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Selection, Characterization, and Biodegradation of Surgical Epoxies

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SUMMARY

A series of epoxy resins has been formulated on the basis of obtaining low water sorption, low water vapor permeability, retention of electrical properties, and resistance to biodegradation by the body. These resins have been tested for these properties both by accelerated aging in 100°C water and in vivo studies.

A literature survey was conducted on the biodegradation of surgical plastics with the findings that nylon lost 80% of its tensile strength after 3 years implantation while Orlon and Dacron deteriorated considerably less in a 2-year period. Teflon, Silastic, and Mylar showed almost no loss in tensile strength after 17 to 22 months.

The epoxies tested on this program showed no loss in strength after 6 months in vivo.

It appears that materials whose chemical structure contain bonds similar to those found in the body (such as amide groups) are susceptible to biodegradation whereas those such as Teflon which contain only C–C bonds or C–F bonds are not.

Two general types of biodegradation can occur on polymers: Attack starting at the end of a polymer chain and proceeding along the chain to produce monomeric fragments (as in polypropylene), and attack at regular intervals along a polymer chain where susceptible cross-linking groups are present to produce macromolecular fragments.

It has been postulated that attack on polymers takes place in the amorphous areas (if they are present) to leave the more crystalline areas of the material intact. Thus, with implantation, these types of materials become brittle.

Histology on the developed epoxies indicated that epoxies containing nonreactive hydrophobic diluents showed a greater foreign body reaction than normal epoxies without such diluents.

INTRODUCTION

In the past decade there has been an ever-increasing use of plastics in the fabrication of medical prostheses for implantation in the body. Plastics as a group have been chosen for such properties as their ease of fabrication, noncorrosiveness, light weight, strength, acceptability by the body, insulation, low curing shrinkage, and hardness. The obvious and most critical criteria for the selection of these materials, however, have been the degree of degradation, or loss of physical properties, suffered by these plastics and the body's response to them.

This paper concerns itself with the selection of epoxy resins that will maintain their good physical properties when implanted. A discussion of biodegradation mechanisms is also included. Though foreign body response to these epoxies is directly related to the biodegradation which they undergo, it is not the purpose of this paper to elaborate on their mechanisms. This will be covered by a subsequent paper.

A series of low permeability, low water sorption, rigid epoxies for the encapsulation of medical prostheses are under development.* Through the proper choice of curing agents and epoxies, resins have been formulated that should prove to be compatible with body tissues. A brief research outline for this program is presented in Fig. 1.

SELECTION OF EPOXY RESINS AND CURING AGENTS

Aside from failure of mercury batteries and breakage of electrical leads at their point of entrance into a prosthesis, the most common cause of

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Development, Characterization, and Biodegradation of Surgical Epoxies

I. Selection of epoxy resins and curing agents based on theoretical considerations.
   A. Selection of epoxy resins.
   B. Selection of amine curing agents.

II. Physical characterization of selected systems.
   A. Water vapor permeability.
   B. Water sorption.
   C. Electrical properties.
   D. Tensile strength.
   E. Hardness.

III. Biodegradation of selected systems.
   A. Tensile strength.
   B. Hardness.
   C. Surface attack.
   D. Biodegradation mechanism.

IV. Tissue compatibility of selected systems.
   A. Toxicity.
   B. Rejection.

Fig. 1. Program outline for development and testing of surgical epoxies.

failure of electrical prosthetic devices is leakage of water and ions from body fluids into the electrical components of the device. These leakages, which occur directly through the encapsulant and at the point of electrical leads, lead to premature failure of the device.

The silastic materials presently used, which have shown good tissue compatibility, are unfortunately unsatisfactory in preventing the transmission of body fluids.

In view of the good adhesive, electrical, and physical properties of the epoxy resins, these polymers appeared to be ideally suited to encapsulation purposes. However, careful selection of the correct type of epoxy resin and curing agent is necessary to obtain the lowest water sorption and water vapor permeability values possible.

Epoxy resins were recently selected for use as dental resins for the fabrication of dentures. Improper selection of materials resulted in swelling of

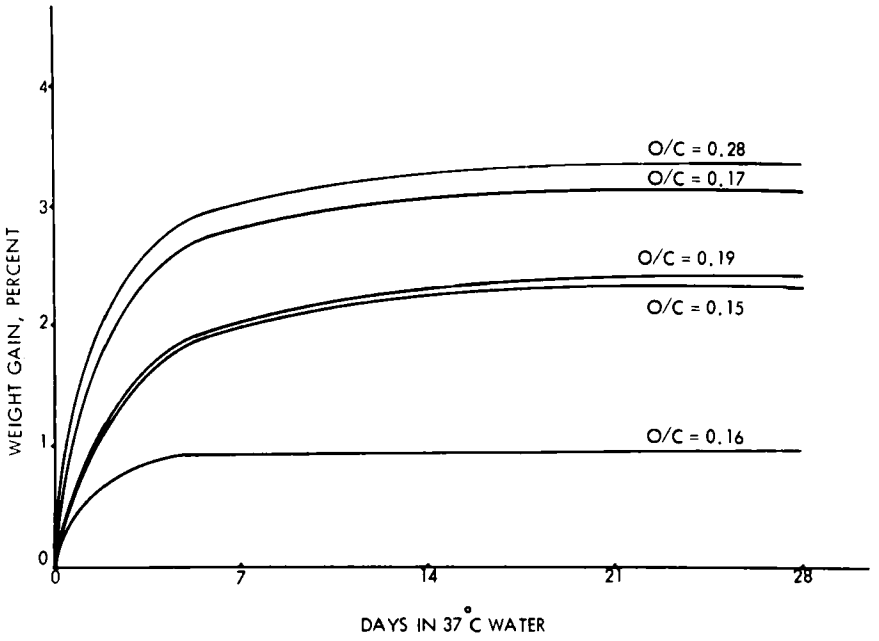

Fig. 2. Water sorption of several aromatic epoxy resins of varying O/C ratios.

the dentures after 1 year in the oral environment. Thus, the need for low-water sorption values is evident, as this leads to ingress of body fluids and biodegradation in addition to loss of insulation and physical properties.

The ratio of O/C or N/C in an epoxy resin or amine curing agent is a measure of the hydrophobicity of that molecule, as oxygen and nitrogen are hydrophilic atoms while carbon is hydrophobic. The O/C ratio can be reduced significantly by methylation of an epoxy.[7] Figure 2 illustrates the hydrophobic effects encountered when epoxies of varying O/C ratios are cured with the same curing agent. Those with lower O/C ratios show reduced water pickup.

Water sorption and water vapor permeability can also be significantly decreased by the halogenation of an epoxy or the addition of a hydrophobic nonreactive diluent to it.

The most promising of these epoxy types were selected for evaluation. They were combined with low N/C dialicyclic diamines and other potentially suitable curing agents.

PHYSICAL CHARACTERIZATION OF SELECTED SYSTEMS

Standard methods of measuring water vapor permeability, such as the Payne Permeability Cup, have proven unable to measure the low transmission values of these epoxies. Permeability has, therefore, been measured using an isotope method. Testing has shown these materials to be low in permeability as compared to the standard epoxies. Water sorption of these systems, given in Fig. 3, shows that these epoxies ranged between 1 and 3%, with the best systems being 1, 3, and 4.

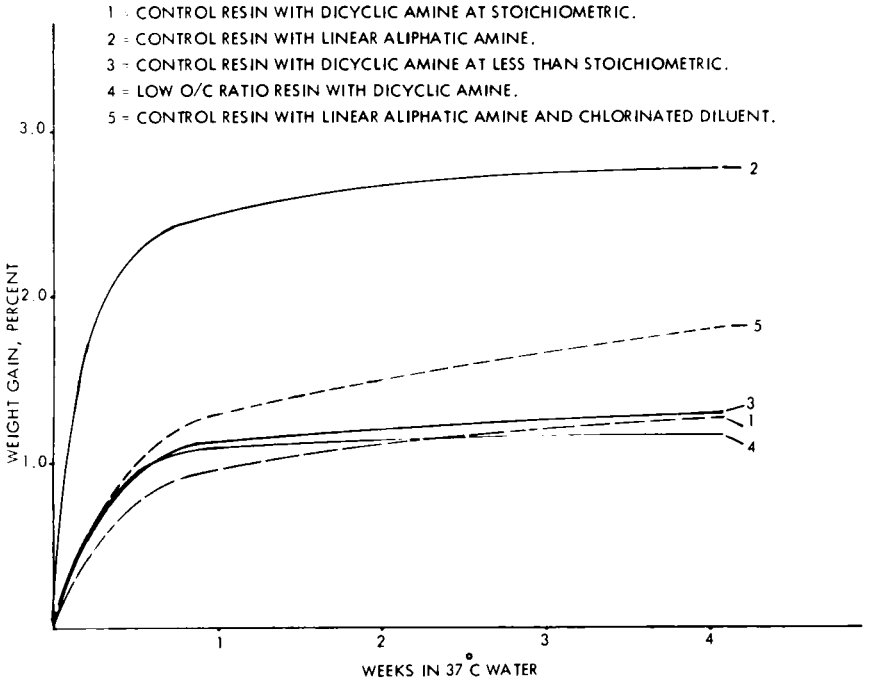

Fig. 3. Water sorption of epoxy encapsulation materials.

The selection of the best encapsulation resin was also based on the results of retention of electrical properties during accelerated aging in 100°C water. Figure 4 illustrates the dielectric loss values for the materials tested. Included in this graph is a control resin (System 1) for comparison. As can be seen, two of the materials screened showed significantly better initial and final dielectric loss factors than the control resin.

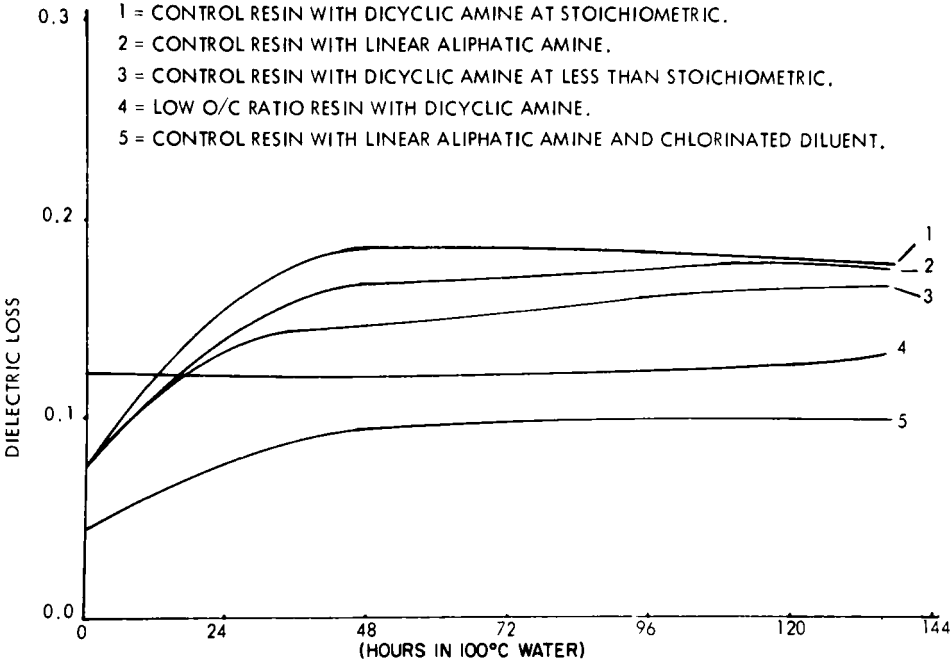

Fig. 4. Dielectric loss of uncoated epoxy encapsulation materials upon accelerated aging.

Tensile strength values for these epoxies were found to range between 7,000 and 11,000 psi, while hardness ranged from 75 to 85 Shore D.

BIODEGRADATION OF SELECTED RESINS (LITERATURE SURVEY)

Probably the most apt description of the available literature pertaining to the biodegradation of surgical plastics is by Leininger who said, "The literature for the past eight years has been surveyed, and only five instances have been found in which measurements of the changes in properties of plastics upon implantation were made. In view of the fact that plastics are used as implants in applications where their physical properties are of vital importance, this lack of information borders on the incredible" [1]. A summary of the literature survey follows.

As could be expected, the information found on biodegradation of physical properties was mostly related to those materials that have been

Table 1. Per cent Tensile Strength Loss of Surgical Plastics after Periods of 17 to 26 Months in vivo [1]

Material	Months in vivo	Tensile strength loss (%)
Thermoplastic polyurethane	8	78
	16	Disintegrated
Nylon (polyamide)	36	81
	17	44
Orlon (polyacrylonitrile)	24	24
Dacron (polyester)	26	11.5
Teflon (polytetrafluoroethylene)	22	6
Silastic (silicone)	17	2.0
Mylar (polyester)	17	0

found to be most accepted by the body. These are silicones, polyethylene and its halogenated derivatives, polyesters, and super-polyamides [2], as shown in Table 1. Though there is an obvious need for standardization in test animals used, size and configuration of test specimens, sterilization procedures before implantation, and methods of testing physical properties, data gathered agree as to the general degree of degradation of a given material [3]. Though implantation times are not at all equal and vary between 17 and 26 months, they can be listed in order of decreasing loss of tensile strength after implantation as follows: thermoplastic polyurethane (disintegrated), nylon (polyamide) (44% loss), Orlon (polyacrylonitrile) (24% loss), Dacron (polyester) (11.5% loss), Teflon (fluorinated polyethylene) (6% loss), Silastic (silicone) (2% loss), and Mylar (polyester) (no loss).

Despite the fact that different animals were used in obtaining data on these materials and specimen size varied from thin to thick sheets and even filaments in some cases, this indicates broad differences in resistance to biodegradation with Mylar, Silastic, Dacron, Teflon, and Orlon proving to be best.

To establish the effect of biodegradation of our epoxy materials, microtensile bars (1/2 scale of ASTM Spec. #D 1708) from 30 to 35 mils in thickness were implanted subcutaneously in experimental dogs. This thickness was used because it has been found, for these rigid materials, to be

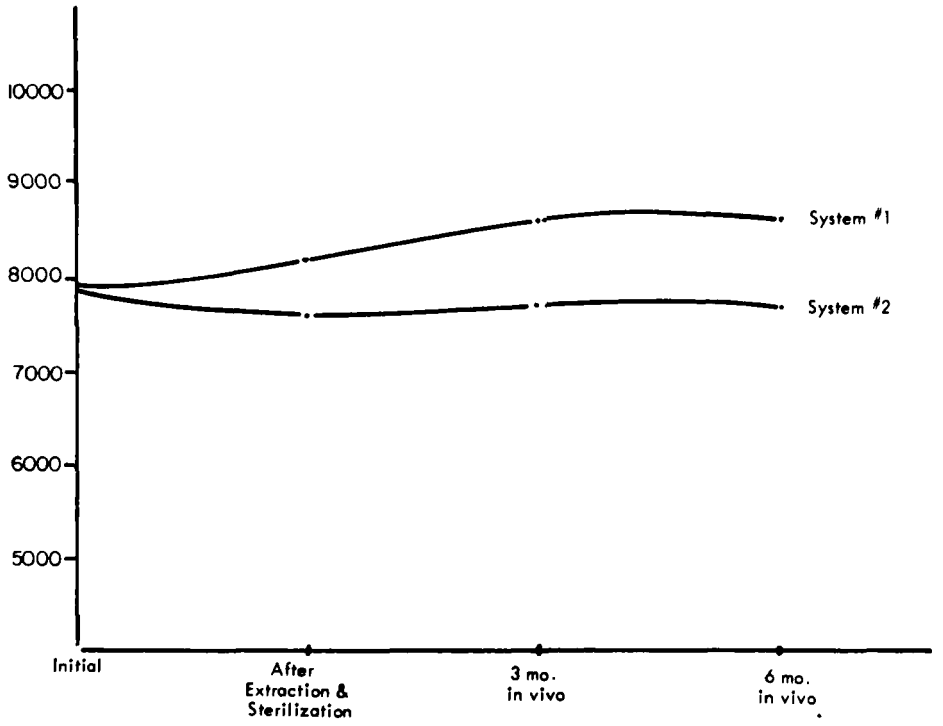

Fig. 5. Tensile strength vs time in vivo of two epoxy encapsulation resins.

the minimum thickness allowable if sufficient strength is to be maintained to prevent breakage during implantation and excision. It remains to be determined if this arbitrary thickness will show significant changes in physical properties. The ideal thickness, of course, would be 0.001 or 0.002 in. where biodegradation effects would be pronounced.

To remove surface contaminants and any unreacted resin components near the surface, all tensile bars received a 16-hr extraction in distilled 80-90°C water in a 2-liter capacity Soxhlet. Sterilization was accomplished in an autoclave at 250°F for 20 min.

Samples were tested after initial cure, after extraction and sterilization, and at regular intervals in vivo.

To date, data from two of these systems after 6 months in vivo has been obtained. Tensile strength is presented in Fig. 5. Tensile values for system #1 dropped from 7960 to 7625 psi, representing a 4.4% decrease. This

Fig. 6. SEM photograph of surgical epoxy after extraction.

material was unaffected by extraction and sterilization. System #2, whose initial tensile strength was 7880 psi, was cured further during the extraction and sterilization cycle, and it gave a tensile strength value of 8213 psi after 6 months in the body. Thus, for a period of 6 months in the thicknesses tested, losses in tensile strength were negligible. Hardness values of 83 and 84 Shore D, respectively, for these two resins were also unchanged.

Figure 4 illustrates the type of accelerated aging which is being conducted to simulate aging in the body and subsequent loss in tensile strength as a result of storage in 100°C water. A direct correlation between days in 100°C water and years in the body will enable quick screening of new materials.

Low permeability and low water sorption were produced in system #1 by the addition of a hydrophobic, nonreactive diluent to the resin. In Figs. 6 and 7 the differences in surface texture of this material after extraction and after 6 months in vivo are shown in scanning electron microscope

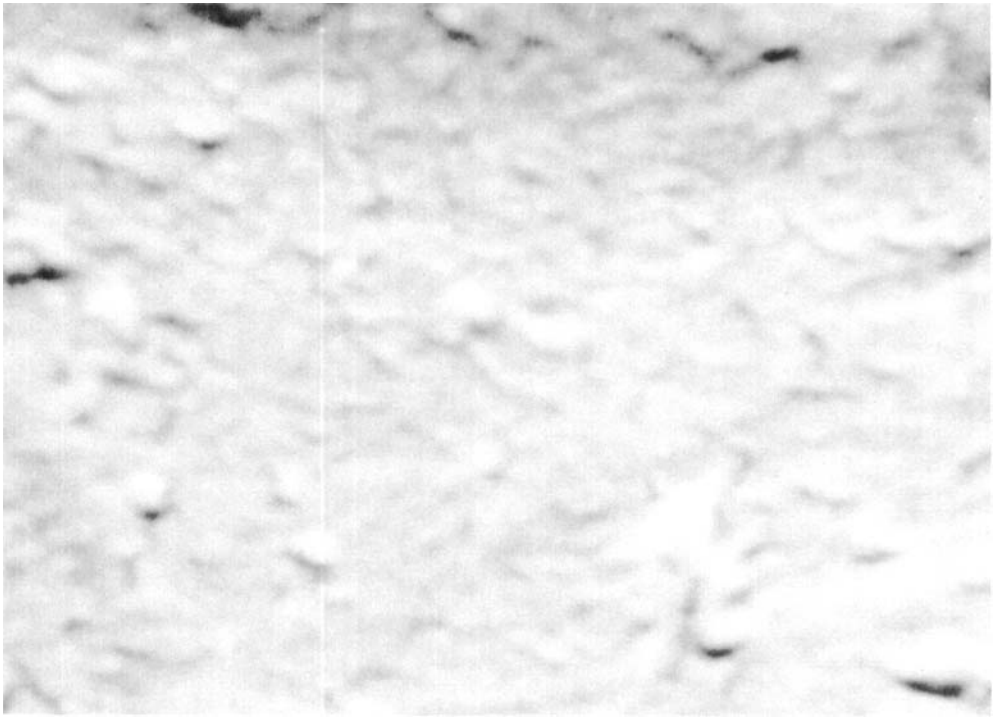

Fig. 7. SEM photograph (3,000X) of medical epoxy after extraction and 6 months in vivo.

photographs. Surface changes between the control sample and the extracted samples were not detectable. However, the increased roughness of the in vivo material as compared to the extracted resin is evident. The body has succeeded in removing susceptible polymer chains and possibly deposition of protein has taken place on the surface.

Turning now to biodegradation mechanisms, Atlas and Mark [4] have proposed that three basic factors influence the extent to which a synthetic polymer will be degraded in the body. These are 1) type of chemical bonds present, 2) steric hindrance and electronegativity effects produced by atoms in close proximity to these chemical bonds, and 3) the supermolecular structure of the polymer (amorphous or crystalline).

In general, chemical bonds in polymeric materials are degraded by the body in exactly the reverse mechanism in which they were formed. Sulfide

(−SO), disulfide (−S−S−), and ester (−C−O−) bonds are sensitive to heat and alkali, acetalic ($-O-CH_2-O-$) groups are sensitive to acids, and urethane groups ($-NH-\overset{\overset{O}{\|}}{C}-O-$) are affected by elevated temperatures. Any of these bonds can be broken through enzyme and/or antibody catalytic action.

It is an interesting theory based on observation, however, that as chemical groups in the polymer become less related to those that might be found in the body, biodegradation decreases. This is well illustrated by the marked loss of physical strength which takes place in nylon (which contains amide groups similar to those found in nucleic acids and other body substances) in contrast to the small effect which the body has on Dacron (polyester). What could be considered the least similar materials to the body are those with carbon-carbon or carbon-halogen bonds such as Teflon and polyethylene. These materials have repeatedly proven to withstand attack by body fluids.

The most inert material appears to be vitreous carbon. This material, a carbonized polymer, is extremely hard and contains no bonds other than carbon-carbon. Unlike polyethylene or polypropylene, which contain only carbon-carbon bonds in helix coils, vitreous carbon is theorized to possess a cyclic (6-membered ring) structure which makes it especially inert. It has been investigated by us and others, and it has been found to exhibit apparently no foreign body response whatsoever. Indeed, the body seems to be unaware of its presence since it cannot find familiar sites for chemical attack.

Atoms which are in close proximity to cross-linking groups also help to shield the group from hydrolysis or oxidation. The chlorinated analog of polyethylene, or Teflon, is more resistant to degradation than polyethylene itself. Thus, methyl groups or halogen atoms on polymers can greatly improve the chemical resistance of these materials by steric hindrance factors and/or electronegativity effects.

The last basic consideration which influences biodegradation in a polymer is the macromolecular configuration. In almost any synthetic polymer, highly crystalline areas are present which are surrounded by amorphous areas where molecular arrangement has little regular geometry. A typical case is that of flexible polyurethanes. Crystalline areas consisting of MDI molecules in close proximity are surrounded by long polyether chains which uncoil to slide by each other and impart elastomeric properties to the material. While the crystalline areas are packed more tightly together as a

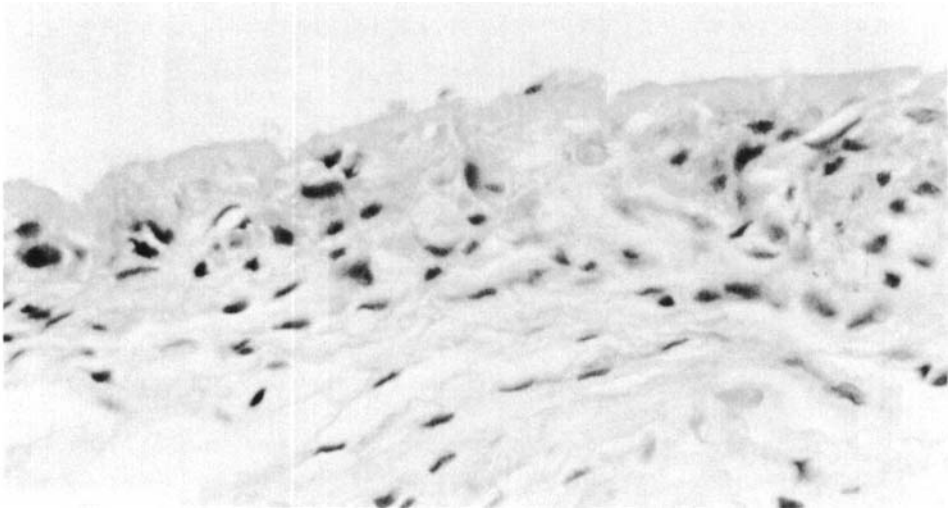

Fig. 8. Cross section of epoxy containing nonreactive diluent after 6 months in vivo.

result of molecular geometry and intermolecular forces, the more amorphous areas of polymer chains are randomly arranged and are more susceptible to passage of body fluids and attack by these fluids. The result is attack of the amorphous areas through chemically susceptible bonds and removal of these polymer chains. Consequently, when the polymer loses its physical properties in this way, it becomes brittle because the more crystalline areas remain in the polymer.

Depending upon the type of polymer, biodegradation can take place by way of two different mechanisms. In the first, polymers made up of small repeating monomeric units such as polyethylene can be attacked at a chain end. A proton is shifted to the next group, and degradation takes place progressively down the chain. Of course, attack can also occur in the center of the chain, from which point degradation then proceeds down the chain. This degradation produces monomeric fragments that are introduced into the blood stream.

In contrast to this, the second type of degradation occurs when polymers consisting of large uninterrupted chains with susceptible cross-linking points at regular intervals are subjected to biodegradation. Degradation in this type obviously occurs at these susceptible bonds and long polymer chains are released into the blood stream.

Though these three factors have been separated for the purpose of a

clear discussion, they are all obviously interacting, and body response is due to these and a host of other factors such as surface potential and distribution of electrical charges on the polymer surface, hardness, cross-linking density, and ionic bonding.

TISSUE COMPATIBILITY

In histological studies, there were signs that the implanted materials were toxic to host tissue as shown in Fig. 8. Inflammatory cells, including neutrophils, round cells, and macrophages, completely surrounded the discs. A fibrous capsule was developed outside of this granulation tissue. There appeared to be a more acute reaction to the resin containing the nonreactive diluent. With the former substance, a mucoid material occupied the space between the inflammatory tissue and the implant surface. This amorphous, extracellular secretion stained strongly with periodic acid-Schiff, indicating that it was probably a glycoprotein.

Evidence that the tissue response was due to toxic chemical effects, and not the result of infection, was provided by the absence of plasma cells and similar leukocytes associated with chronic infection.

It was suggested that the nonreactive diluent was extractable by tissue fluids and was, therefore, responsible for much of the response.

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