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REGENERATION OF SURGICALLY EXCISED SEGMENTS OF DOG ESOPHAGUS US--ETC(U)
JUN 80 M F GROWER, D E CUTRIGHT, E A RUSSELL

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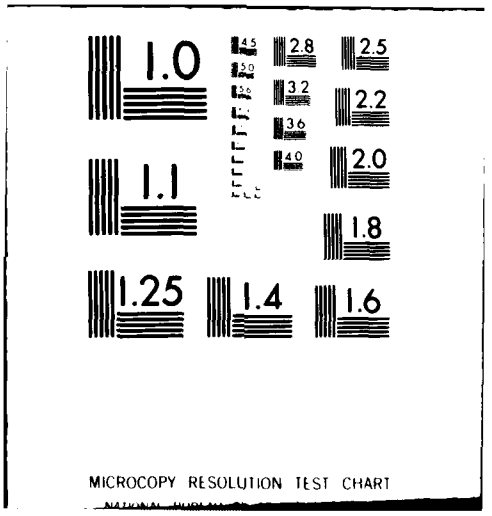
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REGENERATION OF SURGICALLY EXCISED SEGMENTS OF DOG ESOPHAGUS USING BIODEGRADABLE PLA HOLLOW ORGAN GRAFTS

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The widespread multiple site tissue damage to hollow organs which may be produced by the high speed projectiles found in today's battlefield, with the resulting disruption to the vascular supply of the viscera, as well as the need for immediate treatment of the resulting damage, have produced a need for a simple and reliable method for repair of the resulting defects which will yield effective long-term functional results.

The current therapy for repair and replacement of the diseased or avulsed esophagus is by the use of autografts of viscus such as the stomach,(12) the colon,(1) jejunal loops,(3) isolated jejunal segments, (17) or split-thickness skin grafts.(10) None of these procedures produce totally satisfactory results and complications of reconstructive esophageal surgery may include:(14) necrosis of the graft; infection; inadequate blood supply; difficulties in suture retention; leakage at the anastomatic sites; stenosis of the anastomosis between the esophagus and the graft; gastric stasis; reflux; and eating disorders.

The object of this study was to test the feasibility of using a biodegradable polymeric implant constructed from the polymers and copolymers of polylactic acid (PLA) and polyglycolic acid (PGA) to replace an excised segment of the dog esophagus. On a conceptual basis, the use of a biodegradable polymer to fabricate a successful hollow organ graft holds promise, in that, if successful, it would obviate the need for multiple operations and the concern for the vascular integrity of the graft segment. Also, such off-the-shelf grafts would be readily available for immediate repair of a traumatic defect and could be cut to various lengths, depending on the defect to be repaired. Polylactic and polyglycolic acid polymers have been

used as implant materials in the orbital floor,(6) as fixation devices for fractures,(13) and as suture material(4) and in these uses have been shown to exhibit minimal inflammatory response and satisfactory healing response at the implant or suture site. (2,4,5,6,7,8,9,15) The degradation rates of polymers and copolymers of polylactic and polyglycolic acids have been shown to be a function of the type of polymer used as well as different copolymer ratios. (9,15,16)

MATERIALS AND METHODS

The materials used and the working concentration of the solutions employed to fabricate the esophageal grafts were as follows: (1) 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP), (Eastman Kodak Co.). (2) Methylene chloride, analytical grade (Fisher Scientific and Baker Chemical). (3) Polyglactin 910 (90% polyglycolic acid: 10% polylactic acid copolymer) (Ethicon Corp.), [4 g polyglactin 910/50 ml HFIP]. (4) Polylactic acid (DL-PLA), d,l-polylactide (Southern Research Institute), [10 g DL-PLA/100 ml methylene chloride]. (5) Polylactic acid (60% L: 40% DL-PLA), 60% L-polylactide: 40% d,l-polylactide (Ethicon Corp.), [8 g 60% L: 40% DL-PLA/100 ml methylene chloride]. (6) 50% polylactic acid: 50% polyglycolic acid copolymer (50% PLA: 50% PGA) (Batelle Corp.), [8 g 50% PLA: 50% PGA/100 ml methylene chloride]. (7) The templates for fabrication of the esophageal grafts were Teflon cylinders. The Teflon rods used in the fabrication of Group I implants were 150 mm long x 20 mm o.d., while those for Group II were 145 mm long x 26.2 mm o.d. The Teflon templates were constructed from either solid Teflon rods machined to the desired dimensions or from hollow Teflon tubing which had plugs inserted at both ends to facilitate rotation of the tubes.

The esophageal grafts were prepared by building up a hollow cylinder of polylactic acid polymer fibers and films which were reinforced with polyglactin 910 rings by a process of sequential dipping and spraying PLA solutions on a slowly rotating Teflon template. Table 1 gives an example of the steps used in making the Group I grafts listed in Table 2. The PLA solutions were sprayed with a #152 dental atomizer (DeVilbiss Corp.) using 20-30 psi of nitrogen as a propellant at a distance of 10-18 inches from the rotating rod in a fume hood with an air flow of 150 CFM. Spraying of the polymer solutions listed in the materials section produced fibers of 10-25 microns in diameter and 3-10 cm in length which oriented themselves in a circular manner as they attached to each other around the rotating Teflon mandril. Sterilization of the esophageal implants was done using ethylene oxide for six hours at 55C to 60C followed by aeration for eight hours.

The surgical procedures used in this study were done on twelve mongrel dogs under oroendotracheal nitrous oxide, oxygen, and fluo-

Table 1.

Preparation of Series I Esophageal Grafts

1. Dipped 21 mm o.d. x 150 mm length Teflon mandril in DL-PLA solution and allowed to air dry.

2. One end of the coated rod was placed horizontally in the chuck of a slow speed motor, and the other end was put in a glass supporting tube which allowed for rotation of the rod. The motor was then set to turn at a low speed.

3. Sprayed rotating rod with 110 ml PLA solution (90 ml DL-PLA and 20 ml 60% L:50% DL-PLA).

4. Placed 9 polyglactin 910 rings on the PLA-coated mandril. (Polyglactin 910 rings were prepared by spraying polyglactin 910 dissolved in HFIP on a 22.5 mm o.d. Teflon mandril.) The rings were 5 mm in width and were placed 10 mm from each other in groups of 3 to make segments of 45 mm each.

5. Sprayed rod with 10 ml PLA solution (60% L:40% DL-PLA).

6. Dipped rod in 50% PLA/PGA solution and let air dry.

7. Sprayed rod with 40 ml DL-PLA solution.

8. Dipped rod in 50% PLA-PGA solution and let air dry.

9. Sprayed rod with 55 ml DL-PLA solution and placed in sealed jar which was placed in desiccator overnight.

10. Sprayed rod with 72 ml PLA solution (36 ml DL-PLA and 36 ml 60% L:40% DL-PLA).

11. Polymer coated rod was air dried in hood for 2 hours.

12. Placed polymer coated rod in lyophilizer for 48 hours to remove residual methylene chloride solvent.

13. After lyophilization the polymer implant was cut into 3 sections, removed from the Teflon mandril, and stored in a sealed desiccator prior to use.

thane general anesthesia. By a combination of sharp and blunt dissection the cervical esophagus was exposed, mobilized, and retracted from beneath the trachea. A segment of esophagus measuring approximately five centimeters was removed by sharp dissection after placement of umbilical tape slip ties to control secretions from the proximal and distal ends of the transected esophagus. The PLA graft was then anastomosed to the distal end of the esophagus by use of interrupted 000 Dexon sutures (Ethicon Corp.). The proximal end of the esophagus was then anastomosed to the PLA graft in such a manner as to prevent the esophagus from being twisted upon itself. The umbilical tape was removed from the esophagus and the anastomosis inspected for leakage. The surgical wound was closed in the usual layered manner and the suture line sprayed with Topazone (Eaton Veterinary Labs.).

The animals were given Bicillin 1.2 million units intramuscularly for three days post-operatively followed by Keflex, 250 mg three times a day for a period of one week. To prevent dehydration each animal received twice daily subcutaneous feedings of 750 cc of 5% dextrose and water for three days following surgery. On the fourth post-operative day the dogs were fed a liquid diet of canned dog food emulsified in water and fortified with fat (Pig Kalorie Supplement, Haver-Lockhart Labs.).

One of each of the twelve animals was sacrificed at three and nine days and two each at 14, 21, 30, and 56 days with an overdose of barbiturates. Two of the animals were retained for long-term study and as of the writing of this article, one is 10 months post-operative, while the other is 16 months post-operative.

At sacrifice, the graft sites were immediately removed in a cervical block to include the surrounding tissue and at least 2 cm of normal esophagus at either end of the graft. Excess tissue was trimmed off the specimens and they were placed in buffered 10% Formalin. After fixation, the graft sites were grossed serially into 5 to 8 mm transverse segments and photographed. Tissue sections were then prepared at 6 microns thickness and stained with Hematoylin and Eosin for histology.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resource, National Research Council.

RESULTS

Graft Fabrication Table 2 shows the physical dimensions of the biodegradable esophageal grafts that were produced by the sequential spraying and dipping of the Teflon templates with the various forms of polymeric polylactic and polyglycolic acid. Examples of the

Table 2.

Physical Characterization of Biodegradable Esophageal Grafts

Sample	o.d. mm[a]	Wall thickness mm[b]	Length mm	Wt g
		GROUP I		
1	24.5	1.4	44	3.4
2	24.7	1.5	48	3.9
3	24.7	1.6	45	3.4
4	25.4	1.7	52	4.9
5	25.1	1.7	38	3.4
6	25.1	1.7	41	3.7
		GROUP II		
1	33.9	3.7	43	8.6
2	33.4	3.6	39	7.2
3	33.7	3.9	40	8.0
4	31.5	3.0	45	6.8
5	32.0	3.0	45	6.8
6	32.4	3.2	45	6.9

[a] Outside diameter of samples was measured around the polyglactin reinforcing rings. Internal diameter of Group I implants was 20 mm; Group II implants was 26.2 mm.

[b] Wall thickness of polymer between polyglactin 910 reinforcing rings.

(137)

actual grafts produced are presented in Figure 1, A and B. The fabricated grafts were rigid and showed very little tendency to flex. The inner surface of the graft was smooth and tended to be somewhat more solid in nature than the peripheria due to filling up of inter-fibrillar networks by the 50% PLA/PGA dips used in fabrication of the core portion of the implant. This solid core tended to provide a certain rigidity to the implant. The outer half of the implant was composed of a circular network of PLA fibers 10-25 microns in diameter which could be observed as a series of laminations around the inner core as seen in Figure 1A. This fibrillar coating allowed for the rapid infiltration of fibrin and fibrovascular tissue into the implant which resulted in a water-tight seal. These implants exhibited resistance to flex and collapse; however, the consistency of the wall material was fibrillar enough to allow the needle from a 3-0 Dexon suture (Ethicon Corp.) to be placed completely through its wall (Figure 1B). The sutures placed through the graft wall were retained in position and the wall of the graft did not show any tendency to tear after placement of the sutures. Comparison of the physical properties of Group I implants and Group II implants (Table 2) shows that the Group II implants had an inner diameter 6.2 mm greater than Group I and a wall thickness at least two times as thick. These larger implants were constructed to provide more resistance to lumen collapse which was noted in some two-week specimens, and to produce a larger diameter esophageal replacement which would be more resistant to esophageal stricture during the repair phase of healing. Ethylene oxide sterilization of the implants caused an average 4% decrease in length and a 6% decrease in diameter from the dimensions listed in Table 2. This dimensional shrinkage was also accompanied by a slight increase in flex resistance.

Clinical Findings The post-operative periods progressed uneventfully. There was very little swelling at the surgical site. Endoscopic examination of the grafts *in situ* at three days and eight days showed an unobstructed esophageal graft which was in continuity with the rest of the esophagus. Oral administration of slurried canned dog food was thus begun on day four after initial surgery. By the fourth week after surgery, the dogs showed some difficulty in oral feeding and endoscopic examination showed contraction of the repair tissues present in the graft site. Dilation with a series of metal bougies starting at a French #29 (9.5 mm) and ending at a French #45 (14.8 mm) was begun at this time and the graft sites were dilated biweekly until two weeks prior to sacrifice.

The dog presently surviving 16 months (Group I, #5) was dilated biweekly until six months post-surgery. Some esophageal constriction was seen at this time, but was readily relieved by bougienage therapy and a size #45 French dilator freely passed the length of the esopha-

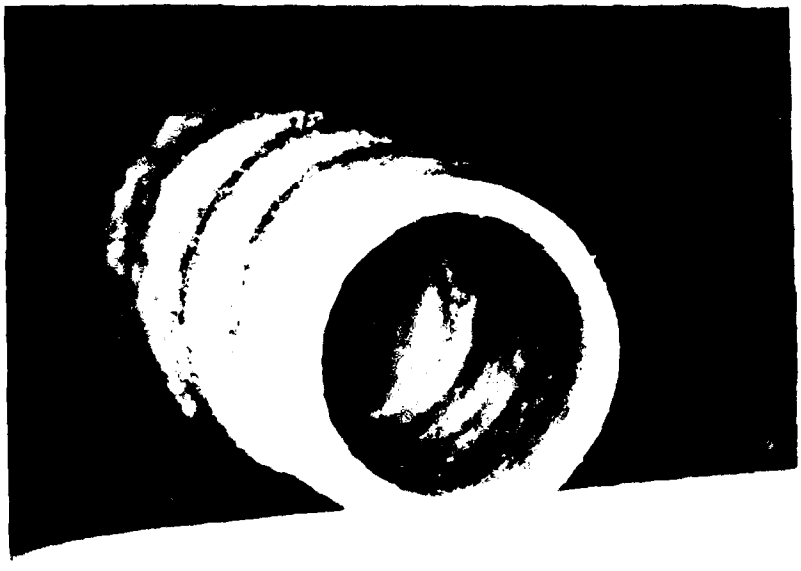

FIGURE 1A. End view of a Group II biodegradable polymer esophageal graft. x1.5

FIGURE 1B. Group I biodegradable polymer graft with 000 Dexon suture placed through wall. x3.0

gus after dilation. This dog was then dilated monthly for the next three months and then one more time two months later. This animal has now gone five months without any further dilation. The dog eats well and has shown an increase in body weight from 45 pounds prior to surgery, to 48 pounds at the present time.

The second surviving dog which had surgery done 10 months ago (Group II, #6) was not dilated until 40 days after surgery and then was dilated monthly for two months up to a size #45 French dilator, after which time it has received no further dilations (over seven months). Endoscopic examination showed that no esophageal constrictions were present and that the epithelium of the graft area was continuous and similar to that of the original esophagus. After an initial weight loss after the esophageal surgery, the dog eventually regained and has maintained his preoperative weight of 40 pounds.

Gross and Histologic Findings The gross morphology of the esophageal grafts after three days of implantation is shown in Figure 2. Gross examination of the implant site did not show any evidence of leakage around the anastomosis between the polymer tube and the esophageal tissue. All the original sutures were present and they showed only minimal inflammatory reaction around them. The implant did not show any evidence of collapse or evidence of loss of structural integrity at this time.

Histologic examination of the original connective tissue wall of the esophagus and the graft itself showed a layer of very early fibroblastic tissue demonstrating hemorrhage with early vascular proliferation. At the interface between the graft and the connective tissue there was evidence of platelet and fibrin accumulation within the interstices of the graft but only very little evidence of organization. The inflammatory response to the graft and sutures was minimal at this time. Although there was no proliferation of the early fibroblastic tissue into the interstices of the graft, there was a definite increase in mitotic activity in the surrounding connective tissues. This was evidenced by an increased number of fibroblasts and small vascular channels proliferating around the edges of the graft.

Nine days after surgery the interface between the connective tissue and the graft showed a marked maturation of the fibrous connective tissue and ingrowth of the vasofibroblastic response into the interstices of the graft material. The thickness of the connective tissue wall measured from the outer surface of the tracheal cartilage rings was 2 mm and the tracheal wall did not show any evidence of erosion due to presence of the graft. Histologically there could be seen a beginning orientation of the connective tissue fibers in a circular manner around the graft site. There was very little tendency to form giant cells surrounding the polymer fibers.

FIGURE 3. Gross section of a 21 day esophageal implant (cross section). (w) regenerated esophageal wall, (l) lumen of esophagus, (i) residual implant material, (t) trachea.

FIGURE 2. Three day gross specimen of the anterior anastomosis of the esophagus with the biodegradable polymer graft (longitudional section).
(e) anterior esophagus, (a) anastomosis site, (g) main body of polymer implant.

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The interface between the graft and the original connective tissue showed an ingrowth of 1.5 mm of fibrous connective tissue into the interstices of the graft itself with minimal inflammation present. At the margins or at the interface between the graft and the esophageal epithelium there was a proliferation of new epithelium at least 3 mm down over the graft site.

Examination of the 14 day samples revealed a vasoblastic connective tissue wall of approximately 3 mm which surrounded the esophageal implant. In certain areas of the connective tissue graft interface there was some mild multinucleated giant cell formation where the polymer had been incorporated into the tissue and this extended back about 1.5 mm from the apparent edge of the graft itself, indicating that the vasofibroblastic ingrowth had penetrated at least 1.5 to 2 mm into the graft. In addition, there was minimal evidence of collagen organization into both circular and longitudinal bands in the implant area as well as epithelial ingrowth down the edges of the graft itself.

Gross examination of the 21-day samples, as seen in Figure 3, showed that there was a vasofibroblastic wall of about 5 mm (measured from the outer tracheal ring) which had formed both as a result of tissue growth around the implant and growth into the implant itself of about 2.5 mm. Histologically, the advancing front of granulation tissue into the graft itself was characterized by occasional multinucleated giant cells which were shown to be phagocytosing the polymer after it had been hydrolyzed. The more solid inner portions of the implants containing the polyglactin 910 supporting rings appeared to have become delaminated from the outer portions which were penetrated by granulation tissue ingrowth. Portions of this residual graft material could be seen in some sections as seen in Figure 3, although in other areas this material was absent. The collagen fibers present in the new esophageal wall showed a variable orientation and there was variable epithelial migration up to 5 mm from the anastomosis along the inner aspect of the graft site.

By eight weeks the graft appeared to be almost completely resorbed and a collagenous tube with a wall thickness up to 5 mm measured from the tracheal rings was present, as seen in Figure 4. In addition, it was evident that the esophageal implants had not affected or caused any erosion of the trachea. The lumen of the esophagus was open although some contraction of the repair tissue was evident as indicated by the narrowing of the esophageal lumen and there was no macroscopic evidence of graft material. Although on microscopic examination (Figure 5) some evidence of residual polymer between the collagen fibers appeared to be present. The Dexon sutures, on the other hand, appeared to have become completely degraded. Only minimal inflammation and slight edema were present at the graft site and the collagen showed a variable orientation with a

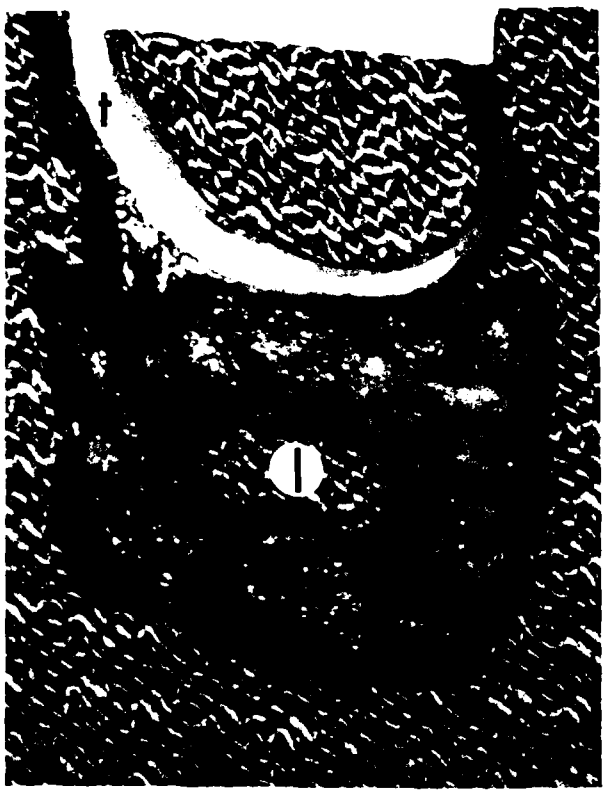

FIGURE 4. Gross section of 8 week esophageal implant (cross section). (w) regenerated esophageal wall, (l) lumen of esophagus, (t) trachea.

FIGURE 5. Histologic section of the 8 week esophageal graft at the graft-esophagus interface.
(e) epithelium of esophagus, (eg) epithelium growing on luminal aspect of graft, (c) collagenous repair tissue, (p) residual polymer, (r) giant cell reaction, (l) lumen of esophagus. x48

small amount of circular orientation. There were islands and sheets of epithelium growing over the surface of the implant throughout much of the graft lumen as seen in Figure 5, although the lumen was not completely epithelialized.

DISCUSSION

This study demonstrated the feasibility of using a biodegradable hollow organ implant fabricated from polylactic acid and polyglycolic acid polymers to regenerate an excised segment of the dog esophagus. The use of an inner core fabricated from polyglactin 910 rings, 100% PLA fibers and laminations of 50% PLA/50% PGA provided for rigidity of the implant. The outer covering of PLA fibers provided for strength and allowed for a vasofibroblastic ingrowth into the graft as well as promoting growth of a collagenous sheath of tissue around the peripheria of the graft. The fabrication of 100% PLA into 10-25 microfibers, as was done in this study, allowed degradation of some polymer in as little as 14 to 21 days (Figure 3) by hydrolysis of tissue fluids and cellular action; although some polymer appeared to be retained for up to 8 weeks (Figure 5). This resorption time is in contrast to the time required for solid PLA plates. Plates are partially resorbed in six weeks and total resorption occurs in six months.(13,16)

The fibrillar esophageal grafts which were constructed in this study were strong, easily handled, and could be trimmed to any required size. They were resistant to leakage, retained sutures well, and showed minimal inflammatory reaction at the anastomotic sites. The ability of these implants to undergo sterilization by ethylene oxide would enable them to be routinely stocked and sterilized in a hospital setting. The minimal shrinkage seen in the implants with ethylene oxide sterilization at 55-60C was probably due to some dimensional change exhibited by the d,l-polylactide fibers (15); however, the use of L-polylactide fibers and polyglactin 910 supporting rings tends to inhibit these dimensional changes.

The PLA polymeric material appeared to have a favorable response on the healing reactions seen as complete repair of the graft site by a collagenous sheath connecting the two ends of the esophagus was achieved by two weeks. Histologically, this repair was by a dense hyalinized type of connective tissue in sheath form.

The connective tissue sheath allowed the animal to eat freely with minimal discomfort until the fourth week after surgery, when some contraction of the new segments was noted. This constriction was readily relieved by dilation of the esophagus with metal bougies. Similar problems may also be seen with autogenous viscus replacements (14) and the course of bougienage therapy used on the long-term surviving dogs is similar to the therapeutic regimens used on human patients with constrictive esophagitis.(11)

The ability of the two surviving dogs to go without dilation for over 5 to 7 months suggests that maturation of the collagen fibers making up the repair may have occurred. The greater resistance to esophageal contraction shown by the dog receiving Graft II, #6 (Table 2) suggests that the wider and thicker grafts used in Series II may provide more optimal healing stimuli than the narrower and thinner grafts of Series I. Dilation of the grafts caused only minimal trauma to the lining epithelium, which rapidly healed. The esophageal grafts in these two long-term animals have also apparently resulted in a functionally effective repair which allowed adequate nutritional support of the dogs, as evidenced by the maintenance and/or increases seen in their initial body weights. This compares favorably with results achieved using viscus grafts in which patients report difficulties in eating and slow weight gain for 12 to 18 months or longer. (14)

In conclusion, it has been shown in this study, for the first time, that: (1) It is possible to construct a completely biodegradable off-the-shelf graft which can replace lost segments of hollow organs; (2) Regeneration of the hollow organ occurred by a new tube of connective tissue lined by epithelium utilizing the technique of neogenesis within a biodegradable polymer-copolymer framework; (3) The replacement supported the dogs' nutritional intake requirements; (4) The replacement showed adequate strength and allowed for maintenance of esophageal diameter by bougienage therapy; (5) It did not appear to exhibit problems such as the need for multiple operations, leakage at anastomosis sites, lack of blood supply, and postoperative infections seen with other therapeutic procedures in current use; and (6) Grafts made of spun biodegradable PLA and PGA polymers meet the requirements for an effective and easy-to-use replacement for traumatized or lost hollow organs which are encountered in combat military surgery, and should be studied further.

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