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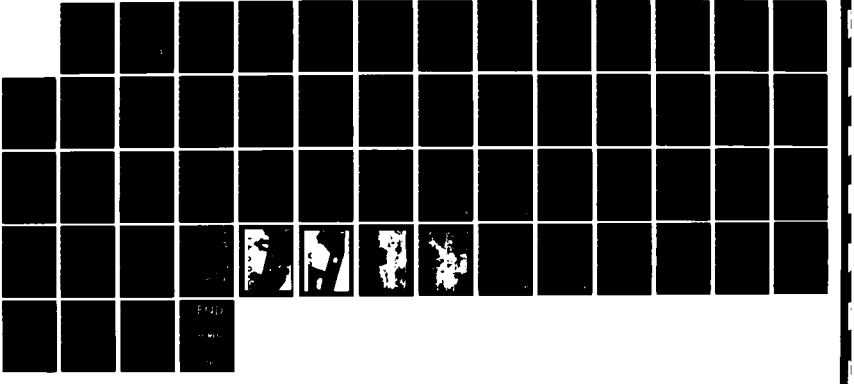

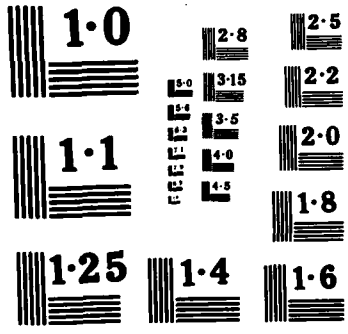

# BIODEGRADABLE BONE REPAIR MATERIALS:

# SYNTHETIC POLYMERS AND CERAMICS

by

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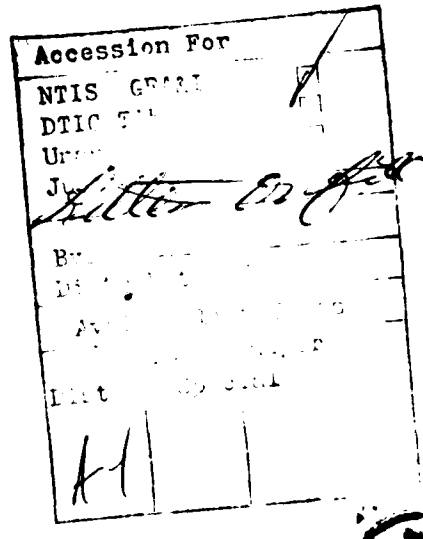
## ABSTRACT

Many different materials have been used by orthopedic and maxillofacial surgeons to repair bony deficiencies. This review was limited to those materials that have been shown to be tissue-tolerant and biodegradable and included certain synthetic polymers and ceramics. Several possible applications for these agents were offered. Some terms and concepts were discussed that were germane to an understanding of polymers and ceramics.



### Key Words

Biodegradable synthetic polymers, biodegradable ceramics, bone repair.

## I. INTRODUCTION

The architectural reconstruction of osseous defects, such as sequellae of infection-induced bony sequestration, developmental malformations, surgical resections, or traumatic avulsions, confront us with an extremely challenging orthopedic task. The need to initiate bone regeneration in order to restore structural deficiency has inspired the development and application of a vast number of materials. Many of these have been reviewed.[33]

Bone repair materials may be classified as either manmade or of natural origin. Manmade agents include certain metals, alloys, ceramics, and synthetic polymers. Those of natural origin consist of bone (i.e., autogenous, allogeneic), bone derivatives (i.e., collagen, bone morphogenetic protein, and other bone matrix proteins), and natural polymers (i.e., collagen). Manmade repair materials are either biodegradable or nonbiodegradable, whereas natural origin compounds will biodegrade completely in the body.

The purpose of this review is to discuss certain biodegradable, manmade (synthetic) polymers and ceramics. A few terms and concepts will be defined, and various properties germane to these materials will be discussed in order to understand the current or potential use of these agents for bone repair.

## II. POLYMERS

Regardless of their origin, most polymers are macromolecules composed of many repeating units (monomers) (Fig.1) that have

carbon atom backbones, although oxygen, nitrogen, silicon, and sulfur also can be present (Table). The reaction that produces a polymer from monomers is known as polymerization. When identical monomers react, a homopolymer is formed (Figs.1,2), whereas a combination of two different monomers can produce a random copolymer, a block copolymer, or a graft copolymer (Fig.3). Poly-para-dioxanone (PDS®) and polyglycolic acid (Dexon®) are synthetic homopolymers used as biodegradable sutures (Figs.2,4).[25,32,-40,49,58,60] The copolymer of polylactic acid and polyglycolic acid (Vicryl® and Polyglactin®) is another type of biodegradable suture (Fig.5).[11,61]

Terpolymerization is defined as a process whereby three different monomers are reacted together, and multi-component copolymerization produces polymers composed of four or more different monomers. Such systems have no current applications in orthopedics.

The physical and chemical properties of the polymers that are used in maxillofacial and orthopedic surgery play an extremely important role in determining how the polymer will function in the body. Some properties of polymers that govern in vivo behavior are molecular orientation, geometric isomerism, conformation, and configuration (Figs.6,7,8).[45] The regularity of the configuration of substituent members surrounding the polymer's backbone atoms (such as a pseudo-chiral carbon) determines

a property known as tacticity (Fig.9), which affects the body's response to that polymer.

Polymers are polydispersions or mixtures of differently sized molecules, therefore, polymer chemists have devised the concept of average molecular weight.[56,63] There are three types of average molecular weights: number-average ($\bar{M}_n$), determined by colligative properties; weight-average ($\bar{M}_w$), determined by light scattering measurements; and viscosity-average ($\bar{M}_v$), obtained from viscosity measurements. Viscosity-average molecular weight is a function of the polymer.[63] Branched polymers are usually more compact than their linear analogs and will, therefore, exhibit lower viscosity.[56] In vivo, high average molecular weight polymers that are highly viscous will undergo slower biodegradation than those with lower molecular weight and lower viscosity.

Polymeric materials may be characterized according to two thermal properties: crystalline melting temperature and glass transition temperature. The crystalline melting temperature (Tm) defines the point where the polymer flows. A rigid, branched polymer with many cyclic units would have a high Tm, whereas a flexible, chain polymer would have a low Tm. The glass transition temperature (Tg) is the temperature at which the polymer acquires the properties of a glassy state; it becomes brittle, stiff, rigid. Tm and Tg are determined by similar factors. Relatively immobile polymer chains favor a high Tg, while mobile

chains are associated with a low Tg. For example, polymethyl methacrylate, a nonbiodegradable, relatively rigid, branched polymer has a Tg of 105°C, whereas the biodegradable, linear polyester poly(DL-lactide) has a Tg of 57°C. The values of the Tm and Tg are good predictors of a polymer's mechanical properties at any particular temperature.

We have defined some terms and mentioned various properties of polymers that have been helpful in guiding our research on osseous repair. For a detailed review of polymer chemistry we have referenced several excellent textbooks.[2,26,31,56,63,65]

## III. TISSUE REACTIONS TO POLYMERS

Various local and systemic reactions can be elicited by the implantation of a polymer. Local tissue responses to biodegradable polymers depend on the rate of degradation and the biocompatibility of the components and degradation products of the polymer. In the case of the slowly biodegradable, biocompatible 50:50 poly (DL-lactide-co-glycolide) copolymer, implantation of a small porous cylinder in a rodent muscle pouch typically induces a transient acute inflammatory response in the adjacent tissue. At 72 hours postimplantation (Fig.10), one observes a narrow zone of fibrinous exudate and edematous granulation tissue enveloping and penetrating the interstices of the implant. There is a mixed infiltrate of polymorphonuclear and mononuclear leukocytes and a modest degree of fibroblast proliferation. Focal degenerative in muscle fibers indicated by swelling, loss of peripheral nuclei,

and altered staining characteristics are probably the result of recent surgical manipulation and/or mechanical irritation caused by the implant. By 7 to 14 days postimplantation (Figs.11,12), progressive maturation of the granulation tissue results in a thin, cellular fibrovascular capsule, incorporating variable numbers of lymphocytes and plasma cells. On the inner aspect of this capsule, histiocytes and a few multinucleated giant cells line the external surface and penetrate the interstices of the implant. At 28 to 35 days postimplantation (Fig.13), a thin rim of histiocytes interspersed with increasing numbers of multinucleated giant cells line the implant surface and interstices. This finding is characteristic of a chronic resorption response to an insoluble, biocompatible polymer. The absence of a significant infiltrate of lymphocytes and/or plasma cells around the implant at this stage of the response attests to the negligible immunogenicity of the copolymer in rat muscle.

There have not been any reports in the literature describing adverse systemic responses to the synthetic biodegradable polymers used for sutures and experimental bone repair. Possible problems could arise if unreacted additives such as polymerization initiators or plasticizers were released into the blood stream as the polymer degraded. These agents could be cytotoxic in high concentration. The authors have not observed deleterious effects from degrading homopolymers or copolymers of polylactic acid and polyglycolic acid.

## IV. BIODEGRADABLE SYNTHETIC POLYMERS

Kopececk and Ulbrick have written an excellent review of experimental and clinically applied biodegradable polymers.[43] Our discussion is limited to polymeric materials that have been investigated for bone repair.

The class of biodegradable polymers known as polyesters has had applications in both medicine and dentistry. Polylactic acid (PLA), polyglycolic acid (PGA), and poly-paradioxanone are three examples of polyesters that have been manufactured in the form of biodegradable sutures.[25,45,49,60] Characterization, degradation rates and pathways, and biocompatibility of these agents have been described.[3,7,8,12,14,15,28,36,44,46,47,52,70] Cutright, Hunsuck, and Beasley used PLA sutures (0.35mm in diameter) for fixation of mandibular symphyseal fractures in Macaca mulatta (rhesus) monkeys.[17] Cutright and his colleagues reported that the fractures healed in a normal manner, the PLA sutures elicited a minimal inflammatory response, and because they were biodegradable, it was not necessary to remove them. PLA in the form of 1.5mm thick sheets was used by Cutright and Hunsuck (1972) to treat blowout fractures in 12 Macaca mulatta (rhesus) monkeys.[16] The authors reported normal eye movements by the monkeys, resorption of the PLA sheets by phagocytic and giant cells with villous projections, and residual PLA after 38 weeks.

Nelson, Stanford, and Cutright prepared $1.5mm^3$ defects in the tibias of 48 adult C.R. Nelson rats.[55] Animals were divided

evenly into four groups and treatment consisted of 1. 50PLA:50PGA in a spheroidal form; 2. 1:1 mixture of spheroidal 50PLA:50PGA plus biodegradable $Ca_3(PO_4)_2$ particles (<0.125mm in diameter); 3. $Ca_3(PO_4)_2$ particles; and 4. no treatment. Nelson and his colleagues determined by histologic examination that at 42 days complete bony repair had taken place in the untreated and $Ca_3(PO_4)_2$ treated groups. There was incomplete healing by 42 days of defects treated with 50PLA:50PGA and 50PLA:50PGA plus $Ca_3(PO_4)_2$. Conflicting results were obtained in experiments recently performed in our laboratory. In our experiments, a copolymer of 50:50 poly (L(+)-lactide-co-glycolide) was prepared in the form of disks for repairing 1.95mm diameter cortico-cancelllous tibial defects in 25 adult Walter Reed rats.[34] In the second experiment, a proteolipid (diphosphoinositide-lysozyme) was added to a 1:12.5 w/vol of 50:50 poly (DL-lactide-co-glycolide) and methylene chloride to produce 1.95mm disks (1). In the same experiment, disks were made from 50:50 poly(DL-lactide-co-glycolide) copolymer. Bilateral cortico-cancellous wounds (1.95mm in diameter) were prepared in tibias of 180 adult Walter Reed strain of rats that were divided equally into three treatment groups: 1. copolymer plus proteolipid, 2. copolymer, and 3. no implant (control). Experimental sites (defects and contiguous bone) were recovered and processed for histomorphometry in both studies to evaluate bone repair rates. The histomorphometric analyses indicated: 1. the proteolipid-copolymer combination produced the most

rapid healing rate; 2. elements of osseous repair were in greater abundance in the copolymer-treated group than in the nontreated controls and; 3. partial degradation of the implant disks was evident at three days. The histomorphometric data that were reported in our experimental studies did not agree with the histological results described by Nelson and his associates. Possible reasons for this disparity will be discussed later in the review.

Because of the promising results observed in rat studies, we prepared rectangular shaped, rigid, porous blocks from a 1% w/w ratio of proteolipid to 50:50 poly (DL-lactide-co-glycolide) for treatment of mandibular discontinuity defects in adult dogs.[35] Radiographic and clinical evidence indicated that by three and one-half to four and one-half months following treatment there appeared to be osseous union (Figs.14a,b and 15a,b). Histologically, the copolymer had completely biodegraded by six months.

Aside from a possible alternative to a bone graft or implant, biodegradable polymers may be useful as internal fixation devices. Many practitioners use metal internal fixation plates that are considerably stiffer than bone, and this has an adverse effect on osseous remodeling.[22,53] Furthermore, a second surgical step often is required to remove the metal device. This procedure, and stress protection induced osteopenia subjacent to the plate, could be obviated by designing biodegradable polymeric devices and screws with an elastic modulus similar to bone.[68] To

determine if this was a feasible approach for fixation, Getter and his associates created fractures in mandibles of six adult beagles.[27] After fracture reduction, fixation was accomplished using biodegradable PLA plates and screws. The authors reported that by 24 weeks post insertion the plates could not be palpated, and at 32 to 40 weeks fracture sites were indistinguishable histologically from contiguous bone. Tortorelli performed a similar experiment and determined that PLA plates warped as they biodegraded.[66] The retaining screws of PLA were loosened and pulled from the bone and rigid fixation was lost. To prevent warping, reinforcement of PLA plates with high modulus carbon fibers has been attempted; however, problems with bioresorbability of fibers militate against such a design.[57] Christel and his colleagues prepared biodegradable fibers from PGA that were embedded within L-PLA plates for added strength.[6] This combination was used with limited success for rigid internal fixation to treat tractures in tibias of sheep. Bioresorbable calcium metaphosphate glass fibers with flexural strengths and moduli acceptable for PLA reinforcement are being developed and studied through collaborative efforts of the United States Army Institute of Dental Research and the Southern Research Institute. As an alternative to reinforcing fibers, Tonc has produced PLA with high inherent viscosities in the range of 3.6 to 7.1.[68] He maintains that high viscosity PLA fixation plates retain high strength for up to 8 to 12 weeks following implantation.

## V. DEGRADATION

Virtually all polymers are susceptible to degradation by heat, oxidation, mechanical perturbation, hydrolysis, enzymatic action, or electromagnetic radiation.[44,56] The process by which the alpha-polyesters such as PLA, PGA, and poly-para-dioxanone biodegrade is principally by hydrolysis (nonspecific hydrolytic scission) (Figs.16a and 16b).[28,43,44,52,69] The lactic acid that is generated when PLA degrades become incorporated in the tricarboxylic acid cycle and is excreted by the lungs as carbon dioxide and water (Fig.17).[3,34] PGA, in addition to being degraded hydrolytically, also is broken down by nonspecific esterases and carboxy peptidases which produce glycolic acid monomers.[7,8,69] Monomeric units of glycolic acid can be excreted in the urine or can be enzymatically converted by glycolate oxidase to glyoxylate which reacts with glycine transaminase. The glycine that is generated can be used for the synthesis of serine which can enter the tricarboxylic acid cycle after transformation to pyruvate (Fig.18).[34]

Several factors govern the rate of hydrolytic scission of polyesters. Kulkarni et al. reported that in tissue culture medium poly(L(+)-lactic acid) is less soluble and less susceptible to degradation than is a racemic mixture.[45] The degree of crystallinity of polymers can affect the rate of water sorption, therefore, the crystalline L form of PLA retards water sorption and degrades more slowly than the less crystalline racemic

form.[28] Copolymers of the alpha-polyester class are less crystalline than their constituent homopolymers and, consequently, degrade more rapidly.[52]

The rate at which PLA:PGA copolymers degrade within the body also depends upon the molar ratio of lactic acid to glycolic acid (Figs.19 and 20).[3,14,52] Methyl groups on the repeating lactic acid units of PLA:PGA protect carbonyl carbons from tissue fluid. The process of lactic acid hydrolysis, consequently, is less rapid than for the glycolic acid units of the copolymer. Therefore, copolymers rich in lactic acid generally degrade more slowly than copolymers rich in glycolic acid.[14] In addition to monomer molar ratios, the sequence of lactic and glycolic acids along the linear chain influences the rate of biodegradation. This is one reason why copolymers of identical molar ratios of lactic and glycolic acids will not degrade at identical rates. For example, it is possible to have blocks of pure lactic acids and pure glycolic acids along a PLA:PGA chain. It also is possible to have alternating lactic acid and glycolic acid units. In both examples the molar ratios of monomer acids may be the same, however, each copolymer will undergo hydrolytic scission at a different rate. These two examples are extremes, one being a block sequence, the other being an alternating sequence. In fact, sequences are probably most often random, and such variability is one of the reasons why there has been disparity in the

literature concerning reported degradation rates of PLA:PGA copolymers.

The sequence of monomers within a copolymer is referred to as the sequence distribution or microstructure of the copolymer. This property is affected primarily by the ability of a monomer to react with itself in contrast to its co-monomer.[9] This propensity is known as the reactivity ratio of the monomer, and it is influenced by the reactive conditions of temperature and catalyst type and level.

The disagreement in the literature concerning absolute values for PLA and PGA homopolymer and copolymer degradation rates can be attributed to the factors mentioned and to polymer variability caused by diverse molecular weight ranges and morphology differences. Furthermore, the physical appearance and characteristics of the end product polymer play a significant role in determining its behavior. For example, in the studies by Hollinger[33,34], implants that were rigid, porous disks had a beneficial effect on osseous repair, whereas Nelson and his associates[55] used spheroidal particles that did not aid in bone regeneration. A positive piezo electric bone healing effect could be generated when a solid implant rather than an amorphous particulate mass is used for repair. In addition, the Nelson group did not describe the copolymer's chemical characteristics in the detail that Hollinger did; therefore, while molar ratios may have been identical, there is no way of knowing if any other similarities existed.

Aside from spheroidal and porous configurations, a smooth, glassy, dense structure (such as the bone plates used by Getter et al.) or film could be produced.[27] Such diversity in physical character leads to differences in surface area available for hydrolysis. That is why degradation rates for polyester suture material differ from cylinders or plates (Fig.21). As the surface area of the polymer increases per its unit volume, the opportunity for hydrolytic scission increases. A porous block, therefore, will degrade more rapidly than a similarly sized glassy and dense block. And, of course, a large implant will be broken down by the body more slowly than will a small implant.

The location where the polymer is placed also will have an effect on degradation. If a biodegradable polymer were to be placed in a highly vascular area subject to active function, its degradation rate would be more rapid than if it were put into a relatively avascular, passive function site.

## VI. BIODEGRADABLE CERAMICS

The list of resorbable, inorganic, alloplastic materials that have been investigated includes $CaSO_4 \cdot 2H_2O$ (plaster of Paris), $CaCO_3$ (argonite), $Ca_3(PO_4)_2$ (beta-whitlockite), and various permutations of calcium phosphate ceramics. Plaster of Paris has had a history of clinical use dating back to at least the turn of the century.[59] Although it does not seem likely that sulfate will see any practical application in resolving bone defects without considerable modification, its reasonable tissue

compatibility, availability, low cost, ease of handling, and ease of sterilization without loss of properties will probably continue to stimulate its study in certain applications.

The porous calcium carbonate structure resulting from the removal of organic material from the genus Porities coral was used by Cheroff et al.[5] as an implant material in the femora and tibiae of dogs. The interconnecting pores of this material were 140 to 160 micrometers in diameter. Bone specimens recovered one year postsurgery revealed complete resorption of the coral skeleton in nine out of twelve cases. However, in most cases, less than half of the repair tissue was mineralized bone. The reasoning behind using the coral structure is the assumption that it is more organized than the random porosity produced in synthetic biomaterials. The use of coral pore structures has been taken a step further in the development of the "Replamineform" technique, a hydrothermal exchange method for producing ceramic replicas of the coral structure. However, there is no convincing evidence that natural structure is better than the synthetic one with respect to bone ingrowth and bioresorption. Klawitter and Hulbert[41] determined that approximately 100 micrometers was the minimum pore size for effective bone ingrowth. Most synthetic porous implant materials in use have a random pore size of 100-500 micrometers.

Phosphate biomaterials have been prepared and investigated in a number of forms. The most widely studied are biodegradable

beta tricalcium phosphate (TCP) and hydroxyapatite. It must be recognized, however, that biodegradable and nonbiodegradable are relative terms, inasmuch as none of the calcium phosphate ceramics should be considered totally nonbiodegradable. A detailed description of the variety of calcium phosphate compositions studied can be found in the recent book edited by deGroot.[19] We will confine our remarks to TCP which is, as stated, biodegradable and is used in vivo in that context, i.e., as a scaffold for bone repair. Perhaps the most consistent and desirable property of TCP, as well as other calcium phosphate ceramics, is biocompatibility.[1,4,13,23,24,30,42,50,51,54] No foreign body reactions, local inflammatory response, or systemic toxicity have been reported. The pathways of calcium and phosphate ions have been traced in serum and urine without any abnormal results.[29] It can be concluded that calcium and phosphate ions of TCP are handled as part of the normal ion pool. In most cases, and particularly with dense nonporous TCP, there is no intervening fibrous tissue between implant and bone.[29] It has been observed, however, that TCP with large pores will display a relatively sudden breakup at nine months post-implantation with some fibrous tissue surrounding the fragmented TCP. A most remarkable property of calcium phosphate ceramics is their ability to bond directly to bone. This phenomenon was first observed by Driskell in studies on TCP.[23] Although not yet fully understood, the

existence of this bond, and to some extent its appearance and composition, is well documented.[20,21,38,39]

A significant limiting factor in the application of TCP is its mechanical properties. Like most ceramics, it is brittle and has low impact resistance. Porous TCP has a compressive and tensile strength similar to, but on the average less than, cancellous bone, depending on the manufacturing process.[37] This limits the application of TCP in stress-bearing circumstances. However, as a bone graft substitute or extender, it has application to the extent that proper fixation can be included during the TCP resorption and bone repair processes.[48] Lemons demonstrated that TCP in granular form can be used as an autogenous bone extender in the repair of long bone discontinuities in rabbits.[48] The surgically created defects filled with 50:50 TCP autogenous bone healed in six weeks as compared with four to six weeks when autogenous bone alone was used. These results indicate that some applications of the granular TCP may be possible in humans where a degree of stress-bearing is a factor. Porous TCP has been applied in block form with some success in mandibular discontinuities in dogs.[67]

The bioresorption of porous TCP is assumed to take place by both solution-driven and cell-mediated processes. The relative significance of these mechanisms is not yet clear. While it is clear that chemical composition is a determining factor in bioresorption, it is also apparent that structural factors may com-

pletely override chemical ones. DeGroot has suggested that the TCP micropores (3 to 5 micrometers) within the larger pore structure (100-500 micrometers) are dependent for their size and numbers on the size of the beginning powder particles and the sintering process which joins these particles.[18]

Although TCP can serve as a scaffold for bone replacement, it does not appear to have osteoinductive capabilities. The ability of TCP to "guide" bone replacement where none would otherwise occur has led some investigators to describe it as being osteoconductive.

The principal clinical application of TCP has been in dentistry. Powdered TCP has been used for initiating apical closure in teeth and for treating periapical defects.[10,62,64] Block materials composed entirely of TCP have thus far not been applied in high stress-bearing situations in humans. Current thought would indicate that the application of choice for degradable ceramics is the filling of spaces caused by trauma and disease where biomechanical strength is not a prime consideration. However, research currently in progress using unidirectional porosity TCP suggests that appropriate design of totally biodegradable block ceramic may make possible its broader application in the segmental replacement of such high stress areas as the mandible. It will be essential that ceramic degradation and bone ingrowth are maintained at rates consistent with a reasonable degree of

mechanical strength throughout the repair process and that the period of ceramic bioresorption is not excessive.

## VII. CONCLUSION

Individuals involved with bone repair must be extremely circumspect when describing where or how to use osseous repair agents. The particular situation in which a specific material may be applied might be very limited. For example, a properly reinforced PLA bone plate may be suitable for rigid, internal fixation, but it has no utility as an osteoinductive material. Conversely, a porous block of PLA:PGA may be useful as a delivery vehicle for an osteoinductive substance to a site of bony deficiency; however, it has no value as a fixation device. The biodegradable ceramics have a narrow range of application in orthopedics. Because of their brittleness, they should not be used in weight bearing, high stress areas. However, as a bone expander, in combination with a bone graft or bone implant, ceramics may be useful.

There is both art and science involved in the synthesis of biodegradable ceramics and polymers. Consequently, variability should be expected from batch to batch synthesis. Considerably more work is required to ensure for product reproducibility. Specific, desired functional properties of the biodegradable polymers can be contrived in the laboratory to render a particular polymer task unique; for example, polymers for augmentation would have different physical and chemical properties than those

for rigid fixation. Tailoring of properties could be accomplished to create a polymer with a uniform pore size by incorporating a surfactant such as triethanol amine into the synthesis. By using different ratios of constituent monomers, a copolymer's properties also can be modified. Altering the weight average molecular weight to produce a polymer of predominantly small sized fragments or prehydrolysis of a polyester could hasten its biodegradation, if such a characteric was desirable.

We believe that the most exciting role for the biodegradables will be as carriers for bone inductive agents or bone cell chemotactic factors. Dipolar microspheres or packets of osteoprogenitor cells donated by an individual may be incorporated within a polymer or ceramic, and in conjunction with characterized bone inductive proteins can be expected to dramatically enhance bone repair and augmentation at any chosen skeletal site.

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## LEGENDS

Figure 1. Many monomers reacted together form a polymer.

Figure 2. Polymerization of identical monomeric units yields a homopolymer. (Commercially used as PDS® suture).

Figure 3. A combination of two different monomers (represented as A's and B's) can produce differently structured polymers.

Figure 4. An example of a homopolymer from glycolic acid known as Dexon®.

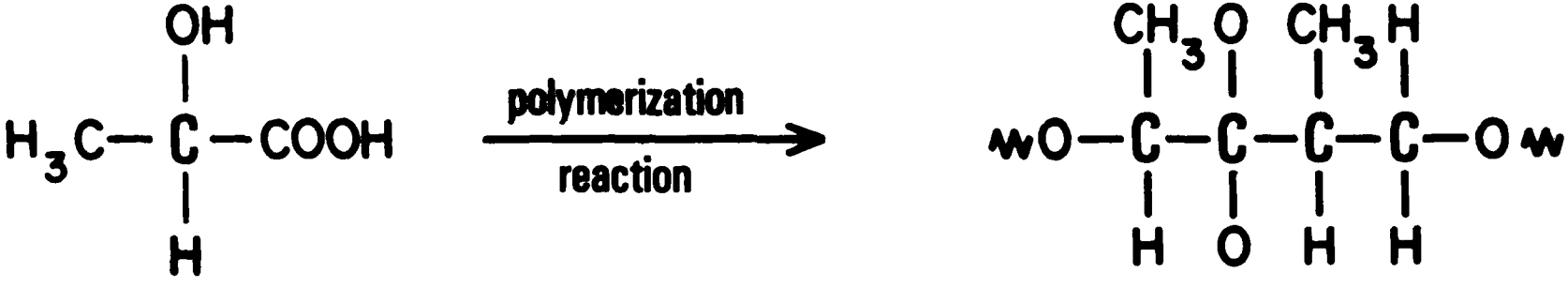
Figure 5. An example of a copolymer from glycolic and lactic acids known as Polyglactin 910®.

Figure 6. The morphology or molecular orientation associated with polymers can be varied; three examples are depicted.

Figure 7. Geometric isomerism (cis and trans forms) arises from different spatial configurations of the atoms of a molecule. Configuration involves different arrangements of atoms and substituents of a molecule that can be interconverted only be breaking and reforming primary chemical bonds.

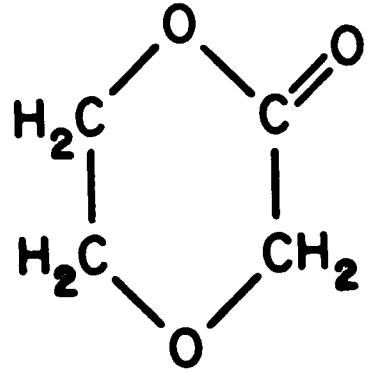
Figure 8. Conformation is the different arrangement of atoms and substituents of a molecule which occur as a result of rotation around single bonds.

Figure 9. When substituent groups along the backbone of a polymer are oriented in a random and unordered fashion, this is called atactic. A polymer is described as isotactic and ordered when the site of steric isomerism in each monomer of the backbone



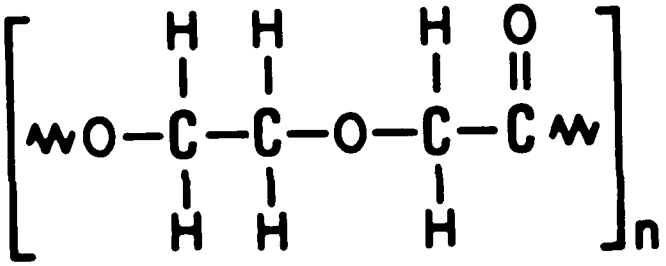

Monomer of lactic acid

Homopolymer of polylactic acid



Monomer of paradioxone

polymerization reaction



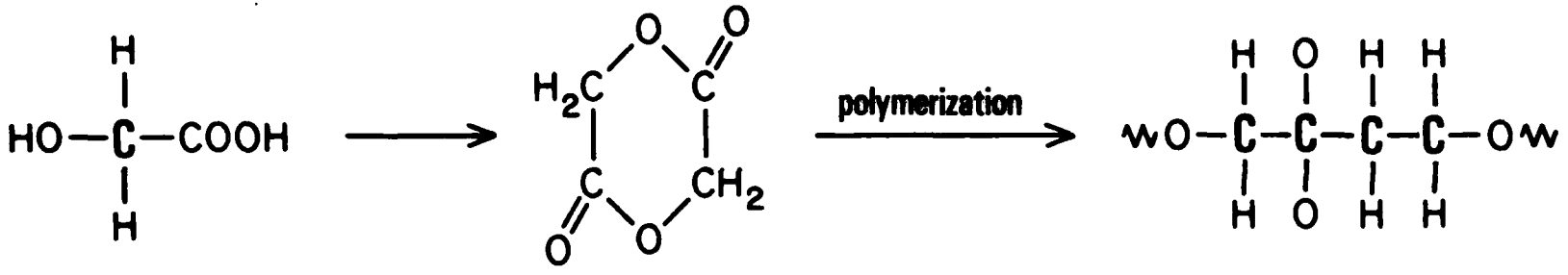
Homopolymer of poly–p–dioxanone

( PDS® )

RANDOM COPOLYMER: ~AABABBBAAABABAB~

BLOCK COPOLYMER: ~AAAAAA~BBBBBB~AAAAAA~

GRAFT COPOLYMER:



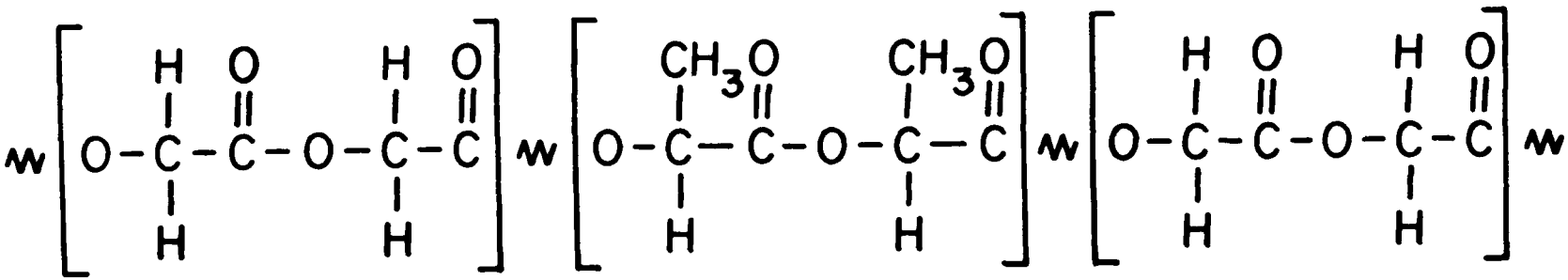

Monomer of Glycolic acid

Glycolide

Homopolymer of Polyglycolic acid (PGA)
(Dexon ®)

4

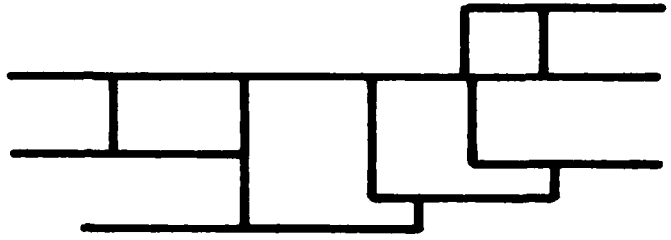
# POLYGLACTIN 910 ®



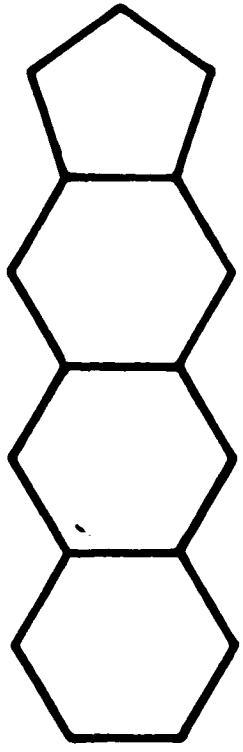
**Diglycolyl Unit** **Dilactyl Unit** **Diglycolyl Unit**

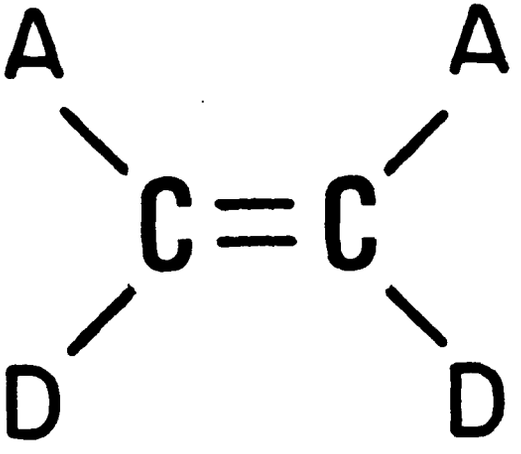
**LINEAR:** ∿ AAAAAAA ∿

**NETWORKS:**



**LADDER:**



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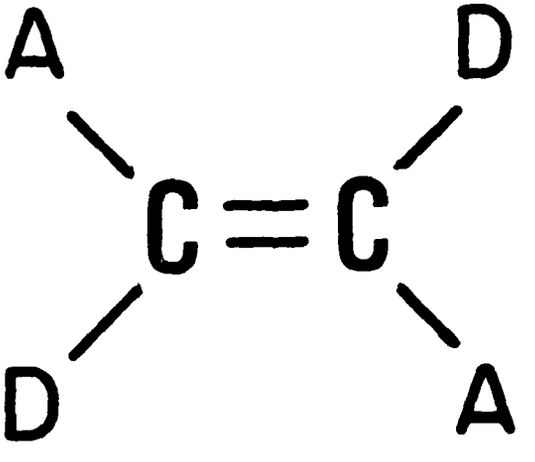
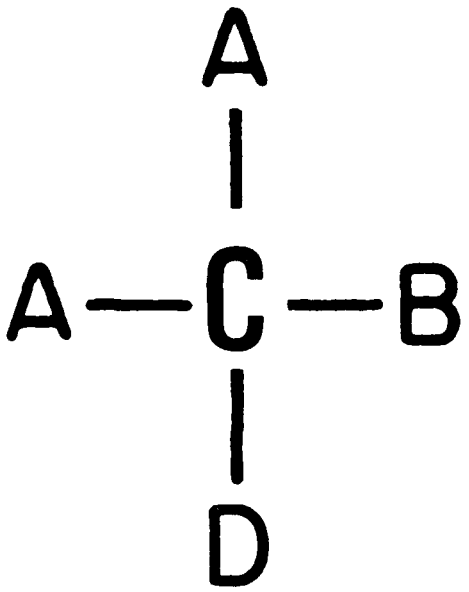
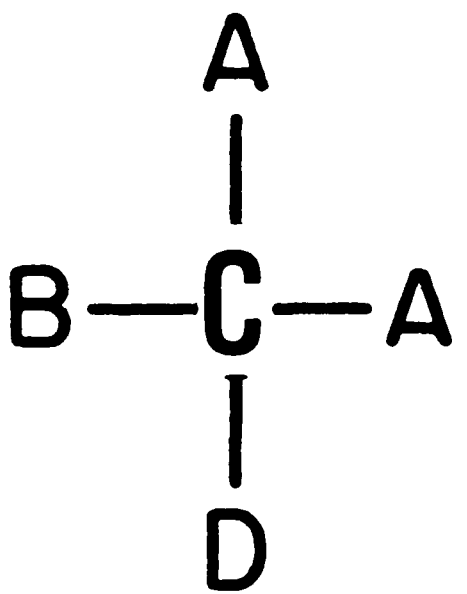


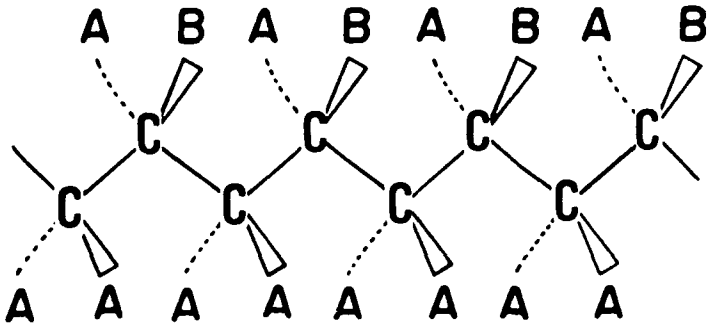

( TRANS )

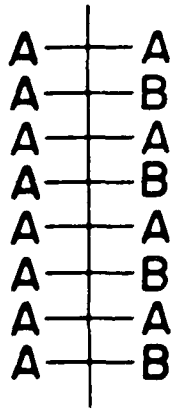
# CONFORMATION



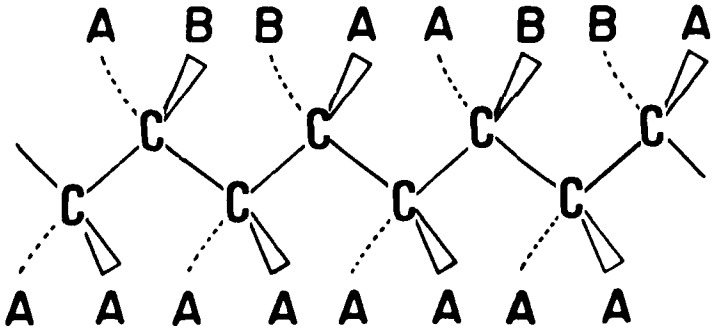



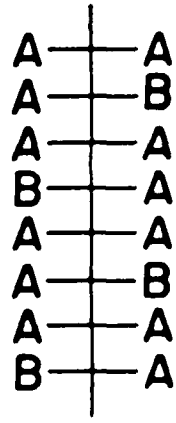
## Isotactic



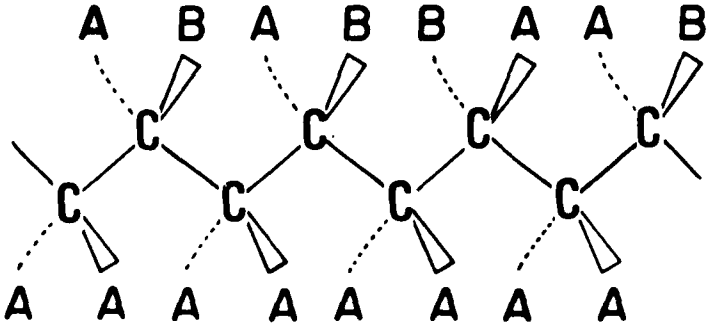



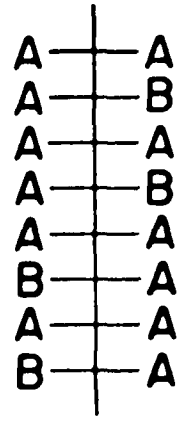

## Syndiotactic




## Atactic




9

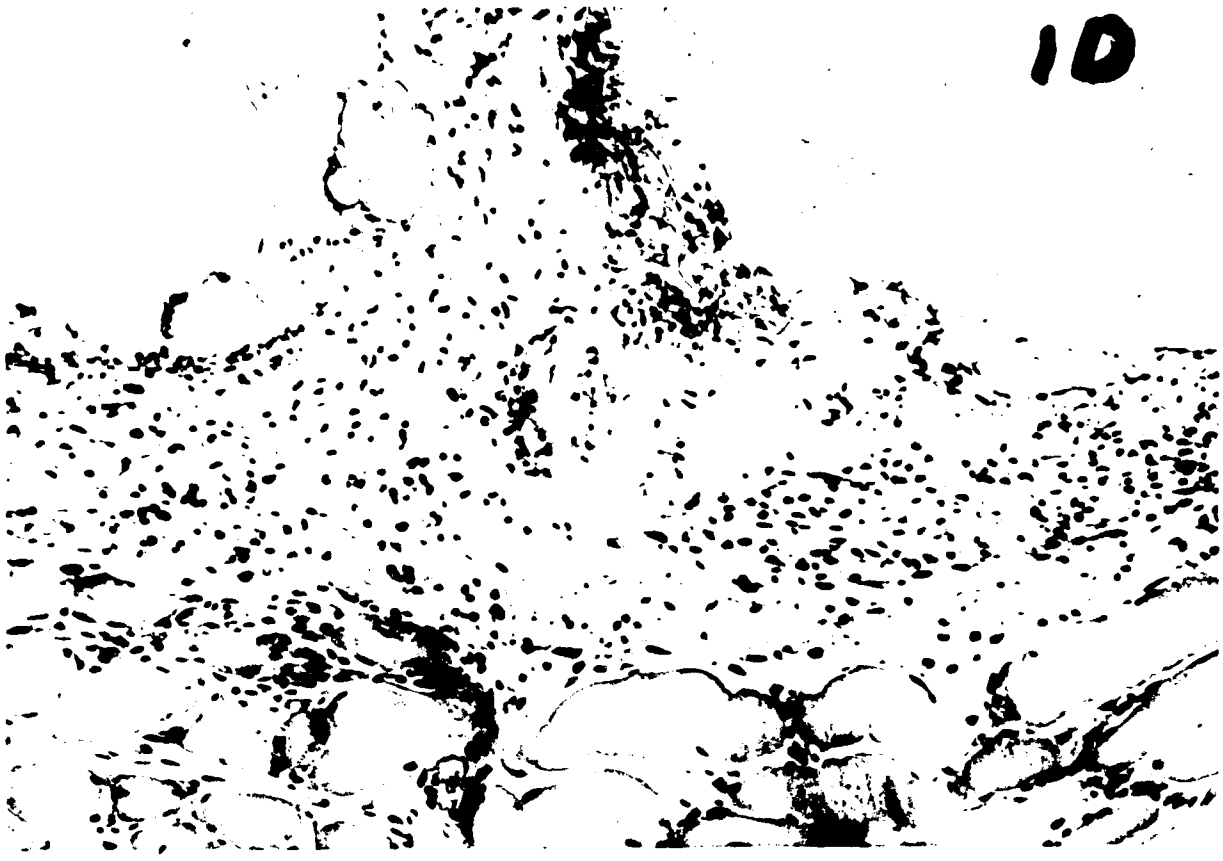
chain has the same configuration. A syndiotactic, ordered polymer has a configuration where the pseudochiral centers alternate from one repeating monomer to the next. The same substituent group would be located alternately on the opposite sides of the polymer chain.

Figure 10. Three-day postimplantation specimen showing host muscle tissue (bottom) and porous copolymer implant (top). A mixture of fibrinous exudate and edematous granulation tissue incorporating numerous inflammatory cells lies between the two and penetrates a pore (arrows) in the surface of the implant. (Hematoxylin and eosin stain. Original magnification, X 150.)

Figure 11. Nine-day postimplantation specimen showing faintly stained host muscle tissue (bottom) and copolymer implant (top). Between the two lies a zone of cellular fibrovascular tissue with a discontinuous single cell layer of epithelioid histiocytes contacting the surface of the implant. (Hematoxylin and eosin stain. Original magnification, X 250.)

Figure 12. Twelve-day postimplantation specimen showing host muscle tissue (bottom) and copolymer implant (top). Between the two lies a zone of cellular fibrovascular tissue incorporating numerous inflammatory cells. A 1-2 cell deep lining of histiocytes, including a multinucleated giant cell (arrow), contacts the surface of the implant. (Hematoxylin and eosin stain.) Original magnification, X 250.)

10



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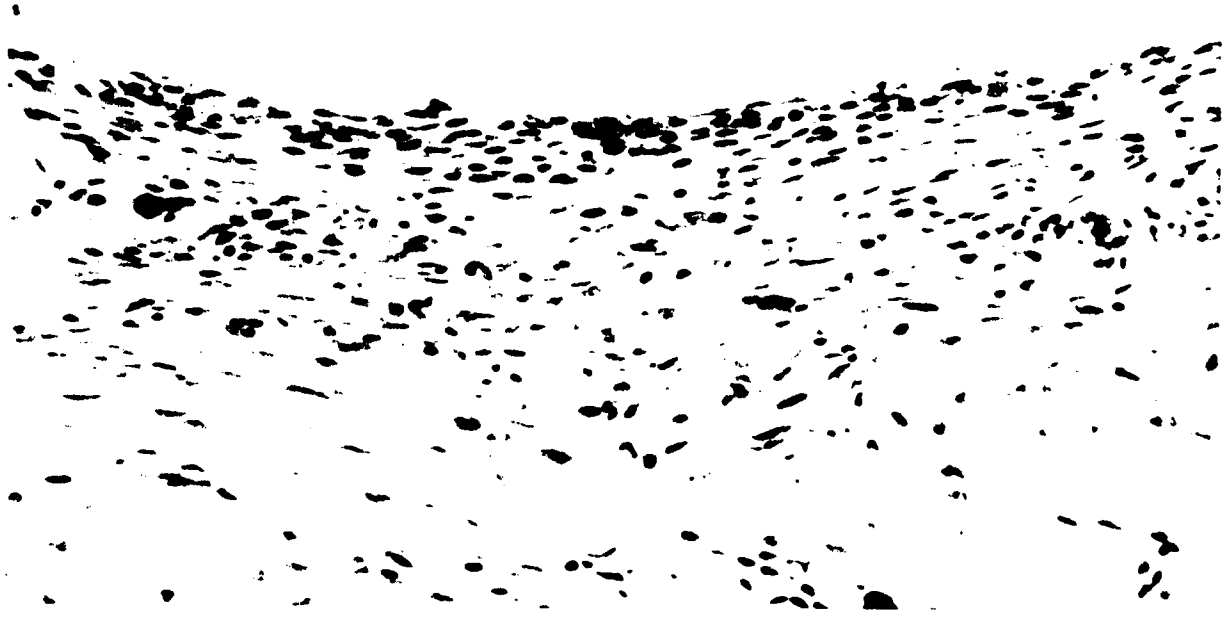

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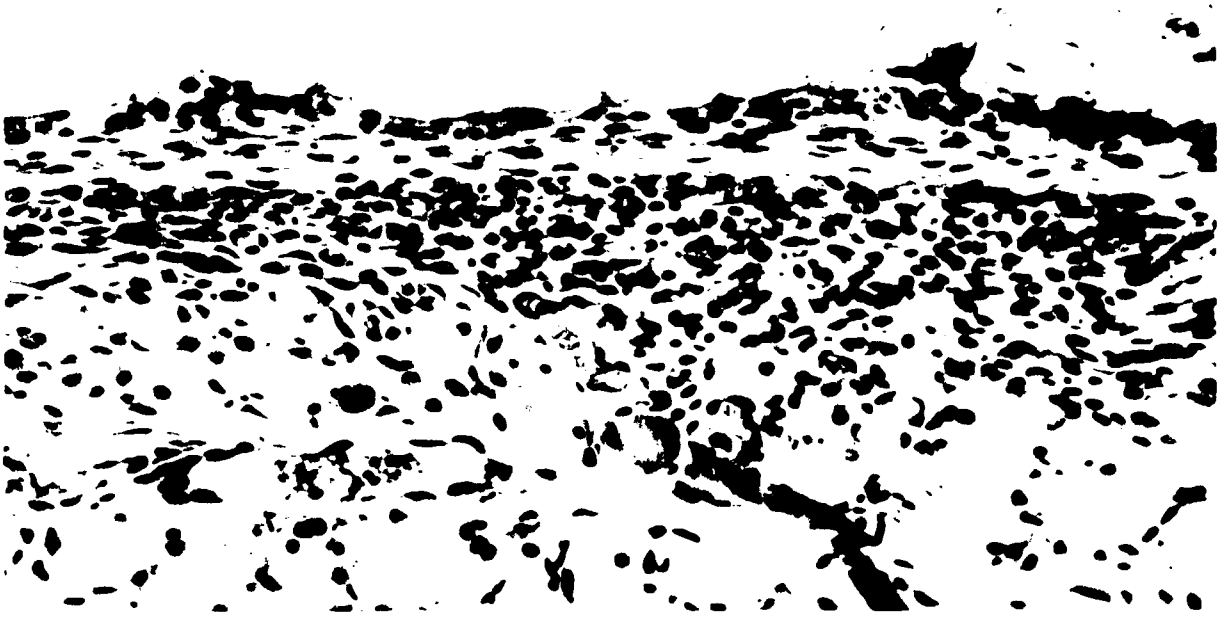

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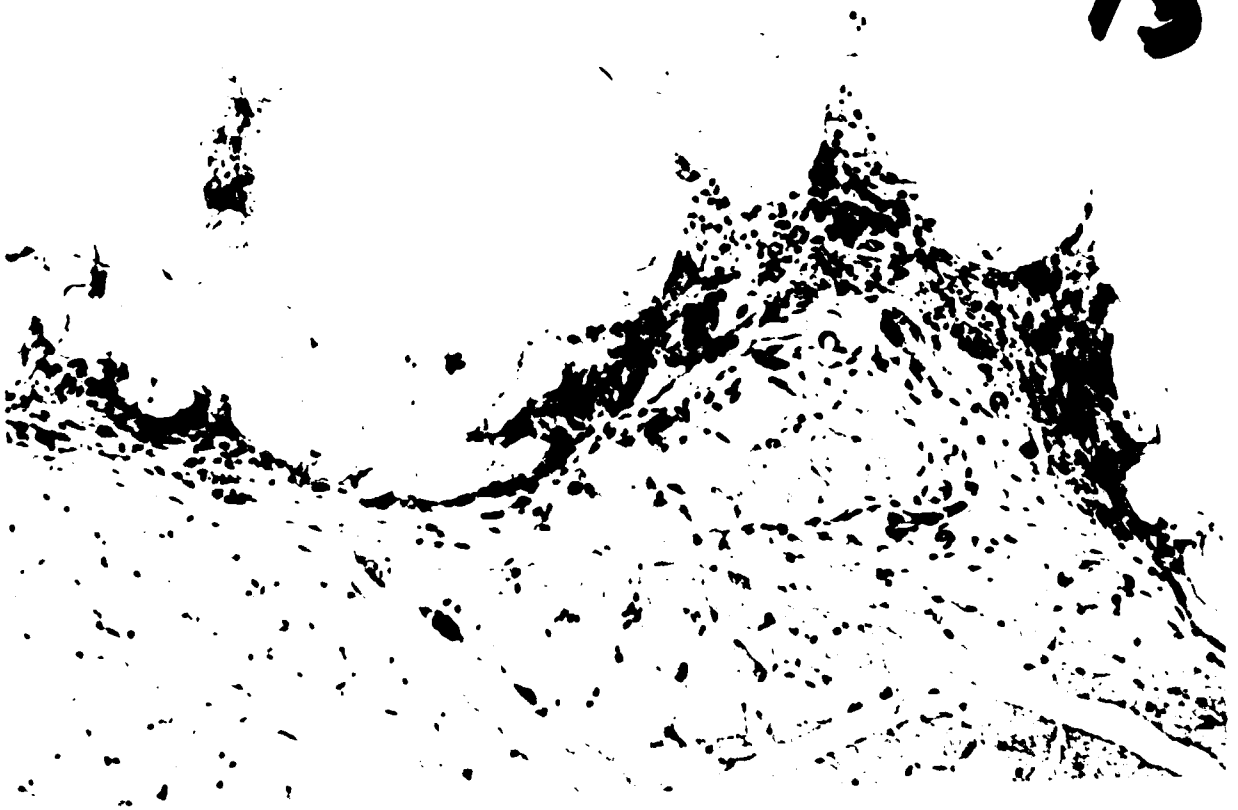
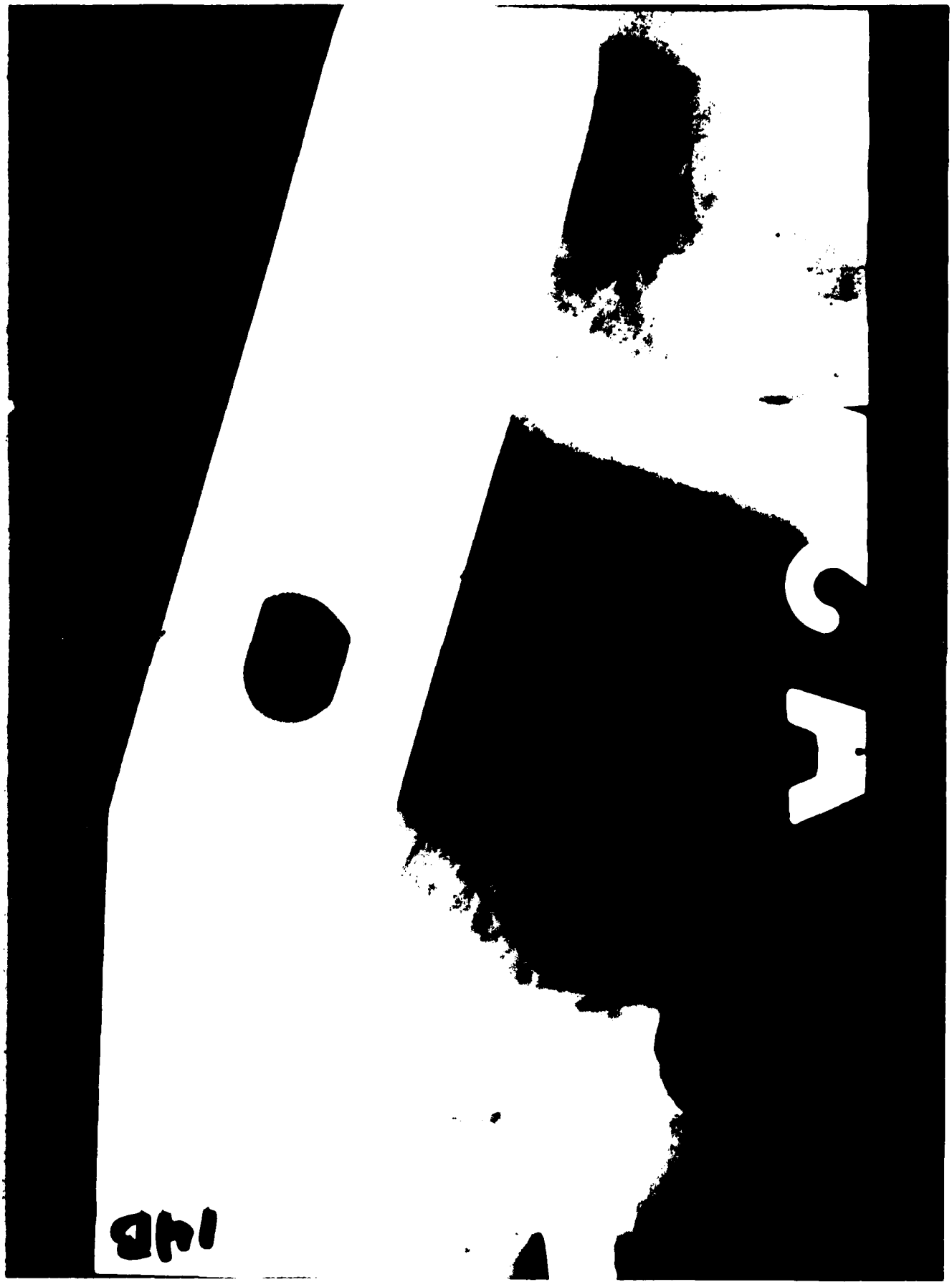
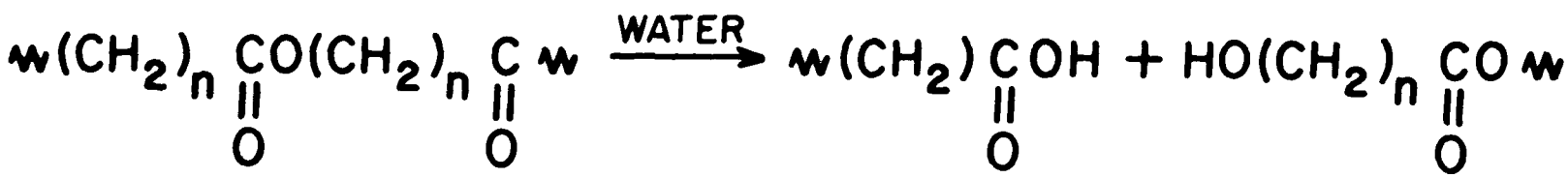


14A

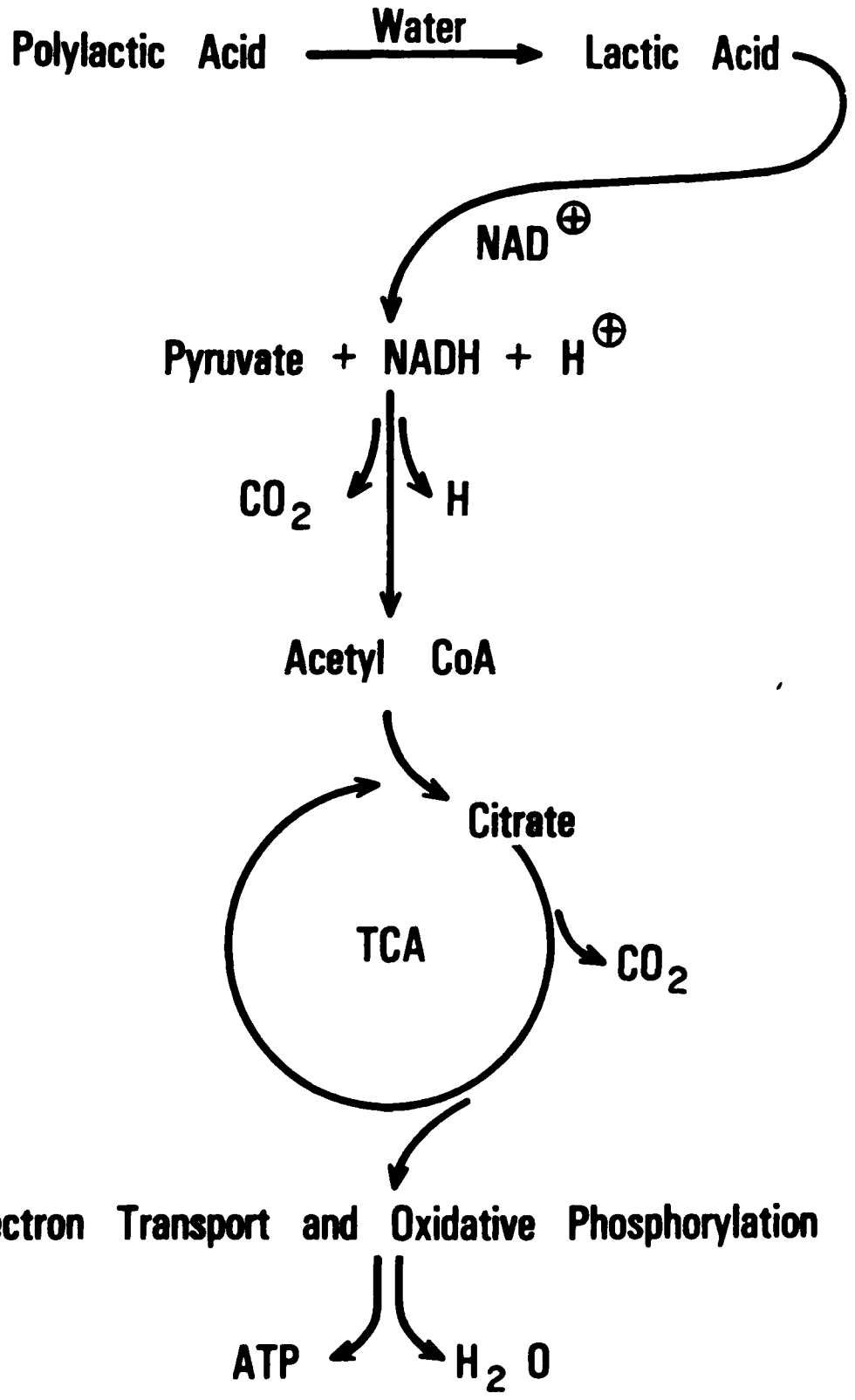


15/

16A




16 B


Polylactic Acid
Water
Lactic Acid
NAD⊕
Pyruvate + NADH + H⊕
CO2
H
Acetyl CoA
Citrate
TCA
CO2
Electron Transport and Oxidative Phosphorylation
ATP
H2 O

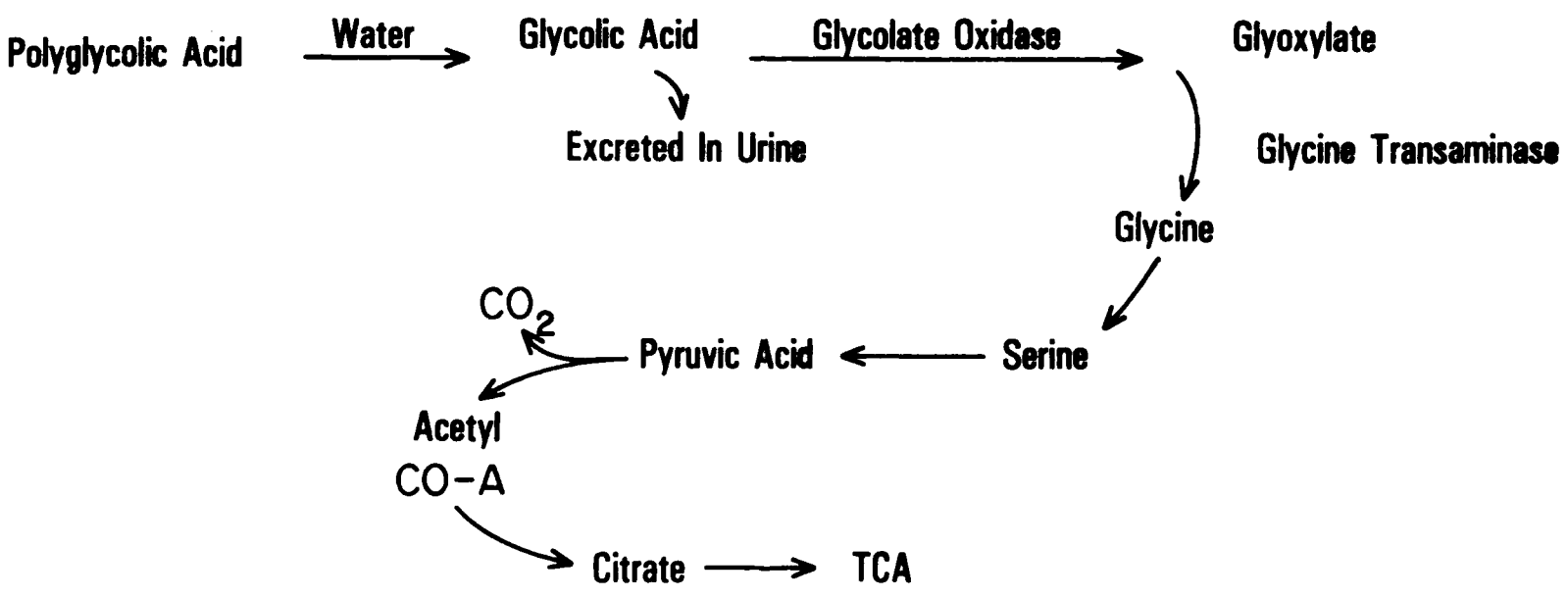


Figure 13. Twenty-eight-day postimplantation specimen showing host muscle tissue (bottom) and porous copolymer implant (top). Many multinucleated giant cells line and penetrate pores in the surface of the implant. (Hematoxylin and eosin stain. Original magnification, X 130.)

Figure 14a. Radiograph of body of mandible showing healing discontinuity (17mm) treated with implant (3 1/2 months).

Figure 14b. Radiograph of body of mandible showing evidence of non-healing defect (17mm) (at 3 1/2 months).

Figure 15a. At necropsy, a bony union is evident in the implant treated mandible (3 1/2 months).

Figure 15b. At necropsy, a non-union of fibrous connective tissue has formed (3 1/2 months).

Figure 16a. Polyesters degrade by the process of nonspecific hydrolytic scission.

Figure 16b. Ester bonds are cleaved by reacting with water, forming carboxy and hydroxy terminal groups.

Figure 17. The monomeric units of lactic acid generated when PLA or PLA:PGA are degraded become incorporated in the tricarboxylic acid (TCA) cycle.

Figure 18. PGA undergoes hydrolytic scission and enzyme hydrolysis to produce monomers of glycolic acid that are excreted in the urine or that can enter the TCA cycle.

# Polymer Degradation

| Ratio | Absorbed ( days ) |
|---|---|
| 25PLA:75PGA | 100 |
| 50PLA:50PGA | 120 |
| 75PLA:25PGA | 180 |
| 100PLA | 220 |
| 100PGA | > 220 |

# Polymer Degradation

| Ratio | Half–life |
|---|---|
| 25PLA:75PGA | ~ 14 days |
| 50PLA:50PGA | ~ 7 days |
| 75PLA:25PGA | ~ 14 days |
| 100PLA | 6.5 months |
| 100PGA, fast cure | 24 days |
| 100PGA, slow cure | 5.0 months |

# Degradation Of Biodegradable Sutures

| Suture | Absorbed ( days ) |
|---|---|
| PGA ( Dexon ) | 60 or 120 |
| 90 PGA: 10 PLA ( Polyglactin 910, Vicryl ) | 60–90 |
| PLA | > 70 |
| CATGUT | > 120 |
| POLYDIOXANONE (PDS ) | 182 |

Figure 19. Degradation of PLA:PGA, PLA, and PGA determined histologically, based upon an in vivo evaluation of plugs 1.6K-1.75K micrometers in diameter (24).

Figure 20. Degradation of PLA:GA, PLA, and PGA determined by using radioisotope labeled specimens in vivo (specimen plugs weighed approximately 5-6mg)(28).

Figure 21. Degradation rates of biodegradable sutures.

# END

# FILMED

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# DTIC