AN INVESTIGATION OF THE TISSUE REACTIONS AND USE OF POLYURETHANE FOAM (OSTAMER) IN EXPERIMENTAL ANIMALS

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by
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Most experimental investigation is a composite of ideas, suggestions and hard work by many individuals and this work was by no means an exception.

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I wish to gratefully acknowledge the helpful criticism and advice given by Dr. W. Zingg throughout the course of this investigation.

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"An implant is a therapeutic agent and should not be used in man until laboratory investigation and animal experiments establish that the final experiment in man has a reasonable chance of success." [1]

John T. Scales.

Herein lies the ultimate goal of this study.

1. Leon Gillis, Modern Trends in Surgical Materials. (London: Butterworth & Co. (Publishers) Ltd., 1958), p. 72.

CHAPTER I

Introduction

Statement of the problem and validation for research

In the last 5 years interest has arisen in the Orthopedic field regarding the development by the plastic industries of several types of industrial bonding agents. The problem of obtaining a suitable synthetic plastic or resin for the treatment of fractures that could be poured or injected in liquid form, set within a reasonable length of time and have the qualities of strength, nontoxicity, osteogenicity, cohesiveness and ease of handling during surgery continues to intrigue the investigator.

Several authors, notably Bloch in Australia (17,18 & 91) Golovin in Russia (41 & 42) and Mandarino & Salvatore in America (63,65,66,67 & 79) have recently published the results of their experimental and clinical investigations on the application of plastic bonding agents to the management of traumatic and pathological fractures, pseudoarthroses, delayed and non-union of fractures, joint arthrodeses and spinal fusions. In some instances the clinical trials with these new plastic materials have followed too closely inadequate experimental investigations. There are conflicting reports on the potentialities and the degrees of success or failure obtainable with these new agents. The final application and results with

these materials is still very much in a state of flux.

Purpose of the study

The purpose of this study was to investigate the use of these new plastic materials in experimental fractures of long bones in large animals, to assess tissue reaction to the material, and to investigate its effect on callus formation in healing fractures in rats with special reference to its potentialities as a framework for ingrowth of soft tissue and bone. The material investigated was Polyurethane foam (Ostamer), first described in the medical literature by Mandarino & Salvatore (64) and manufactured by the William S. Merrell Company, Cincinnati, Ohio, U.S.A.

CHAPTER II

Review of the Literature

Plastic materials

Definition

It behooves the surgeon to know the physical, chemical and biological reactions of any material which he proposes to use and therefore a brief resume of the technological aspects of plastics and related materials is not felt to be remiss at this point.

For the most part plastics are organic substances - that is to say, they are based on carbon compounds. It is not easy to isolate them rigorously by definition. Generally, however, plastics, like metals, deform elastically under initial load to the yield point and then deform plastically, undergoing a permanent deformation. With increasing temperature the transition from elastic to plastic deformation will occur at lower loads.(5)

Classification

Industrially, plastics are usually classified into two types. (4) The thermoplastic type is one which is capable of being deformed by the application of heat and pressure, taking up a new shape under these combined influences. This process is reversible, that is, upon renewed application of heat and pressure the moulded material can again be deformed

either to its original or some other state and this process can be repeated any number of times.

A thermosetting plastic is also one which is capable of being deformed by the application of heat and pressure, taking up a new shape under these combined influences. However, the process is not reversible. Once the deformation has taken place the chemical change brought about in this class of material by heat and pressure, renders the material infusible and incapable of further deformation. Borderline cases occur in which some materials exhibit the properties of both types.

Ingraham, et al (57) classify plastic materials into synthetic resins, natural resins, for example shellac, cellulose derivatives and protein derivatives. The synthetic resins in turn may be either thermosetting or thermoplastic. Blum (19) & Blaine (15 & 16) in 1944 and 1946 respectively published their observations on the use of absorbable (protein) and non-absorbable (non-protein) plastics in bone surgery.

For a very complete review of the use of plastics in surgery articles published by Jens Bing (13 & 14) in 1950 and Cobey (25) in 1956 may be consulted. Further discussion of the technology of plastics and related materials would be outside the realm of this communication but is, however, available in standard scientific texts (3 & 8).

Polyurethane foam

Definition

Polyurethane foams are expanded, high molecular weight plastics having a distinct cellular structure. (1) They are thermoplastics and in general are characterized by low weight, low thermal conductivity, good strength - weight ratios and in many cases good water resistance. (40) Industrially they are found useful in refrigeration insulation, buoyancy agents, sandwich structures, building and aircraft construction.

Methods of production

Polyurethanes are produced by two methods - condensation with elimination of water and polymerisation. (2) The latter method involves the linkage of many molecules (up to 5,000 in the linear chain) of a monomer into a high molecular weight polymer which has the same percentage composition as the monomer.

Historical development

In 1848 Wurtz (2) discovered that the isocyanates not only react with the reactive hydrogen atom of hydroxyl and amino groups but also of the carboxyl group:

$$CH_3 - COOH + O = C = N - C_2H_5 \longrightarrow CH_3 - CO - NH - C_2H_5 + CO_2\uparrow$$

Here the acid amide is formed by splitting off carbon dioxide to yield a plastic foam with high strength. When a

diisocyanate is mixed with a polyester prepared from a dicarboxylic acid and trihydroxy alcohol and containing free hydroxyl as well as carboxyl groups, the honey-like substance starts reacting at a temperature of only 50° C. with the formation of urethane and acid amide linkages and simultaneously splitting off carbon dioxide. This causes the substance to rise like dough and harden as the cross-linking progresses.

Bayer (2) in 1937 discovered and developed polyurethane polymerization, also known as the diisocyanate method. Polyurethanes are available as linear products (Perlon-U suture material), lacquers with strong adhesive properties and as plastic foams which can be produced with high strength and in any desired elasticity.

Ostamer

Composition, properties and use.

To produce a dense, rigid, cellular foam with the properties essential for orthopedic use a "prepolymer" is prepared by reacting a trihydroxy resin with an excess of 2-4 diisocyanate.(92) This prepolymer is then reacted at the time of surgery with a liquid catalyst (a mixture of aliphatic tertiary amines and water in precise ratio). The resultant exothermic reaction liberates carbon dioxide and produces a rigid, expanded, white polymer with a closed lacunar-like system of pores and having approximately twice

the volume of the original liquids.

The physical properties of density, tensile, compressive, shear and flexural strengths of Ostamer will vary to some degree. (93) The variables that can affect the reaction of the prepolymer and catalyst can alter the final product substantially. The recommended mixing temperature and mixing time have been in a state of flux. The presently recommended temperature of 100° F and mixing time of 7 seconds allow for ease of handling. Inadequate mixing, the presence of exogenous moisture and incomplete reaction can alter the properties of the final product.

Ostamer is recommended for use primarily in non-union, pathological fractures or complicated acute fractures occurring in any long bones and even in uncomplicated acute fractures where the technique of handling the material has been mastered. It is recommended wherever adjunctive stabilization of bone fragments is considered necessary.

Operative technique

Briefly the operative technique with Ostamer involves routine surgical exposure and reduction of the fracture, removal of a cortical inlay graft, curetting and drying of the medullary canal, secural of adequate hemostasis and application of previously sterilized prepolymer and catalyst mixed for seven seconds in the correct ratio followed by replacement of the cortical inlay graft. The Ostamer is

allowed to expand within the medullary canal and following a 20 minute setting interval the wound may be closed, providing adequate stabilization has been obtained. Ancillary metal fixation in the form of intramedullary Kirschner wires, or Mandarino rods and discs is recommended where the medullary canal is less than half an inch in diameter. After immobilization for 48 hours it is said that weight bearing, in the case of the lower extremity, may be considered.

Ultimate fate in the organism

The ultimate fate of Ostamer within the body is not completely understood although it is stated that it is slowly absorbed over a period of 18 - 24 months. Preliminary isotope studies with tritium tagging indicate it is eliminated in part in the urine and faeces. (30) How the substance is mobilized is unknown at present.

Foreign material implantation and tissue reactions

The problems of Ostamer implantation within the body is the problem of any foreign material placed within the human organism. (60 & 82) Up to 1955 there were over 1,440 separate articles on the use of foreign substance implants in reconstructive surgery reported in the literature. (44,45,46,47 & 48)

A material to be implanted in the body must fulfill

the following criteria: (5)

1. be chemically inert;
2. not be physically modified by tissue fluids;
3. not excite an inflammatory or foreign body cell response in the tissues;
4. be non-carcinogenic;
5. not produce a state of allergy or hypersensitivity;
6. be capable of standing up to mechanical strains imposed upon it;
7. be capable of being fabricated in the form required with reasonable ease and at relatively low cost;
8. be capable of being sterilized.

Few materials approach all these specifications. Many investigators (12,27,37,51,53 & 54) have reported on the use of various implant materials at various sites both in the experimental animal and man with special reference to subsequent tissue reactions. Oppenheimer et al (71,72, 73,74 & 75) have shown that many of the plastics which are in use today can at one time or another, and to a greater or lesser degree produce malignant changes in rats. So far there are no reported instances in which the embedding of plastic material in humans has resulted in the development of neoplasia.

Plastics are complex materials. The simple chemical monomer units which form the plastic by polymerization are themselves sometimes irritant. The synthesis of

plastics, polyurethanes not excluded, is often brought about by catalysts or accelerators. Other substances such as fillers, pigments, anti-oxidants, and stabilizers may be added for a variety of reasons. While the final resin or polymer may be inert the additives may leach out of the plastic and cause cytotoxic reactions.

There are diverse responses to the physical as well as the chemical properties of an implant. Le Veen & Barberio (61) have shown that the surface area of both the foreign substance and the tissue exposed are important in determining tissue reaction. They found that chemically inert plastics which cannot be wet with water produced the least tissue response.

Cohen (26) in discussing the difficulties of assaying foreign body reaction states that difficulties arise in determining qualitatively the degree of tissue reaction in the various tissues and in characterizing the nature of the stimulus.

The epoxy resins currently used by Bloch (18) and Golovin (41 & 42) in the bonding of fractures, and Bowen (22) in dental work, have been reported to cause severe contact dermatitis (55) and other hypersensitivity reactions. (59) The toxicology of both the cured, and uncured epoxy resins and associated curing agents is well tabulated. (28,43,68 & 81)

Histologically the tissue reaction to Ostamer both in man and experimental animals has been reported as minimal and limited largely to a moderate fibrous tissue reaction and multi-nucleated giant cell formation.

It has been said that no resin and hardener system capable of reacting at normal temperatures can be regarded as physiologically inert. It is impossible to produce such a system which is completely non toxic since chemical and biological activity are inseparable. (21)

Previous investigations with Ostamer & related materials.

Although the problem of bonding foreign materials to living bone is an intriguing one it is by no means new. In 1931 Nedri (52) reported good results with "Osseeol" a bone glue which he employed in the treatment of fractures and pseudoarthroses by open reduction or by injecting the material between the bone ends. No further articles have appeared in the literature following this one isolated paper.

In 1956 Bloch (17 & 18) published his experimental observations on the use of epoxy resin adhesives in the bonding of fractures in sheep, along with a report of its use in three patients. The technology of epoxy resins, the technique employed in their use and their further application in a research project were clearly outlined in his monograph published a year later. (91) Golovin (41 & 42) in the

Russian literature has reported on his experimental and clinical results with "Osteoplast" a resorcinal epoxy resin compound. He says that this method is now used extensively in a number of Leningrad clinics with apparently good results.

Mandarino and Salvatore (63,64,65,66 & 67) have carried out extensive experimental and clinical investigations with polyurethane foam (Ostamer). They claim that Ostamer is a chemically and physiologically inert substance which creates mechanically superior fixation by bonding to bone; thus minimizing postoperative immobilization. They further claim, as does the manufacturer, that the lacunar-like system of Ostamer will provide a framework for the endochondral proliferation of new bone. There are no reports in the literature at this date of toxicity to Ostamer or its precursors in tissue cultures, experimental animals or man.

Redler (77 & 78) and Drompp (34) have also reported on their clinical experience with Ostamer. Their high incidence of failures and complications is appalling and is further conclusive evidence that this new material should continue to remain within the realm of experimental investigation only.

Sataloff (80) has employed Ostamer in the repair of middle ear ossicular defects in 25 cadavers and 2 patients. It was used successfully in restoring the continuity of the ossicular chain. In the case of the 2 living patients a

substantial improvement in hearing occurred.

N.R. Crozzoli (29) has reported poor results with his first attempts at experimental bonding of fractures with commercial adhesives.

The ability of Ostamer to act as a framework for ingrowth of soft tissue and particularly new bone is at the moment a controversial and experimentally unproven point. Similar investigations have been carried out on polyvinyl-formal (Ivalon) sponge. In 1949 Grindlay and Clagett (49) reported fibrous tissue infiltration into Ivalon sponge when used as plombage in dogs following pneumonectomy. In 1951 Grindlay and Waugh (50) reported that Ivalon sponge would act as a framework for fibrous tissue ingrowth. These findings were followed in 1955 by Struthers et al (86,87 & 88) stating that Ivalon was well tolerated by skeletal tissues, that new bone would infiltrate it from adjacent surfaces of cancellous bone and that this ingrowth of bone was increased by the addition of chips or small particles of autogenous bone to the sponge implant. These results have stimulated others (20,38,39 & 83) to investigate its potentialities as a tissue substitute in thoracic (56 & 62) and vascular surgery (10,58 & 59), mammaplasty (35) and in the jaw to overcome resorption of the alveolar margin following tooth extraction. (9,11 & 33)

In 1958 Bryan, Janes & Grindlay (23) reported that Ivalon sponge delayed bone healing in dogs up to a period of one year although it did act as a framework for ingrowth of soft tissue and bone.

Ostamer however is chemically and physically different from Ivalon sponge and no analogies can be drawn in this regard, except that they are both materials foreign to the body. Nevertheless these experiments with Ivalon sponge serve to outline the course of investigation to be followed with Ostamer.

Addendum:

W.G.Hueper (55a) has reported briefly in the J.A.M.A., 173: 860, 1960 that polyurethane foam when implanted into the abdominal cavity of rats either in the form of a sponge or powder produced sarcomas and adenocarcinomas of the cecal mucosa at the site where the polymer was in contact with and had become adherent to the intestinal wall. The carcinomas of the cecum occurred as early as 10 months following implantation of the polyurethane foam.

CHAPTER III

Materials & Methods

Experiment 1. : The use of Ostamer in experimental fractures in large animals.

Seventeen procedures were carried out on 8 cross-bred Oxford and Suffolk sheep, 4 mongrel dogs and 2 cross-bred Brown Swiss & Holstein calves weighing between 16 and 80 kg. The tibia was the operative site chosen in all procedures except 5, in which the femur was selected.

Under pentobarbital sodium anesthesia an incision was made to expose the bone. The periosteum was then incised and elevated and an osteotomy was performed in the region of the mid-shaft. A cortical inlay graft was removed across the osteotomy site with an electric bone saw. The exposed medullary canal was curetted, and dried, and Gelfoam sponge inserted into the canal above and below the graft site to prevent oozing. Adequate hemostasis was obtained without a tourniquet.

Table I on page 22 shows the variables existing in all the operative procedures because of changes that were made as we became more familiar with handling this new material and as successes or failures arose.

The size of the cortical inlay graft varied according to the animal and operative site chosen but

generally speaking a substantial size graft was removed in all cases.

The obvious importance of obtaining a dry, fat-free field led to the use in 3 cases of an inert gas heater as described by Bloch (18) to dry the bone ends. In 4 procedures the bone ends and marrow cavity were swabbed with ether to remove excess fat.

After reduction and immobilization of the bone ends with Lowman clamps ancillary internal metal fixation was used in 11 cases and consisted of either intramedullary Steinmann pins, Sherman SMO bone plates or as in one case transfixing screws. Six procedures were performed using Ostamer alone. In 3 instances repeat procedures were performed following failures of bonding with obvious instability.

Previously sterilized Prepolymer and Catalyst were heated to 100° F in a water bath. Exactly 14 cc. of catalyst were added to the jar of prepolymer and mixed with an electric rotary beater. The mixing temperature varied according to the recommendations concurrent at that time. The final recommended temperature of 100° F appears to be the best compromise between ease of handling and speed of setting.

Mixing time varied from 7 seconds to one minute by the clock depending on the temperature of the Prepolymer and Catalyst. All poor mixtures, as judged by color and presence of unmixed ingredients, were discarded.

The Ostamer was then immediately poured into the prepared site, the cortical inlay graft was replaced and the material allowed to set. After 5-7 minutes excess Ostamer was either removed with a scalpel or moulded about the osteotomy site. Twenty minutes after pouring stability was checked and if felt to be satisfactory periosteum was approximated where possible and the wound closed in layers.

None of the animals were immobilized postoperatively nor were splints applied. Only the dogs received antibiotics postoperatively. (500,00 u. crystalline penicillin and 0.5 gm. streptomycin on 3 successive days). The animals were followed clinically, radiologically and at post mortem.

Experiment 2. : The subcutaneous implantation of Ostamer in rats.

Under ether anesthesia sterile, standard size (10 mm. x 4 mm. x 1 mm.) Ostamer implants were placed subcutaneously in the paraspinal region of 30 pure line strain Wistar rats of undetermined sex weighing between 120 and 200 gms. No transfixing sutures were placed through the implant and the skin was closed with a continuous 4-0 silk suture. Simple skin incisions in 4 rats without implants served as a control for the first 2 weeks to assess the degree of inflammatory reaction due to trauma alone.

The rats were sacrificed by ether overdosage at predetermined time intervals between one and 26 weeks. All

specimens then underwent multiple sectioning at 6 to 7 microns and routine staining with hematoxylin and eosin.

Experiment 3. : The implantation of Ostamer at tibial fracture sites in rats.

Under ether anesthesia standard size Ostamer implants were placed at tibial fracture sites in 42 pure line strain Wistar rats of undetermined sex weighing between 120 and 249 gms. The implants were in one of two forms - small onlay type grafts measuring 5 mm. x 3 mm. x 1 mm. and small tubes of Ostamer measuring 6 mm. in length with a wall thickness of 1 mm. which acted as tiny collars at the fracture sites. It was hoped that the tubes would remain in more intimate contact with the fracture site than would the onlay graft type of implant.

The tibiae were fractured after a method described by Selye (84). The skin was shaved in the inguinal region and an incision 2 cm. in length was made through the skin just above the inguinal canal. The skin was then pulled down to the level of the tibia; this can easily be done in the rat because of its loose subcutaneous connective tissue. The middle third of the tibia was then freed of surrounding muscles and transected with scissors. In the rat the distal end of the fibula forms a synostosis with the tibia and consequently the fibula acted as a splint which maintained the two ends of the tibial fracture in position. After

severance of the bone an onlay graft of Ostamer or an Ostamer tube was applied across the fracture site and the skin closed with a continuous 4-0 silk suture. The indirect approach was used in order to minimize the danger of infection, which is always great when a bone fracture is placed just under a skin incision.

Control tibial fractures without implants were carried out in 15 rats. The normal healing of fractures in rats is well recorded in the literature. (32,36,76,85 & 90)

All rats were sacrificed by ether overdosage at predetermined time intervals between 1 and 38 weeks.

All specimens were then decalcified using the formic acid and cation exchange resin method (31), multiple serial sections made at 7.5 to 10 microns and then stained with hematoxylin and eosin.

CHAPTER IV

Results

Experiment 1. : The use of Ostamer in experimental fractures in large animals.

The results are tabulated in Table I on page 22 and ranged from failure at operation or shortly thereafter to complete success with clinical and radiological union. A failure was classified as clinical or radiological evidence of instability and movement occurring at the osteotomy site.

All the procedures using Ostamer alone or in combination with intramedullary pins failed except in one instance which although initially infected and draining went on to subsequent union. This animal is now 6 months postoperative. The skin is healed with no drainage and the animal is moving about normally.

The most successful results were obtained in those animals in which Ostamer plus Sherman SMO bone plates or transfixing screws were used. There were 4 successes and 4 failures.

Three repeat procedures all went on to subsequent failure.

The series was not without infection all 4 dogs developing it postoperatively despite antibiotics.

Soft tissue healing did not appear to be delayed except in the infected animals although there was

considerable postoperative swelling in the extremity of all animals for a variable period of several days to 2 weeks.

At the time of this writing there are 2 sheep, 2 dogs and one calf which are alive and walking normally with no apparent ill effects.

In all postoperative radiographs the callus formation was mainly subperiosteal with no evidence of callus invading the Ostamer, which remained radiolucent.

At postmortem of 9 sacrificed animals the intramedullary plug of Ostamer could readily be removed with no apparent bonding to bone.

TABLE I

Comparison of the Methods & Results with Ostamer in Experimental Fractures in Large Animals.

Procedure	Animal	Weight (kg.)	Osteotomy Site	Method	Temp. (°F)	Inert Heater	Ether	Graft Size (in.)	Result
1	Sheep A	62	Femur	Ostamer	120°			3 x ½	Failure 6 days postop.
2	Repeat A			Ostamer & intramed. pin	120°				Failure 2 days postop.
3	Sheep B	71	Femur	Ostamer	120°			3 x ½	Failure 10 days postop.
4	Sheep C	60	Tibia	Ostamer	100° & 120°		+	2½ x ⅜	Failure at operation after 2 trials
5	Sheep D	60	Tibia	Ostamer & bone plate	120°	+	+	3½ x ⅜	Successful union. Bearing weight 4 weeks postoperatively.
6	Sheep E	48	Tibia	Ostamer & bone plate	100°			3 x ½	Failure 7 days postop.
7	Sheep F	80	Tibia	Ostamer & bone plate	110°			3 x ⅜	Failure 7 days postop.

TABLE I (continued)

Comparison of the Methods & Results with Ostamer in Experimental Fractures in Large Animals.

Procedure	Animal	Weight (kg.)	Osteotomy Site	Method	Temp. (F°)	Inert Heater	Ether	Graft Size (in.)	Result
8	Sheep G	70	Tibia	Ostamer & bone plate	100°			3½ x ⅜	Successful union. Bearing weight 3 weeks postoperatively
9	Sheep H	68	Tibia	Ostamer & bone plate	100°			4 x ⅜	Failure 3 hrs. postop.
10	Calf A	70	Tibia	Ostamer & transfixing screws	120°		+	3⅛x⅜	Successful union. Bearing weight 4 weeks postoperatively.
11	Calf B	54	Tibia	Ostamer & bone plate	100°			4 x ½	Anesthetic death. No bonding
12	Dog A	16	Femur	Ostamer	100°			4 x ½	Failure 2 days postop.
13	Repeat A			Ostamer & intramedullary pin	100°		+		Failure 4 days postop. Infected.

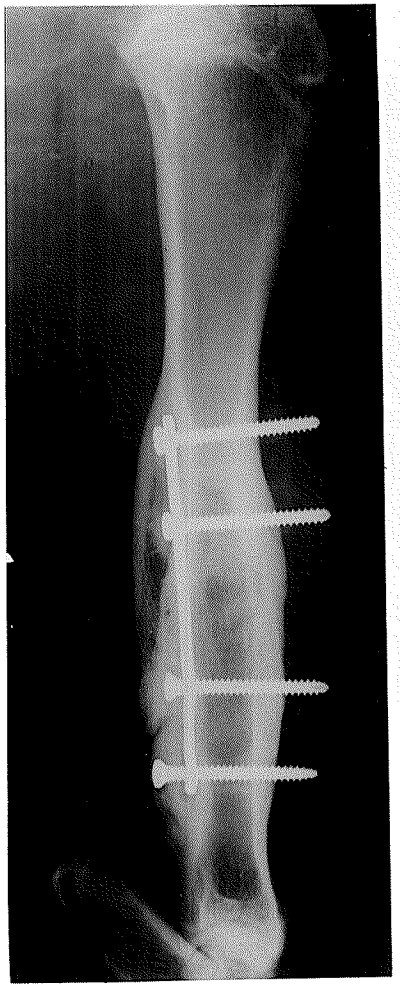
TABLE I (continued)

Comparison of the Methods & Results with Ostamer in Experimental Fractures in Large Animals.

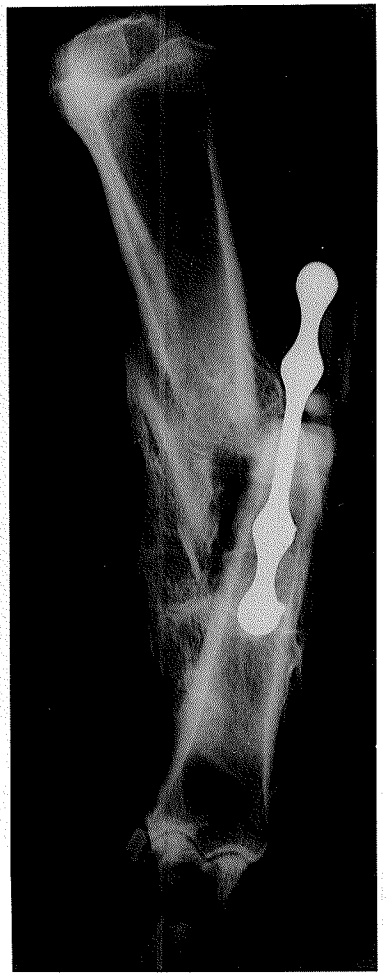
Procedure	Animal	Weight (kg.)	Osteotomy Site	Method	Temp. (F)	Inert Heater	Ether	Graft Size (in.)	Result
14	Dog B	30	Tibia	Ostamer	120°	+		$4\frac{1}{2} \times \frac{3}{8}$	Failure 7 days postop. Infected
15	Repeat B			Ostamer & intramed. pin	120°				Failure 7 days postop.
16	Dog C	26	Tibia	Ostamer	120°	+		$3\frac{1}{2} \times \frac{3}{8}$	Successful union 4 months postop. Infected
17	Dog D	29	Tibia	Ostamer & bone plate	120°			$3\frac{1}{8} \times \frac{3}{8}$	Successful union 3 months postop. Infected

FIG. 1

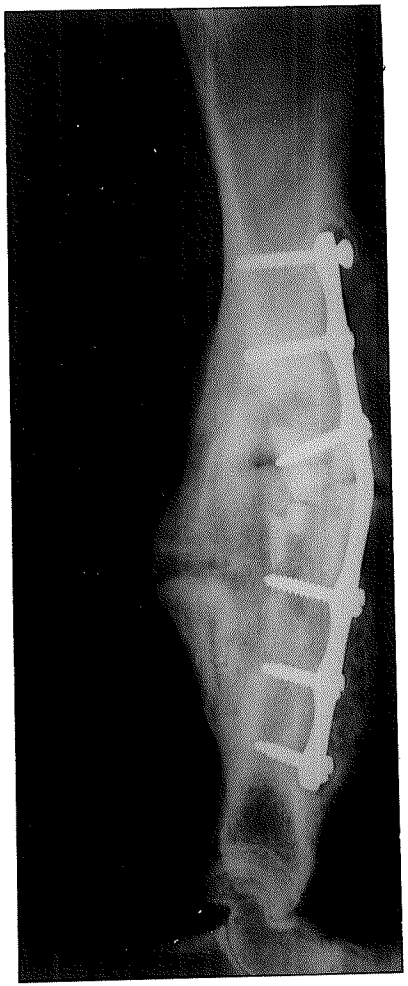
Radiographic results of Ostamer & Sherman bone plates in fractured sheep tibiae.
See Table I, p. 22.



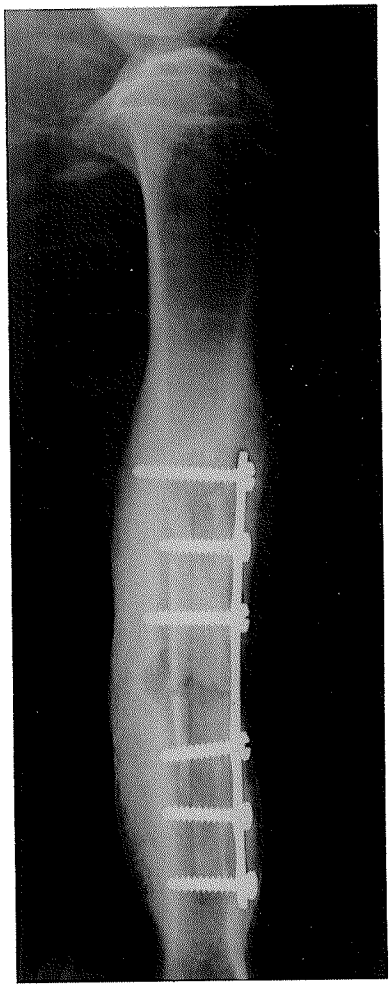
Sheep D
20 weeks postop.



Sheep E
14 weeks postop.



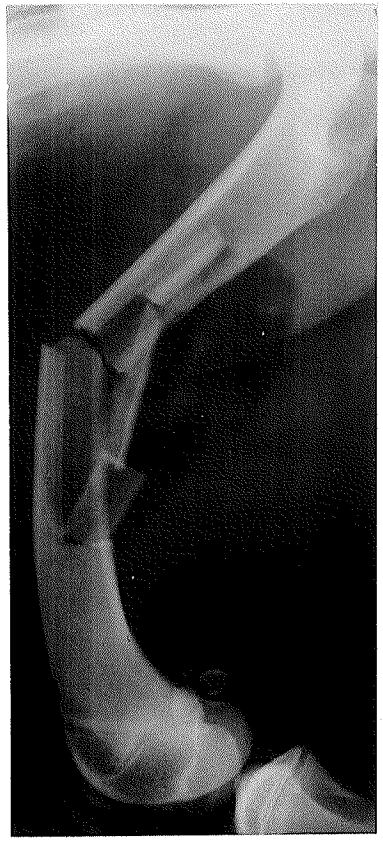
Sheep F
13 weeks postop.



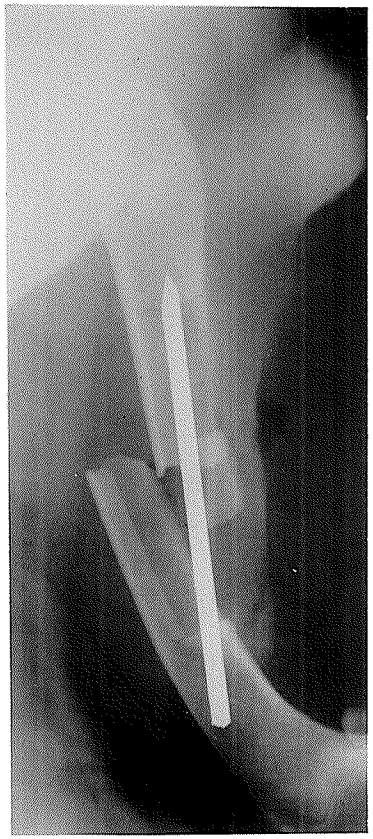
Sheep G
10 weeks postop.

FIG. 2

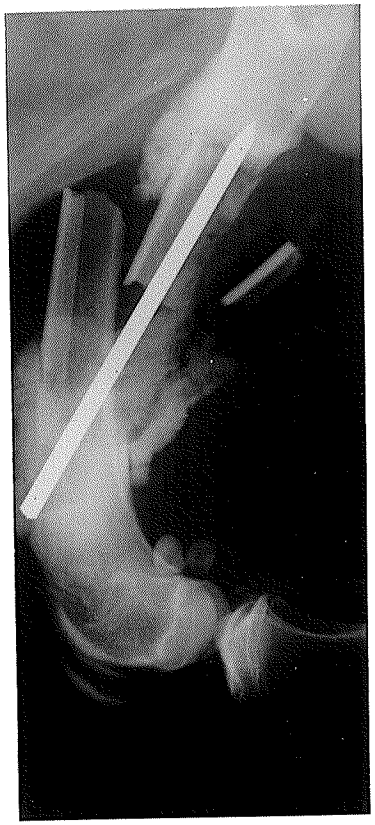
Radiographic results in dog A (procedures 12 & 13).
See Table I, p. 22.



Procedure 12
Ostamer
2 days postop.



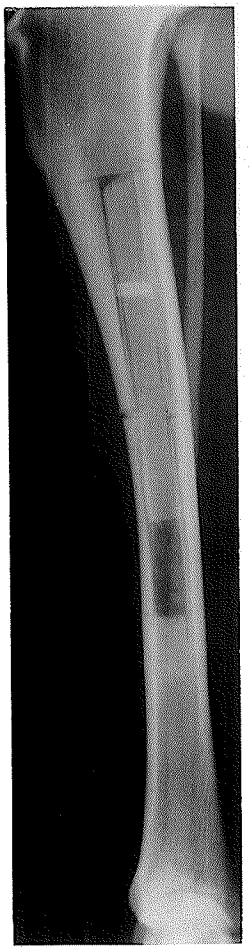
Procedure 13
Ostamer + intra-
medullary pin
4 days postop.



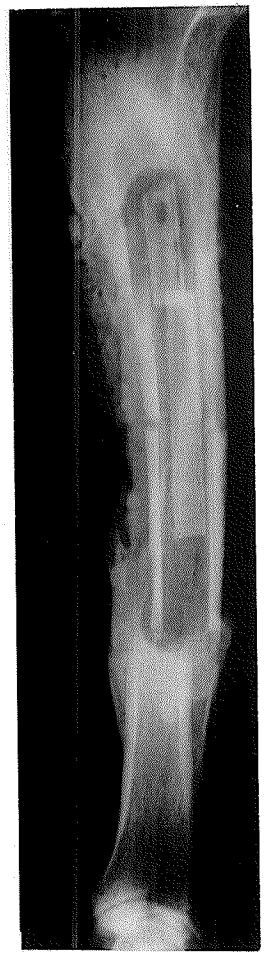
Procedure 13
4 weeks postop.

FIG. 3

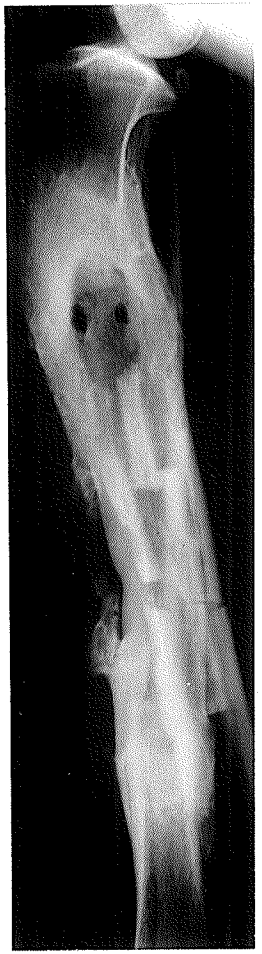
Radiographic results in dog C (procedure 16).
See Table I, p. 22.



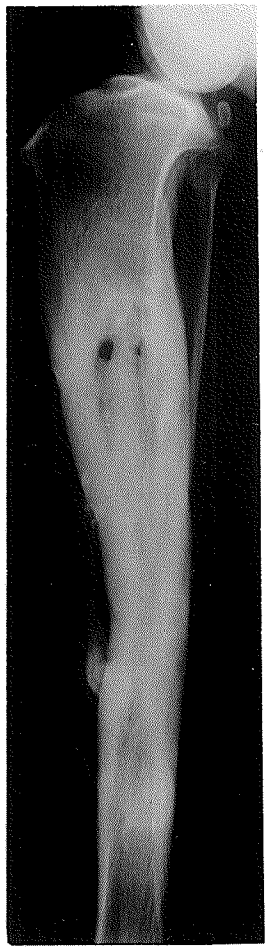
1 week postop.



7 weeks postop.



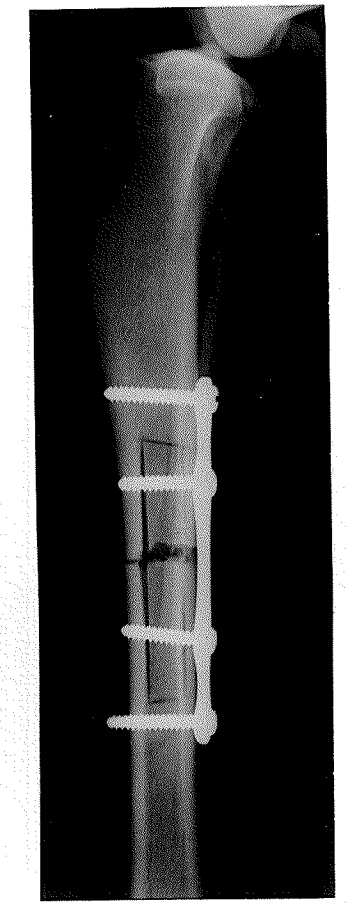
12 weeks postop.



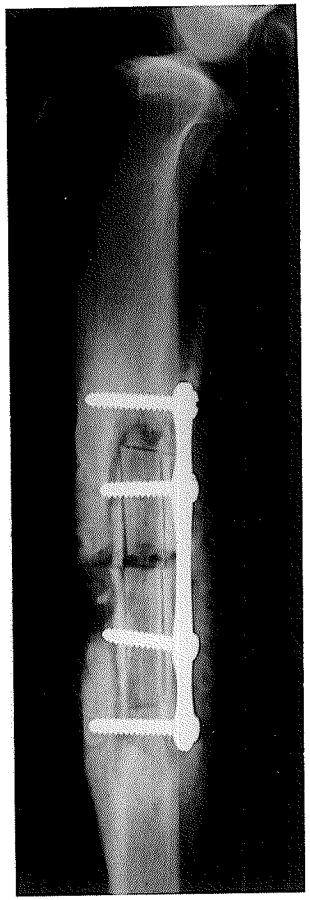
19 weeks postop.

FIG. 4

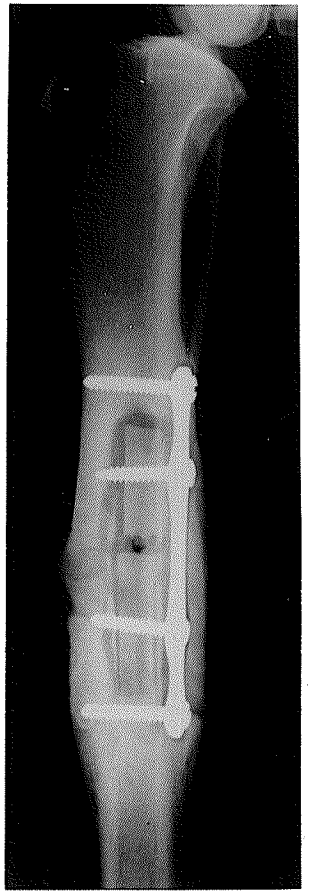
Radiographic results in dog D (procedure 17).
See Table I, p. 22.



1 week postop.



6 weeks postop.



12 weeks postop.

Experiment 2. : The subcutaneous implantation of Ostamer in rats.

The overlying skin in all the subcutaneous implants of Ostamer healed by first intention. There was considerable swelling at the implant sites for one to 2 weeks, more marked than in the simple control incisions. At 1 week the tissues were adherent to the implants and small blood vessels were apparent coursing over the surface of many of the implants. At no time were local fluid pockets observed around the implants.

Histological sections of the subcutaneous implants showed an initial, minimal, acute inflammatory reaction followed by fibrous tissue encapsulation of the implant evident at one week. During the 2nd - 4th week the fibrous capsule became more organized and a few foreign body giant cells were apparent. By this time the acute reaction had subsided and only occasionally was there evidence of a chronic lymphocytic inflammatory reaction. At 4 weeks the fibrous tissue had invaded only the outermost lacunae to a depth of 50 microns or less. At 5-6 weeks small blood vessels and capillaries could be seen in intimate contact with the implants. The Ostamer implants, in many cases, at approximately 20 weeks, showed histological evidence of early dissolution and break-up associated with a more vigorous fibrous tissue and vascular ingrowth. In all sections

examined the smaller fragments of Ostamer evoked a more marked tissue reaction.

This histological picture remained fairly constant over the observed period of 26 weeks. Only the outermost lacunae were invaded by fibrous tissue and in some instances small blood vessels and capillaries. None of the more central portions of the implants showed fibrous tissue ingrowth unless the implants were showing evidence of disintegration. In all observed specimens the central lacunae were either empty or filled with an amorphous material stained pink by eosin.

There was no appreciable change in size of the implants during the observed period of 26 weeks nor evidence of the development of neoplasia.

Experiment 3. : The implantation of Ostamer at tibial fracture sites in rats.

The overlying skin healed in all 42 fracture site implantations except 4, in which there was pressure necrosis of the overlying skin with partial extrusion of the Ostamer. Generally the position and alignment of the healed fractures was better in the control rats than in the experimental rats. This was thought to be due to the manipulation required in placing the implant in contact with the fracture site in the experimental series. The tubes of Ostamer remained in

more intimate contact with the fracture sites than did the onlay grafts but they also excluded the surrounding soft tissues and may thus have jeopardized normal callus formation.

All the tibial fractures with Ostamer implants united and the development of callus and subsequent union compared favorably with that seen in the control tibial fractures without implants and also recorded in the literature. (32,36,76,85 & 90) The foreign body giant cell reaction appeared more marked however. It was also noted whenever the Ostamer implant remained in intimate contact with the healing fracture that fibrous union, as well as bony union, occurred to a greater or lesser degree. The space occupying nature of the material also prevented dense bony union.

Ostamer provoked only a slight, local, acute inflammatory reaction followed by a peripheral rim of fibrosis apparent at 2 weeks. Neither the onlay grafts nor the tubes of Ostamer participated in the healing reaction.

Only the outermost lacunae in all implants observed between one and 38 weeks showed fibrous tissue ingrowth. The central lacunae remained empty or were filled with an amorphous pink staining material. A few sections at 38 weeks showed small "buds" of new bone occupying the outermost lacunae of the implant. None of the sections examined between 1 and 38 weeks showed any evidence of osteoblastic

activity within the closed lacunae of Ostamer even when the implant remained in intimate contact with bone.

There was no appreciable change in size of the implants and no evidence of neoplastic development.

FIG. 5

Subcutaneous implant of Ostamer at 1 week. Implant surrounded by granulation tissue and fibrous tissue invading the lacunae. Hematoxylin and eosin stain 100X.

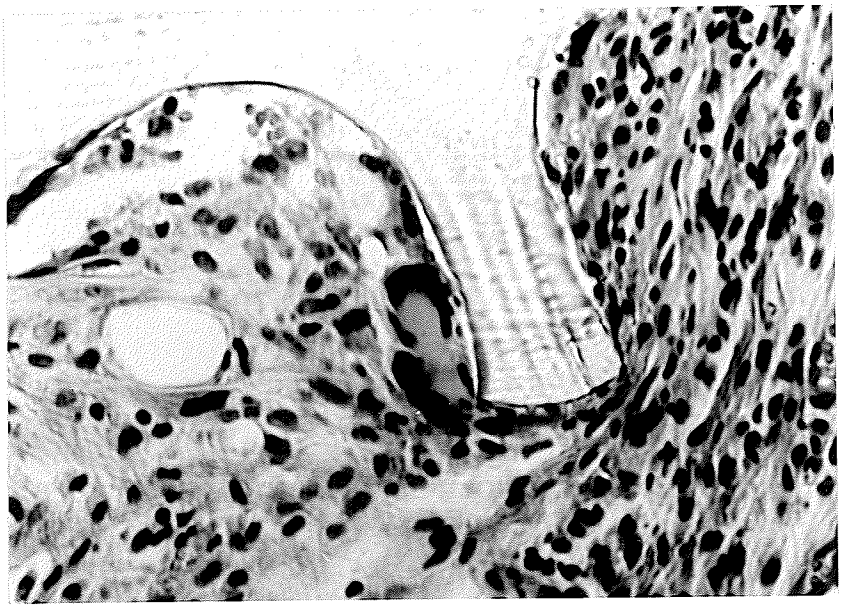


FIG. 6

Subcutaneous implant of Ostamer at 1 week. Multinucleated foreign body giant cell in intimate contact with Ostamer spicule. Hematoxylin and eosin stain. 400X.

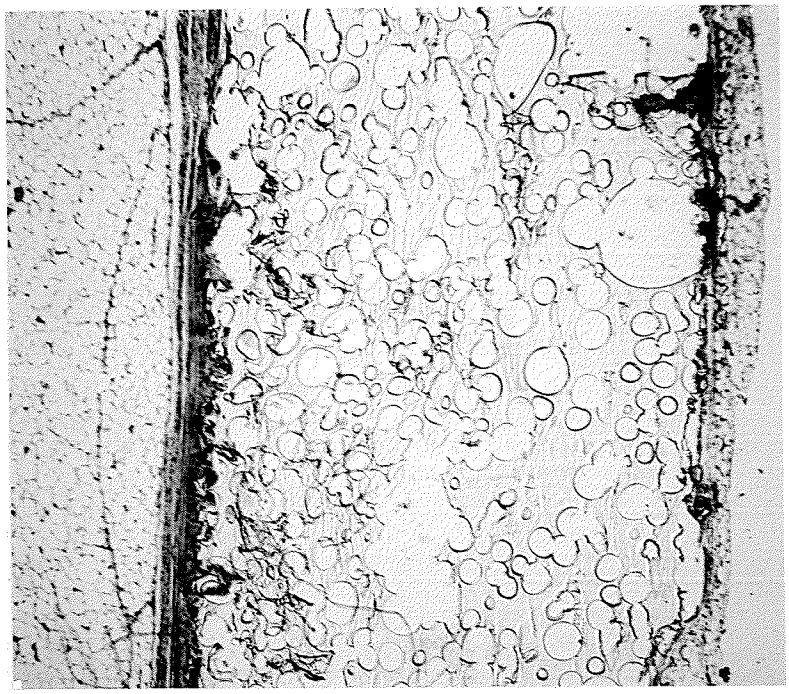


FIG. 7

Subcutaneous Ostamer implant at 2 weeks. Implant encapsulated with minimal soft tissue ingrowth into the outermost lacunae. Hematoxylin and eosin stain. 40X.

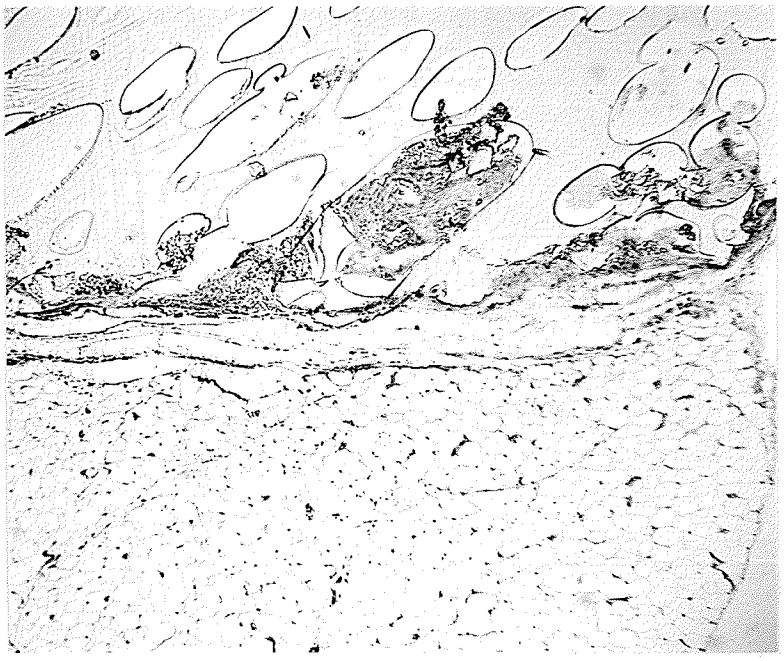


FIG. 8

Subcutaneous implant of Ostamer at 14 weeks. Fibrous tissue ingrowth limited to the outermost lacunae of the implant. Central lacunae empty. Note that the lacunae in the implant are "closed" with few interconnecting channels. Hematoxylin and eosin stain. 40X.

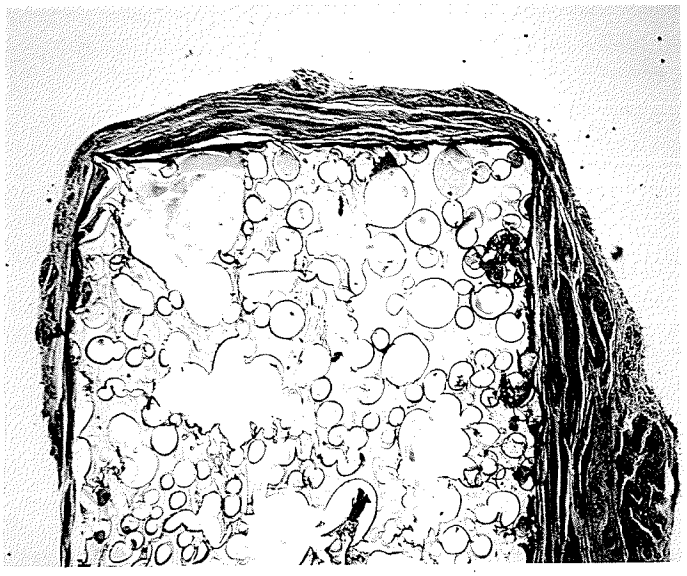


FIG. 9

Ostamer implant at 21 weeks. Implant well encapsulated with no evidence of soft tissue ingrowth. Hematoxylin and eosin stain. 30X.

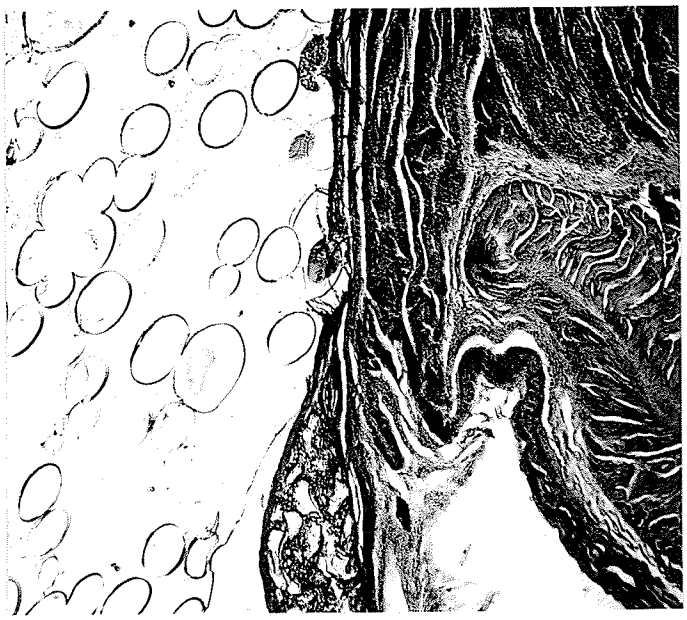


FIG. 10

Ostamer implant at 21 weeks. Muscle shows no tendency to invade the implant. Narrow fibrous tissue capsule with more marked reaction around the smaller Ostamer fragments. Hematoxylin and eosin stain. 30X.

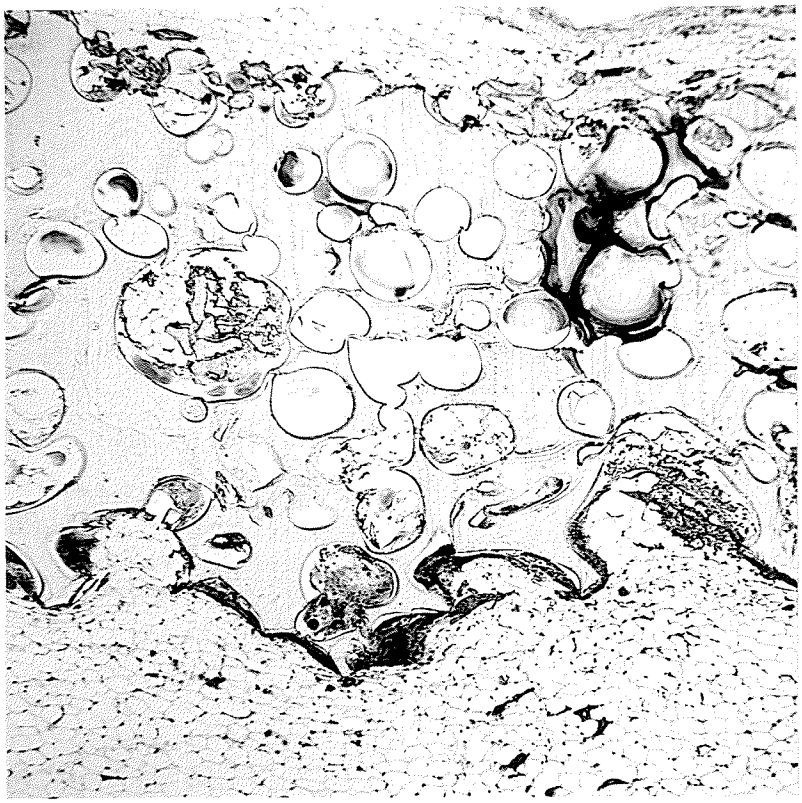


FIG. 11

Subcutaneous implant of Ostamer at 22 weeks. Fibrous tissue ingrowth limited to only the outermost lacunae. Considerable amorphous pink staining material in central lacunae. Hematoxylin and eosin stain. 50X.

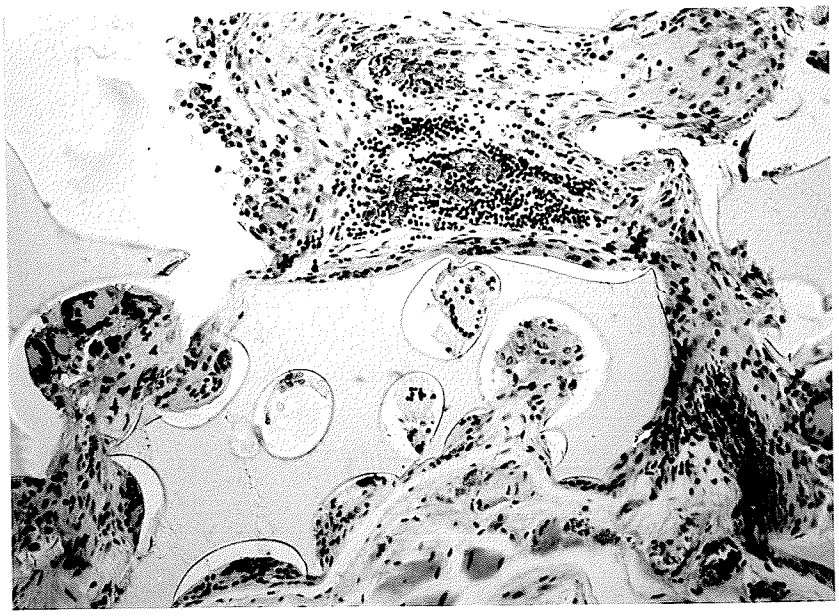


FIG. 12

Subcutaneous implant of Ostamer at 22 weeks.

Multinucleated foreign body giant cell reaction.

Hematoxylin and eosin stain. 150X.

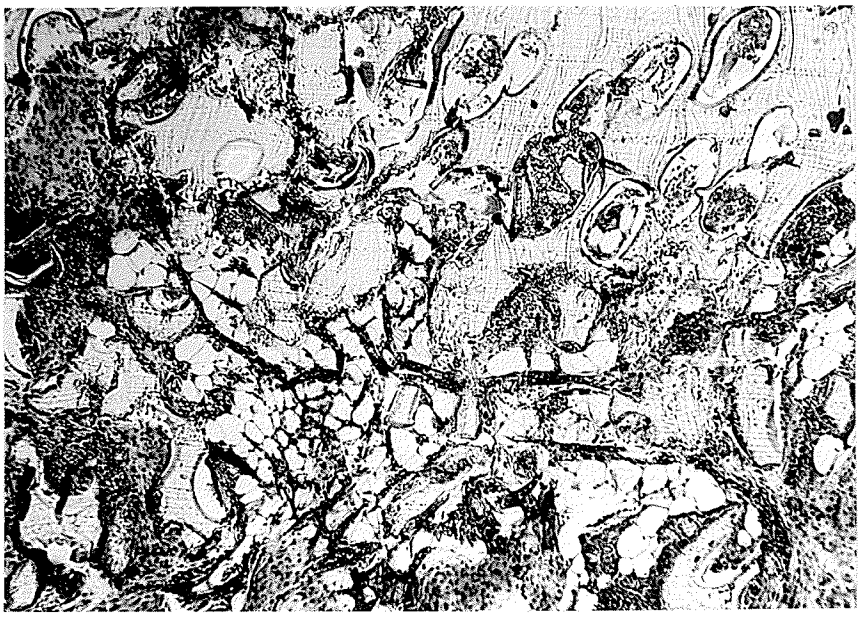


FIG. 13

Subcutaneous Ostamer implant at 24 weeks. Ostamer breaking up with vigorous fibrous tissue and small blood vessel ingrowth. Hematoxylin and eosin stain. 50X.

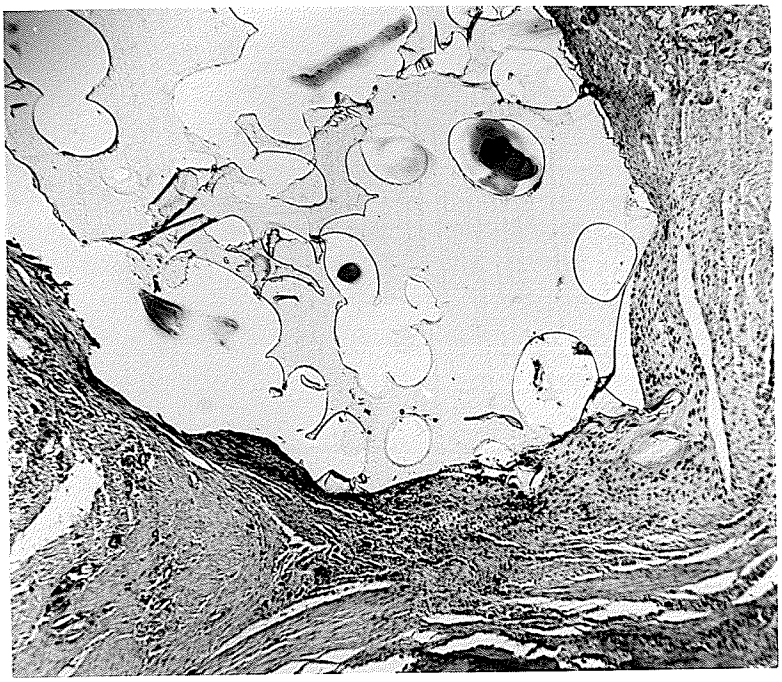


FIG. 14

Tibial fracture site implant of Ostamer at 3 weeks. Ostamer is not taking part in the healing reaction and there is no evidence of soft tissue or osseous ingrowth. Hematoxylin and eosin stain. 40X.

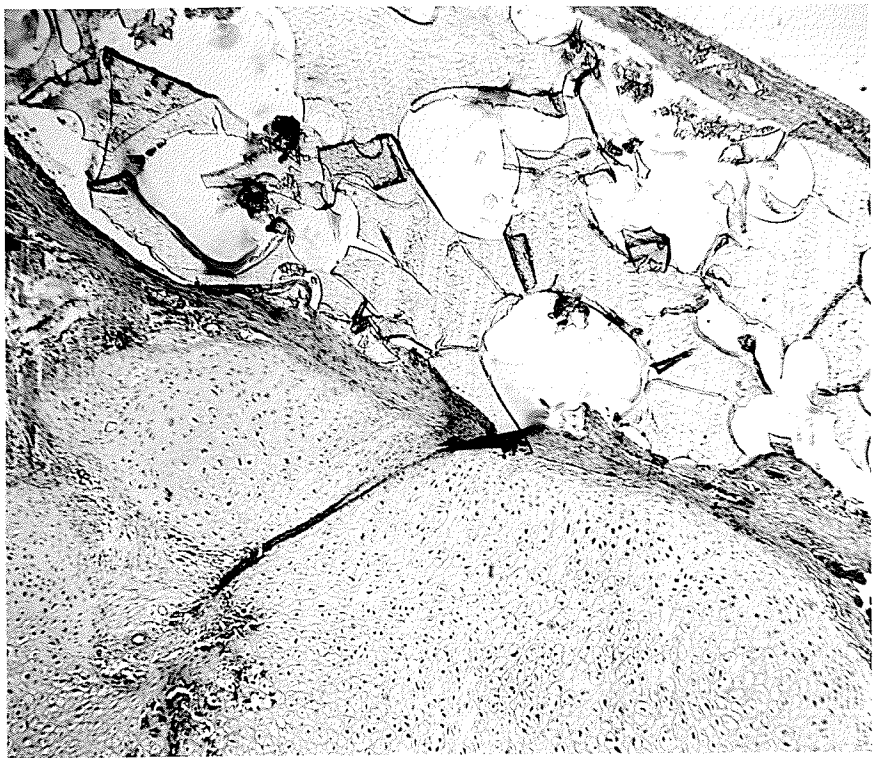


FIG. 15

Tibial fracture site implant of Ostamer at 3 weeks. Implant well encapsulated. Cartilage shows no tendency to invade the lacunae. Hematoxylin and eosin stain. 40X.

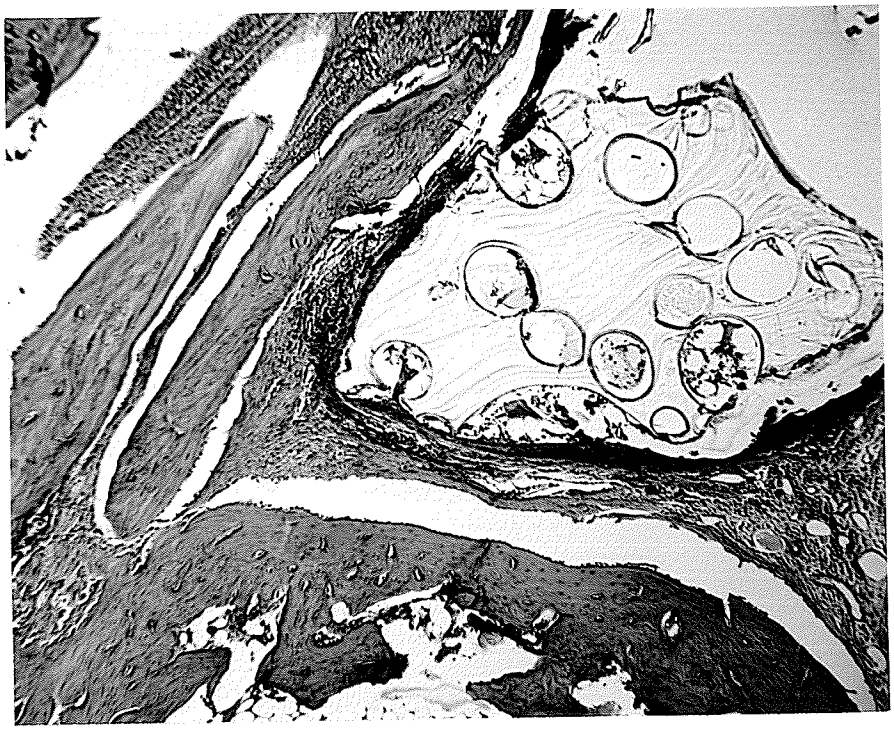


FIG. 16

Tibial fracture site implant of Ostamer at 13 weeks. Implant well encapsulated by inflammatory reaction. Hematoxylin and eosin stain. 40X.

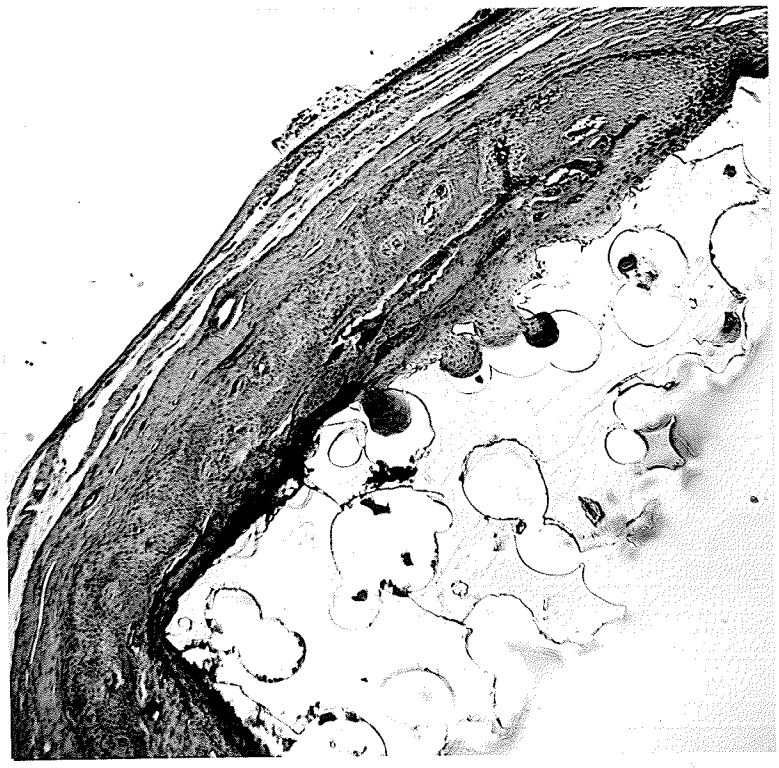


FIG. 17

Tibial fracture site implant of Ostamer at 21 weeks. Buds of new bone invading the outermost lacunae of the implant. Hematoxylin and eosin stain. 40X.

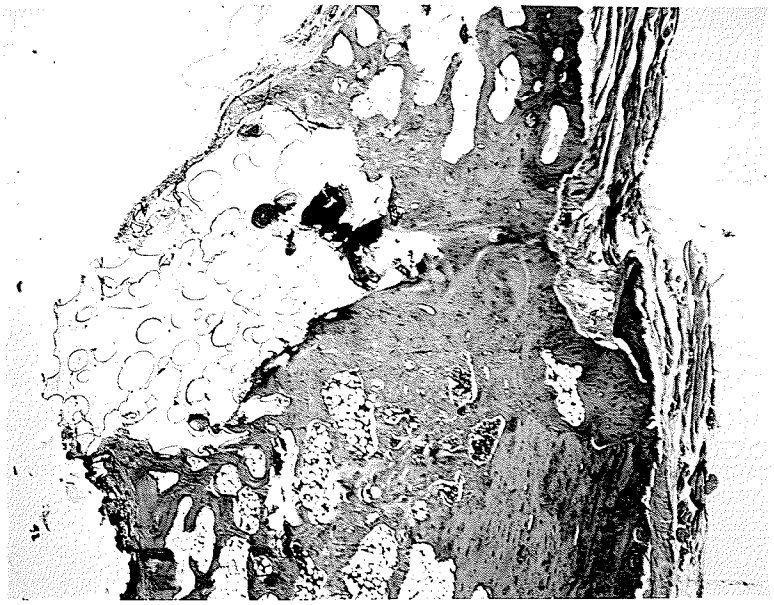


FIG. 18

Tibial fracture site implant of Ostamer at 34 weeks. Ostamer has not taken part in the healing reaction and appears to be preventing union of the fracture on one side. Bone invades only the outermost lacunae of the implant. Hematoxylin and eosin stain. 15X.

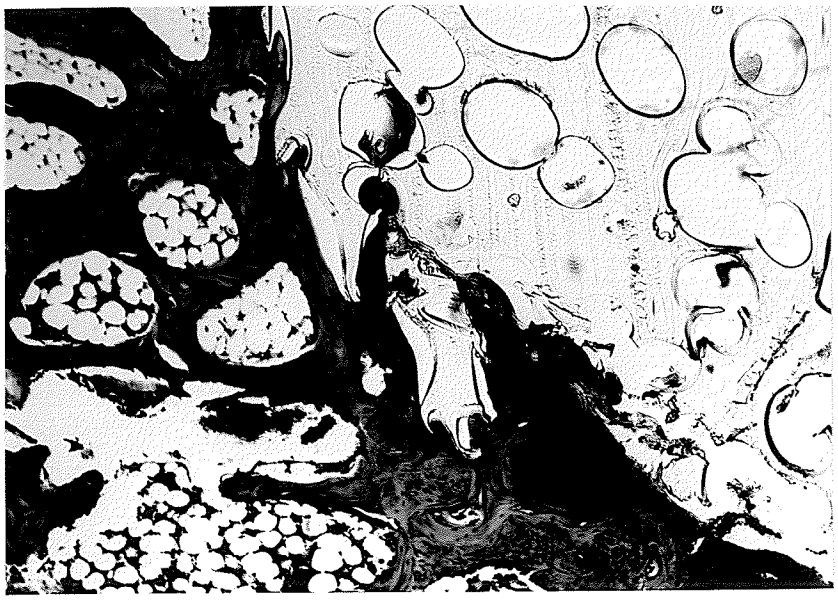


FIG. 19

Tibial fracture site implant of Ostamer at 34 weeks. New bone invading the outer lacunae of the implant. Hematoxylin and eosin stain. 50X.

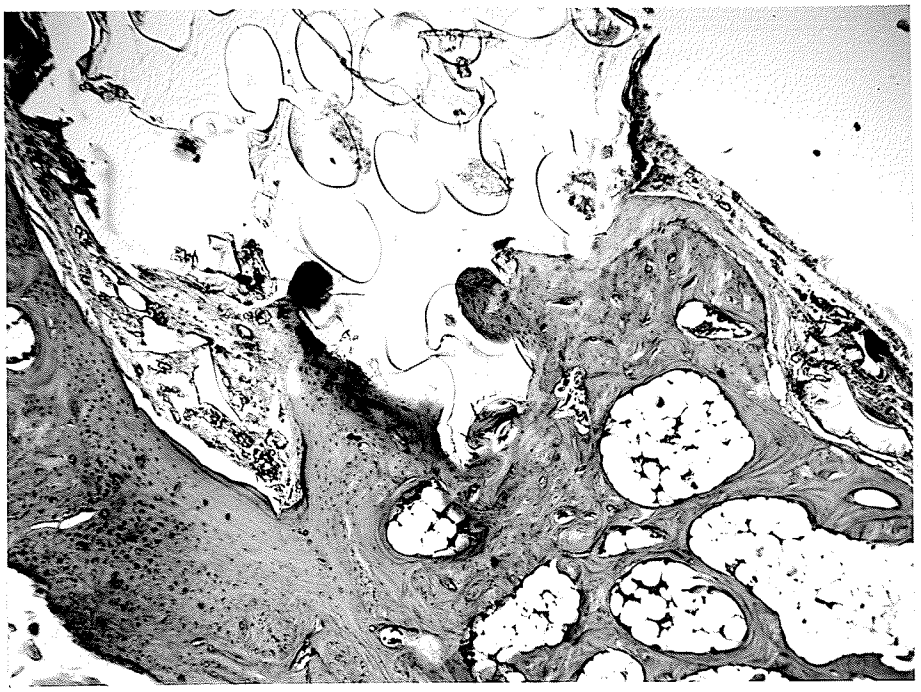


FIG. 20

Tibial fracture site implant of Ostamer at 38 weeks. Ostamer in intimate contact with new bone. Outermost lacunae show bony invasion. Hematoxylin and eosin stain. 40X.

CHAPTER V

Discussion

Ostamer is to be regarded as the prototype of future materials which are primarily adapted to orthopedic use. These early trials have been with commercial adhesives which are neither chemically nor physically adapted to use in the human body. It is only recently that the medical field has become aware of the potentialities of these newer materials and there is consequently a wide gap in our technical knowledge. It took 50 years or more of intensive experimental investigation to find a metal suitable for implantation in the human body and it will probably take as long, or longer, to find a plastic material embodying the properties we seek.

The use of Ostamer in human material at our present level of knowledge is open to severe criticism and perhaps tragedy. Its early effect on healing tissues appears minimal; but the very late effects are still unknown. The use of Ostamer alone is a very different problem from the use of Ostamer in conjunction with the inert metals.

There are many technical errors possible in using Ostamer. The physical properties of the final product are dependent on proper temperature control and thorough mixing. Addition of small amounts of water, serum and blood during

the in vivo reaction are known to alter its physical properties, particularly tensile strength. Many plastics are known to "leach out" one or more of their constituents and this possibility is compounded in the case of Ostamer where the reaction takes place in vivo. Unreacted or even partially reacted prepolymer and or catalyst may cause tissue reactions, react with the inert metals or form degradation products with harmful effects.

The final product in all our experiments with large animals was very brittle and had little, if any, adhesive properties. It is difficult, if not impossible to obtain an absolutely dry, fat-free, blood-free field in operative orthopedic surgery and not jeopardize or do harm to the tissues that one is handling. Any one of these factors will serve to compromise the adhesive properties of Ostamer. The problem of adhesion in vitro is a complex one (3 & 4) and in vivo the problem is even more complex.

It is difficult at this time to conceive of any foreign, inert material bonding or adhering to a living, dynamic tissue such as bone. Bone is continually undergoing dissolution and recrystallization, in fact surface phenomena dominate the chemical behaviour of bone mineral. (7 & 69) Furthermore bone resorption occurs to some extent in all acute fracture sites and this will further jeopardize any bonding or adhesion.

The large quantity of foreign material necessary across the fracture site in order to provide sufficient tensile strength and stability prevents normal hematoma and subsequent callus formation occurring at the fracture. Extensive exposure is necessary with the present method of application and it lies at the extremes of operative interference. The reaction occurring after mixing the Prepolymer and Catalyst is exothermic to a variable degree and this may further harm tissues in intimate contact with the reactants.

Finally in our zealous haste to mobilise orthopedic patients the importance of soft tissue healing is too often overlooked.

Ostamer is reported to be absorbed over a period of 1-2 years in vivo (29, 92 & 93) and to have a biological half-life in experimental animals of 10 months. (34) It is not known how it is mobilised. Tagging with radioactive tritium in experimental animals and one patient have shown it to be excreted in part in the urine and faeces.

Continued careful and thorough investigation is warranted before Ostamer or related materials are relegated to further use in humans. John T. Scales phrased it very succinctly when he said:

"Assuming that a material is biologically compatible and mechanically suitable, the problem remaining is the union of living with dead, inert material."[1.]

1. John T. Scales, Problem of Materials in Bone Replacement, J. Bone Joint Surg. (Brit.), 35: 6, 1953.

CHAPTER VI

Summary & Conclusions

1) The use of Ostamer in experimental fractures of long bones in large animals failed to substantiate the claims that it acts as a bone adhesive.

2) Ostamer acts as an intramedullary rod conforming to all the bony irregularities within the marrow cavity and thus providing some measure of mechanical stability.

3) Used alone without adequate ancillary metal fixation it is not of sufficient strength to allow early ambulation of quadruped animals.

4) When used in conjunction with internal metal fixation or external splints the same criteria for mobilisation and weight bearing should be used as in other standard methods of fracture treatment.

5) Callus formation is not affected by its proximity to Ostamer but it is delayed due to the space occupying nature of the material and its fibrous tissue stimulating property.

6) Ostamer evokes minimal tissue reaction and minor foreign body giant cell reaction in rats observed over a period of 38 weeks.

7) Although it may serve as a framework for fibrous tissue and small blood vessel ingrowth this is limited by the closed lacunar system of Ostamer.

8) This study failed to show histological evidence of osteoblastic activity within the closed lacunae of Ostamer.

9) Ostamer offers no advantages over our presently accepted methods of fracture treatment and because of the many complications occurring in this study and reported in the literature its use at the present time should be limited to experimental investigation in animals.

10) Further experimental research on Ostamer and related materials is required before they can be accepted for use in the human organism.

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