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Polymers in Contact with the Body

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The clinical use of polymeric materials in the body to repair and restore damaged or diseased tissues and organs is substantially increasing on an annual basis. Concomitant with this use is an increase in materials related research on medically used polymers. Information on the historical and current clinical use of polymeric materials is provided in order to establish a basis for the philosophy and problems encountered in assessing the acceptability of various polymers in the biological system. The requisite properties which must be demonstrated by a polymer in contact with the body are discussed from two viewpoints, i.e., the effects of the material on the stability of the host and the effects of the host on the stability of the material. In addition, the effects of synthesis, processing, storage, sterilization, implantation, and possible degradation of polymers are discussed, poly(ethylene terephthalate) being used as an example.

The use of materials in the body to repair or restore damaged, diseased, or ravaged tissue and organs is not new (*1*). First recorded use was from the Edwin Smith Surgical Papyrus, nearly 4000 years old, describing the use of stitches (sutures) in wound repair. Extensive use of a variety of suture materials such as braided horsehair, leather strips, cotton fibers, animal sinews, and bark from the Ashmantaka tree was recorded in ancient Indian literature nearly 2500 years ago.

The first recorded use of nonbiological materials came in 1550, with the use of gold wires as sutures. This was followed shortly by the first use of a biomedical device, a gold plate to repair a cleft palate. Later in the 1800's there were numerous reports of metal plates and pins to fix broken bones. During the last several decades, advancements in the field of materials and surgery has enabled the surgeon to literally rebuild many parts of the human body with artificial parts, organs, and other supporting structures. The large increase in the variety of implants was concurrent with the expansion of the polymer industry and the availability of polymeric materials having properties more similar to the body than their metal counterparts.

The recent use of polymers in surgery have been quite broad: temporary assist materials, such as sutures, surgical adhesives, plasma extenders, relatively simple artificial parts of a more permanent nature, such as vascular grafts, heart valves, hydrocephalic drain tubes, joints, tendons, reinforcing meshes, as well as a variety of soft tissue replacement materials for cosmetic surgery; and the more complex devices such as the artificial kidney, the artificial lung, the artificial heart, etc., which can simulate some physiological process. Indeed, the imagination and skill of the surgeon, and more recently the support and technical assistance of scientists and engineers, have resulted in a great variety of devices and parts being commercially available (*2*).

However, this progress has not been without failure. Most failures have been due to improper choice or processing of the material for the intended use. For example, silicone rubber heart valve poppets can absorb fatlike substances from the blood stream, causing malfunction, fracture of the ball valve, and ultimately, death of the patient (*3*). Also, a number of total hip prostheses whose acetabular cups were made of Teflon required reoperation and removal of the implant because continued compressive stresses caused the polymer to

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flow and distort and to wear severely. The end result was failure of the device after one or two years (*4*).

In many instances, the proper material for a given application has yet to be developed. Those polymers most often used are those readily available from many commercial processes, and practically all are intended for uses and environments which vastly differ from that found in the body. By proper engineering of the implant, however, a successful part for limited use may be obtained. Vascular grafts represent a good example of this.

Early work on synthetic polymer vascular grafts involved solidwall tubes (*5*). However, thrombus and/or damage to the soft vessel walls at the junction with the rigid tube, lead to minimal success (*6*). More extensive studies in adapting these synthetic polymers to vessel wall replacement focused on the findings that porosity appeared to be a necessary requirement (*7,8*) and was most easily achieved by the use of polymer fibers processed in fabrics or knitted into tubings.

A number of commercial fibers were explored. Of these, poly(ethylene terephthalate), or Dacron, appeared to be the better material in terms of its minimal toxicological response, its durability, and its mechanical properties. There were problems, however, such as seepage of blood because of the porosity; occlusion of the vessel in smaller diameter grafts, or in grafts in the venous system; and a process of fibrous ingrowth, contraction, calcification, etc., which occasionally caused failure. The latter appears to be the result of a normal wound healing response within the graft structures. Nevertheless, an acceptable arterial prosthesis was now available to the surgeon (from a nonblood-compatible polymer) even though there were limits to its use in terms of graft internal diameter, and location in the vascular system.

Concurrent with these studies have been the improvements in development of artificial lung devices, artificial kidneys, and arteriovenus shunts which allow repetitive extracorporeal dialysis, heart valves, and more recently the artificial heart and various heart assist devices. As a result of these developments, there is an increased emphasis on biomedical materials. A recent paper (*9*) describes 17 new potentially blood-compatible surfaces, none of which were available prior to 1960. However, of these only the polyurethane types have reached some degree of availability in devices.

Of the many problems associated with biomedical polymer research, the need for a better understanding of the environment in which a polymer is used is perhaps most important. Even with this knowledge an improper device design or an improper implantation technique can often mask a good material. Thus the search for new biomedical polymers must truly be an interdisciplinary activity.

Many of the problems reported for polymeric implants could conceivably be eliminated if "pure" high molecular weight polymers were used. The large amounts and infinite variety of additives in polymers are perhaps the most significant contributors to the biological response evoked after their implantation. For example, a variety of additives, such as plasticizers, antioxidants, ultraviolet and radiation stabilizers, antiozonants, residual monomers, and catalysts, and in the case of textiles, sizing and finishing agents, whiteners, antistatic agents, and even flame retardants are occasionally released by the polymer at the site of implantation. While some investigators have attempted to make these polymers more medically acceptable for their studies by an extensive series of washings and extractions in an attempt to eliminate the additives, these processes are only successful to a point. The mechanical properties of the polymer are often affected by the extraction process. Thus, a compromise must be reached between the relative impurity levels in the material and the retention of adequate mechanical behavior. Also, the remaining concentrations of impurities can still effect the overall biotolerability of the implanted polymer.

These additives are not needed in implant polymers. However, because of the low poundage of polymer needed in these applications, many device makers have been forced by economics to use nonmedical grade materials. This lack of a large commercial market for biomedical polymers has deterred large commercial companies from entering the field. In addition, the general shortage of materials scientists who have interacted with medical research has also been a major factor in the slow development and use of new polymeric materials designed specifically for biomedical applications.

During this last decade, however, a considerable awareness of the inherent problems associated with polymeric implants has developed, and a more unified approach to the problem of the use of a synthetic material as an implant has evolved. This considered the implanted material from two standpoints: the effect of the particular implant upon the body, from the cellular to the systemic level, and the effect of the body on the implant. The latter is important in determining the long-term performance of the implant in the body environment.

Complete answers to these effects are not available this time. The considerable amount of empirical information currently available on the use and performance of a variety of materials in the body and related physiological environments does, however, make it possible to outline the characteristics that must be considered when investigating polymers for biomedical applications (*1*).

In determining the effect of the implant on the body, the characteristics of the material that must be considered are: toxic or irritational qualities of the material or its breakdown products (molecular level), or of additives incorporated into the material; mechanical characteristics of the material; fabricability of the material into the desired implant form and the effect of fabrication on altering the material, i.e., oxidation of the surface, residual solvent, mold contamination, etc.; quantity of the material (systemic level); size and shape of the material (tissue level); surface structure of the material (cellular level); sterilizability of the material; possible antigenicity of the material (immunological response); thrombogenicity; antileukotaxis (infection predisposition); carcinogenesis.

In determining the effect of the body on the implant, the material must be examined for changes such as: degradation or other changes in molecular structure (i.e. crosslinking or phases); changes in mechanical properties; wear particles; state of hydration; elution of low molecular weight species; protein saturation or oxidation of the surface; cellular ingrowth; calcification.

As one can see, an implant polymer is exposed to a variety of microenvironments within the body; the degree of response which is acceptable depends on how long the implant must remain functional. One area of response that is influenced by many of the synthesis and processing variables discussed in the earlier papers of this symposium is the degradation of the polymer in the physiological environment. The degradation of poly(ethylene terephthalate) or PET, can be used as an example.

Because of its extensive use as a textile fiber, much is known regarding the nonphysiologic degradation mechanisms of PET. These include thermal (*10*), oxidative (*11*), radiation-induced (*12*), and hydrolytic (*13*) degradations. Application of these mechanisms to the analysis of PET as an implant material produces interesting implications, especially when considering the environment to which an implant is subjected, i.e., storage, sterilization (and in some cases repeated sterilization), and implantation.

The storage environment, for example, of an implant is obviously a point worthy of consideration. However, far too many variables are present, such as environmental conditions of the storage area, materials stored with the implant, lighting facilities, and even initial packaging procedures, to lend any concrete evidence to degradation resulting from storage. Interesting enough, however, are the facts that information or instructions are almost never listed on packaged implants regarding their storage, and that most are supplied as "sterile" packages with no indication of prior sterilization procedures.

Sterilization effects on polymeric materials are very seldom given proper attention. Most polymers are not sufficiently thermally stable to withstand a dry heat sterilization technique (160–180°C). In the case of PET textile materials, ethylene oxide sterilization requires long waiting periods (several days in some cases) before the residual traces of the gas are removed from the implant after its exposure. γ-radiation sterilization (often used in sterile packaging) could lead to severe degradation reactions, depending on the dosage and time of exposure. Thus, the method of choice is usually steam sterilization at temperatures ranging from 120°C to 135°C (*14*) for time periods which average 15 to 20 min. In some cases, such as flash autoclaving, even higher temperatures are used for shorter periods of time.

Thus, it is conceivable that even before the PET has been implanted, it may have been

sufficiently degraded so that meaningful predictions of its function life are not possible. Not all of this results from hydrolysis of the labile ester linkages in PET, but also involves abnormal linkages present in the chain due to the thermal nature of the PET polymer synthesis. As a result of these linkage variations, Buxbaum (*11*) has proposed that oxidative degradation can occur in PET at a temperature as low as 100°C. The mechanism he proposes is based on the attack of abnormal diethylene glycol segments within the chain reported to be present in concentrations of 2.0–2.5 mole-% (*15*). Miyagi (*13*) has shown that extensive hydrolytic attack of PET with water can take place at 130°C in 24 hr, mainly concentrated in the amorphous regions of the polymer. Asmus and Fleissner (*16*) report that ester bonds in PET are prone to hydrolysis and recommend that the permanent use of the material in steam or water above 70°C should be avoided. Furthermore, Scales and Lowe (17) have reported that autoclaved PET disintegrated after refluxing in a normal saline solution. As a further extension of degradation mechanisms, virtually nothing is known regarding the susceptibility of PET to attack under physiologic conditions by enzymes, proteins, etc.

Thus, much more research must be done in the area of both short-term and long-term degradation effects of polymer implant materials in order to establish viable performance standards. While this has not been a serious problem with implants thus far, it remains to be seen whether its significance is justified.

In summary, what we hope to have accomplished in this brief review of polymers in contact with the body is a demonstration of the complexity of the interaction of the body and the polymer implant. While careful, meaningful research in the bioengineering field is difficult and extremely time-consuming, it must be accomplished if serious health hazards are to be kept to a minimum in the future.

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