A Review of Material Properties of Biodegradable and Bioresorbable Polymers and Devices for GTR and GBR Applications

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Use of bioresorbable and biodegradable materials for guided tissue and guided bone regeneration is under intense investigation and is being tested in clinical trials. This study presents a basic overview of material properties of bioresorbable and biodegradable polymers and devices for guided tissue and guided bone regeneration treatment. Collagens and aliphatic polyesters, such as poly(glycolic acid), poly(glactic acid), and polycaprolactone, are discussed, as well as biocompatibility, mechanical properties, and sterilization. (Int J Oral Maxillofac Implants 1996;11:667-678)

Key words: biocompatibility, bioresorbable device, bioresorbable polymer, guided bone regeneration

During the last two decades, experimental and clinical studies on periodontal wound healing have resulted in the development of a regenerative treatment modality called guided tissue regeneration (GTR). The principle of the treatment is the placement of a membrane between the periodontal defect and the gingival tissues (GTR) or between the bone defect and the gingival tissues (guided bone regeneration [GBR]). One disadvantage of the most commonly used GTR and GBR devices is that they are nonresorbable. Therefore, they must be removed for GTR in 4 to 6 weeks and for GBR in 6 to 9 months after placement. This requires a two-stage procedure, which has a certain psychologic impact on the patient and increases the costs of medical treatment. The obvious advantage of bioresorbable devices for GTR and GBR treatment is the obviation of the surgical intervention after the device has fulfilled its mission. Bioresorbable and biodegradable membranes and foils, made of natural and synthetic materials, are under intense investigation and are being used in clinical trials. Some of them are already commercially available. Little is mentioned in the common GTR and GBR literature of the material properties of these devices. This study gives a basic overview of the material properties of biodegradable and bioresorbable polymers and devices for GTR and GBR treatment.

The earliest reports of the use of biomaterials came from the Edgar Smith papyrus, which reports the use of sutures and other wound closure devices around 4000 BC and the use of metals in bone repair around 2000 BC. Ancient Indians are reported to have used silk and hair as suture materials. Chu referred to a chromizing
technique for natural collagen suture developed by Lister in 1840. Natural tissues such as amnion and placenta were suggested in 1900 as skin replacement.\textsuperscript{3} Biomaterials used in surgery may be synthetic, materials such as poly(amino acids), polyanhydrides, polyester, polyorthoester, and polyphosphazenes; or they may occur naturally, such as albumin, chitin and chitosan, collagen and gelatin, and polysaccharides. The synthesis and commercial applications of bioresorbable, manmade polymers in the 1960s resulted in a number of useful products. The most widely recognized products are synthetic bioresorbable sutures.

Collagen

Collagens comprise the most substantial group of structural proteins in connective tissue and represent about one third of total body proteins. To date, more than 13 types of collagen have been isolated, some of which have been completely characterized, and others, only partially characterized (Table 1).\textsuperscript{4-6} The individual types differ in their preliminary structure as well as in their macromolecular arrangement.\textsuperscript{7,8} However, they can generally be classified as interstitial or fibril-forming collagens, collagens of the basement membrane, and so called “minor collagens,” which appear in relatively small amounts in the tissue.\textsuperscript{9}

Of the naturally occurring or biologic polymers used in surgery, collagen is, by far, the polymer that is most intensely studied. In general, it is derived from submucosa of bovine or bovine intestine, hence the name gut. The collagenous tissue so derived is treated in an aldehyde solution, which crosslinks and strengthens the preparation. In addition, this chemical treatment makes the collagen more resistant to enzymatic degradation. Suture material treated in this way is called plain gut. If the suture is additionally treated in chromium trioxide, it becomes chromic gut. Chromic gut suture is more highly crosslinked and, hence, is stronger and more resistant to biodegradation. Salthouse\textsuperscript{10} has demonstrated that the mechanism by which gut or other collagen implant materials degrade is by sequential attack by lysosomal enzymes. In most locations, the initial attack is by acid phosphatase, with leucine amino peptidase activity increasing later during the degradation period. Collagenase is also thought to play a role in the enzymatic degradation of collagenous materials. In fact, the activity of collagenase is much higher for the processed, denatured protein than for the naturally occurring native collagen.\textsuperscript{11} The activity of collagenase can be reduced, however, if the collagen is crosslinked either with metal ions, which act as enzyme poisons, or with aldehydes. Consequently, treatment with glutaraldehyde, formaldehyde, or chromic salts greatly improves the degradation kinetics of these collagen-based materials.

The pure triple-helical collagen molecule does not elicit a strong antigenic response. However, associated cellular debris, ground substance, or the associated nonhelical telopeptide region of the collagen molecule can evoke a rather strong antigenic response.\textsuperscript{12} In an effort to reduce the antigenic response of processed collagen-based materials, methods of dissociation, purification, and reconstitution of
collagen have been developed. The source of such collagen is usually animal tendon or hide. The reconstitution process yields a pure, less antigenic collagen. Through an extrusion method, fine plain and chromic sutures are produced primarily for microsurgery. Aqueous dispersions of reconstituted collagen may be crosslinked with an aldehyde to produce a hemostatic collagen foam. Gelatin, one of the degradation products of collagen, can also be used to produce hemostatic gelatin foams. Injectable aqueous dispersions of reconstituted collagen are used in esthetic surgery to ameliorate superficial skin defects. Collagen-based sutures and hemostatic sponges are well known to most surgeons and need not be discussed in any detail here. However, a topic of increasing interest to periodontists, restorative implant dentists, and maxillofacial surgeons is the use of natural collagen materials as membranes and foils for guided tissue regeneration (GTR) and guided bone regeneration (GBR). The experimental and clinical results of collagen membranes and foils from a biocompatibility and material point of view are discussed in another report.

**Synthetic Polymers**

Synthetic polymers offer several advantages over naturally occurring materials. Synthetic materials can be prepared reproducibly under carefully controlled conditions and can be made available, if needed, in almost unlimited quantities. Synthetic polymers are available with a wide range of physical, chemical, and mechanical properties that may be easily altered by simple chemical modifications. A search for a simplified synthetic alternative to collagen began in the early 1960s. Prior to this time, collagen was the only commercially available biodegradable material. The alpha polyamides, polyglycine and polyprolene, were synthesized. However, these materials were found to not be bioresorbable or biodegradable. Schmitt and Palistina recognized that the alpha polyester analogs of the alpha polyamides might indeed be bioresorbable and, hence, a useful material for surgical applications.

**Aliphatic Polyesters**

Aliphatic polyesters (Fig 1) constitute the most attractive family among which poly(α-hydroxy acids) has been extensively studied. Poly(α-hydroxy acids) constitute a class of polymers represented by the general formula –(–O–CHR–CO–)–n.

**Poly(glycolic acid).** The simplest alpha polyester is poly(glycolic acid) (PGA). Poly(glycolic acid) was first synthesized in the 1930s by William Carothers, the father of nylon. At that time, it was noted that the major limitation of this polymer was its hydrolytic instability. It was this hydrolytic instability that attracted Schmitt and Palistina.

In the 1960s, Frazza and Schmitt perfected procedures for the synthesis of high-molecular weight PGA and the next homolog in this series of alpha polyester, poly(lactic acid) (PLA). Poly(glycolic acid) is polymerized from alpha acetic acid,
commercially called glycolic acid. On mild heating, glycolic acids form cyclic
diamers called glycolides. When subjected to a catalytic ring-opening procedure,
these alpha glycolides polymerize to form high–molecular weight PGA. Its most
characteristic property is its high crystallinity, which gives rise to a high melting
point (230°C) and low solubility in organic solvents. Poly(glycolic acid) was used in
the first synthetic bioresorbable suture by American Cyanamid.¹⁷ Poly(glycolic acid)
sutures have been commercially available under the trade name Dexon (Braun
Melsungen, Melsungen, Germany) since 1970. Dexon sutures resorb rapidly and
tend to lose their mechanical strength during a period of 2 to 4 weeks after
implantation.

Poly(lactic acid). With its asymmetric carbon atom, lactic acid is optically
active. It forms optically active cyclic diamers or lactides. As in the case of
glycolides, a ring-opening procedure is used to produce the polymer. Poly(lactic
cid) is more hydrophobic than poly(glycolic acid) because of the presence of an
extra methyl group. This limits the water uptake and reduces the rate of backbone
hydrolysis as compared to PGA.¹⁸,¹⁹ In addition, PLA is more soluble in organic
solvents than is PGA. Since lactic acid is a chiral molecule, it exists in two
stereoisomorphic forms that give rise to four morphologically distinct polymers.
Poly(D-lactide) and poly(L-lactide) are the two stereoregular polymers.
Poly(D,L-lactide) is the racemic polymer obtained from a mixture of D and L lactic
acid, and poly(meso-lactide) can be obtained from D,L-lactide. The polymers
derived from the optically active D and L monomers are semicrystalline materials,
while the optically inactive poly(D,L-lactide) is always amorphous. This fact has
important practical ramifications. The amorphous poly(D,L-lactide) is usually
considered for applications such as drug delivery, when it is essential to have a
homogeneous dispersion of the drug within a monophasic matrix. On the other hand,
the semicrystalline poly(L-lactide) is preferred in applications when higher
mechanical properties are required for items such as, for example, sutures, staples,
and orthopedic devices.²⁰-²³

The synthesis by the ring-opening procedure of PGA and PLA is identical.
Therefore, PGA and PLA can be copolymerized to form high–molecular weight
copolymers. Copolymers of PGA and PLA have been intensively investigated.¹⁸,¹⁹ A
copolymer of glycolic and lactic acids in a 9:1 ratio is often called polyglactin 910. It
has adequate mechanical strength and biocompatibility for use as a material for
bioreversible sutures.²⁴-²⁶ Polyglactin 910 sutures are marketed under the trade
name Vicryl (Ethicon, Norderstedt, Germany).

It is noteworthy that there is no linear relationship between the ratio of glycolic
acid to lactic acid and the physicomechanical properties of the corresponding
copolymers. Poly(glycolic acid) is highly crystalline, whereas crystallinity is rapidly
lost in copolymers of glycolic acid and lactic acid. These morphologic changes lead
to an increase and decrease in the rates of hydration and hydrolysis, respectively.
**Poly(ε-caprolactone).** Poly(ε-caprolactone) was one of the earliest polymers synthesized by Carothers in the early 1930s.\textsuperscript{27} It became available commercially following efforts to identify synthetic polymers that could be degraded by microorganisms.\textsuperscript{28} Poly(ε-caprolactone) can be prepared either by ring-opening polymerization of caprolactone using a variety of anionic, cationic, and coordination catalysts or via free radical ring-opening polymerization of 2-methylene-1-3-dioxepane.\textsuperscript{29} Poly(ε-caprolactone) is a semicrystalline polymer. Its crystallinity tends to decrease with increasing molecular weight. The high solubility of polycaprolactone, its low melting point (59°C to 64°C), and its exceptional ability to form blends\textsuperscript{30} has stimulated research on its application as a biomaterial. Poly(ε-caprolactone) resorbs at a slower pace than does poly(D,L-lactide) and can be used, therefore, in drug delivery devices that remain active for longer than 1 year. The release characteristics of poly(ε-caprolactone) have been investigated in detail by Pitt and coworkers.\textsuperscript{31} The Capronor system, a 1-year implantable contraceptive device, has become commercially available in Europe and the United States. The toxicology of polycaprolactone has been extensively studied as part of the evaluation and clinical approval of Capronor. Based on a large number of tests and studies,\textsuperscript{29-32} ε-caprolactone and polycaprolactone are currently regarded as nontoxic tissue-compatible materials. In Europe, poly(ε-caprolactone) is already in clinical use as a resorbable staple for wound closure, and it stands to reason that polycaprolactone, or blends and copolymers containing poly(ε-caprolactone), will be used for additional medical applications in the future. For example, poly(ε-caprolactone) could be used as a plasticizer in a copolymer or in a blend with L-PLA to design a membrane or foil for GTR and GBR.

**Polydioxanone.** Polydioxanone (PDS) is a homopolymer of p-dioxanone, prepared by polymerization in the presence of an Et₂Zn catalyst.\textsuperscript{33} Poly(glycolic acid) and Vicryl sutures are more flexible than cat gut, but less flexible than silk sutures.\textsuperscript{34} These materials are quite stiff for generalized use and can be used only in fine sizes. In colonic surgery, bioresorbable sutures lose strength too rapidly to be used alone. Braided materials produce prolonged tissue reactions. Polydioxanone was investigated as a material free from these problems.\textsuperscript{34} It is a monofilament suture material that elicits a low tissue reaction.\textsuperscript{26,34} It can be regarded as a modified PGA. It retains a resorbable character because of the presence of the ester bond, and its flexibility is improved as a result of the change of one ester linkage to an ether linkage. It retains 60% of its strength after 4 weeks; the total strength loss is after 8 weeks. The time of complete resorption is approximately 4 to 6 months. Other applications of PDS are a fixation pin for unloaded fractures, as staples, and as foil to reconstruct the orbital wall.

**Trimethylene carbonate.** The search for bioresorbable materials that hydrolize into physiologically neutral components led to the development of a family of aliphatic carbonate-based block and random copolymers. Polymers are synthesized
by ring-opening copolymerization of either cyclic carbonates alone or with lactones. Cyclic carbonates 1,3-dioxan-2-one (TMC) and 5,5-dimethyl-1,3-dioxan-2-one (DMTMC) are used as only or primary monomeric components, and TMC is used as a minor component in Maxon sutures. Preliminary characterization in vitro and in vivo of a random copolymer of dimethyltrimethylene carbonate (DMTMC) and trimethylene carbonate (TMC) was performed by Shieh et al.

Hürzeler et al assessed the utility of a copolymer of poly(D,L-lactide) and trimethylene carbonate in a GBR model in monkeys. In eight monkeys, atrophic ridges were surgically created. After a healing period of 3 months, subperiosteal tissue expander was placed, and tissue in the edentulous area was expanded for 3 weeks. Titanium dental implants were placed in the alveolar ridge with large circumferential osseous defects. On the control side, an expanded polytetrafluoroethylene (e-PTFE) augmentation material was placed; on the other side, a trimethylene carbonate copoly(D,L-lactide) 70:30 foil was used. Soft tissue dehiscences were seen only on the control side, whereas on the experimental side, no dehiscences could be detected. The histologic sections 4 months after the augmentation procedures revealed significant bone gain on the control side compared to the experimental side. The authors concluded that the trimethylene carbonate-copoly(D,L-lactide) 70:30 foil on its own cannot be recommended for the purpose of GBR. In an experimental pilot study, Lundgren et al tested a plasticized poly(lactic acid) against a copolymer of poly(lactic acid) and trimethylene carbonate in cranial bone defects.

Biodegradation and Bioresorption

The meaning of the words bioabsorbable, biodegradable, and bioresorbable are often used misleadingly in the literature of GTR and GBR. Definitions were given by Vert and Vert et al: Biodegradable refers to solid polymeric materials and devices that break down as a result of macromolecular degradation with dispersion in vivo, but there is no proof of elimination from the body. (This definition excludes environmental, fungal, or bacterial degradation.) Bio degradation polymeric systems or devices can be attacked by biologic elements so that the integrity of the system and, in some cases but not necessarily the macromolecules themselves, is affected and gives fragments or other degradation by-products. Such fragments can move away from their site of action but not necessarily from the body.

Bioresorbable refers to solid polymeric materials and devices that can degrade and further resorb in vivo, ie, that are eliminated through natural pathways either because of simple filtration of degradation by-products or after their metabolization. Thus, bioresorption is a concept that reflects total elimination of the initial foreign material and of degradation by-products (low–molecular weight compounds) with no residual side effects. The use of the word bioresorbable assumes that elimination is shown conclusively.

Bioabsorbable refers to solid polymeric materials or devices that can dissolve in
body fluids without any polymer chain cleavage or molecular mass decrease. Slow dissolution of water-soluble implants in body fluids is an example. A bioabsorbable polymer can be bioresorbable if the dispersed macromolecules are excreted.

**In Vitro Degradation.** In vitro degradation of poly(α-hydroxy acids) in aqueous media proceeds via random, bulk hydrolysis of ester bonds in the polymer chain. This is accompanied by a decrease in molecular weight and, on prolonged exposure to the degrading media, by weight loss (Fig 2). Products of degradation are monomeric carboxylic acids, which catalyze the degradation process. The aqueous solution diffuses into the amorphous region, but not into the crystalline region. Therefore, the amorphous region is more susceptible to degradation than is the crystalline region. Any change in the degree of crystallinity is likely to affect degradation kinetics. The degree of crystallization changes during the process of degradation. It is believed that degradation of crystalline or semicrystalline polymers proceeds through two main stages: the first in the amorphous regions; then in the crystalline regions. Crystallinity first increases and reaches a maximum at the end of the first stage. Then degradation of the more compact crystalline region begins, and the degree of crystallinity decreases. Usually, the rate of polymer degradation and resorption is lower for polymers with high molecular weight, high crystallinity, and a strong orientation. Large implants resorb slower than those with small cross-sections. Porous materials containing impurities and additives (eg, plasticizer) degrade and resorb faster than nonporous and pure ones.

**In Vivo Degradation and Resorption.** In vivo, implant materials are exposed to various body tissues and fluids. The main constituents of body fluids are aqueous solutions containing proteins, enzymes, and salts. In vivo degradation and resorption of aliphatic polyesters is described as a loss of physical and/or chemical integrity resulting from the interaction of a material with the living tissue because of the hydrolysis process. Kronenthal described four stages: hydration; hydration and degradation; degradation; and resorption.

Hollinger reported that there is a difference in the metabolism of lactic and glycolic acids. Lactic acid takes part in the Krebs’ cycle and is consequently excreted by the lungs as carbon dioxide. Glycolic acid is first acted upon by glycolate oxidase and is transformed into glycoxylate. Then glyoxylate reacts with glycine transaminase to yield glycine, which may take part either in protein synthesis or in the Krebs’ cycle (Fig 3).

The presence of enzyme molecules has been reported to affect the resorption kinetics of PGA, PLA, and elastomeric poly(ε-caprolactone). From physical and physiochemical view points, enzymes that are large molecules cannot penetrate solid synthetic polymers. Poly(α-hydroxy acids) have ester linkages that are likely to be hydrolyzed by aqueous media alone or by esterase enzymes. Salthouse and Matlaga studied the effect of an aqueous medium on several suture materials. They concluded that degradation and resorption kinetics depend on the total time spent in
an aqueous environment, regardless of whether the time is totally in vivo or a combination of in vitro and in vivo. This implies that the biodegradation process of a bioresorbable polymer is purely a hydrolytic process and that enzymes have no effect on it. However, these studies show that the degradation by-products during the resorption process may be metabolized by enzymes. Holland et al\textsuperscript{49} have critically examined the literature dealing with the contribution of enzymes to aliphatic polyester degradation and resorption, and they came to the conclusion that, for glassy polymers, nonsignificant enzyme involvement is expected in the early stages. The involvement can be more pronounced in the later stages, however, as erosion and physical fragmentation occur. In contrast, for polymers in the rubbery state, enzymes can play a significant role in their degradation and resorption process.

In general, when in vitro and in vivo degradation and resorption kinetics are compared, or when enzyme-free and enzyme-containing buffer media are compared, as is generally done in the literature, differences can be expected for many reasons other than the enzymatic degradation of macromolecules. The approximate time for the bioresorption of poly(\(\alpha\)-hydroxy acids) is as follows:

1. Poly(L-lactide), 18 to 36 months
2. Poly(D,L-lactide), 4 to 6 months
3. Polyglycolide, 3 to 4 months
4. D,L-lactide-co-glycolite (50:50), 2 to 3 months
5. D,L-lactide-co-glycololite (85:15), 2 to 4 months
6. D,L-lactide-co-caprolactone (90:10), 2 to 3 months
7. Polydioxanone, 4 to 6 months

It is often quite difficult to compare exact degradation and resorption kinetics from various independent in vitro and in vivo studies. The rates of in vitro and in vivo degradation and resorption of polymers can be influenced by the following factors:\textsuperscript{39}:

1. Chemical structure
2. Chemical composition
3. Distribution of repeat units in multimers
4. Presence of ionic groups
5. Presence of unexpected units or chain defects
6. Configurational structure
7. Molecular weight
8. Molecular weight distribution (polydispersity)
9. Presence of low–molecular weight compounds (monomers, oligomers, solvents, plasticizers, drugs, etc)
10. Method and conditions of processing
11. Design
12. Method of sterilization
13. Morphology (amorphous versus semicrystalline, presence of microstructures, presence of residual stresses)
14. Annealing
15. Storage history
16. Site of implantation
17. Adsorbed and absorbed compounds (water, lipids, ions, etc)
18. Physiochemical factors (ion exchange, ionic strength, pH)
19. Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress and solvent induced, crackings, etc)
20. Mechanism of hydrolysis (enzymes versus water)

Therefore, bioresorbability and biocompatibility depend very much on the same factors.

**Biocompatibility.** Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility is generally evaluated through cell culture systems; experimental, histologic, and pathologic examination of the peri-implant; and host responses such as immunogenic, carcinogenic, and thrombogenic responses. The complexity of these host responses results from the series of processes involving many closely interdependent mechanisms of material-tissue interactions. It is these interactions that finally control the ultimate performance of a material in a biologic environment.

In the field of biostable materials and permanently implanted devices and prostheses, the primary goal is minimizing and adjusting material-tissue interactions. The interaction of the living environment and the material should be acceptable and stable for long-term therapies and performances. In the field of biodegradable and bioresorbable materials, the situation is the opposite because of the degradation by-products, which are able to strongly interact with living systems. From this point of view, biodegradable and bioresorbable polymers must be regarded as much closer to pharmacology than to material science.

In the past three decades, several studies\(^2,17,24,26,34,41,47\) have been published to
present general data and results of studies regarding the biocompatibility of sutures made of aliphatic polyesters. The material composition of commercially available sutures is polyglycolide (Dexon), poly(L-lactide-co-glycolide) 10:90 (Vicryl), poly(glycolide-co-trimethylene carbonate) 67.5:32.5 (Maxon), and polydioxanone (PDS). In the case of suture materials, inflammatory response is more pronounced for Dexon and Vicryl (mononuclear cells, polymorphonuclear leucocytes and lymphocytes, histiocytes, and multinucleated giant cells) than for Maxon and PDS (mononuclear macrophages, a few neutrophils, multinucleated giant cells, organized collagenous capsule).

The development of implantable drug delivery systems is probably the most widely investigated application of bioresorbable, biodegradable, bioerodible, and bioabsorbable polymers. The use of these polymers as drug delivery systems has been reviewed by Langer and Chasin and Langer in detail and will, therefore, not be described in further detail here.

Kulkarni et al., Kulkarni et al., Cutright et al., and Cutright and Hunsuck were the first to report preliminary experiments on the use of poly(lactic acid) in the design of internal fixation devices. Kulkarni et al. used extruded pins of L- and D,L-PLA for the reduction of mandibular fractures in dogs and, they confirmed the minimal inflammatory responses for both polymers. Cutright et al. and Cutright and Hunsuck reported data on mandibular fracture reduction in monkeys using transosseous ligatures with poly(lactic acid) suture materials. Animals were sacrificed from 2 to 12 weeks. After 12 weeks, early features of bony union appeared, and the sutures became infiltrated by cellular connective tissue with fibroblasts, endothelial cells, mononuclear phagocytes, and giant cells. Sutures were progressively replaced by bands of young collagen and vascular connective tissue. Tissue reaction was limited to the immediate perisutural area.

A historic survey of the early work on PLA- and PGA-based internal fixation devices has been published by Vert et al. As stated by Vert et al, the early work was characterized by a careless description of fundamental polymer properties such as polymer source, molecular weight, molecular weight distribution, and processing parameters. Consequently, conflicting data on degradation and resorption kinetics, retention of mechanical strength, and degree of inflammation of PLA- and PGA-based implants and devices were published. A comprehensive review of the use of bioresorbable, biodegradable, and bioerodible polymers and composites for internal bone fixation has been published by Daniels et al. By 1990, about 40 different formulations involving copolymers and composites had been developed, and numerous clinical studies using self-reinforced PGA rods, polydioxanone pins, or experimental devices made of PLA had been reported.

Thus far, however, only two major products have been approved for routine clinical use in the United States and Europe. One product is the self-reinforced PGA rod, which is marketed under the trade name Biofix; the other product is a
polydioxanone pin, which is marketed under the trade name Orthosorb (Johnson & Johnson, New Brunswick, NJ) in the United States and Ethipin (Ethicon) in Europe.

The biodegradation and biocompatibility of self-reinforced PGA materials were examined by Böstman et al\textsuperscript{58} in a histopathologic study of biopsy specimens from some of his patients. A review by Böstman\textsuperscript{59} summarized a number of clinical studies involving hundreds of patients. Among 516 patients treated with the Biofix, six patients (1.2\%) required reoperation because of device failure, and nine patients (1.7\%) suffered from bacterial infection of the operative wound. Local fluid accumulation was seen in 41 patients (7.9\%). This late noninfectious inflammatory response warranted operative drainage and was manifested by swelling, redness of the skin, and sometimes pain. Furthermore, the author\textsuperscript{59} reported that local fluid accumulation can lead to a transient sinus formation, if not treated properly.

The main disadvantages of the polydioxanone pin are the insufficient mechanical properties and degradation kinetics. The polydioxanone pin tends to lose its mechanical properties within a time interval too short to guarantee bone healing.\textsuperscript{55} Both the self-reinforced PGA rod and the polydioxanone pin are poorly visible on conventional radiographs and do not allow postoperative radiographic examination of the implant.

During the last 3 years, there has been a trend toward the development of increasingly sophisticated bioresorbable implants, the so-called polymer-designed implants. Claes et al,\textsuperscript{60} Helling et al,\textsuperscript{61} and Rehm et al\textsuperscript{62} developed a bioresorbable pin to overcome the described disadvantages of the polyglycolide pin and the polydioxanone pin. For their pin, they selected a poly(L-lactide-co-D,L-lactide 70:30) with a bending strength of 123.7 MPa. Decrease of the mechanical properties of poly(L-lactide-co-D,L-lactide 70:30) starts at 9 months and ends at 18 months.\textsuperscript{60-63} The mass volume (mass loss) is metabolized by the body after 24 months.\textsuperscript{61} A radiopaque marker allows determination of the pin location in a radiograph assessment of the degradation and resorption process. The design of the pin allows the application of slight compression forces on the fragments. Biocompatibility testing of the pin showed, in comparison to the Biofix, no signs of inflammatory reaction.\textsuperscript{61} Histologic evaluation revealed no foreign-body reaction to the circonium IV oxide during the mass degradation and resorption of the poly(L-lactide-co-D,L-lactide 70:30) pin.\textsuperscript{61}

Bioresorbable and biodegradable fracture fixation devices for maxillofacial surgery have been reviewed by Suuronen.\textsuperscript{64} She concluded that all studied materials were well tolerated by living tissue; however, mild inflammatory reactions have frequently been seen around the implants. Bergsma et al\textsuperscript{65} and Bergsma et al\textsuperscript{66} reported foreign-body reactions to poly(L-lactide) bone plates and screws. Six of 10 patients had to reundergo operations after postoperative periods between 35 and 44 months because of swelling at the implantation site. The authors reported that no discoloration of the overlaying tissue was observed, and no signs of acute or
subacute inflammation, such as an increase in temperature or pain on palpation, could be detected. Light microscopic analysis of the soft tissue showed a foreign-body reaction without signs of inflammation around the poly(L-lactide). On the outer part of the poly(L-lactide), a few polymorphonuclear leucocytes were present; the inner part was surrounded by dense connective tissue lying within macrophages, foreign-body giant cells, and fibrocytes. The authors hypothesized that the observed foreign-body reaction is a combination biochemical and biomechanical reaction of the crystallike poly(L-lactide) fragments. Pistner et al. and Gutwald et al. studied two amorphous and one crystalline poly(L-lactide) in the paravertebral muscle of rats. The crystalline poly(L-lactide) remained almost stable in form and structure during a period of 116 weeks. No signs of inflammation and a mild foreign-body reaction were observed. After 116 weeks, the amorphous poly(L-lactide) of higher molecular weight resorbed nearly completely. The amorphous poly(L-lactide) of lower molecular weight was metabolized. During the degradation and resorption period, a mild to moderate histiocytic inflammation was found.

The gradual shift from nonresorbable membranes to biodegradable and bioresorbable membranes represents one of the most significant trends in GTR and GBR research. Functional requirements demanded of nonresorbable, biodegradable, and bioresorbable membrane materials used in GTR and GBR procedures are the same. Material properties and characteristics, eg, chemical, physical, and biochemical, may and must be different to allow performance of the intended function.

Biodegradation and bioresorption kinetics can be dramatically affected by the presence of additives such as plasticizers. These plasticizers, such as citric acid esters, are mainly used in the food industry in plastic bags and foils. During the aging process of polymer bags and foils, the plasticizer diffuses into the packaged food. Conclusively, they are incorporated in people through the food chain. Biocompatibility includes biologic phenomena such as immune response, carcinogenicity, and thrombogenicity. The biomaterial literature of bioresorbable polymer additives is rather poor regarding these points, which should be scientifically considered in the future for complete understanding of plasticizer and plasticized polyester behavior in vivo.

Two bioresorbable membranes for GTR procedures, namely Resolut Membrane (WL Gore, Flagstaff, AZ) and Guidor Membrane (Guidor AB, Huddinge, Sweden), were recently approved by the US Federal Drug Administration (FDA). Several other membranes are under experimental and clinical investigation. Most of them are defined by the FDA as generally regarded as safe (GRAS) until their final clinical success has been approved by the FDA. The experimental and clinical results of bioresorbable membranes and foils from a material, biocompatibility, and design point of view are discussed in detail in another publication.
In general, bioresorbable materials are well tolerated by living tissue. It appears that biocompatibility of bioresorbable polyesters depends primarily on factors other than the polymers themselves. The leaching of low–molecular mass compounds, either because of degradation or because of the presence of leachable impurities, is the major source of triggering inflammation. The massive release of acidic degradation and resorption products contributes to the observed inflammatory reactions of bioresorbable polymers and implants. One other important factor is the location of the implantation. If the capacity of the surrounding tissues to eliminate the by-products is low because of poor vascularization or low metabolic activity, chemical composition of the by-products may lead to temporary local disturbances. One example of this is the increase of osmotic pressure or pH manifested by local fluid accumulation or transient sinus formation. Hence, problems of biocompatibility of bioresorbable polymers such as aliphatic polyesters is definitely related to biodegradability and bioresorbability.

**Mechanical Properties**

In many fields of surgical application such as sutures or internal fixation devices, the strength of the material is an important aspect. In general, the mechanical properties of aliphatic polyesters are similar to other polymers but quite different from the strength of bone or metals (Table 2). Mechanical properties of polymers are strongly dependent on their molecular weight, orientation, and crystallinity; material purity; the presence of defects, voids, and/or reinforcing elements in the material; as well as the polymer chemical structure. Polymer tensile strength and moduli increase with increasing molecular weight up to a plateau of molecular weight, which differs for different polymers. The increase in polymer crystallinity and orientation enhances mechanical properties in the direction of the orientation. The presence of reinforcing structures, such as fibers and whiskers, improve mechanical properties. The presence of impurities and/or additives make it worse. Aliphatic polyesters are viscoelastic materials. Independent of the degradation process, such materials show time-related changes in their mechanical behavior such as creep and relaxation. This must be taken into consideration for the function of bioresorbable implants and devices. Polymers that are relatively stiff at room temperature become more and more flexible and elastic until they reach their glass transition point. These properties are used to improve the malleability of bioresorbable membranes at body temperature.

**Sterilization**

The susceptibility of aliphatic polyesters to hydrolysis presents problems when using conventional methods of sterilization. Because these polymers are heat, moisture, and radiation labile, choosing the right method of sterilization is a major problem. Steam and dry heat sterilization lead to unacceptable changes of implant shape and design. Electron beam irradiation and low temperature plasma sterilization still need to be researched further. Currently available methods for the sterilization of
bioresorbable, biodegradable, and bioerodible implants include gamma irradiation and ethylene oxide (EtO) sterilization. 69

**Gamma Irradiation.** A viable alternative method of sterilization for bioresorbable, biodegradable, and bioerodible polymers and implants is provided by gamma irradiation. This procedure is known to induce structural changes such as main chain scission and/or cross-linking in the irradiated polymer. Numerous studies of the radiation degradation of polymers that have oxygen atoms in the main chain have been reported in the literature. These polymers exhibit exceptionally high sensitivity to radiation. 69-71 Similar studies 71,72 on polymers containing oxygen in the backbone have also been done. Some researchers 73 observed that the quaternary C atom plays an important role during the radiation degradation of such bioresorbable polymers and implants. These changes may, in turn, affect the polymer and implant properties such as mechanical strength, degradation kinetics, molecular weight, and implant design. Therefore, it is advisable to have controlled environments, such as a nitrogen atmosphere and a low polymer moisture content, when gamma irradiation is to be used for sterilizing bioresorbable, biodegradable, and bioerodible polymers and implants.

**Ethylene Oxide Sterilization.** Ethylene oxide is used extensively for the sterilization of medical supplies and devices that are heat sensitive. Because EtO is known to be a very reactive agent, residuals of EtO are considered to be a risk for patients. This is particularly true in continuously or repeatedly applied medical devices such as bioresorbable and biodegradable implants. Protracted aeration (ie, degassing) times are necessary after sterilization to reduce EtO residues to an acceptable level. The US FDA published proposed residue limits for medical devices in 1978. These limits vary from 25 to 250 ppm, depending on device application. However, there is a strong tendency to lower this range. According to a recommendation from the German Bundesgesundheitsamt (BGA), medical devices and implants should only be sterilized with EtO if the polymer materials do not allow any proven alternative method. In addition, the BGA requires that medical devices and implants not contain any EtO that can be measured by a method sensitive to 2 ppm. The specific aeration time necessary for a particular polymer material or implant depends on many variables, eg, the composition, weight, form, and design, as well as the type of EtO sterilization system employed. A study by Hutmacher et al 69 showed that it takes approximately 6 to 8 weeks of degassing to reduce an initial EtO residue level of 40 ppm to the tolerable level of 2 ppm for a bioresorbable minipin made of poly(L-lactide-co-D,L-lactide) 70:30 ( Fig 4). This injection-molded nonporous device was developed for the fixation of bioresorbable and biodegradable membranes. The minipin had an intrinsic viscosity of 2.0 dL/g and a mass volume of 0.015 g. For polymers with a glass transition point (Tg) lower than 40°C, the influence of implant shape is also a problem. The necessary prehumidification during EtO sterilization also affects the highly hydroscopic polymers. Residual moisture in the permeable foil or paper bag could lead to the
initiation of a slow degradation process in the stored product.


### Table 1 Types of Collagens

<table>
<thead>
<tr>
<th>Type</th>
<th>Class</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>α1, α2 (I)</td>
<td>Skin, tendons, bone</td>
</tr>
<tr>
<td>II</td>
<td>α1 (II)</td>
<td>Cartilage</td>
</tr>
<tr>
<td>III</td>
<td>α1 (III)</td>
<td>Skin, internal organs, vessels</td>
</tr>
<tr>
<td>IV</td>
<td>α1, α2 (IV)</td>
<td>Basement membrane</td>
</tr>
<tr>
<td>V</td>
<td>α1, α2, α3 (V)</td>
<td>Cell-associated, skin, muscles</td>
</tr>
<tr>
<td>VI</td>
<td>α1, α2, α3 (VI)</td>
<td>Microfibrils</td>
</tr>
<tr>
<td>VII</td>
<td>α1 (VII)</td>
<td>Anchoring fibrils</td>
</tr>
<tr>
<td>VIII</td>
<td>α1 (VIII)</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>IX</td>
<td>α1, α2, α3 (IX)</td>
<td>Cartilage</td>
</tr>
<tr>
<td>X</td>
<td>α1 (X)</td>
<td>Cartilage (hypertrophy)</td>
</tr>
<tr>
<td>XI</td>
<td>α1, α2, α3 (XI)</td>
<td>Cartilage (type V equivalent)</td>
</tr>
<tr>
<td>XII</td>
<td>Similar to type X</td>
<td>Cartilage</td>
</tr>
<tr>
<td>XIII</td>
<td>α1 (XIII)</td>
<td>Cartilage, bone, skin</td>
</tr>
</tbody>
</table>

### Table 2 Mechanical Properties of Different Materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Tensile strength (N/mm²)</th>
<th>Bending strength (N/mm²)</th>
<th>Modulus (N/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(L-lactide)</td>
<td>70</td>
<td>120</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Poly(D,L-lactide)</td>
<td>50</td>
<td></td>
<td>3,000,000</td>
</tr>
<tr>
<td>Polydioxanone</td>
<td>30</td>
<td></td>
<td>200,000</td>
</tr>
<tr>
<td>Polyhydroxybutyrate</td>
<td>40</td>
<td></td>
<td>4,000,000</td>
</tr>
<tr>
<td>Poly(methyl methacrylate)</td>
<td>80</td>
<td>140</td>
<td>3,000,000</td>
</tr>
<tr>
<td>Steel 316L</td>
<td>1,000</td>
<td></td>
<td>200,000</td>
</tr>
<tr>
<td>Titanium</td>
<td>700</td>
<td></td>
<td>100,000</td>
</tr>
<tr>
<td>Titanium alloys</td>
<td>900</td>
<td></td>
<td>125,000</td>
</tr>
<tr>
<td>Bone</td>
<td>200</td>
<td></td>
<td>20,000</td>
</tr>
</tbody>
</table>
used for synthesis of aliphatic polyesters.

Fig. 1 Monomers

versus mass volume loss.

Fig. 2 Molecular weight decrease
Fig. 3 Krebs’ cycle.

Fig. 4 Ethylene oxide residue level analysis of an injection-molded nonporous device—namely, a bioreabsorbable minipin for GTR and GBR applications.