Evaluation of Tissumend II Sterile as a Multipurpose Absorbable Tissue Adhesive

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ABSTRACT

Radiochemically sterilized Tissumend II Sterile was evaluated as an absorbable tissue adhesive/sealant for: 1) repairing corneal defects in rabbit models; 2) augmenting kidney incisional wounds in rabbits; and 3) sealing lacerated lung tissue in cats and dogs. Immediate post-surgical evaluation of treated sites indicated timely curing of tissue adhesives. Retrieved tissues from application sites were evaluated for histological changes 1 to 3 weeks following surgical procedures. Available data indicate a moderate tissue response at 1 week that subsided at 2 and 3 weeks. All surgical sites were almost completely healed at 3 weeks. All animals survived, reflecting excellent functional performance of adhesive.

INTRODUCTION

The use of tissue adhesives as alternative or adjunct means to sutures and staples in tissue repair has been suggested by surgeons for a number of decades. In fact, tissue adhesives are preferred over mechanical devices in surgical procedures associated with tissues that are soft and/or sensitive to minor mechanical deformation. Typical examples of some soft tissues are those of the lung, liver, and kidney. The retinal and corneal tissues are examples of those whose functional performance can be easily compromised by minor mechanical distortion that can be encountered during suturing or stapling. Based on these facts and recent success associated with the use of Tissumend II Sterile (Veterinary Products Laboratories, Phoenix, Arizona, USA) as an absorbable tissue adhesive in topical veterinary applications, as well as the availability of the radiochemically sterilized version of the adhesive, the pursuit of the present study was prompted. This report deals specifically with the use of Tissumend II Sterile in repairing corneal defects and kidney lacerations in rabbits, and lung lobe lacerations in cats and dogs.

MATERIALS AND METHODS

Tissumend II Sterile was supplied by Veterinary Products Laboratories (Phoenix,

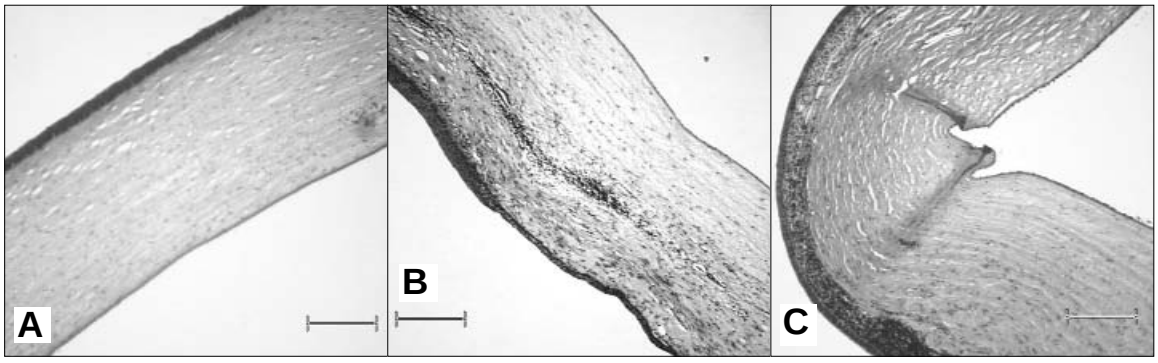

Figure 1. Histological photomicrographs of untreated rabbit corneas at Week 1 (A) and treated rabbit corneas at Week 3 (B) and Week 4 (C) post-surgery.

AZ). The study protocols for the rabbit cornea and kidney were approved by the Institutional Animal Care and Use Committee of Clemson University. The study protocol for the cat and dog lung was approved by the Institutional Animal Care and Use Committee of the University of Tennessee.

Adhesive Repair of the Rabbit Cornea

Eight New Zealand white rabbits with normal eyes were anesthetized with ketamine-valium or xylazine, and a topical anesthesia, proparacaine, was applied to the eye. After rinsing the conjunctival cul-de-sac with dilute Betadine® solution (1:50; Purdue Pharma L.P., Stamford, Connecticut, USA) and placing a pediatric wire lid speculum, a superficial keratectomy (utilizing a 5-mm ophthalmic corneal trephine set for a depth of 0.2 mm) was performed in the axial cornea. The trephined button was dissected from the base with a disposable Beaver keratectomy blade. The surgically created ulcer was dried with a cellulose spear and adhesive applied to the ulcer bed.

Post-operative evaluation was performed twice daily for the first 5 days with the amount of ocular discharge, blepharospasm, conjunctival hyperemia, corneal neovascularization, pupil size, aqueous flare, and adhesive retention noted. The eyes were then examined at least once a day until the corneal adhesive was extruded or the animal euthanized.

The rabbits were euthanized and the eye dissected, removed, and placed in 10% neutral buffered formalin for histological evaluation. Retrieval of the globe of the eye occurred at 1, 3, and 4 weeks post-surgery. For histological evaluation of the treated and control site, the entire globe of the eye was used for preparing the sections following a standard protocol.[1] Stained sections were examined using optical microscopy and the micrographs were prepared.

Adhesive Repair of Rabbit Kidney Lacerations

Prior to sterilization, aliquots of the tissue adhesive, Tissumend II Sterile, contained in sealed polyolefin dispensers, were packaged with Tyvek® (DuPont, Wilmington, Delaware, USA) pouches containing Celcon M-90 (Ticona, Summit, New Jersey, USA) as a precursor of radiolytically generated formaldehyde. The sterilization was conducted using about 5 kGy of gamma radiation. The sterilized adhesive packages and non-sterile control were tested, as described previously.[2]

Six New Zealand white rabbits were used in 3 sets of 2. For the surgical procedure, a single abdominal incision was made exposing the left kidney. For the experimental animals, 2 separate 2-cm incisions were made in the left kidney approximately 1- to 2-cm apart. The edges of the tissue were reapproximated and closed using either Tissumend II Sterile, Vicryl® suture (Ethicon, Inc., Somerville, New Jersey, USA), or PDSII® suture (polydioxanone surgical; Ethicon, Inc., Somerville, New Jersey, USA). For the control animals, 2 interrupted incisions were made in the left kidney approximately 1- to 2-cm apart. One inter-

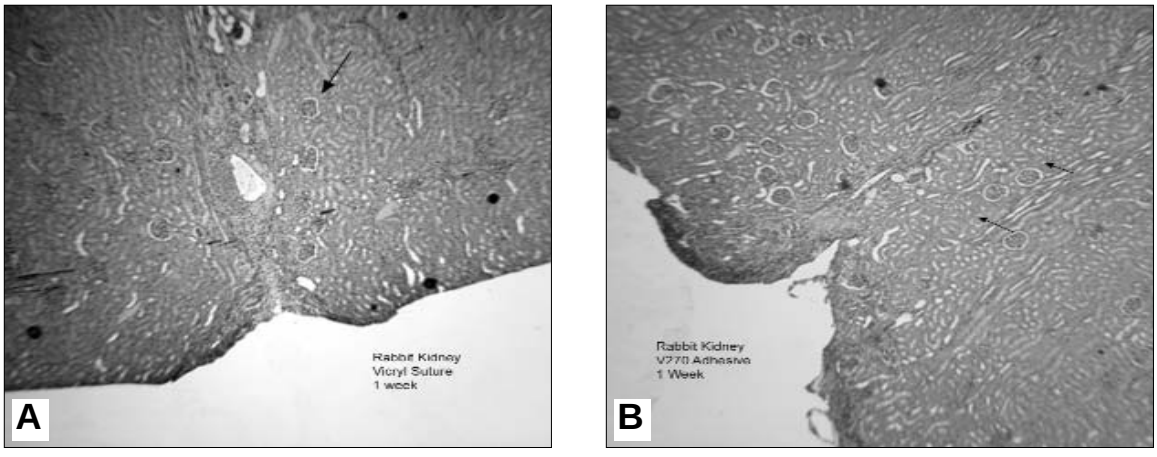

Figure 2. Histological micrographs of repaired rabbit kidney with Vicryl® (A) and Tissumend II Sterile (B) at Week 1 post-surgery.

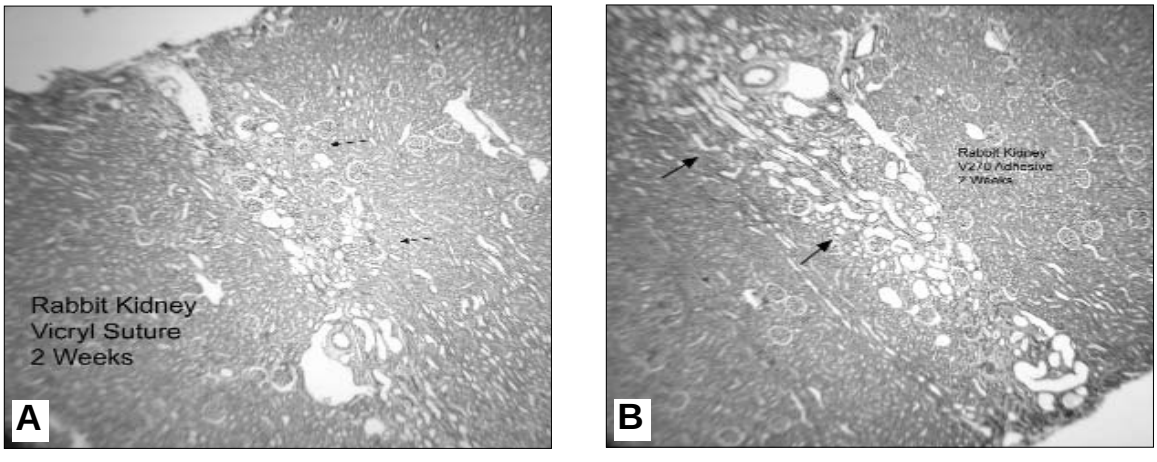

Figure 3. Histological photomicrographs of repaired rabbit kidney with Vicryl® (A) and Tissumend II Sterile (B) at Week 2 post-surgery.

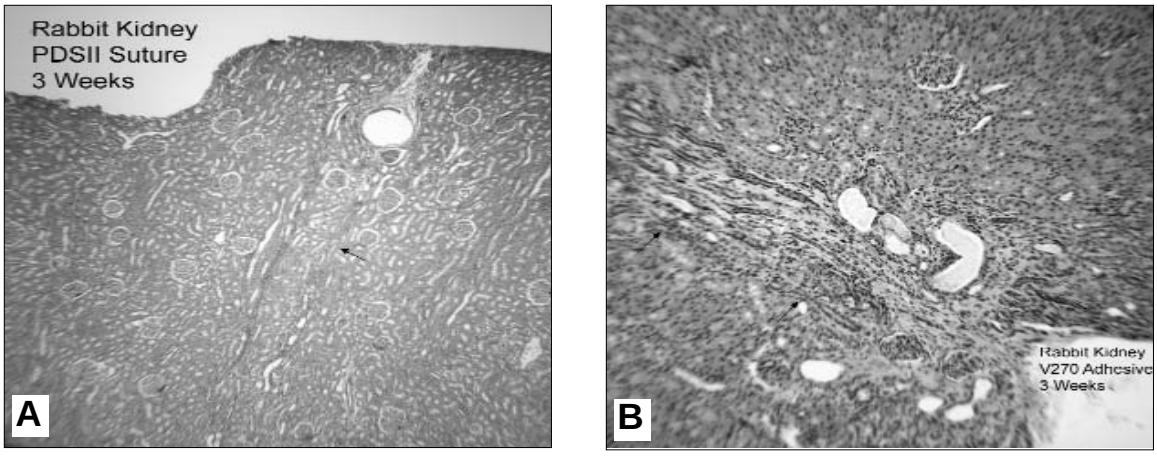

Figure 4. Histological photomicrographs of repaired rabbit kidney with PDS II® (A) and Tissumend II Sterile (B) at Week 3 post-surgery.

rupted incision set was closed with Tissumend II Sterile and the other closed with suture. The control rabbits served to observe side-by-side the local tissue response of intact and incised tissue to the tissue adhesive. Following post-operative recovery times of 1, 2, or 3 weeks, the animals were euthanized and the kidneys dissected and placed in formalin for histological processing. The specimens were

Table 1. Pathology Summary of Cat Lung Closures Using Tissumend II Sterile and Suture.

	Day 7						Day 14						Day 21					
Pathology	**CS**	**MS**	**CA**	**MA**	**CC**	**CC**	**CS**	**MS**	**CA**	**MA**	**CC**	**CC**	**CS**	**CS**	**MA**	**MA**	**CC**	**CC**
Multifocal neutrophilic infiltrate		2	2	3			4	3	1	1					1			
Multifocal necrosis		3	2				4	3										
Fibroplasia		4					3	3	3					3				
Alveolar type II cell hyperplasia								3		1					3			2
Mesothelial cell hypertrophy	1	3	2	1				1	2				1					2
Alveolar macrophage accumulation	1												2		3			
BALT hyperplasia											2			3		3	2	
Pleural fibroplasia	2		3	4			3			3								4
Bronchiolization of subpleural alveoli		2		3			3			2								
Suture granuloma		P					P											

CS = cranial suture; MS = middle suture; CA = cranial adhesive; MA = middle adhesive; CC = caudal control; BALT = bronchus-associated lymphatic tissue; P = present; 1 = minimal; 2 = slight/mild; 3 = moderate; 4 = moderately severe; 5 = severe/high.

subjected to standard protocol for sectioning and staining[1] and examined by an optical microscope.

Adhesive Repair of Cat and Dog Lung Lobe Lacerations

Surgical incisions were made in the ventral half of the right lung lobes of 6 cats and 6 dogs. Doyen clamps were used to reduce hemorrhage.

Cats

The lacerated lung tissue was apposed and Tissumend II Sterile was applied at the wound edges. The bonding time and set-up was 3 to 20 seconds (median, 8 seconds) with a total application median time of 4.5 minutes. Suturing was more difficult on the cat lung due to the thin lung tissue and took 1.5 to 2 minutes. Two cats each were euthanized on Days 7, 14, and 21 following the operations. Lung tissue samples were preserved in neutral buffered formalin, sectioned, and stained with hematoxylin and eosin.

Dogs

Tissumend II Sterile was applied as in the cats. The set-up of the adhesive ranged from 8 to 12 seconds (median, 11 seconds) with total application time ranging from 3 to 5 minutes. Suturing was easier on the dog lung due to the thickness of the lung and the median time for closure was 70 seconds. Two dogs each were euthanized on Days 7, 14, and 21 following the operations. and tissue samples were prepared as in the cats.

RESULTS

Adhesive Repair of the Rabbit Cornea

In all cases, the applied adhesive adhered well to the treated site. However, it adhered poorly to the intact cornea and eventually

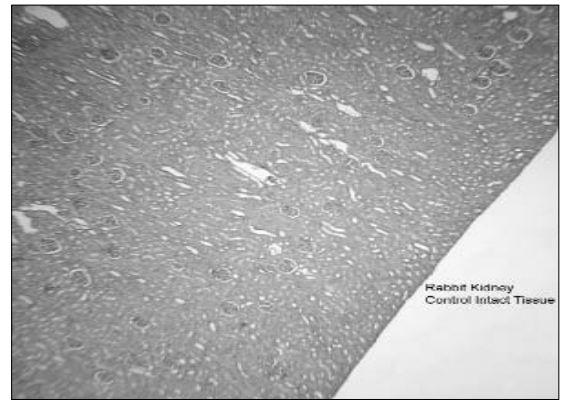

Figure 5. Histological photomicrographs of rabbit kidney control.

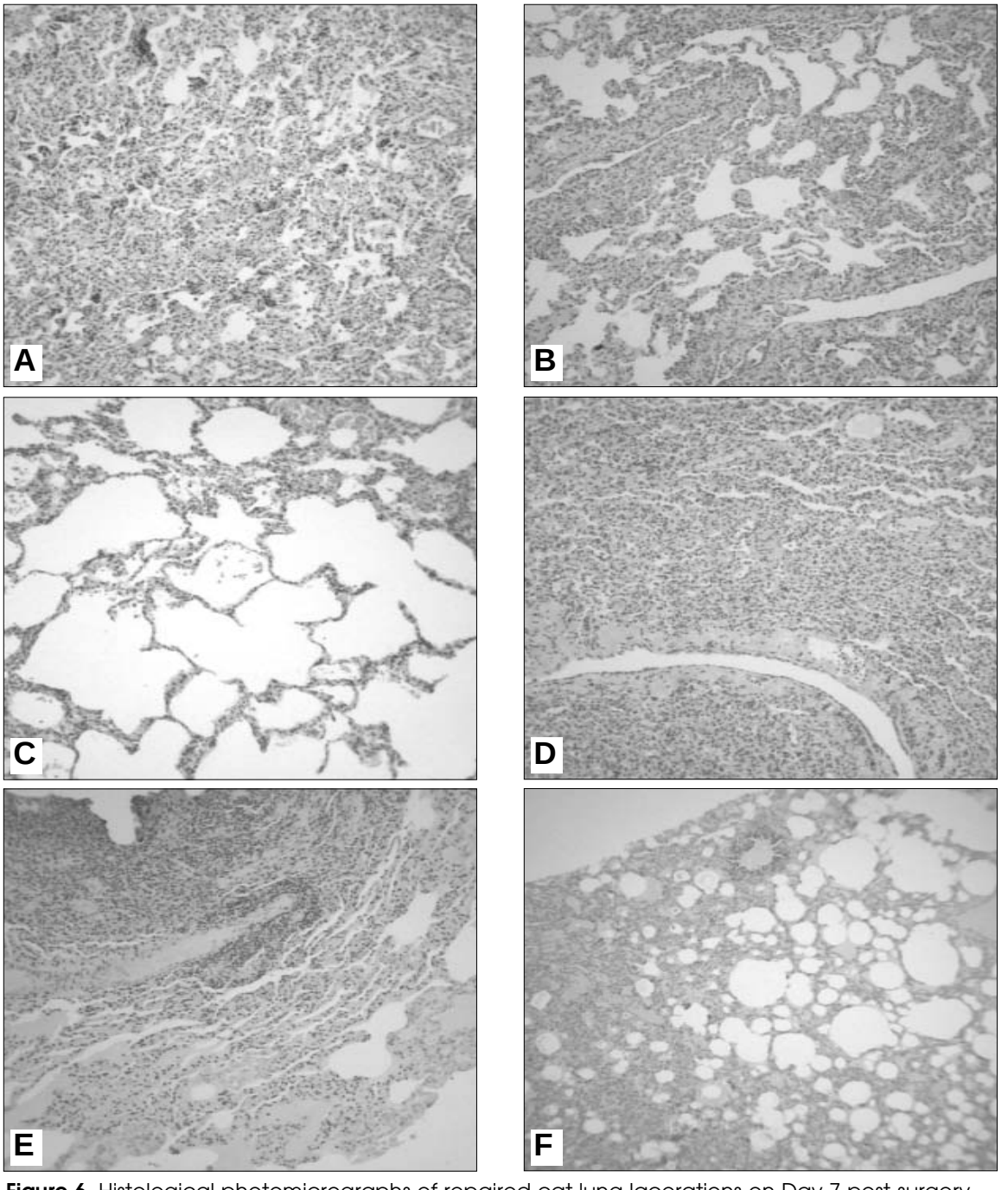

Figure 6. Histological photomicrographs of repaired cat lung lacerations on Day 7 post-surgery. Cranial suture (A), middle suture (B), and caudal control (C); cranial adhesive (D), middle adhesive (E), and caudal control (F). All images 100×.

migrated from the application site. During the study period, the animals were monitored for subjective evaluation of the treated eyes and overall well-being. All animals appeared to revert to normal behavior 1 day after surgery. The treated eye in most of the rabbits appeared normal at 1 week and became indistinguishable from the intact control eye at 2 weeks. Typical histological photomicrographs of treated and control rabbit corneas are shown in Figure 1. The tissue response to the adhesive in the treated site was slight and comparable to any soft tissue response that is repaired with an absorbable suture.[2] The histological photomicrographs of treated and control rabbit corneas at 3 and 4 weeks indicate normal wound-healing patterns, with a fully healed

Table 2. Pathology Summary of Dog Lung Closures Using Tissumend II Sterile and Suture.

	Day 7						Day 14						Day 21					
Pathology	**CS**	**MS**	**CA**	**MA**	**CC**	**CC**	**CS**	**MS**	**CA**	**MA**	**CC**	**CC**	**CS**	**MS**	**CA**	**MA**	**CC**	**CC**
Multifocal neutrophilic infiltrate		3	4	4			2		3				2					
Multifocal necrosis			2	2														
Fibroplasia			5	5				2										
Alveolar type II cell hyperplasia			4	4				5										
Mesothelial cell hypertrophy	2	2	2	2			1		2	2		3	2		3	2		
Alveolar macrophage accumulation		3	3	3					5						2			
BALT hyperplasia																		
Pleural fibroplasias	3	4	5	5			3		3	5			3	3	5	5		3
Bronchiolization of subpleural alveoli	2	4	5	5			2		3	2						2		2
Suture/foreign material granuloma	3		3	3					3	5			3		5	4		2
Fibrin			4	4														
Eosinophilic infiltrate		2																
Giant cells			3	3					3	3			1		3	1		
Hemosiderin															3			

CS = cranial suture; MS = middle suture; CA = cranial adhesive; MA = middle adhesive; CC = caudal control; BALT = bronchus-associated lymphatic tissue; P = present; 1 = minimal; 2 = slight/mild; 3 = moderate; 4 = moderately severe; 5 = severe/high.

site at Week 4. Figure 1 shows that the wound site at 4 weeks is approaching the appearance of the untreated control at 1 week.

Adhesive Repair of Rabbit Kidney Lacerations

The surgical procedures were pursued uneventfully and adhesives appeared to adhere within 60 seconds to the wound edges. Shortly after, sufficient strength appeared to develop to stabilize adjoined wound edges. Histological photomicrographs of the repaired tissue sections and a control are shown in Figures 2–5. In Figure 2, the incisions repaired with tissue adhesive appear to elicit a tissue response similar to that repaired with Vicryl® suture. In fact, the tissue adhesive appears to result in a higher quality of wound edge approximation as compared to the Vicryl® suture. A similar tissue response and wound repair quality was observed at 2 weeks as shown in Figure 3. For the 3-week study, the adhesive is compared with PDS monofilament suture, which is normally less reactive than Vicryl®, and shows that PDSII® and the adhesive yield a similarly healed wound with comparable quality (Figure 4). The tissue reaction at 3 weeks is practically non-existent; tissues appear to be quite comparable to an intact tissue control (Figure 5).

Adhesive Repair of Cat and Dog Lung Lobe Lacerations

Cats

All cats experienced extremely active recoveries and were difficult to handle both before and after the surgery. No lung leakage was observed and all had persistent negative intrathoracic pressure 2 or more hours

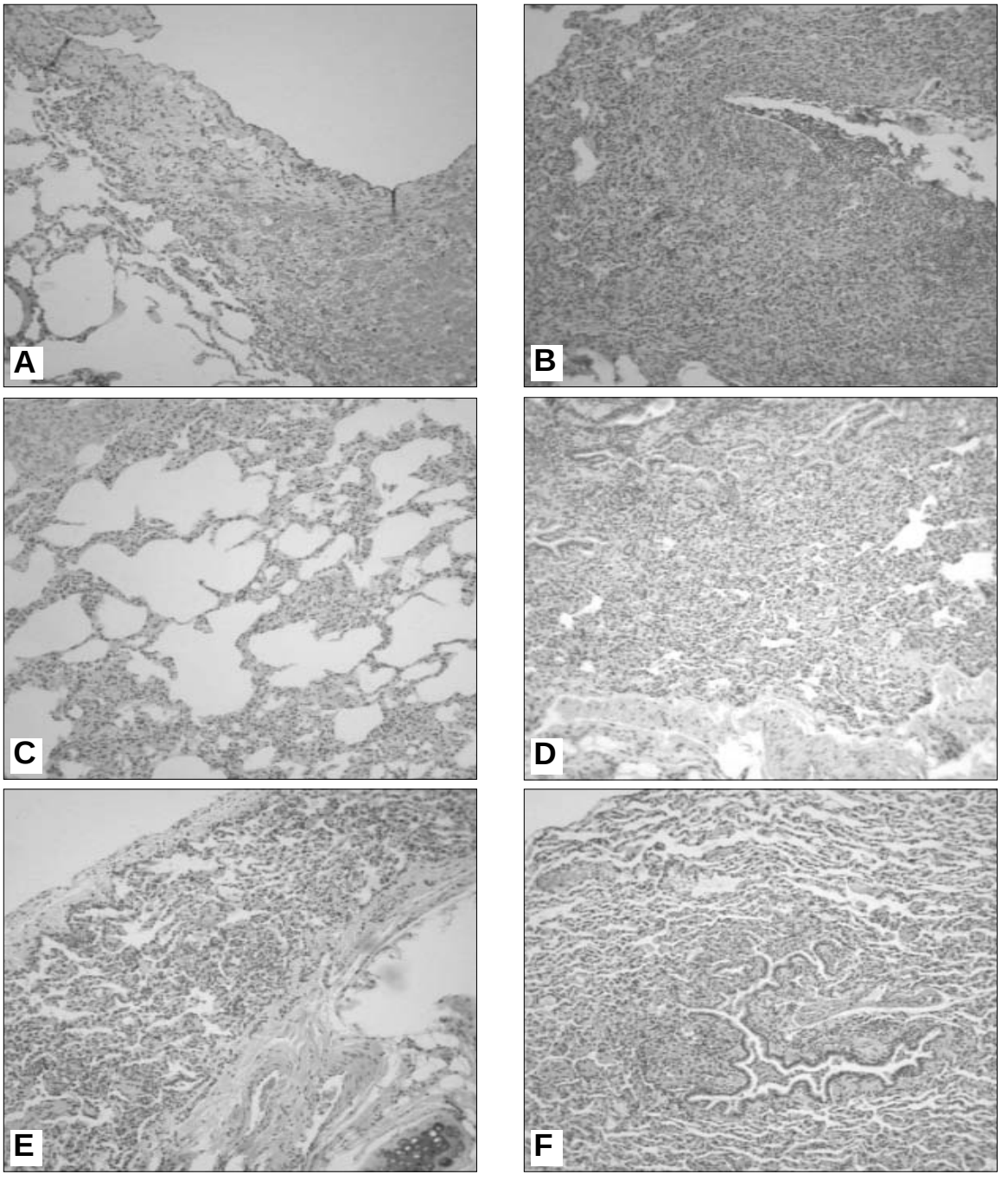

Figure 7. Histological photomicrographs of repaired cat lung lacerations on Day 14 post-surgery. Cranial suture (A), middle suture (B), and caudal control (C); cranial adhesive (D), middle adhesive (E), and caudal control (F). All images 100×.

after surgery. Two days after surgery, all cats returned to normal pre-operative behavior. Necropsy at post-operative Day 7 showed that both cats had minimal adhesions of the lung to the thoracic wall. On Day 14, the lobe of 1 cat sealed with Tissumend II Sterile adhered to the thoracotomy site. On Day 21, the lung lobes of both cats were adhered to the site.

Histological evaluation of the tissue from both closure methods showed typical wound healing (Figures 6–8). No difference between adhesive and suture groups was detected as described in the pathology summary (Table 1).

Dogs

No complications following surgery were

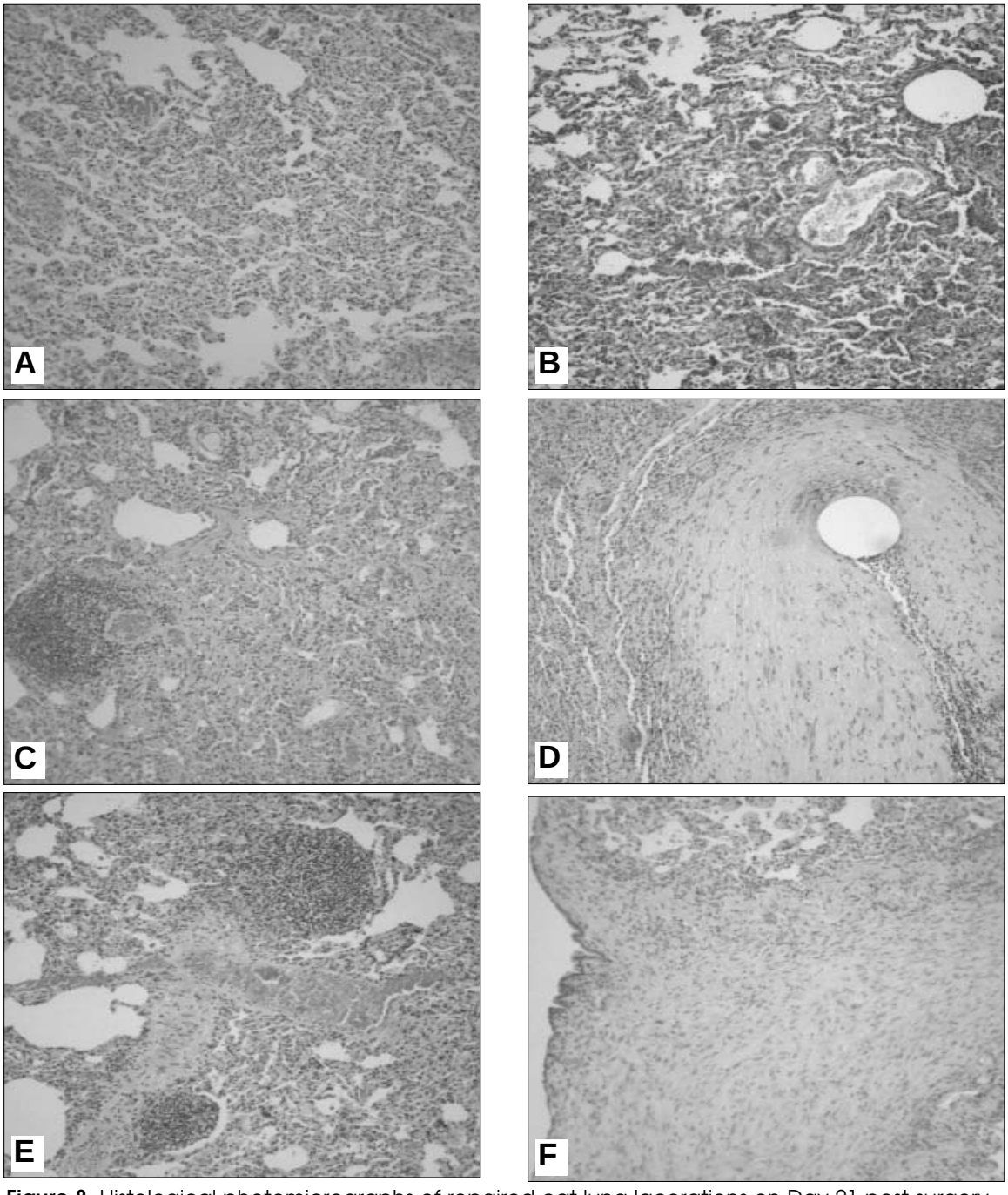

Figure 8. Histological photomicrographs of repaired cat lung lacerations on Day 21 post-surgery. Cranial suture (A), middle adhesive (B), and caudal control (C); cranial suture (D), middle adhesive (E), and caudal control (F). All images 100×.

noted in the dogs. Necropsy at Day 7 indicated the lobe lacerations repaired with the adhesive in both dogs were adhered to the thoracotomy site. On Day 14, the sutured and adhesive sites of 1 dog were adhered to the chest wall. In the second dog, the sutured site was adhered to the chest wall and the adhesive site was adhered to the other lung lobe. On Day 21, both adhesive and suture lobes of 1 dog were adhered to the pericardium. In the second dog, the middle and caudal lobes repaired with the adhesive were adhered together and the sutured lobe was adhered to the thoracotomy site.

Histological changes for each closure method were consistent with wound healing (Figures 9–11). Early tissue response was more marked in the wounds closed with tissue adhesive than in those closed with suture as described in the pathology summary (Table 2).

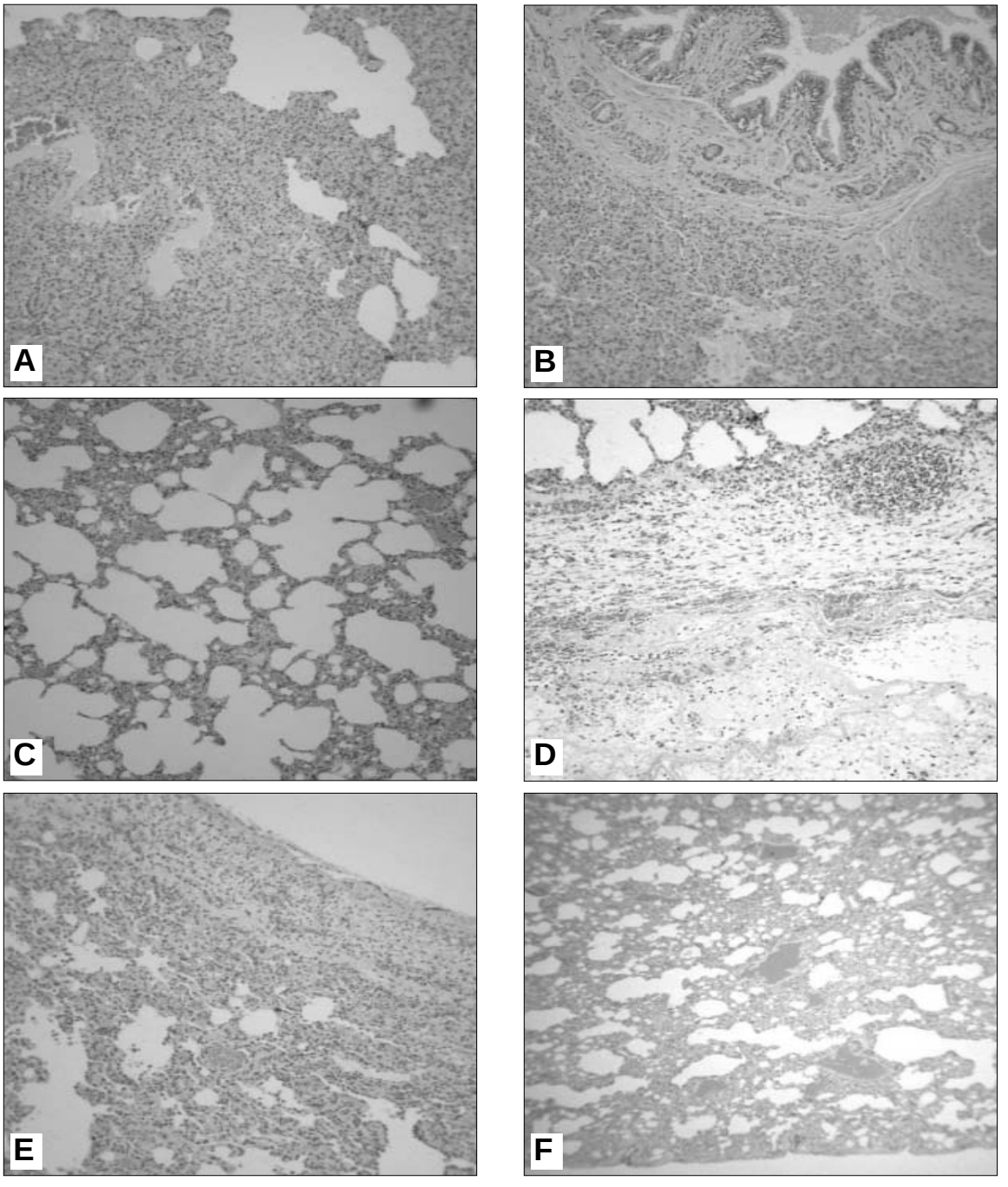

Figure 9. Histological photomicrographs of repaired dog lung lacerations on Day 7 post-surgery. Cranial suture (A), middle suture (B), and caudal control (C); cranial adhesive (D), middle adhesive (E), and caudal control (F). All images 100×.

DISCUSSION

Over the past few years, researchers in our laboratories have demonstrated that low-dose radiochemical sterilization (RCS) can be used successfully to achieve sterility in absorbable devices that normally undergo unacceptable degradation upon using the standard, high-energy radiation sterilization at a nominal dose of 25 kGy.[3,4] The RCS protocol entails the use of low-dose gamma radiation or E-beam of about 5 to 10 kGy in the presence of radiochemically generated formaldehyde gas from unstabilized polyformaldehyde (Celcon®) in a closed, dry package and preferable in a nitrogen atmosphere. Availability of a sterile, absorbable tissue adhesive prompted exploring its first use for internal wound repair applications.

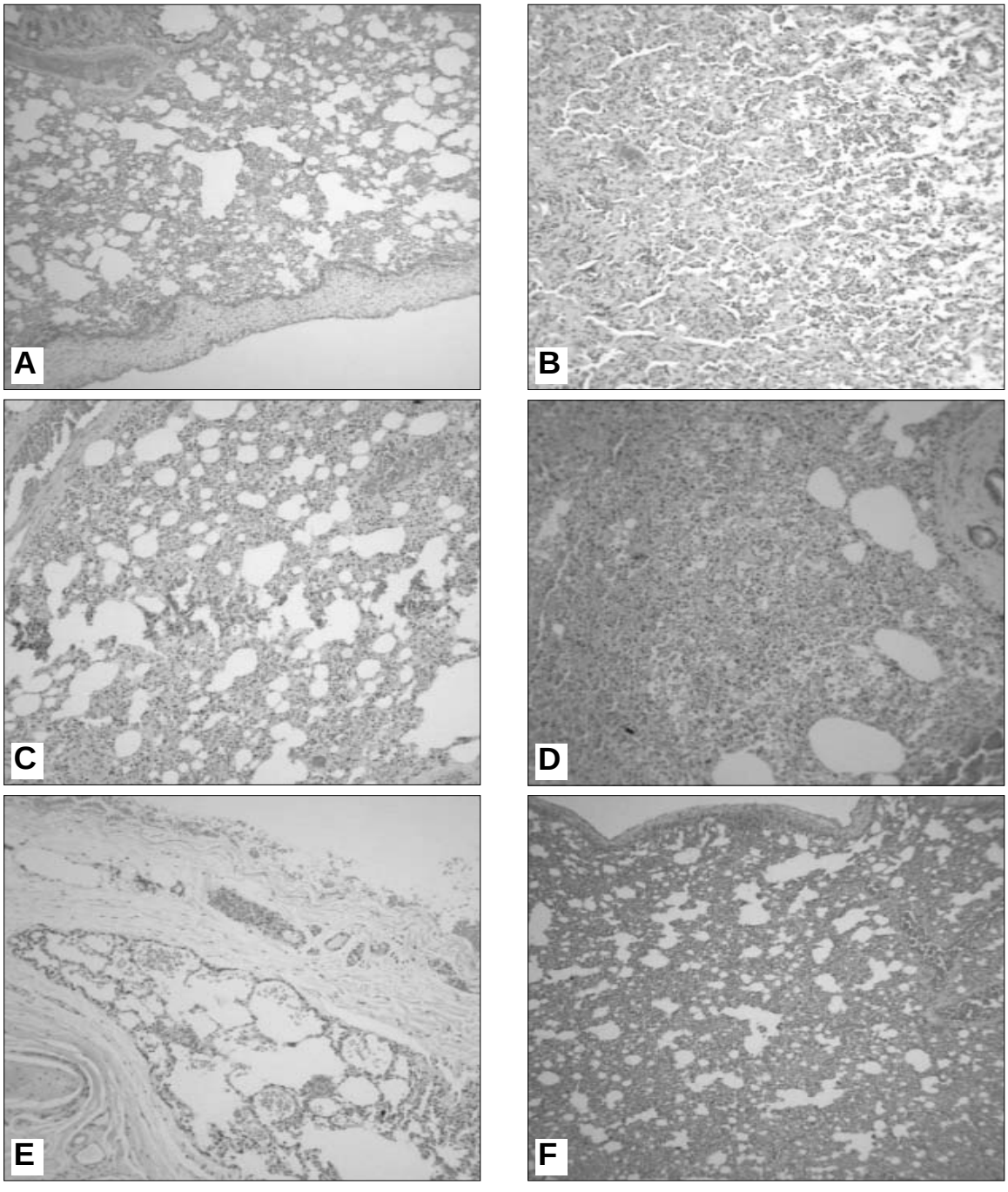

Figure 10. Histological photomicrographs of repaired dog lung lacerations on Day 14 post-surgery. Cranial suture (A), middle suture (B), and caudal control (C); cranial adhesive (D), middle adhesive (E), and caudal control (F). All images 100×.

The results of this study indicate that the use of Tissumend II Sterile is well suited for repairing corneal abrasions and kidney lacerations using a rabbit model and can be used as a suitable alternative to sutures in exceptionally soft lung tissue as illustrated in cats and dogs by this study. Tissumend II Sterile worked well on distal lung lobe laceration in both the cat and dog lung tissue and was easier than suturing lung lacerations in the cats. Post-operative leakage was minimal and tissue reaction to the wound was similar for both closure methods.

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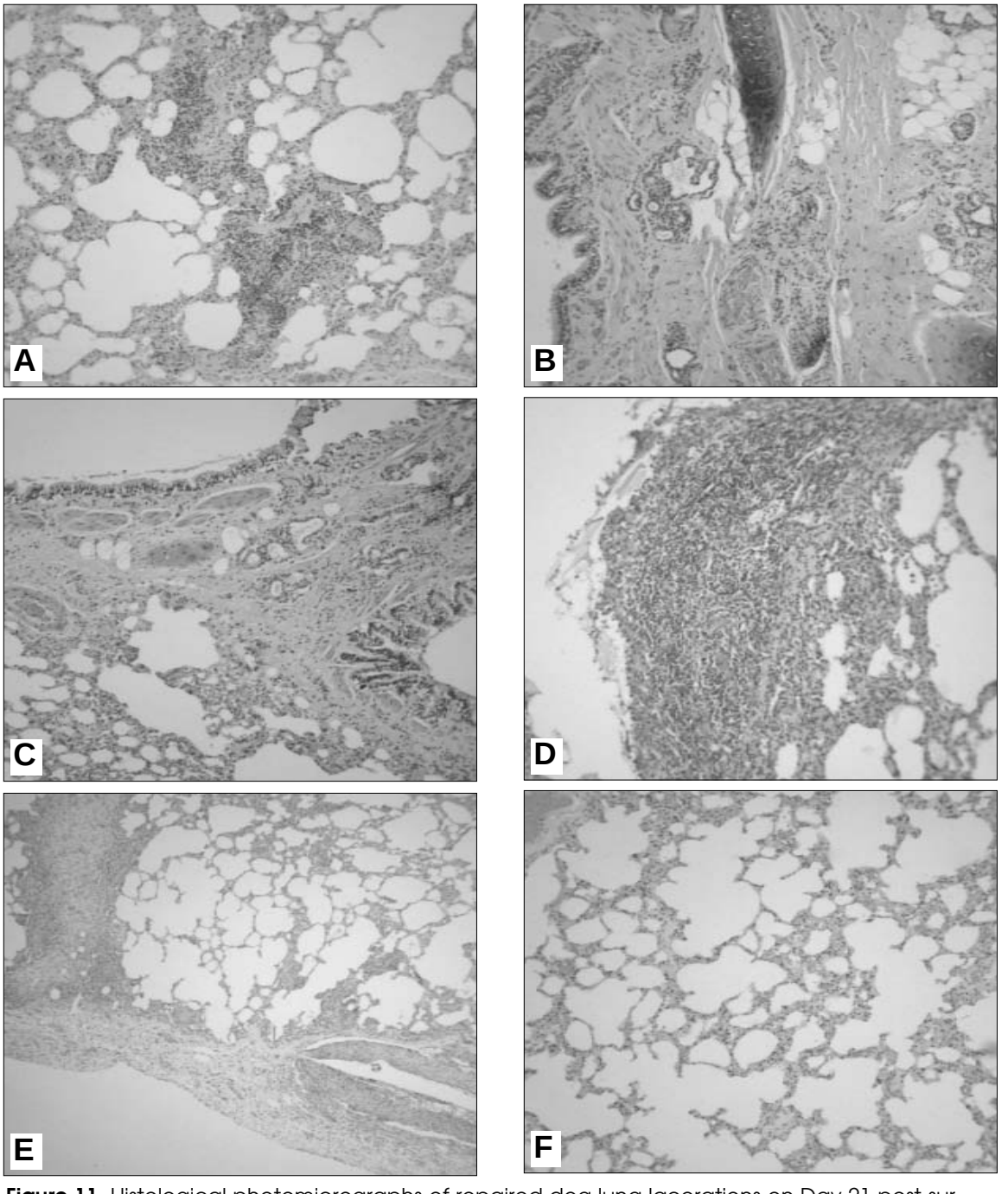

Figure 11. Histological photomicrographs of repaired dog lung lacerations on Day 21 post-surgery. Cranial suture (A), middle suture (B), and caudal control (C); cranial adhesive (D), middle adhesive (E), and caudal control (F). All images 100×.

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