THE UNIVERSITY OF MICHIGAN

SCHOOL OF DENTISTRY
Department of Oral Surgery

Annual Progress Report

STUDIES OF FRACTURE HEALING

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PART I

INTRODUCTION

(Figs. 1-8)

Experimental work with the Macaca Mulatta Rhesus monkey in 1965-1966[1,2] resulted in the development of a reliable fracture model[3] responsive to the influences of altered treatment modalities. After investigation of several healing factors and methods of fixation, we were attracted to the bone adhesive potentials of Isobutyl Cyanoacrylate Monomer, supplied by the Ethicon Corporation. The prototype "Eastman 910 Adhesive" developed in 1960 was methyl-2-cyanoacrylate monomer with various additives. The product[4] was purified by the Ethicon Corporation and supplied to several qualified investigators. The methyl form of cyanoacrylate was investigated extensively in animal surgery and in rare human trials. It was applied to small vessel anastomoses, heart and aorta surgery, and in procedures on the lungs, skin, eye, kidney, ureter, bladder, G.I. system, liver, and spleen.[5,13] Work on bone and tendon, with one exception,[14] was limited to long bones. By 1965, further investigation revealed diminished toxicity achieved by an increase in the length of the alkyl chain.[15,16] The isobutyl form proved to be least irritating to tissues.[17]

Our pilot studies first involved the use of the material in soft tissue incisions and mucoperiosteal flaps in the rhesus monkeys.[2] Healing was satisfactory at 6- and 12-week intervals and showed a minimum of inflammatory response.

Our primary interest was the tissue reaction to the acrylate monomer placed in bone. Further pilot studies involved the incorporation of a small amount of the material in the mandibular fracture model of our experimental animals. The adhesive was also used with an autogenous bone graft from tibia to the mandible. Marrow response to the monomer was determined by the injection of a given amount of the material into the medullary portion of the tibia.[2] Severe inflammatory response indicated a need for further investigation. In the mandibular fracture, the tissue response included medullary inflammatory reaction to the acrylate 6 weeks following the placement of the adhesive.

On the basis of these preliminary observations, a study design included two groups of six monkeys to determine several responses: (1) the effect that Isobutyl Cyanoacrylate Monomer has on the healing of bone in the healing mandibular fracture at 3, 6, and 12 weeks healing intervals. (2) To compare the reaction of a cyanoacrylate on the adherent stable tibial bone

grafts. (3) To determine the reaction of bone when the monomer was placed on stainless steel screws set in position, both in stable situations and under conditions of a constant displacing force. (4) To discover what beneficial effects cyanoacrylate may have in the temporary protection of severely compounded fracture injuries and open facial wounds during the period preceding that of definitive treatment.

MATERIALS AND METHODS

ANESTHESIA

Intramuscular phenylcyclidine hydrochloride (Sernylan) was used in all operative procedures. Early problems of inadequate anesthesia or convulsions due to overdosage have been eliminated by a dosage range of 2 milligrams per Kg of body weight. Anesthesia occurs within 10 minutes following intramuscular injection and lasts approximately 2 hours. No endotracheal tube has been necessary; the animal can swallow, cough, and clear any obstruction which might appear.

SURGICAL PROCEDURE

Mandibular Fracture (Figs. 9-10-11)

Approximately 2 weeks following the extraction of the mandibular right second bicuspid or primary second molar and preoperative lateral jaw radiographs, the animal was anesthetized, shaved, and prepared with hexachlorophine soap. The operator scrubbed and gowned, and the animal was draped in the usual sterile manner for the extraoral procedure.

The body of the right mandible was exposed by sharp and blunt dissection through a 3 cm incision inferiorly. The cut was made with a No. 6 carbide bur in the region of the previous extraction. The section was continued vertically through medullary bone up to but not including the lingual cortex. Following adequate sectioning, the fracture was completed through the lingual cortex with the twist of an elevator. The fracture was not compounded into the oral cavity. Mobility was demonstrated by manual manipulation. Exactly 2 drops of Isobutyl Cyanoacrylate Monomer was measured from the sterile applicating mechanism supplied by the Ethicon Corporation and placed in the open fracture site. After adequate hemostasis, the soft tissue was closed in layers and the skin sutured with interrupted 4-0 braided silk sutures.

Tibia Bone Grafts (Fig. 12)

The anterior surface of the right tibia was exposed in the same 6 animals and a 1 x 1-1/2 x 1/2 cm block of cortical bone was removed. The cortical bone block was returned and stabilized with one drop of the adhesive monomer.

Stainless Steel Screws (Figs. 13-18)

Two holes, approximately 30 mm apart, were drilled with a Clev-Dent No. 12 bone bur in the left tibia of one animal. Stainless steel screws were placed in these holes. The proximal screw was withdrawn and moistened with one drop of acrylate and immediately replaced. Tissues were closed in layers.

The right tibia of two animals was exposed and holes were drilled with their centers exactly 29.5 mm apart. Two screws were set in a similar manner, the adhesive added to the proximal screw and loaded with a previously constructed appliance designed to produce a constant displacing force.

Compounded Mandibular Fractures (Figs. 19-26)

In the second group of 6 monkeys, a standard mandibular fracture was produced. The reflected soft tissue flap was sutured to expose the bone and simulate a compounded war injury. The animals were divided into three pairs. One of each pair was sprayed with Isobutyl Cyanoacrylate monomer by a method developed by Leonard, et al.[18] The second specimen of the pair served as a control. The animals were returned to their cages. Following a prescribed length of time (2 to 9 days) the animals were reanesthetized and the wounds were thoroughly debrided and closed in layers. The animals were sacrificed following 6 weeks of healing period.

POSTOPERATIVE MANAGEMENT

After surgery, the animals were placed in their cages with the head hyperextended for recovery from the anesthetic. During the course of healing, all monkeys received a commercial soft diet preparation. Weights were recorded three times in the experimental course. All animals maintained their weight during the healing period observed.

EVALUATION METHODS

Radiographs

Lateral jaw radiographs were exposed: (1) pre-operatively following

tooth extraction, (2) postoperatively at the time of fracture, and (3) at the time of sacrifice. Films were exposed 65 kV and 0.4 seconds on Kodak Morlite occlusal dental film.

SACRIFICE PROCEDURE

After the prescribed healing period, a veterinary lethal solution containing pentobarbital and alcohol vehicle was injected intravenously. The fracture was immediately evaluated for clinical union. The mandible was disarticulated and again a clinical impression for fracture stability was obtained. Following lateral jaw radiography, the specimen was placed in a 10% neutral buffered formalin solution for histological preparation.

Histologic Technique

The remaining segments were decalcified, dehydrated, infiltrated and embedded in paraffin, serial sections were taken on a horizontal plane. They were mounted and stained alternately with hemotoxyline and eosin, and with masson tri-chrome stain, then covered for histologic study.

EVALUATION TECHNIQUES

CLINICAL IMPRESSION OF UNION

The firmness of the healed fracture was determined immediately after sacrifice by manual manipulation.

RADIOGRAPH EVALUATION

The amount of bony bridge across the fracture site was estimated from lateral jaw radiographs.

HISTOLOGIC EXAMINATION

The microscopic sections were evaluated from the standpoint of bony union, fibrous union, or nonunion. The presence of osteoblastic activity and a calcified bond was designated as a bony union.

A section showing active osteoblastic proliferation and new bone formation, absence of inflammatory elements in the bone, and the presence of minimal fibrous tissue running perpendicular to the fracture site was classified as fibrous union.

A diagnosis of nonunion was made in the absence of osteoid or osteoblastic activity. Osteoclasis and/or inflammation in dense fibrous tissue running parallel to the fracture line was also classed as nonunion.

RESULTS

MANDIBULAR FRACTURES (Figs. 27-29)

All six specimens of this group demonstrated a clinical bony union and a satisfactory healing of the extraoral incision site. Lateral jaw X-rays demonstrated a bony ridge in the 6 and 12 week specimens and a slight bridge in the fracture which was given 3 weeks of healing time.

In all histologic sections, bony union was demonstrated in the lingual cortex.

There were numerous voids in the medullary and buccal cortex regions previously occupied by adhesive material. There was fibrosis with a frequent inflammatory cellular response. Osteogenesis was diminished in adjacent areas. The large collection of monomer apparently served to impede the progress of bone formation.

The sections of the 3, 6, and 12 week specimens were essentially similar, although the 3 week specimens showed a more acute response, more giant cells, and some eosinophiles.

TIBIAL GRAFTS (Figs. 30-31)

In a situation not subjected to stress, the results were somewhat different. Histological bony bridging was adequate but still with some isolated voids which represented nondegraded monomer. The voids were not as numerous or as severe as observed in the fracture segments (mandibular).

STAINLESS STEEL SCREWS

The cross section through the hole occupied by the control screw was unimpressive. Cellular response was absent at the end of 3 weeks following the placement of the screws. Areas of bony regeneration were observed. The section of the hole occupied by the screw upon which adhesive was placed showed cellular response in one monkey similar to that observed in the mandibular fracture. Giant cells were more numerous here than in any other sections.

No clinical difference could be found in the tibia containing the screws placed under constant load. The screw set with adhesive and the control screws appeared the same. Both were firmly anchored 6 weeks following placement. Histologic sections showed little variation between the control screw and the screw placed with adhesive. Small voids were discovered in the latter, but did not appear to significantly alter the histologic pattern.

COMPOUNDED MANDIBULAR FRACTURES (Figs. 32-35)

Spray application of the adhesive monomer to the compounded fracture site was accompanied by rapid control of bleeding surfaces. The adhesive immediately solidified when contacting the warm, moist bony and soft tissues forming a rather noticeable shield. The period of delay before treatment varied from 2 to 9 days with little variation noted in the six animals. At the time of secondary closure, there was little gross evidence of adhesive. There was no evidence of infection in the control or experimental specimens.

Healing in all animals proceeded uneventfully and, at the time of sacrifice 6 weeks later, all demonstrated clinical and radiographic union.

Histologic union was again demonstrated primarily in the lingual cortex. Bony union was accompanied by formation of cartilage in some specimens. As seen with the preceding six animals, the buccal and medullary areas of bone exposed to the adhesive had voids varying in size.

DISCUSSION

Application of the adhesive to the fracture site by the drop method was difficult. Although minimal hemorrhage was controlled, residual bleeding from the medullary areas simply carried the adhesive away from the fracture site. Contact with moisture caused immediate coagulation of the monomer; therefore, to successfully use the material in a fracture site, hemorrhage must be controlled and the fracture must be held in a reduced position. Under these conditions, the monomer would be drawn into the fracture site by capillary action. In the adhesion of large fragments, the monomer exhibited very little stabilizing effect.

The presence of the monomer in the fracture did not appear to influence healing on clinical or radiographic aspects. Histologically, bone healing appeared to require removal of the acrylate monomer and, therefore, the ability of the bone to absorb or exteriorize the monomer to periosteal tissues. Monomer in osseous tissue was characterized by a void surrounded by varying degrees of cellular response from mild fibrosis to acute inflammatory cellular

elements including polymorphonuclear leukocytes, eosinophiles, and giant cells. Whether the acute inflammatory response was due to the monomer or was secondary to the surgical procedure cannot be validated.

In the case of the small relatively stable fragments, such as the tibia bone graft, the adhesive was found to be of some clinical adhesive value. If requirements of hemostasis and adequate reduction were met, the adhesive was drawn into the fracture line and stabilized the graft in position. Histologic response varied from normal healing to an inflammatory reaction and an excess of monomer may be responsible for this cellular change.

During the application of stainless steel screws in the tibia, limited clinical value could be found in the use of the adhesive. Actually, the coagulated adhesive in the screw hole seemed to form a lubricating interface which resulted in less resistance to removal of the screw by the screwdriver. The loaded and unloaded specimens were all retained and were tight at the time of sacrifice. There is some question that the great difference observed histologically in the first unloaded specimen might be due to artifact in the control screw. Very little difference could be noted clinically or histologically in the control and adhesive incorporated screws in the loaded specimens. No tissue or marrow response was seen.

A practical spray method was developed to apply the adhesive to an open wound. The immediate hemostasis observed was dramatic and a significant barrier was indeed present. Unfortunately, our choice of experimental animal in this aspect was poor and we are convinced that the monkey did not allow the adhesive covering to remain for any length of time. The copious blood supply to the area also diminished the possibilities of infection in our control or experimental specimens. In further studies, we would recommend the small of the back of an animal be used where the possibility of interference with the healing of the wound is minimized. Fractures healed better in areas where the adhesive was effectively eliminated as observed in previous specimens.

SUMMARY AND CONCLUSIONS

1. Cyanoacrylate monomer did not stabilize large mobile fracture segments.

2. Careful application of a small amount of adhesive seemed to mechanically stabilize small bone grafts.

3. Osteogenesis proceeded effectively as the adhesive was eliminated, but necessitated a delay in repair.

4. The monomer produced an inflammatory response that was not predictable or constant.

5. The adhesive did not improve the reaction of bone to stainless steel screws in bony cortex or to their retention.

6. The spray application of adhesive to compounded wounds afforded temporary protection before definitive therapy. Further work is required utilizing better controls for unmolested healing of the wound.

7. Cartilage formation seemed to be related to delayed healing or tissue ischemia. Further study of cartilage forming significance is indicated.

8. An inflammatory cellular response was seen in bone marrow in some animals. This was due to the presence of monomer, tissue contamination or surgical interference. Further investigation is indicated. Whether this reaction was specific for the monomer was not consistently demonstrated and was clouded by other variables.

9. From the studies to date, cyanoacrylate monomer adhesive did not assist in the technical control of fracture fixation.

10. Although not a major deterent to osteogenesis, the adhesive did not enhance the repair process of bone defects studied.

PART II

A STUDY OF CARTILAGE PRODUCTION AND CALLUS FORMATION IN HEALING FRACTURES

Throughout studies of mandibular fracture repair, cartilage has frequently been observed histologically in the fracture callus of the nonunion animals. Presence of the consistent association of the cartilage with fracture nonunion has stimulated research interest in the relationship between these factors.

The literature has described cartilage production to be related to a number of variables such as size of the fracture defect, mobility of the bone fragments, species and age of the experimental animal, anatomical variation, blood supply to the area, oxygen consumption of the tissues, and metabolic requirements. Although the specific cause is uncertain, the presence of cartilage in a repairing fracture site seems to represent a secondary pathway to the eventual production of mature bone. Cartilage which is produced during repair must eventually be replaced by bone through a process of endochrondial ossification thus increasing the healing time to bony union. The ultimate goal in treating fractures should be to promote primary bone repair, that is, repair which progresses directly to intramembranous type of bone formation without an initial cartilage phase.

Primary osteogenesis may be produced through induction substances and extensive study is currently under progress in this area. However, another area for fruitful investigation involves the stimulation of factors responsible for primary osteogenesis and the elimination of those factors which allow secondary or endochondral ossification to occur. Studies of this type may contribute to clinical methodology which will stimulate fracture healing at an advanced rate.

A pilot study was instituted to investigate factors responsible for the presence of cartilage in the fracture site during the repair process. The study was designed to evaluate (1) The relationship of cartilage to the size and position of bone defects. (2) Relationship of mobility to cartilage production. (3) Bone anatomical variations and cartilage production, and (4) Species and age differences which may be related to cartilage in the callus.

It was deemed necessary to evaluate the bone repair process in the rhesus monkey in a situation in which mobility of bone was eliminated. This was done by creating three standardized defects at the inferior border of the mandible through the buccal and lingual cortices inferiorly to the inferior alveolar canal. The cut of 5 mm was placed near the angle of the

mandible and defects of 9 mm and 12 mm were placed in the mid-portion and anterior mandible (Fig. 36).

Similar size defects were made in the tibia (Fig. 37) and frontal bone (in a limited number of animals) with the use of trephine burs. This was done to evaluate anatomical differences between bones which developed through either intramembranous or endochondral type formation.

In order to test the hypothesis that certain species of animals are so-called "cartilage formers" similar bone defects were made in the mandible and tibia of rabbits under pentobarbital anesthesia.

Previous studies had shown that defects of this size would "heal" in approximately 6 weeks in the monkey and 15 days in the rabbit. Therefore, the animals were sacrificed at 3 weeks and 8 days respectively in order to study healing activity at the optimum time. The specimens were decalcified, embedded, cut, and stained with (1) Hematoxylin and Eosin, (2) Toluidine Blue, and (3) a combination of Alcian Blue and Chlorantine Red. These stains were used in an effort to differentiate newly formed cartilage and osteoid.

RESULTS

The study is still in progress and most specimens are in the decalcification stage, but preliminary results suggest that cartilage production is greatly dependent upon mobility of the bony fragments and disruption of blood supply and is not related to the type of bone, the position or size of the defect, or the species of animal utilized for investigation. Further evaluation is currently underway at the time of this submission and will be reported in detail in our next quarterly report.

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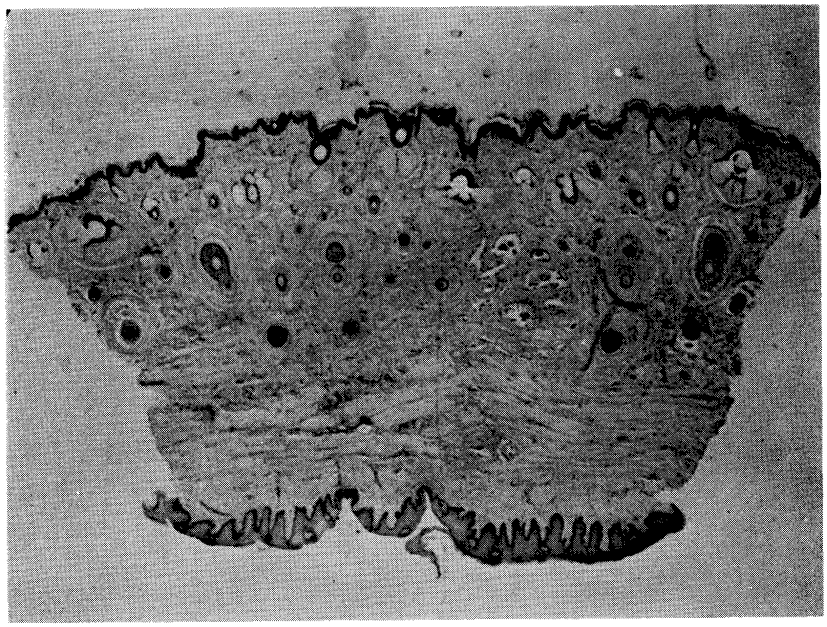

Figure 1. Midline of upper lip six weeks following application of adhesive. Note minimal foreign body response in muscular layer.

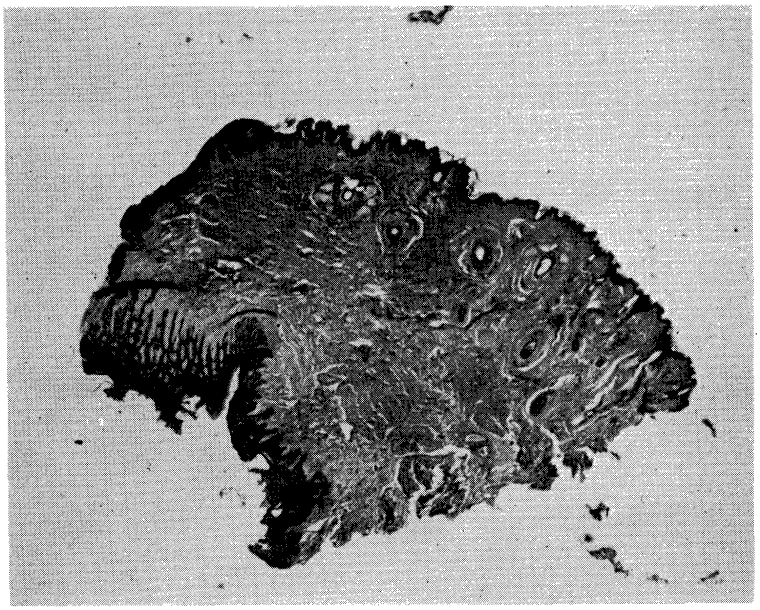

Figure 2. Midline of upper lip twelve weeks following application of adhesive.

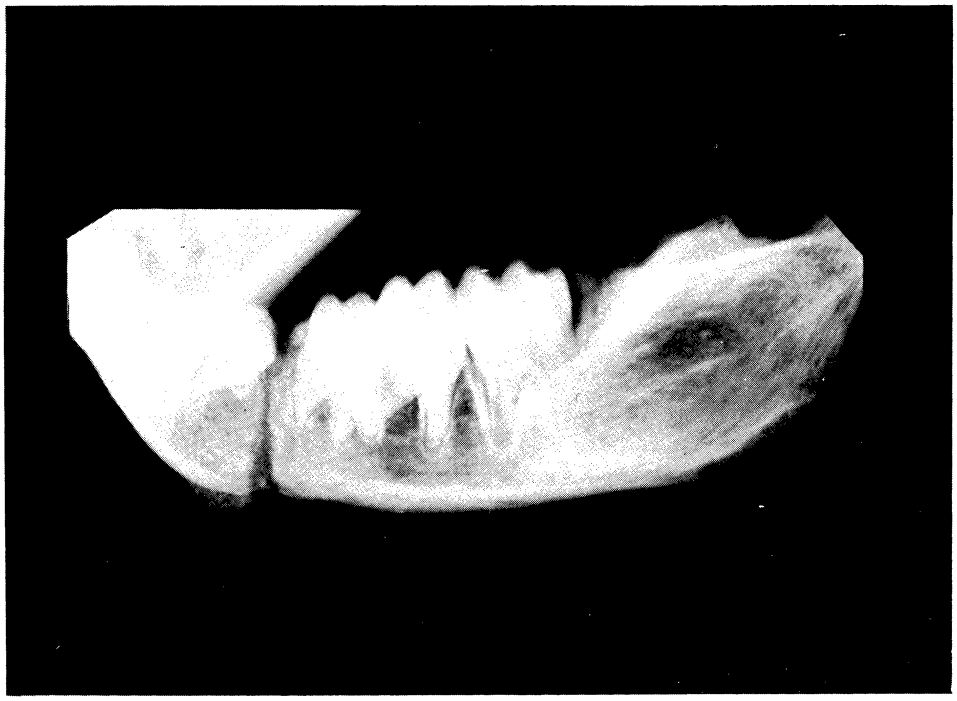

Figure 5. Radiographic evidence of nonunion, six weeks after incorporation of adhesive to the fracture site.

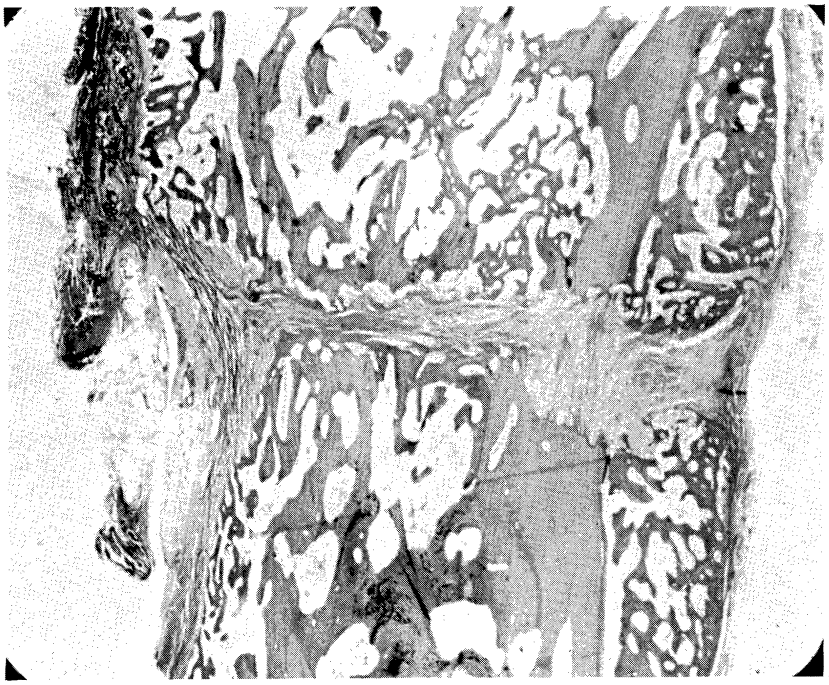

Figure 6. Histologic section of the mandibular fracture six weeks after inclusion of adhesive. Concentration of adhesive seen at left (buccal cortex).

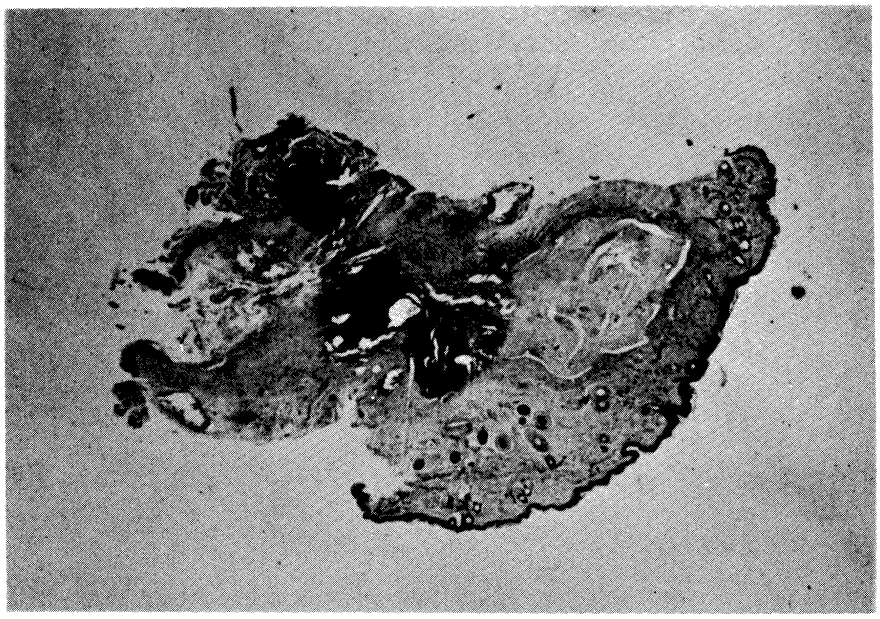

Figure 7. Subcutaneous abscess associated with mandibular fracture. Intense lymphocytic and polymorphonuclearcytic infiltration was noted.

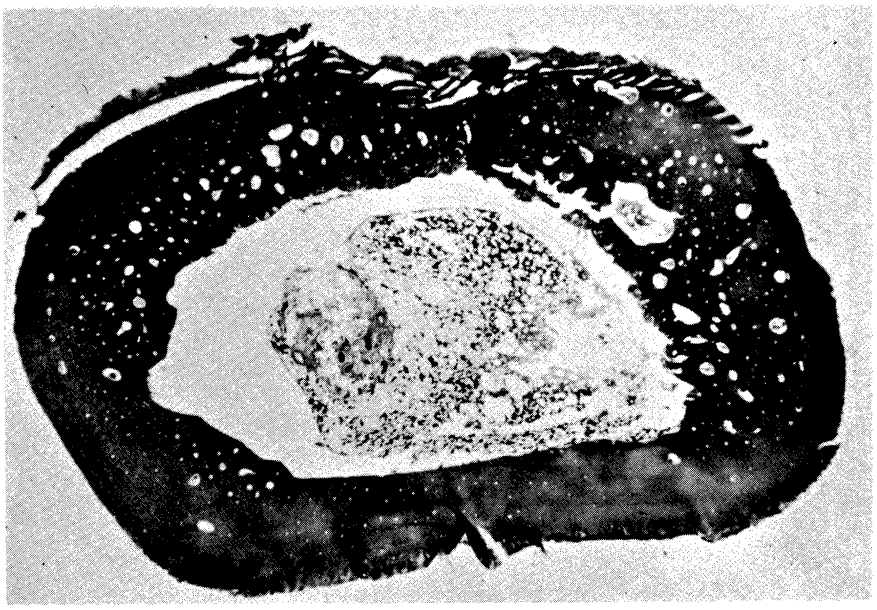

Figure 8. Tibia medulla six weeks after injection of adhesive. Reaction to adhesive can be seen on the right.

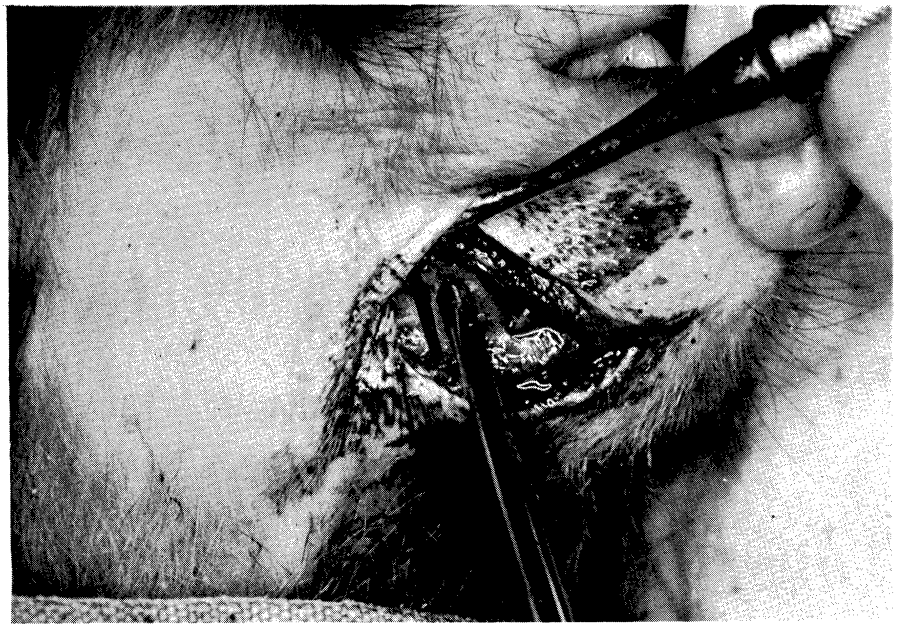

Figure 9. Completed mandibular fracture.

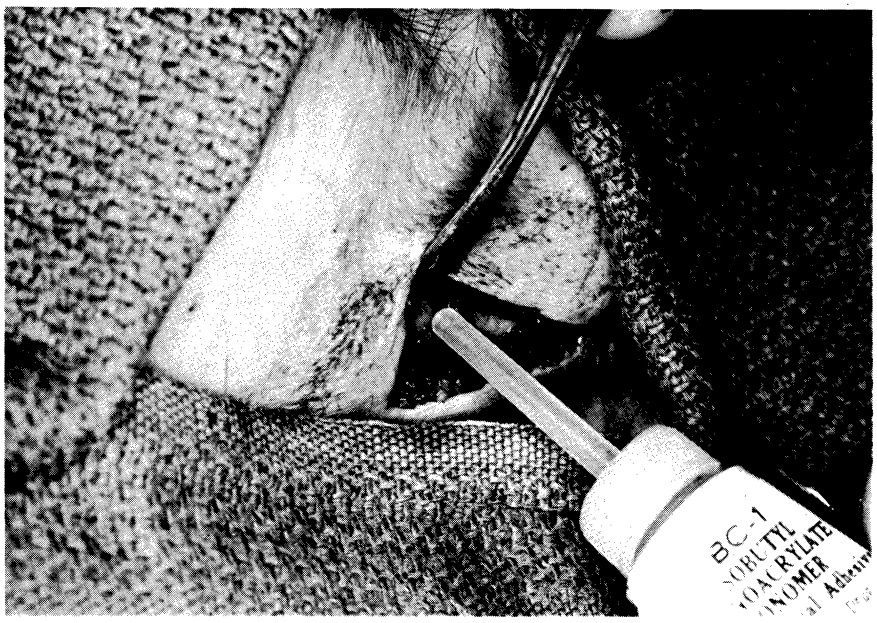

Figure 10. Application of isobutyl cyanoacrylate adhesive to the Model II mandibular fracture.

Figure 11. Sutures placed at the completion of the first stage of the Model II operation.

Figure 12. Placement of a tibia autogenous bone graft to the freshly prepared site at the base of the left mandible.

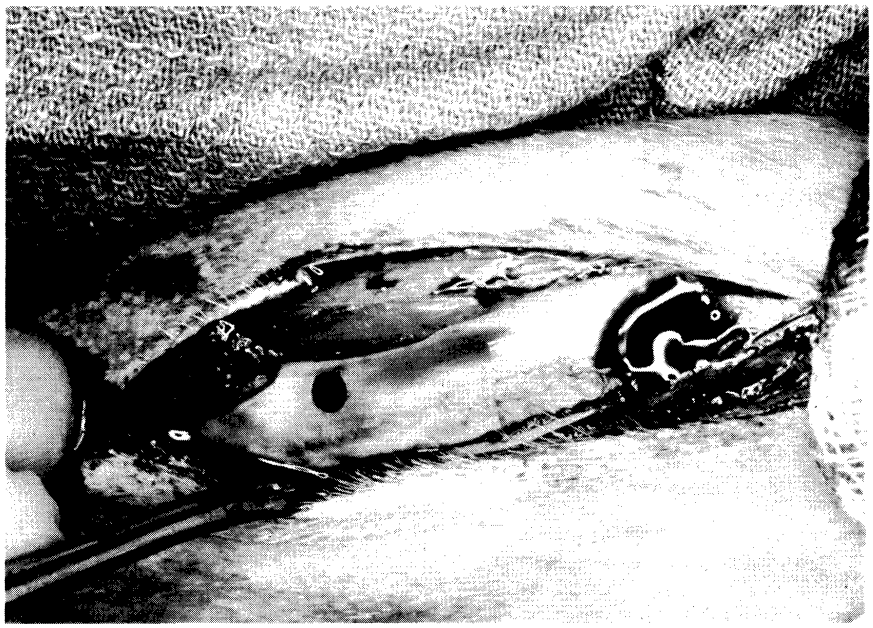

Figure 13. Placement of screw holes in the tibia.

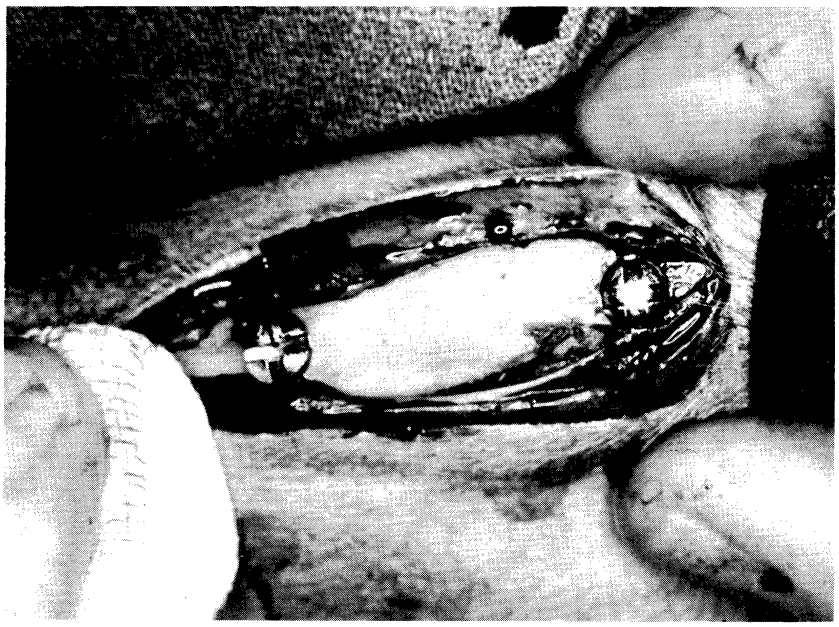

Figure 14. Placement of screws.

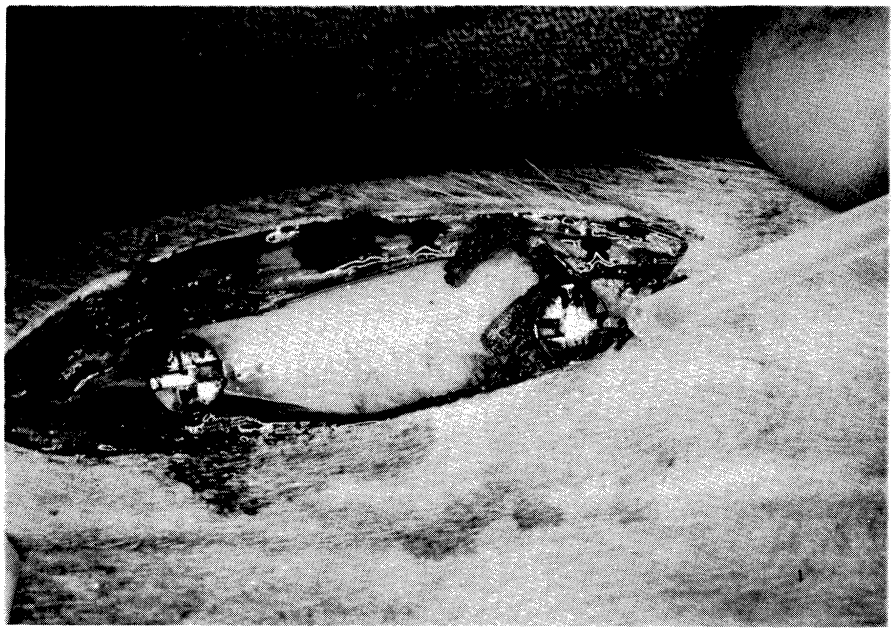

Figure 15. Placement of screws and adhesive.

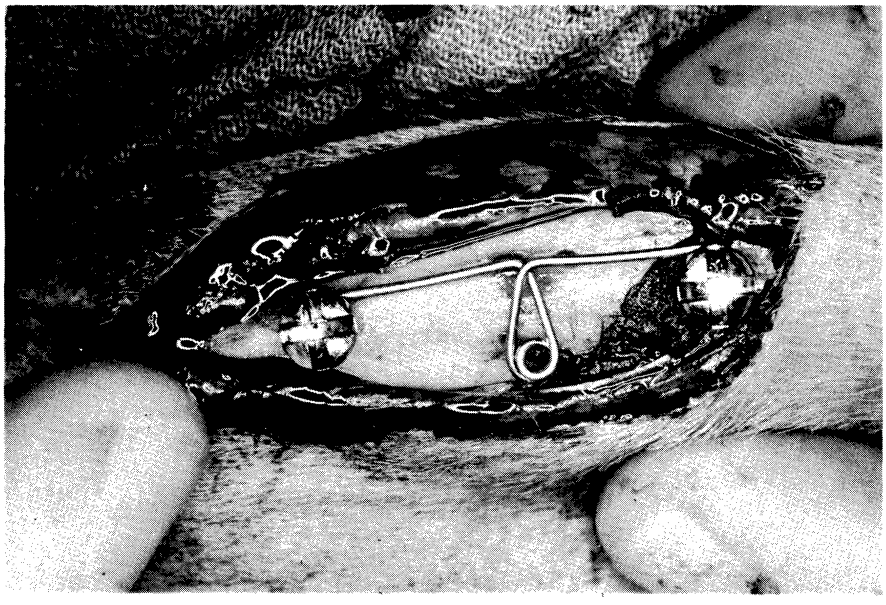

Figure 16. Loading the screws with the wire appliance.

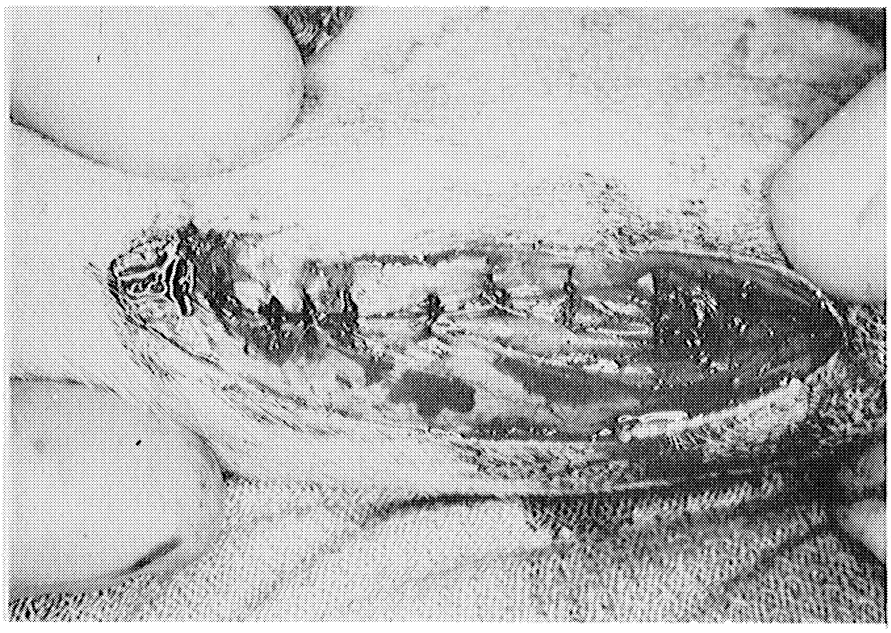

Figure 17. Closure.

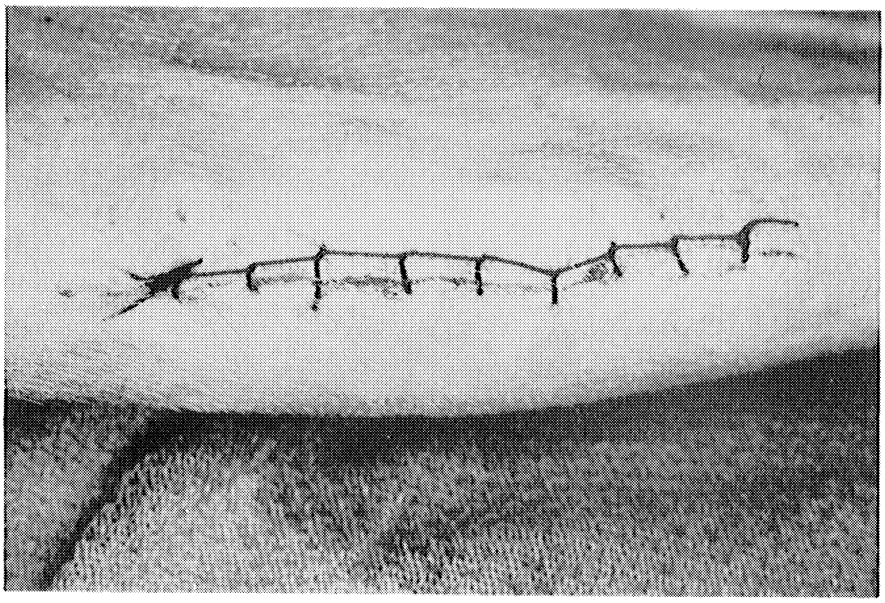

Figure 18. Closure.

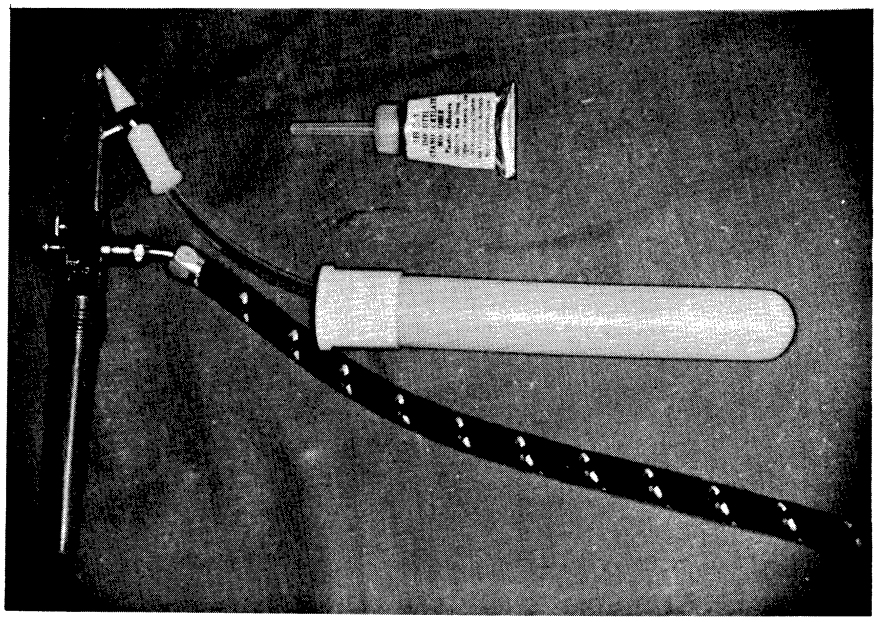

Figure 19. Equipment utilized in the spray application of the isobutylcyanoacrylate.

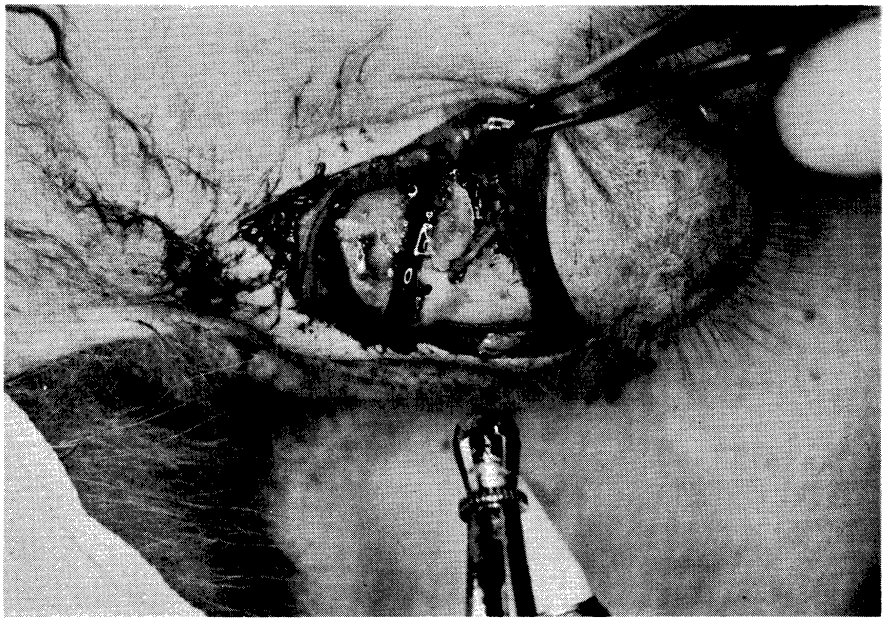

Figure 20. Spraying of the fracture site.

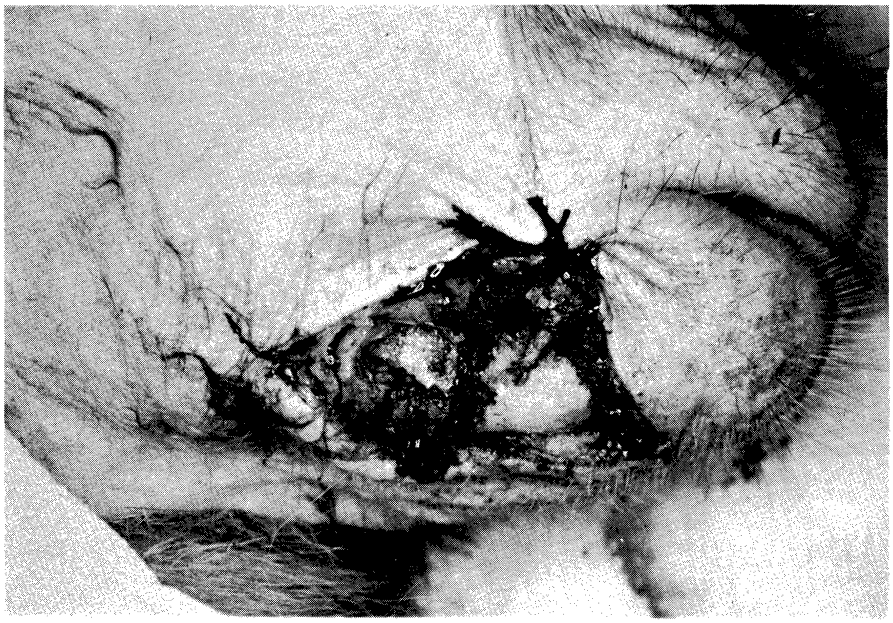

Figure 21. Fracture site immediately after spraying.

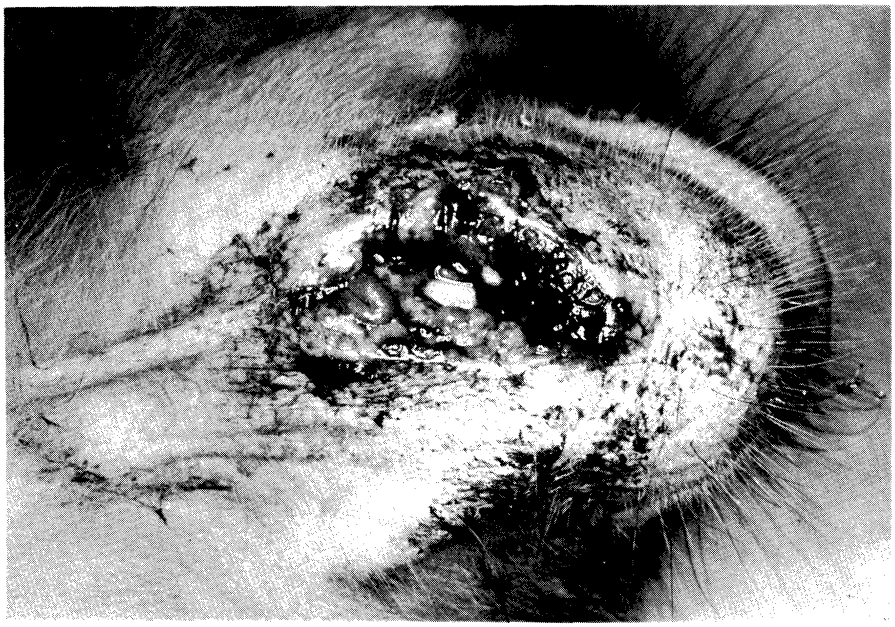

Figure 22. Specimen No. 69 immediately after spraying.

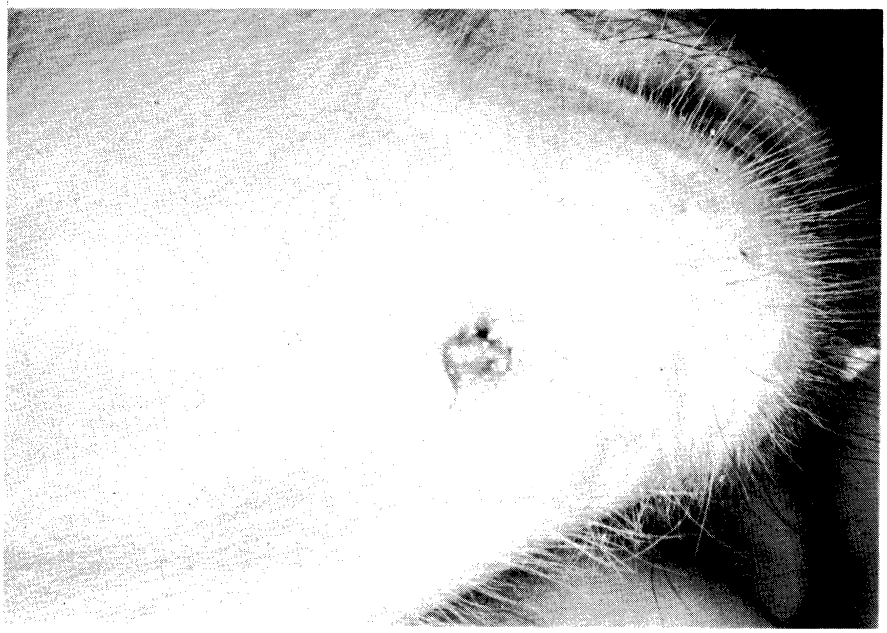

Figure 23. Specimen No. 69 nine days following the spray.

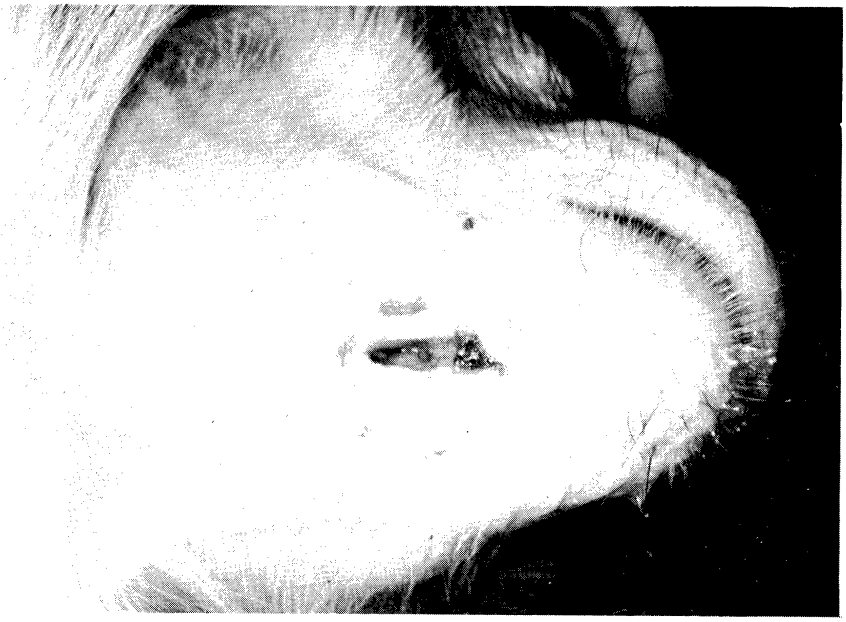

Figure 24. Specimen No. 70 nine days following compounded fracture without the use of adhesive.

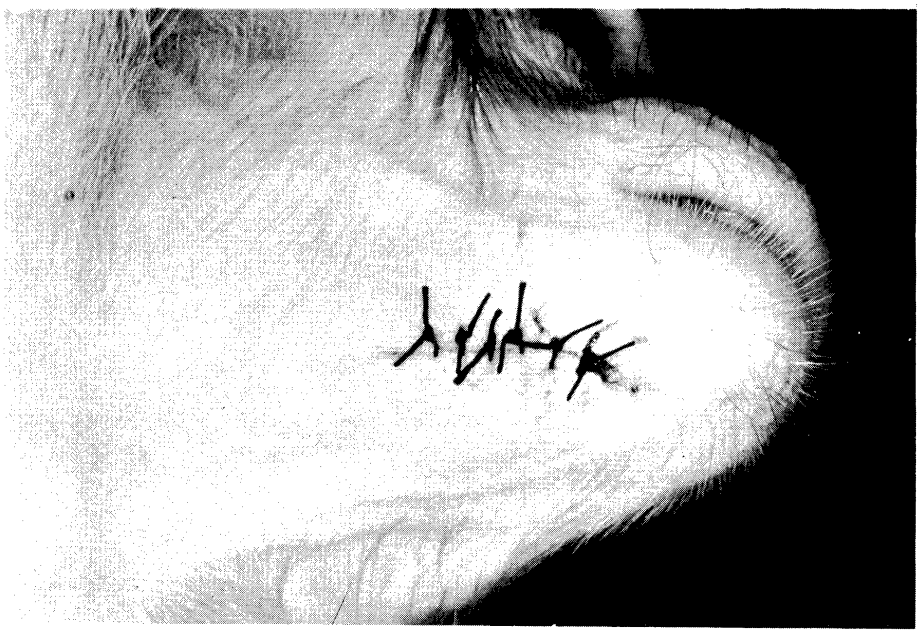

Figure 25. Specimen No. 69 following debridement and closure.

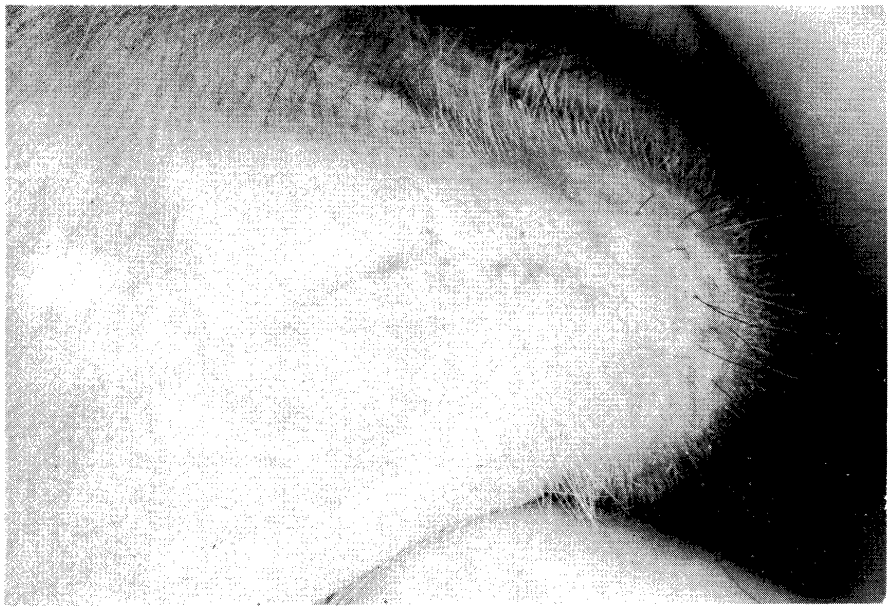

Figure 26. Specimen No. 69 six weeks later at time of sacrifice.

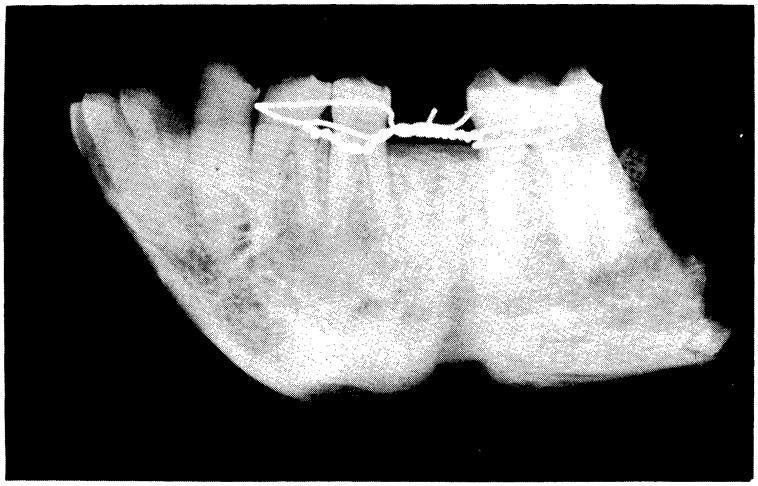

Figure 27. Lateral jaw X-ray twelve weeks following body fracture into which the cyanoacrylate monomer was incorporated.

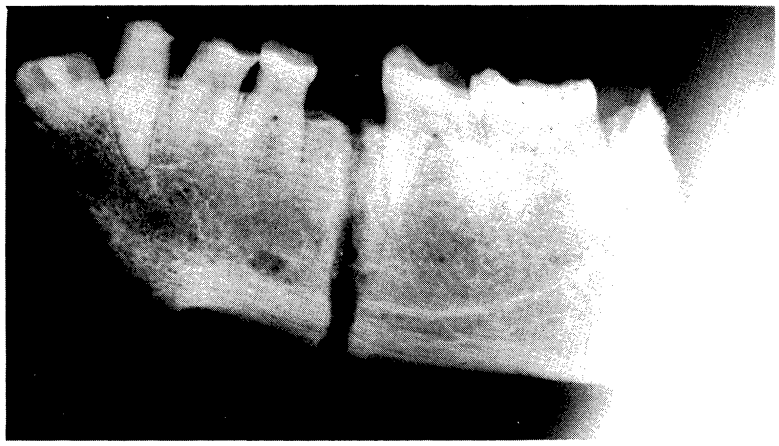

Figure 28. Lateral jaw X-ray six weeks following fracture into which cyanoacrylate monomer was incorporated.

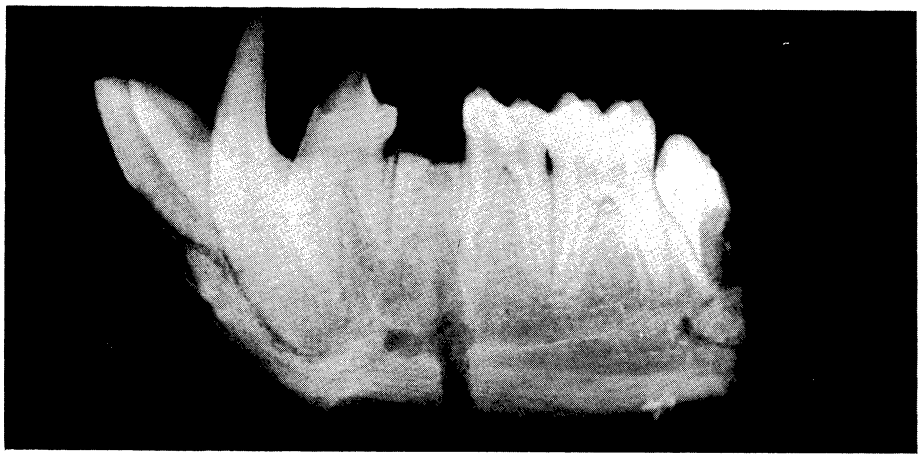

Figure 29. Lateral jaw X-ray three weeks following fracture into which cyanoacrylate monomer was incorporated.

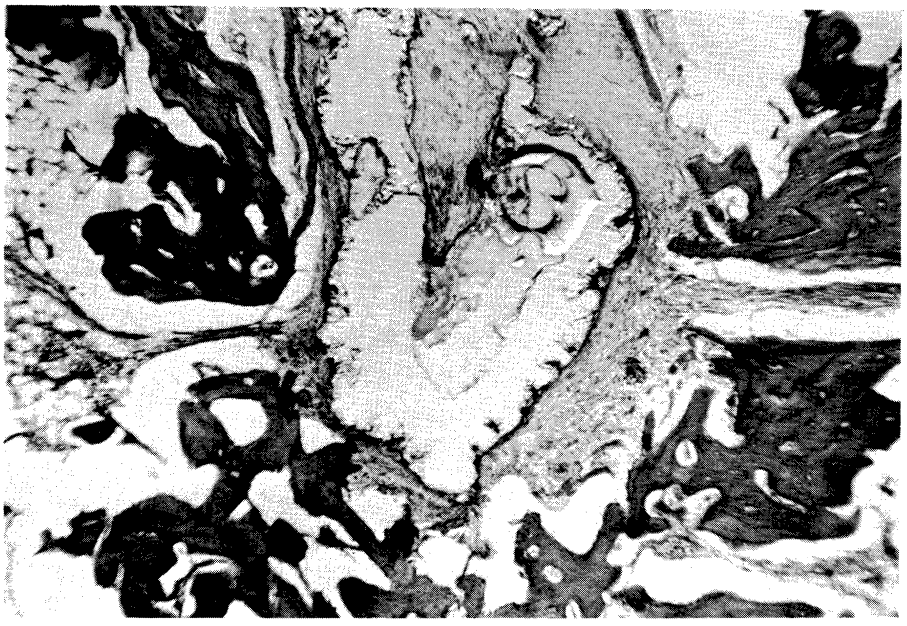

Figure 30. Residual isobutyl cyanoacrylate monomer present between the host bone and tibial graft. Note the minimal inflammatory response which was characteristic in the bone grafting procedures.

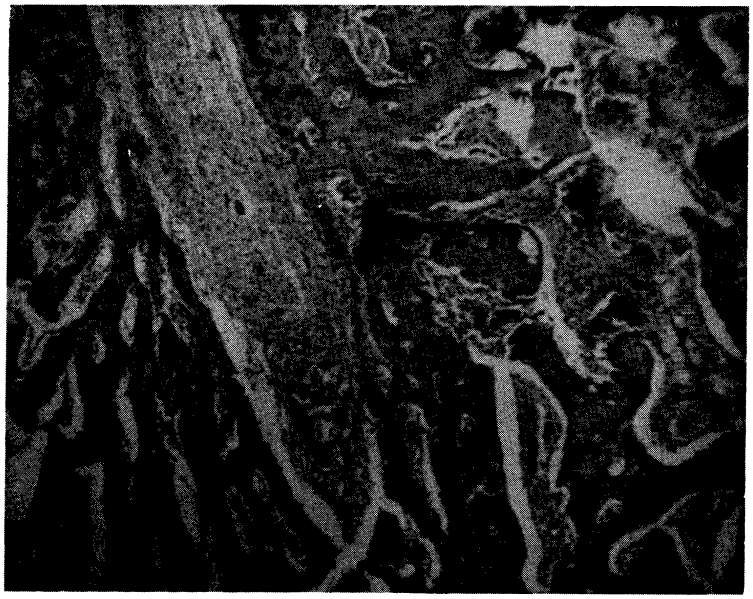

Figure 31. Bony union in a mandible graft. Fibrous connective tissue is noted in the center of the photomicrograph with areas of monomer and debris.

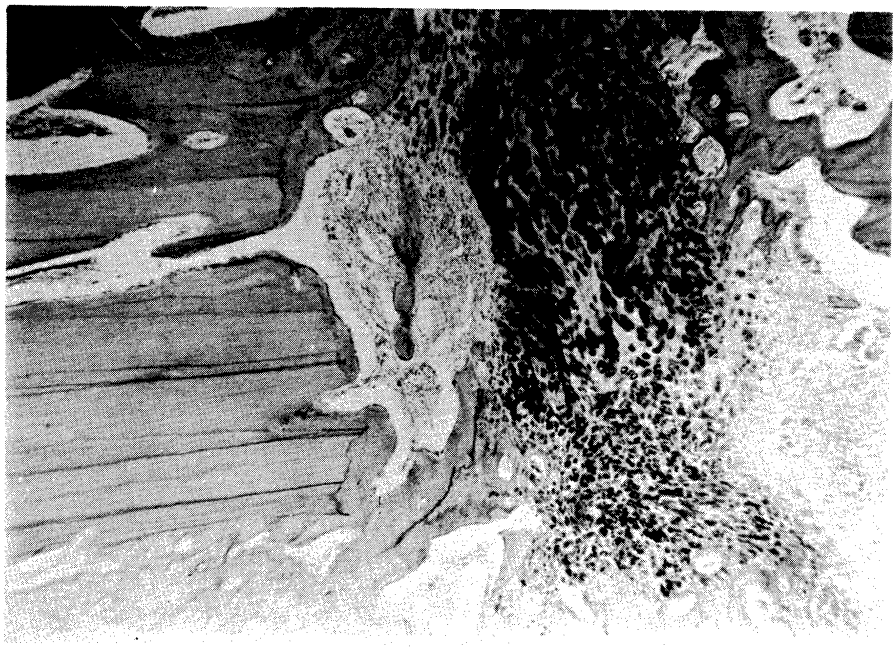

Figure 32. Low power (40x) photomicrograph of a compounded fracture sprayed with adhesive. Note the intense cartilage formation between the fracture sites.

Figure 33. Low power (40x) photomicrograph of a compound fracture nonunion. Note the fibrocellular response on the buccal surface with areas of residual monomer.

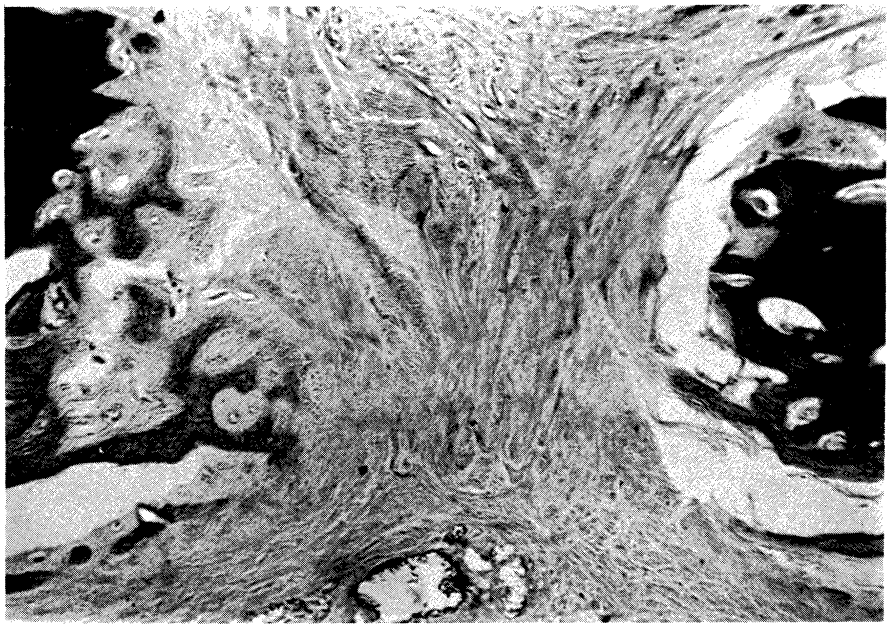

Figure 34. Photomicrograph (40x) demonstrating delayed healing in a compound fracture of the mandible. Note the dense fibrous connective tissue in the center of the section with ostenogenesis occurring on the left.

Figure 35. Compound fracture of the mandible sprayed with monomer in which treatment was delayed five days. Note the presence of monomer at the lower border of the photomicrograph.

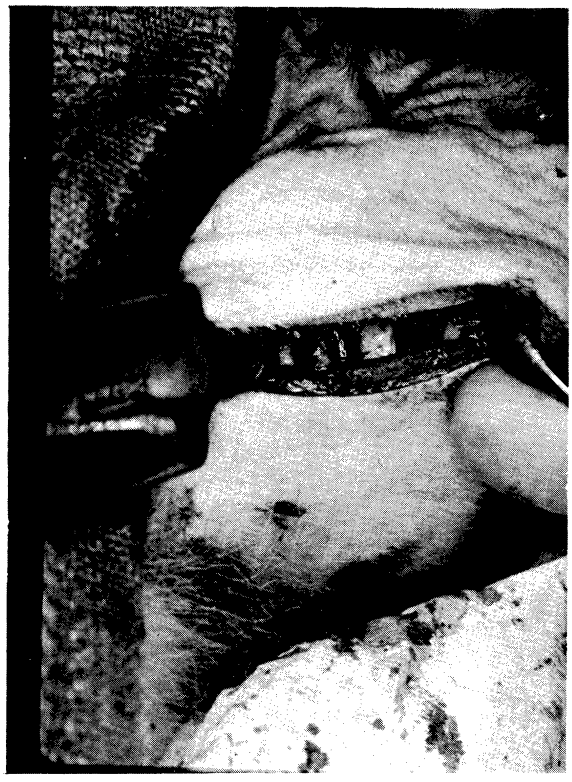

Figure 36. Three defects created at the lower border of the monkey mandible. The largest defect is most anterior in position.

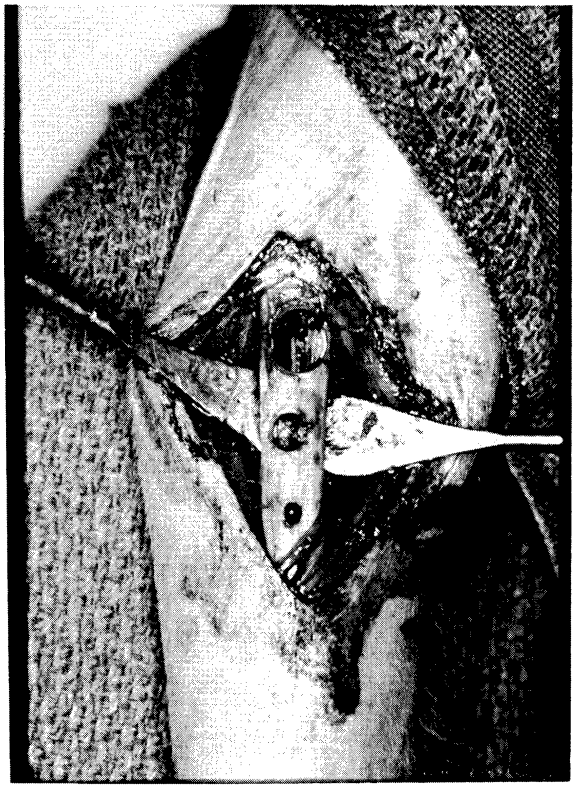

Figure 37. Three trephine defects in the monkey tibia. The largest defect is most caudal in position.

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13. ABSTRACT

Investigations were designed to determine the effects of Isobutyl Cyanoacrylate Monomer on: (1) healing mandibular fractures, (2) tibial bone grafts, (3) the stability of stainless steel bone screws, and (4) severely compounded fractures and facial injuries.

The experimental animals used were the Macaca Mulatta Rhesus monkeys, and the results obtained were evaluated by clinical, radiographic, and histologic methods.

Results demonstrated that adhesive would stabilize small bone grafts but not mobile fractures. The cyanoacrylate monomer tended to retard osteogenesis and did not aid in the retention of bone screws under tension. Application of the monomer to compounded wounds aided in hemostasis and offered temporary protection to the wound.

Further studies were designed to evaluate the functional role of fibrocartilage in the healing callus. Preliminary results indicate that cartilage production is dependent upon bone mobility and disruption of adjacent blood supply and periosteum and is not related to the type of bone, position or size of the defect, or species of animal.

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Mandible Fracture Rhesus monkeys Isobutyl cyanoacrylate monomer LDH activity Aerobic Anaerobic						

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