, DeMeester's score values at the postimplantation period decreased significantly but were normalized in only 1 of 10 patients. A possible explanation could be that reflux episodes, while not completely eliminated, were reduced significantly to a degree that did not produce symptoms.

In the initial follow-up period, the implantation of PMMA resulted in an obvious relief of GERD-related symptoms in 9 out of 10 patients and was recorded as a statistically significant decrease in the mean symptom severity scale score. With the current median follow-up of 14.5 months, 7 out of 10 patients remain off any medication. Considering the novel nature of the study and the effect of the learning curve on the results, we believe that there is a place for implantation treatment in the management of GERD. Further investigation will determine the exact volume of material and site of implantation that can optimize the results. Regarding the long-term effects of implantation, it could be speculated that once the process of connective tissue formation is completed, the maintenance of improvement would be durable.

It is reasonable to expect a general concern regarding the use of novel endoscopic techniques to treat GERD [38]. Results must be established on the basis of randomized, well-designed studies with the longest possible follow-up; however, pilot studies are valuable in the initial assessment of a new technique and provide the experience needed to overcome technical difficulties.

Acknowledgments

References

[1] National Digestive Diseases Data Working Group. Digestive diseases in the United States. Epidemiology and impact. In: Everhart JE, editor. US Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication no. 94–1447; May 1994.

[2] Klingman RR, Stein HJ, DeMeester TR. The curent management of gastroesophageal reflux. Adv Surg 1991;24:259–91.

[3] Bloom BS, Jayadevappa R, Wahl P, et al. Time trends in cost of caring for people with gastro-esophageal reflux disease. Am J Gastroenterol 2001;96:S64–9.

[4] Dimenas E, Glise H, Hallerback B, et al. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regiments? Scand J Gastroenterol 1993;28: 681–7.

[5] Stein HJ, DeMeester TR, Naspetti R, et al. Three-dimensional imaging of the lower esophageal sphincter in gastroesophageal reflux disease. Ann Surg 1991;214:374–83.

[6] Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux. N Engl J Med 1982;307:1547–52.

[7] DeMeester TR, Peters JH, Bremner CG, et al. Biology of gastroesophageal reflux disease: pathophysiology relating to medical and surgical treatment. Annu Rev Med 1999;50:469–506.

[8] Kahrilas PJ, Shi G, Manga M, et al. Increased frequency of transient lower esophageal relaxation induced by the gastric distention in reflux patients with hiatal hernia. Gastroenterology 2000; 118:688–95.

[9] Society of American Gastrointestinal Endoscopic Surgeons (SAGES). Guidelines for Surgical Treatment of Gastroesophageal Reflux Disease (GERD). Committee on Standards of Practice. Surg Endosc 1998;12:186–8.

[10] Harris DR, Iacovou JW, Lemberger RJ. Periurethral silicone microimplantats for the treatment of genuine stress incontinence. Br J Urol 1996;78:722–8.

[11] Harrison SC, Brown C, O'Boyle PJ. Periurethral Teflon for stress urinary incontinence. Br J Urol 1993;71:25–7.

[12] Colombo T, Augustin N, Breinl E, et al. The use of polymethhylsiloxane in the treatment after radical prostatectomy. Br J Urol 1997;80:923–6.

[13] Puri P. Ten years experience with subureteric Teflon injection (sting) in the treatment of vesico-ureteral reflux. Br J Urol 1995;75:126–31.

[14] Puri P, Granata C. Multicenter survey of endoscopic treatment of vesicoureteral reflux using polytetrafluoroethylene. J Urol 1998;160:1007–11.

[15] Tabata Y, Ikada Y. Effect of the size and surface charge of polymer microspheres on their phagocytosis by macrophages. Biomaterials 1988;9:356–62.

[16] Apple DJ, Mamalis N, Brady SE, et al. Biocombatibility of implant materials: a review and scanning electron microscope study. J Am Intraocular Implant Soc 1984;10:53–9.

[17] Lopez AE, Padron OF, Patsias G, et al. Transurcthral PTFE injection in female patients with urinary incontinence. J Urol 1993;150:856–8.

[18] Ireland AC, Holloway RH, Toouli J, et al. Mechanisms underlying the anti-reflux action of fundoplication. Gut 1993;34:303–8.

[19] Aragona F, D'Urso L, Scremin E, et al. PTFE giant granuloma and adenopathy. J Urol 1997; 158:1539–42.

[20] Lemperle G, Gauthier-Hazan N, Lemperle M. PMMA-microspheres (Artecoll) for long-lasting correction of wrinkles: refinements and statistical results. Aesthetic Plast Surg 1998;22:356–65.

[21] Lemperle G, Gauthier-Hazan N, Lemperle M. PMMA microspheres for skin tissue augmentation. Part 2: clinical investigation. Plast Reconstr Surg 1995;96:627–34.

[22] Schopf BW, Blair G, Dong S, et al. A porcine model of gastroesophageal reflux. J Invest Surg 1997;10:105–14.

[23] Feretis C, Benakis P, Dimopoulos C, et al. Endoscopic implamentation of plexiglas (PMMA) microspheres for the treatment of GERD. Gastrointest Endosc 2001;53:423–6.

[24] Veldhuyzen van Zanten SJ, Tytgat KMAJ, PollacK PT, et al. Can severity of symptoms be used as an outcome measure in trials of non-ulcer dyspepsia and Helicobacter pylori associated gastritis? J Clin Epidemiol 1993;46:273–9.

[25] Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45: 172–80.

[26] Donahue PE. Basic considerations in gastroesophageal reflux disease. Surg Clin North Am 1997; 77:1017–40.

[27] Buhl K, Schlag P, Herfath C. Quality of life and functional results following different types of resection for gastric carcinoma. Eur J Surg Oncol 1990;16:404–9.

[28] Hirsch DP, Tytgat GN, Boeckxstaens GF. Transient lower oesophageal sphincter relaxations—a pharmacological target for gastro-eosophageal reflux disease? Aliment Pharmacol Ther 2002; 16:17–26.

[29] Horgan S, Pellegrini CA. Surgical treatment of gastroesophageal reflux. Surg Clin North Am 1997;77:1063–82.

[30] Little AG. Mechanism of action of antireflux surgery: theory and fact. World J Surg 1992;16: 320–5.

[31] Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg 1999; 86:405–10.

[32] Hinder RA, Filipi CJ, Wetscher G, Neary P, DeMeester TR, Perdikis G. Laparoscopic Nissen fundoplication is an effective treatment for gastroesophageal reflux disease. Ann Surg 1994; 220:472–81.

[33] Sandbu R, Khamis II, Gustavsson S, et al. Long-term results of antireflux surgery indicate the need for a randomized clinical trial. Br J Surg 2002;89:225–30.

[34] Triandafilopoulos G, DiBaise JK, Nostrant TT, et al. Radiofrequency energy delivery to the gastroesophageal junction for the treatment of GERD. Gastrointest Endosc 2001;53:407–15.

[35] O'Connor KW, Lehman GA. Endoscopic placement of collagen at the lower esophageal sphincter to inhibit gastroesophageal reflux: a pilot study of ten medically intractable patients. Gastrointest Endosc 1988;34:106–12.

[36] Shafik A. Intraesophageal polytef injection for the treatment of reflux esophagitis. Surg Endosc 1996;10:529–31.

[37] Fillipi CJ, Lehman GA, Rothstein RI, et al. Transoral, flexible endoscopic suturing for treatment of GERS: a multicenter trial. Gastroinetst Endosc 2001;53:416–22.

[38] Hogan WJ. Endoscopic treatment modalities for GERD: technologic score or scare? Gastrointest Endosc 2001;53:541–5.