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Osseous Reactions to Three Hemostatic Agents

Reacciones Oseas a Tres Agentes Hemostaticos

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The effects of bone wax, Surgicel, and Gelfoam on bone healing were evaluated microscopically using two different intraosseous implantation techniques. Experimental defects were made in both tibias of rats. Test materials were placed in defects in right tibias and were left in situ for the duration of the experiment. Likewise, materials were placed in left tibial defects and then were removed as completely as possible after 10 min. All three hemostatic agents affected healing when left in situ. Bone wax inhibited osteogenesis. Surgicel markedly slowed the rate of repair and caused inflammation. Gelfoam was usually completely resorbed and healing was complete 120 days after surgery. Residues of test materials were observed in most left tibial defects and they elicited reactions that were qualitatively similar but quantitatively less involved than those observed in the right tibias. These results indicate that careful removal of hemostatic agents during periapical surgery aids healing.

Se evaluaron microscópicamente los efectos de cera para hueso, Surgicel, y Gelfoam en la cicatrización osea usando dos técnicas de implantación intraósea diferentes. Los defectos experimentales fueron hechos en las dos tibias de ratas. Los materiales de prueba fueron colocados en los defectos de las tibias derechas y se dejaron in situ durante todo el experimento. De la misma forma, se colocaron materiales en defectos de las tibias izquierdas y se removieron todo lo que fue posible a los 10 minutos. Los tres agentes hemostáticos afectaron la cicatrización cuando se dejaron in situ. La cera ósea inhibió la osteogénesis. Surgicel disminuyó marcadamente la velocidad de reparación y causó inflamación. El Gelfoam en casi todos los casos se reabsorbió completamente y la cicatrización se completó a los 120 días de la cirugí. Se observaron residuos de los materiales de test en la mayoría de los defectos de las tibias izquierdas y produjeron reacciones que fueron cualitativamente similares, pero cuantitativamente menos importantes que las que se observaron en las tibias derechas. Estos resultados indican que la remoción cuidadosa de los agentes hemostáticos durante la cirugía periapical ayuda a la cicatrización.

The use of hemostatic agents in periapical surgery has proven to be an efficient means of maintaining a dry surgical field and can aid in the scavanging of debris from the surrounding tissues (1–4). However, it is possible fragments of the hemostatic agent could inadvertantly be left behind and contaminate the surgical site. There is evidence that residual masses of foreign materials can induce inflammation and affect tissue healing (5, 6). Therefore, the following experiment was designed to evaluate and compare the effects of Gelfoam (The Upjohn Co., Kalamazoo, MI), Surgicel (Johnson & Johnson, New Brunswick, NJ), and bone wax (Ethicon, Somerville, NJ) on the healing of osseous defects in rat tibias.

Gelfoam is a gelatin-based sponge that is water insoluble and biologically resorbable. Its mode of action is to promote platelet fracture and support fibrin strands (7). Gelfoam has been extensively used in oral surgery (8) to control excessive hemorrhage. Studies (9, 10) have demonstrated that this material initially provokes an inflammatory reaction but has no long-term deleterious effects on bone formation.

Surgicel is made by the oxidation of regenerated cellulose. It is soluble in alkaline solutions, but insoluble in water or acidic solutions. Its mode of action is not completely understood, but it is believed to have a mechanical effect rather than to have an effect on the normal clotting mechanism (11). Nappi and Lehman (12) found that Surgicel inhibited osteogenesis in the resected ribs of rabbits. Johnson & Johnson (13) do not recommend implantation of Surgicel in bony defects because of the possibility of interference with the formation of a bony callous and the theoretical possibility of cyst formation.

Bone wax is composed of a mixture of beeswax and

a softening agent (isopropyl palmitate). Its method of action is purely mechanical and has no effect whatsoever on the clotting mechanism. Animal studies have demonstrated that bone wax inhibits osteogenesis (14, 15). There have been reports of foreign body reactions to bone wax in humans (16, 17). Ethicon (18) warns that bone wax should not be used where rapid osseous regeneration and fusion are desired.

This study was designed to evaluate and compare the effects of these three hemostatic agents on the healing of experimental osseous defects under two conditions. The test materials were placed in openings of rat right tibias and were left in place for the duration of the experimental period. This method of implantation was designed to assess the maximal effect of the hemostatic agents on bone repair. The same test materials were placed in defects made in the contralateral tibias in an identical manner. However, after 10 min, the materials were carefully removed. This procedure was designed to mimic the use of hemostatics in periapical surgery and to determine if all of the applied material could be consistently removed from the surgical site.

MATERIALS AND METHODS

Fifty male (400- to 450-g) Sprague-Dawley rats were divided into three groups, each consisting of 15 animals (groups 1 to 3) and one group consisting of 5 animals (group 4). All rats were housed in shoebox cages with ad libitum access to lab chow and tap water at a constant ambient temperature of 21 ± 1°C and a 12-h dark, 12-h light cycle. At surgery, each animal was anesthetized by intraperitoneal injection of 0.025% solution of Avertin (tribromoethanol) at a dosage of 0.015 ml/g body wt. The incision site was cleaned with 70% ethanol and a 2- to 3-cm incision was extended distally from the tibial tubercle. The medial surface of each tibia was exposed and an opening that extended through the cortex into the medullary cavity was made in the middle of each surface 5 mm distal to the tibial tubercle with a number 8 bur in a slow-speed handpiece. Hemostatic agents were placed in the defects in the tibias of animals in groups 1, 2, and 3 in the following manner. The material was inserted into defects in the right tibias and left in place for the duration of the experimental period. In the left tibias, the test material was placed in the defect and then removed after 10 min. The area was completely curettaged in an attempt to mimic the conditions that occur in periapical surgery. Identical surgery was performed on animals in group 4 except that no test materials were placed in the bony defects. Incisions were closed with 4-0 gut sutures placed 3 mm apart.

Bone wax was the test material in group 1. Surgicel was placed in the bony defects of group 2 and Gelfoam was the test material in group 3. Group 4 served as controls.

Three animals from groups 1, 2, and 3 and one animal from group 4 were killed by ether overdose at 3 days, 7 days, 14 days, 40 days, and 120 days after surgery. Appropriate areas of the tibias were isolated by gross dissection and placed in 10% formaldehyde. Following fixation, the specimens were decalcified in a 15% formic acid solution and processed for routine paraffin embedding (19). Seven-micrometer sections were cut and stained with hematoxylin and eosin (19). All sections were examined with a Zeiss universal microscope.

RESULTS

Microscopic examination of the 3-day control specimens demonstrated that the osseous defects were filled with fibrin clots and an influx of inflammatory cells was seen. By 7 days, active bone formation was noted throughout the control defects and some neutrophils and lymphocytes were observed. At 14 days, thicker trabeculae of immature bone occupied most of the defect and there was little sign of inflammation. In the 40-day specimens, bone regeneration was complete. The defect was filled by remodeling compact bone that was delineated from older bone by cement lines. By 120 days, the appearance of the operative site was basically the same as that of the 40-day specimens.

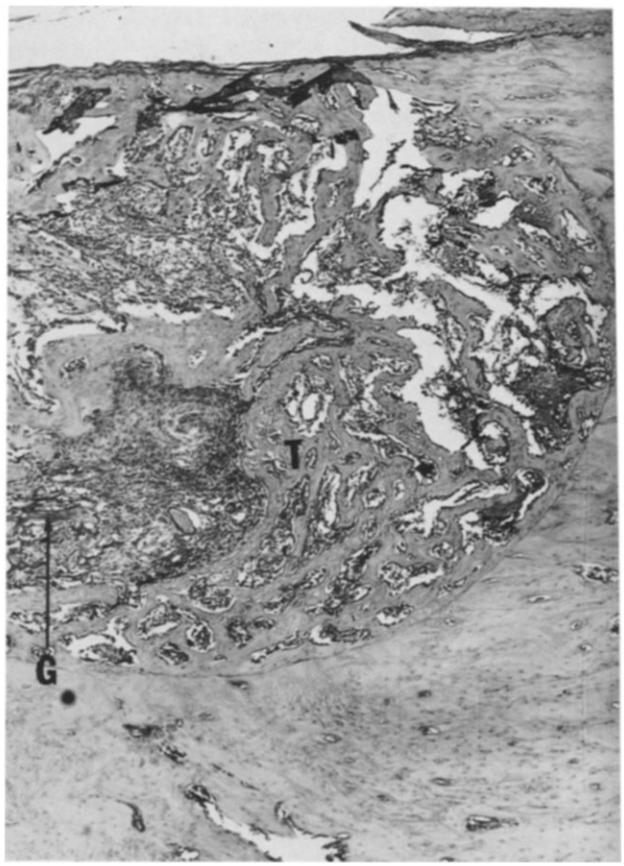

FIG 1. This section of a 14-day Gelfoam (left tibia) specimen demonstrates trabeculae (*T*) of immature bone. Gelfoam (*G*) residues are also evident. Hematoxylin and eosin; original magnification ×40.

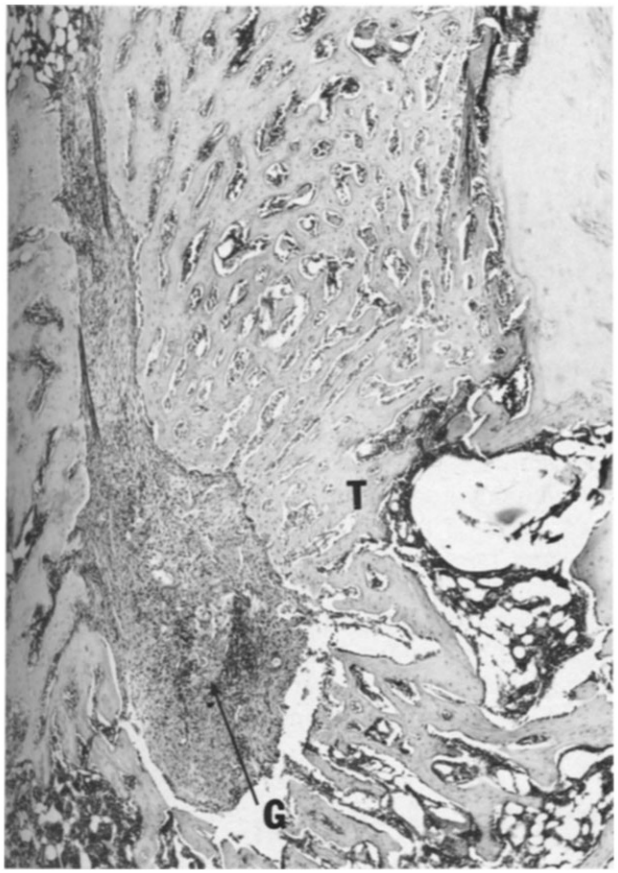

FIG 2. This section of a 40-day Gelfoam (left tibia) specimen demonstrates thick bony trabeculae (*T*) filling most of the defect. Gelfoam (*G*) residues are also evident. Hematoxylin and eosin; original magnification ×40.

The defect had completely healed with no signs of inflammation.

Histological examination of the experimental bone defects demonstrated that distinct osseous reactions occurred depending upon the hemostatic agent utilized and whether the material was removed 10 min after implantation (left tibias) or left in situ (right tibias) for the duration of the experiment. Healing of the Gelfoam implant sites occurred more rapidly in the left tibias than in the right tibias. Three days after surgery, the defects made in the left tibias were filled with fibrin clots which showed evidence of organization. An inflammatory infiltrate was evident and occasional Gelfoam residues were noted. By 7 days, immature bony trabeculae were observed and pieces of Gelfoam were seen. Inflammatory cells were scattered throughout the defect site. At 14 days, thick trabeculae of immature bone were observed throughout the test cavities and remnants of the material were still evident (Fig. 1). Inflammatory cells were still observed. At 40 days, most of the defect was filled with bony trabeculae (Fig. 2). Occasionally, Gelfoam residues were encountered and inflammatory cells were observed. Osseous regeneration was complete by 120 days and no Gelfoam remnants were observed. Reversal lines demarcated the regenerated bone filling the defect, from adjacent, unmanipulated cortical bone (Fig. 3).

At 3 days, the defects in the right tibias showed an inflammatory infiltrate. Gelfoam was interspersed throughout the fibrin clot that filled the experimental defects. By 7 days, trabeculae of immature bone were observed surrounding the material but no bone deposition was observed in the area physically occupied by Gelfoam (Fig. 4). An inflammatory infiltrate composed of lymphocytes and neutrophils was observed. In the 14-day specimens, bony trabeculae were seen peripheral to remaining masses of Gelfoam. At 40 days, thick bony trabeculae were observed peripheral to remaining masses of Gelfoam. Numerous lymphocytes, as well as some macrophages, were seen in the vicinity of the material. By 120 days, cortical replacement was complete. Complete resorption of the material had occurred in all but one specimen which showed a small amount of Gelfoam inside the marrow cavity which was surrounded by osseous trabeculae (Fig. 5). However, this remnant of Gelfoam did not interfere with regeneration of cortical bone.

Healing at the Surgicel implant sites was more thorough in the left tibias than in the right tibias. Examination of histological sections from left tibias demonstra-

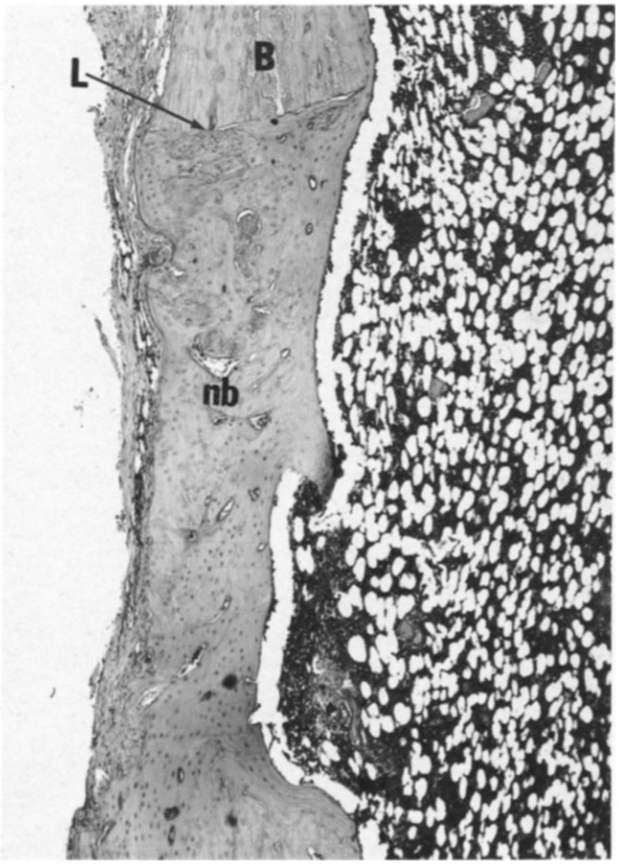

FIG 3. This section of a 120-day Gelfoam (left tibia) specimen demonstrates cement lines (*L*) demarcating the newly formed bone (*nb*) from adjacent unmanipulated cortical bone (*B*). Hematoxylin and eosin; original magnification ×40.

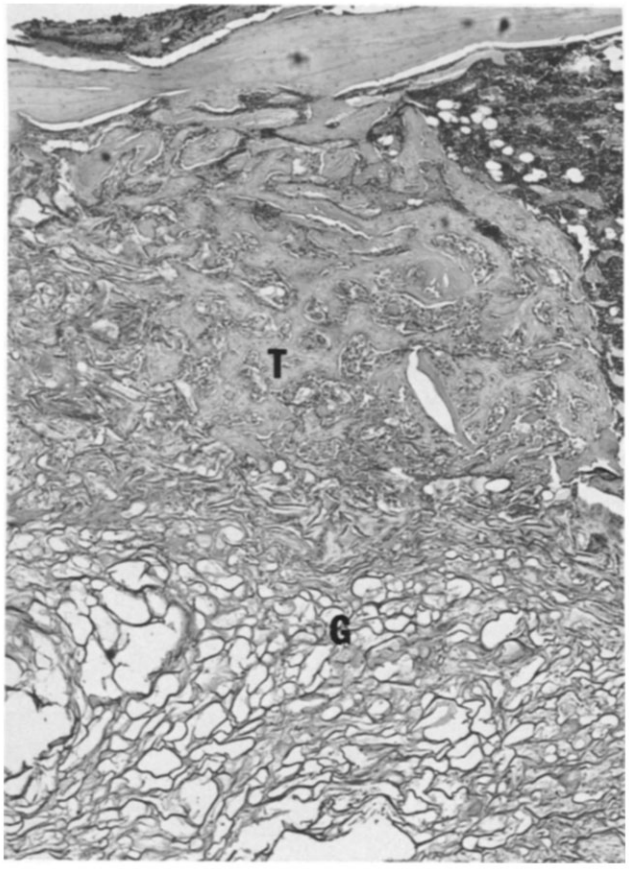

FIG 4. This section of a 7-day Gelfoam (right tibia) specimen demonstrates the Gelfoam (*G*) implant surrounded by immature bony trabeculae (*T*). Hematoxylin and eosin; original magnification ×40.

ted that by 3 days, the defects were filled with a fibrin clot which showed evidence of fibroblastic invasion. Occasional Surgicel residues were encountered and inflammatory cells were evident. At 7 days, bony trabeculae were noted throughout the defect and neutrophils and lymphocytes were observed. Surgicel residues were occasionally noted. In the 14-day specimens, thicker trabeculae occupied a larger portion of the test cavities (Fig. 6). Surgicel residues were observed and there was evidence of inflammation. By 40 days, occasional Surgicel remnants were observed. Osseous regeneration was advanced and cement lines delineated the area of repair (Fig. 7). Occasional Surgicel remnants were observed and inflammatory cells were rarely noted. At 120 days, the defects were filled with mature bone with reversal lines demarcating the site of osseous regeneration. One of the specimens showed residual masses of Surgicel which were surrounded by bony trabeculae.

Specimens from right tibias showed that at 3 days, the Surgicel implant occupied a large portion of the test cavity. Dense aggregations of inflammatory cells were observed surrounding the Surgicel. At 7 days, the structural integrity of the material was still evident. No signs of new bone deposition were noted and many inflammatory cells were observed. In the 14-day specimens, bone deposition was still not apparent. Foci of cartilage were noted inside the defect and Surgicel remnants were observed throughout the defects. Fragments of acellular material were interpreted as remnants of a fibrin clot (Fig. 8). An inflammatory infiltrate composed of lymphocytes, neutrophils, macrophages, and multinucleated giant cells was observed. At 40 days, there was evidence of new bone deposition and Surgicel fibers were still observed. At 120 days, the test material was seen in the defect and was isolated by a palisade of bony trabeculae (Fig. 9). Lymphocytes, macrophages, and multinucleated giant cells were observed.

Bone wax greatly impaired osseous regeneration for the duration of the experiment. Observation of the left tibial specimens showed that by 3 days the test cavities were filled with fibrin clots. Some inflammatory cells were observed. A 7 days, bony trabeculae were seen throughout the defect. Fibrous connective tissue lined clear irregular spaces which contained bone wax residues (Fig. 10) and neutrophils and lymphocytes were

FIG 5. This section of a 120-day Gelfoam (right tibia) specimen demonstrates a Gelfoam (*G*) residue within the marrow (*M*) cavity. Thick bony trabeculae (*T*) surround the material. Hematoxylin and eosin; original magnification ×40.

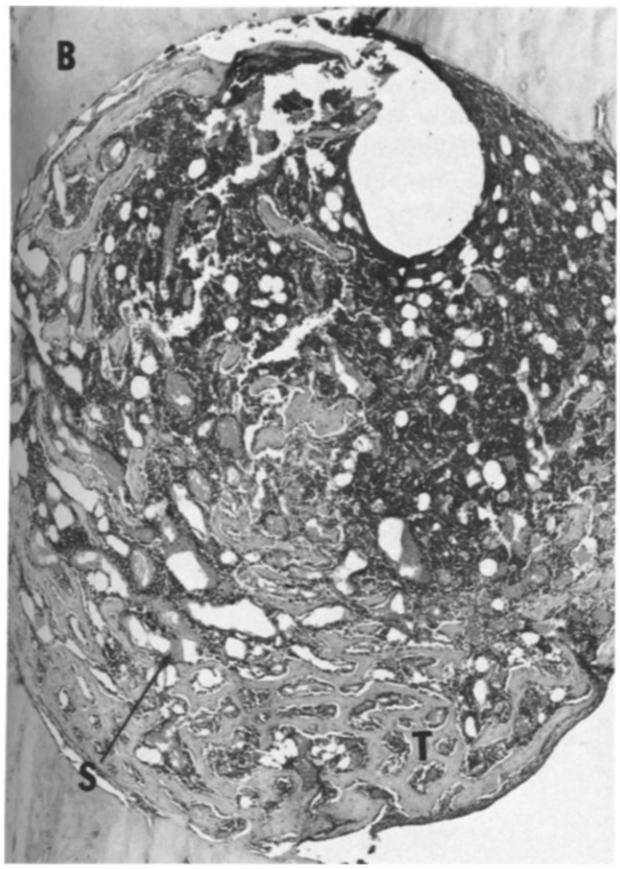

FIG 6. This section of a 14-day Surgicel (left tibia) specimen demonstrates bony trabeculae (T) throughout the defect, Surgicel (*S*) residues, and compact unmanipulated bone (*B*). Hematoxylin and eosin; original magnification ×40.

observed. In the 14-day specimens, thicker trabeculae were observed throughout the test cavities. Clear irregular spaces which contained bone wax remnants were lined by fibrous connective tissue. There was an inflammatory infiltrate. By 40 days, thick trabeculae were observed throughout the experimental defects. Fibrous connective tissue lined irregular clear spaces that contained bone wax remnants and lymphocytes and macrophages were observed. At 120 days, mature bony trabeculae were demarcated from the surrounding unmanipulated cortical bone by cement lines. Clear irregular spaces were lined by fibrous connective tissue and contained bone wax vestiges (Fig. 11). Macrophages and multinucleated giant cells were occasionally observed.

Observation of the right tibial specimens demonstrated that by 3 days, large empty cavities containing bone wax residues occupied most of the surgical site. Fibrous connective tissue was observed lining the periphery of these spaces. Some inflammatory cells were seen at the periphery of the test cavities. At 7 days, some bony trabeculation was seen at the periphery of the test cavities. Fibrous tissue intervened between the bone and the spaces containing bone wax (Fig. 12). Inflammatory cells were observed. At 14 days, spaces similar to those of the 7-day specimens were observed and bone wax residues were associated with macrophages and multinucleated giant cells. An area of fibrous proliferation was evident. The 40- and 120-day specimens were similar, showing large empty cavities lined by fibrous connective tissue. Bone wax remnants were evident (Fig. 13). Macrophages and multinucleated giant cells were occasionally observed and there was complete inhibition of bone regeneration at the implantation sites.

DISCUSSION

The healing of control defects in rat tibias was similar to that described by other investigators (14, 20). Three days after surgery, a fibrin clot showing signs of organization filled the experimental defect and osteogenesis was evident by 7 days. Bone regeneration was essentially complete 40 days after surgery. The sequence of events in the healing of rat tibias was comparable to that observed in the repair of postextraction sites in

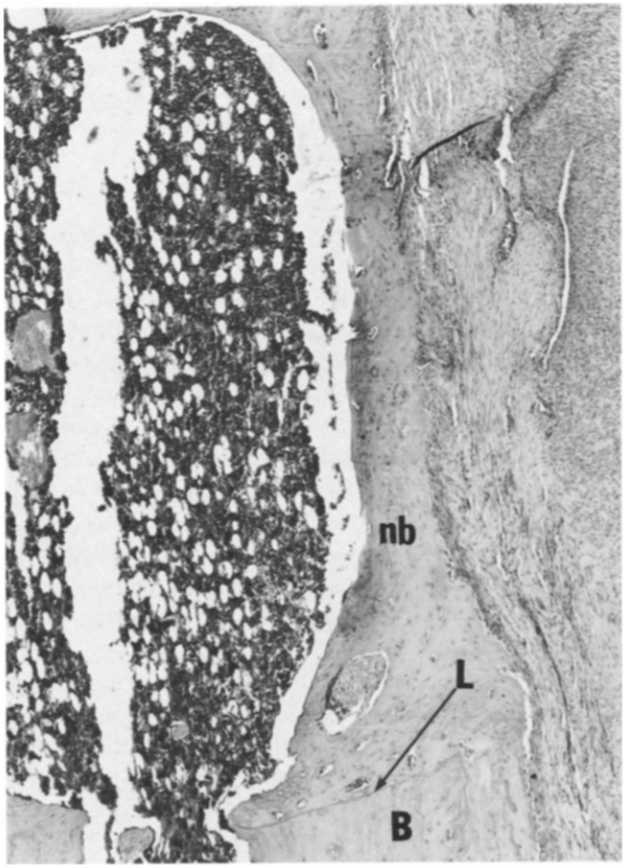

FIG 7. This section of a 40-day Surgicel (left tibia) specimen demonstrates reversal lines (*L*) demarcating the newly formed bone (*nb*) from surrounding unmanipulated cortical bone (*B*). Hematoxylin and eosin; original magnification ×40.

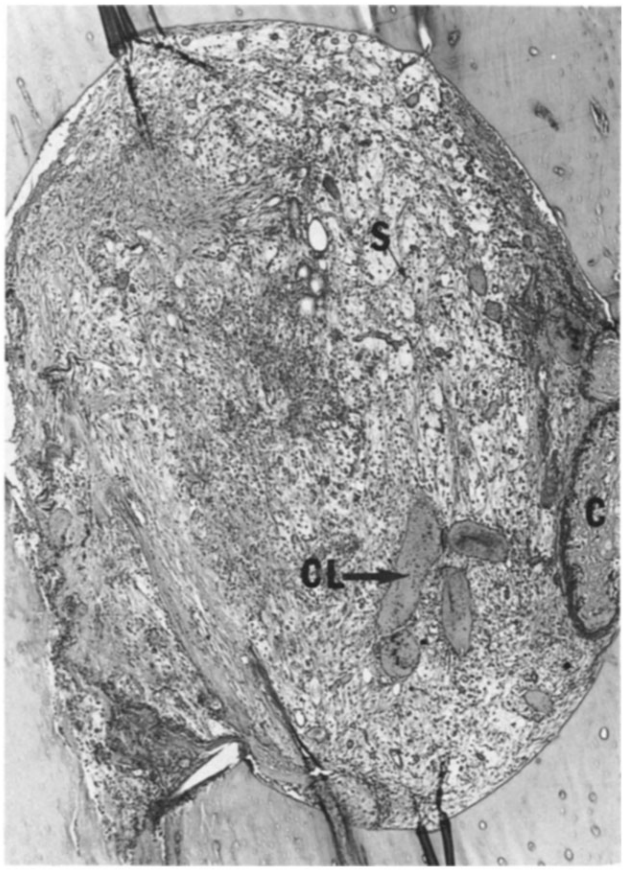

FIG 8. This section of a 14-day Surgicel (left tibia) specimen demonstrates Surgicel (*S*) remnants, cartilage (C), and clot (CL) residues. Hematoxylin and eosin; original magnification ×40.

alveolar bone. Initially the alveolar socket is filled with a fibrin clot. Thereafter, organization of the clot occurs and then osteogenesis takes place. These defects are filled with new bone in approximately 40 days (21). Therefore, it may be possible to extrapolate the results of the present study to healing of alveolar bone.

The experimental design utilized in right tibias in which the hemostatic agent was left in situ was designed to create a situation in which any deleterious effects of implanted materials would be maximized. Such a condition would not usually be expected to occur clinically, but the results may clarify some of the complications of surgery that can occur when these materials are used. In this study, bone wax left in situ had the most harmful effect on bone regeneration. This material is not biologically resorbable and causes a foreign body reaction. One-hundred twenty days after surgery, the implanted bone wax was still present and was surrounded by a fibrous capsule (Fig. 13) peripheral to which were scattered macrophages and giant cells. These results were interpreted as indicating that the physical presence of bone wax in osseous tissue impairs osteogenesis and provokes a foreign body reaction. These results agree with the observations of other investigators. Howard and Kelley (14) found that bone wax prevents the healing of bony defects and elicits a mild foreign body reaction. Johnson and Fromm (22) report that bone wax can persist at the implantation site for long periods of time and act as a foreign body that prevents clearing of bacteria from cancellous bone. Bone wax residues have been associated with sinus tracts that developed following surgery (15, 16), suggesting that care must be exercised to ensure the complete removal of this material from the surgical site.

Surgicel left in situ caused the most intense inflammatory response of the three hemostatic agents evaluated in this study. Surgicel also impaired osseous regeneration. There was little resorption of this material by 120 days (Fig. 9). Geary and Frantz (15) state that the acidity of oxidized cellulose undoubtedly decreases the pH of surrounding tissues and delays the "alkaline tide" essential to the function of alkaline phosphatase in the deposition of calcium. The physical presence of Surgicel and the possible effect of this material on tissue pH could account for the delayed healing observed in this study. Bony trabeculae were observed peripheral to the implanted Surgicel (Fig. 9). It is also interesting that cartilage deposition was observed in one of the

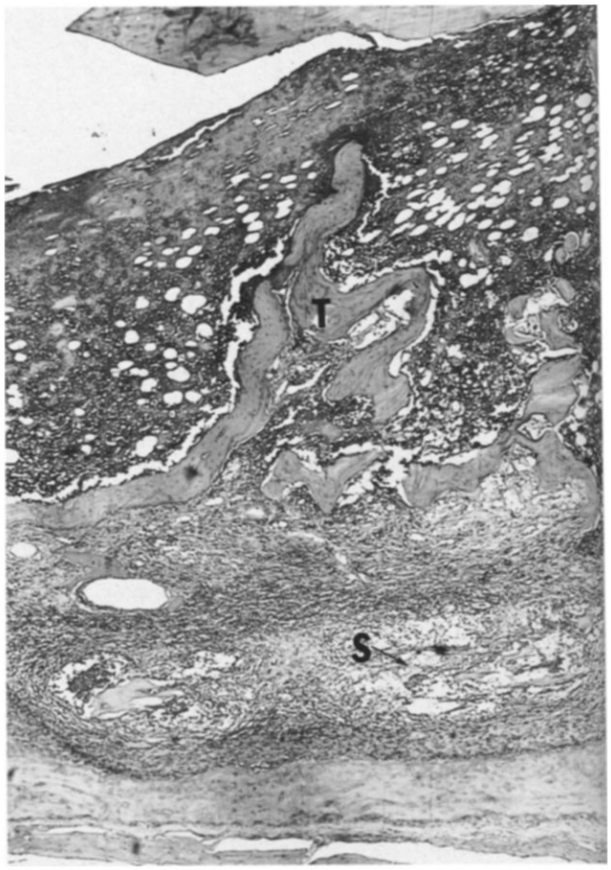

FIG 9. This section of a 120-day Surgicel (left tibia) specimen demonstrates a residual mass of Surgicel (*S*) surrounded by dense bony trabeculae (*T*). Hematoxylin and eosin; original magnification ×40.

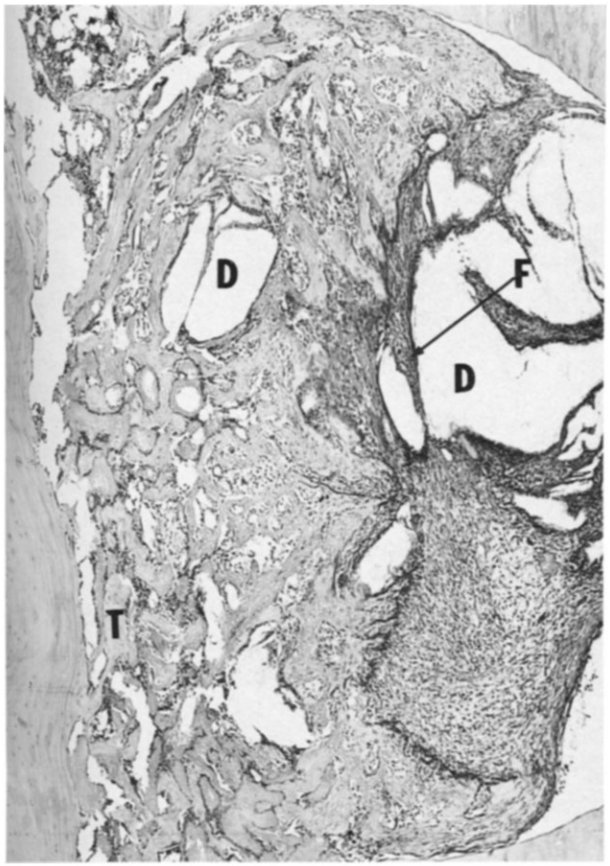

FIG 10. This section of a 7-day bone wax (left tibia) specimen demonstrates defects (*D*) lined by fibrous connective tissue (*F*) and some bony trabeculation (*T*). Hematoxylin and eosin; original magnification ×40.

14-day Surgicel specimens (Fig. 8). Although cartilage formation is associated with the development of the external callous of fractures (27) in this study, it was not observed in control specimens or in specimens from tibias in which bone wax or Gelfoam had been implanted.

Gelfoam slowed repair of osseous defects at early postsurgical intervals in this study but did not have any chronic effects on osteogenesis. There was a transient inflammatory response and Gelfoam was completely resorbed in all but one of the 120-day right tibia specimens (Fig. 5). However, healing of all experimental defects was complete by the conclusion of the study. These results are in agreement with Laskin et al. (9) who report that Gelfoam does not have any long-term deleterious effects on bone regeneration.

The experimental manipulation of left tibias in the present study was designed to mimic clinical utilization of these hemostatic agents in periapical surgery and, therefore, the materials were removed 10 min after placement. Our observations indicate that complete removal of the hemostatic agent was not accomplished by the procedures used in this study. In spite of careful curettage of the surgical sites, histological examination revealed that some residues of the materials were left behind. These residues provoked tissue reactions that were qualitatively similar to those observed in right tibias. However, the intensity of the reactions to residual fragments of the materials was usually much less than when large masses of the hemostatic agents were intentionally left in situ. Bone wax residues inhibited bone regeneration. The amount of bone inhibition was proportional to the size of the residues left behind. Bony trabeculae formed in areas where the bone wax was successfully removed (Fig. 11). Residual pieces of Surgicel elicited an inflammatory response, but complete repair was observed in two of the three 120-day specimens. Surgicel residues in the third experimental animal caused a foreign body reaction. This discrepancy could be explained by the successful removal of the material in two of the specimens. Healing of the surgical sites in which Gelfoam was placed and then removed was similar to that of control defects. Repair was evident by 40 days after surgery (Fig. 2) and

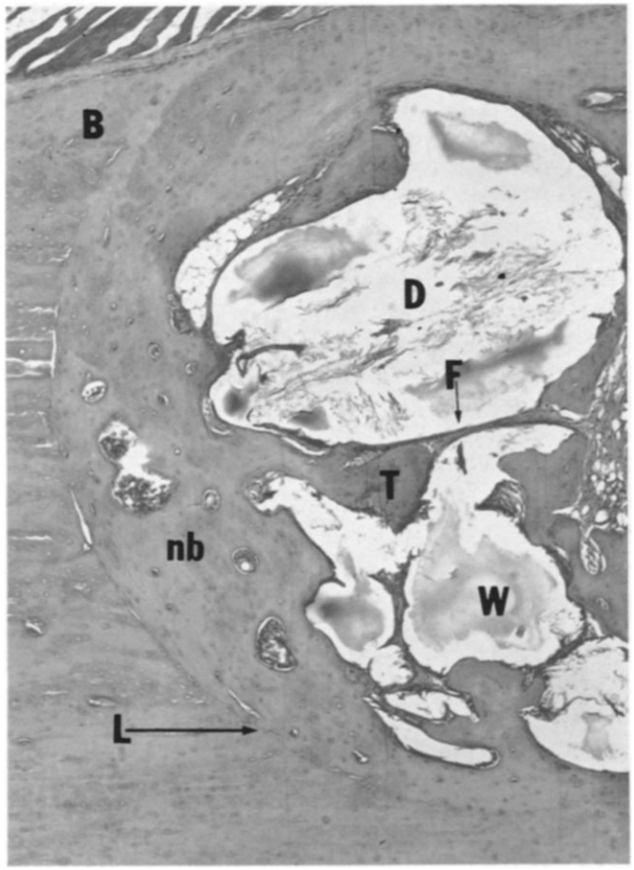

FIG 11. This section of a 120-day bone wax (left tibia) specimen demonstrates cement lines (*L*) demarcating newly formed bone (*nb*) from surrounding unmanipulated cortical bone (*B*). Defects (*D*) are lined by fibrous connective tissue (*F*) and contain bone wax (*W*) residues. Hematoxylin and eosin; original magnification ×40.

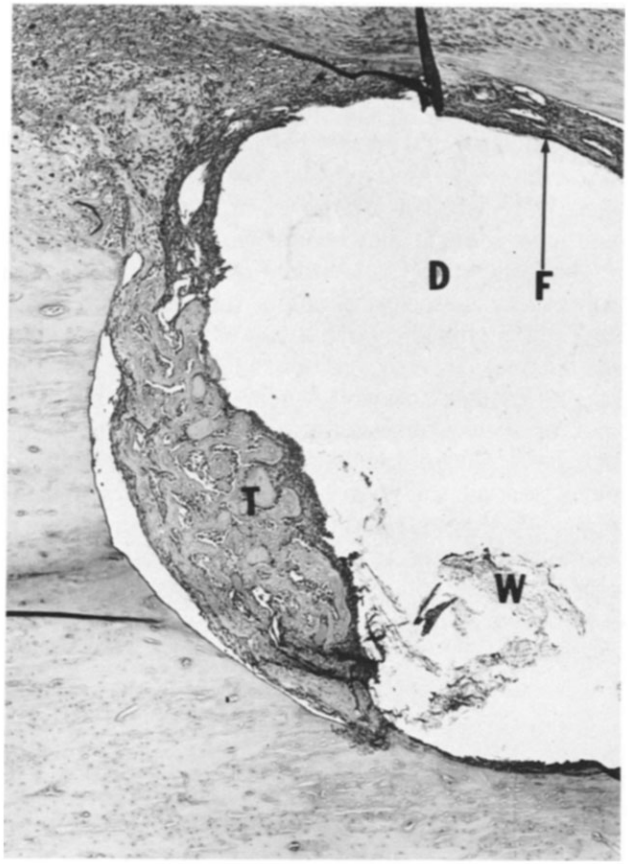

FIG 12. This section of a 7-day bone wax (right tibia) specimen demonstrates some bony trabeculation (*T*), a large defect (*D*) lined by fibrous connective tissue (*F*), and bone wax (*W*) residues. Hematoxylin and eosin; original magnification ×40.

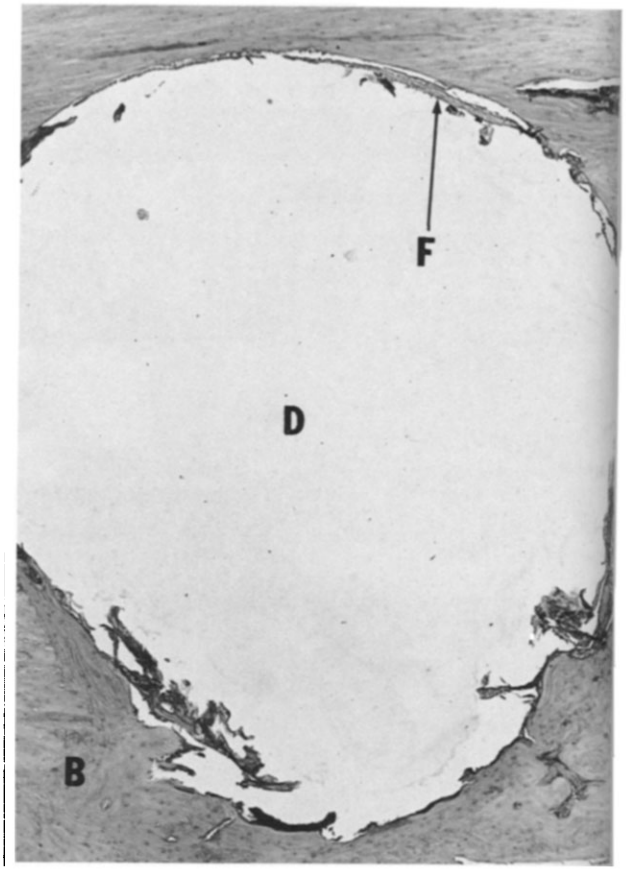

FIG 13. This section of a 120-day bone wax (right tibia) specimen demonstrates a large defect (*D*) lined by fibrous connective tissue (*F*). Unmanipulated cortical bone (*B*) is seen in the vicinity of the defect. Hematoxylin and eosin; original magnification ×40.

complete by 120 days (Fig. 3). There were no signs of any residual Gelfoam 120 days following surgery.

The hemostatic agents evaluated in this study were effective in controlling hemorrhage. However, the results of this study indicate that bone wax and Surgicel can induce a foreign body reaction and inhibit osteogenesis. This finding, coupled with reports that foreign bodies can initiate and perpetuate periapical lesions (5, 6), indicates that care must be exercised to ensure removal of as much of the material as possible. Gelfoam did not have any long-term effects on bone regeneration, but careful removal hastened the healing process.

SUMMARY

The results of this study demonstrated that bone wax and Surgicel left in situ greatly inhibited osteogenesis and caused a foreign body reaction. When Gelfoam was left in situ, complete resorption of the material was observed in two of three 120-day specimens. However, this remnant did not interfere with osseous repair of the experimental defect. Attempts to remove bone wax left residues that interfered with bone deposition and caused a foreign body reaction. Attempts to remove Surgicel left residues in one of three 120-day specimens. These remnants interfered with osseous regeneration and provoked a foreign body reaction. The other two specimens showed evidence of osseous regeneration. Successful removal of the material could account for this finding. Defects in which Gelfoam was placed and then removed demonstrated total repair in all 120-day specimens.

Curettage of the experimental defects did not prevent residues of the hemostatic agents used in this study from remaining in the surgical area. These residues produced similar but less severe reactions than those observed in the specimens in which the materials were left in situ. These results indicate that of the three hemostatic evaluated in this study, Gelfoam is the most acceptable. The hemostatic benefit of bone wax and Surgicel is offset by the deleterious effect that these agents can have on bone regeneration. It is recommended that clinicians using these hemostatic agents during periapical surgery be particularly attentive to the meticulous removal of the material.

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