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Review
Biodegradation of surgical polymers

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This work combines a review of the literature on the degradation of polymers in the physiological environment with a description of a series of experiments concerned with the role of components of that environment, such as enzymes, lipids and bacteria, on such degradation.

1. Introduction

Polymeric materials have been used in medical and surgical applications for 30 to 40 years [1–6], often in situations where there is intimate contact with living tissues. Although the specific materials requirements will differ according to the nature of the application, it is a fundamental requirement in each and every case that the polymer should display adequate biocompatibility. This implies that, for permanent implant applications, the material should not degrade within the physiological environment, nor should it have any adverse effect on the tissue, and that for short-term intentionally degradable prostheses, the rate of degradation and the release of degradation products should be physiologically tolerable.

In theory, polymeric-based materials have one significant advantage over metals, since, although the isotonic saline solution that comprises the extra-cellular fluid is extremely hostile to metals, it is not normally associated with the degradation of synthetic high molecular-weight polymers. Since the tissue response to an implanted material is often associated with the degradation of that material and the release of degradation products, this physiological inertness augurs well for good overall biocompatibility. Such a prediction is generally upheld by practical and clinical experience and it is commonly observed that the implantation of pure homo-chain high molecular-weight polymers elicits minimal response from the tissues.

In many situations this minimal response is regarded as ideal, but there are several points which deserve attention in this respect.

(a) The above generalization does not hold good for all polymers and there are some, and especially the hetero-chain polymers, which are not totally resistant to environmental degradation and have the potential for initiating a greater response.

(b) As noted above, there are some applications where it is actually desirable that the polymer degrades either in the course of its particular function (such as controlled drug release via matrix erosion) or after a specific function has been performed (such as after bone union in disposable fracture plates).

(c) Although strictly controlled, surgical polymeric materials may have to contain some additives, such as plasticizers, which themselves have a potential to irritate the tissue, especially if they are leached out from the plastic.

(d) It is not correct to assume that the physiological environment is a simple isotonic saline solution and it cannot be modelled in such a way. The extracellular fluid itself is complex, containing a variety of anions, cations and organic species, while the cells themselves may play very important parts in some reactions. It is, therefore, necessary to consider the degradation of polymers in the light of this more complex environment.

In the present work the degradation of surgical polymers is reviewed and some recent experimental work on the subject is discussed. Frequently, any degradation process that occurs in the body is referred to as biodegradation. This is not strictly correct, since biodegradation implies an active role for the biological media. Any changes produced

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simply by the aqueous extracellular fluid not involving any vital function of the host, (such as simple hydrolysis) are not examples of biodegradation. Emphasis is placed in this paper on this latter aspect and a distinction is drawn between conventional degradation in a physiological environment and biodegradation.

2. Susceptibility of polymers to degradation under physiological conditions

All polymers are susceptible to degradation [7], but the conditions under which this occurs and the kinetics of the reactions are extremely variable. The degradation processes can generally be divided into two types. Firstly, there are those which involve the absorption of some kind of energy to cause disruption of primary covalent bonds to form free radicals, which then cause the propagation of molecular degradation by secondary reactions. Secondly, there are hydrolytic mechanisms where the depolymerization process can be seen as the reverse of polycondensation.

The conditions under which the first of these general processes takes place include elevated temperatures, especially in the presence of oxygen to give thermal oxidation, electromagnetic radiation (i.e., γ-rays, X-rays or ultra-violet radiation), mechanical stress at elevated temperatures giving thermo-mechanical degradation and ultrasonic vibration. Clearly, the physiological environment within the human body does not offer any of these conditions to an implanted polymer; hence, the optimistic statement that most polymers should be stable upon implantation.

Hydrolysis, on the other hand, is quite feasible in the aqueous extra-cellular fluid. A number of conditions have to be met in this respect. Firstly, the polymer has to contain hydrolytically unstable bonds. Secondly, for any significant degradation to occur, the polymer should be hydrophilic, otherwise the medium producing hydrolysis will have very limited opportunity for gaining access to the hydrolysable bonds. Thirdly, the hydrolysis has to take place at a physiological pH (around 7.4).

Thus, polymers can be placed in a ranking order of predicted susceptibility to *in vivo* degradation [8] in the sequence:

hydrophobic, no hydrolyzable bonds – most stable;

hydrophilic, no hydrolyzable bonds – may swell, but little or no degradation;

hydrophobic, hydrolyzable – surface activity only; and

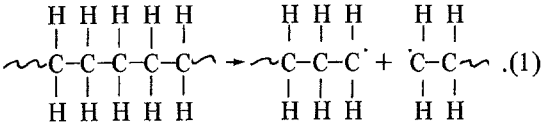
hydrophilic, hydrolyzable – bulk degradation.

The validity of these predictions is discussed below under the two headings of non-hydrolyzable and hydrolyzable polymers.

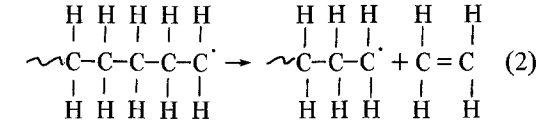
3. *In vivo* degradation of non-hydrolyzable polymers

The types of polymer used in surgery and included here are: some polyolefins (polyethylene and polypropylene), halogenated hydrocarbon polymers (most notably polytetrafluoroethylene) polyacrylic acids and their esters (such as polymethyl- and polyethyl-acrylates), some polyether urethanes and certain silicone polymers (notably polydimethyl siloxane).

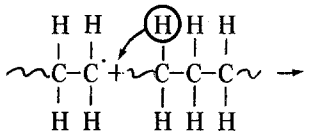
Each degradation process involves initiation, propagation and termination stages. During initiation, energy is absorbed from the external source, causing the breaking of a covalent bond (either the primary chain bond or a cross-link) and the formation of active radicals. Thus, thermal degradation occurs when the vibrational, rotational or translational energy exceeds the activation energy required to break a carbon–carbon bond on increasing the temperature. Considering the polyethylenes as examples, the thermal degradation of pure polyethylene provides one of the simplest cases, with a random chain scission initiation phase:

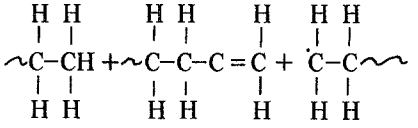


Propagation takes place as follows:



or free radical transfer may take place to terminate the process in any one molecule according to



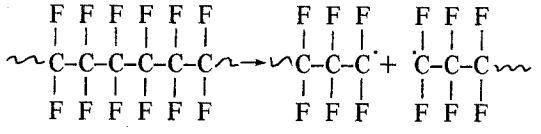


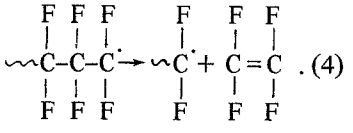
(3)

and termination may take place by either a disproportionation or combination process.

The result will be a mixture of chain fragments of varying sizes and some monomer. If the free radical transfer predominates over the unzipping propagation, then there will be little monomer produced. The activation energy for the degradation varies with physical and chemical factors. According to Madorsky [9], the activation energy for a polyethylene of molecular weight of 23 000 is 66.1 kcal mol^{-1} and that for a molecular weight of 11 000 is 46 kcal mol^{-1}. An unbranched polyethylene will have a higher activation energy than a branched material. The activation energy for polypropylene degradation has been given as 58 kcal mol^{-1}.

With polytetrafluoroethylene the C–F bond is much stronger than the C–H bond so that no free radical transfer is possible during thermal degradation. Chain scission occurs as before, but propagation takes place entirely by unzipping, to yield virtually 100% C_2F_4:





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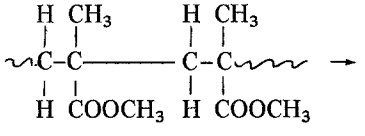
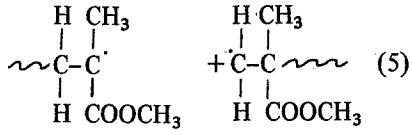
The activation for this reaction is 80.5 kcal mol^{-1}.

The thermal degradation of polymethylmethacrylate is rather similar, involving random chain scission and unzipping to yield substantial amounts of monomer,





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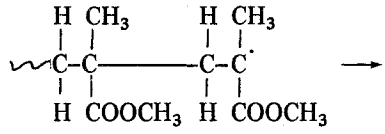
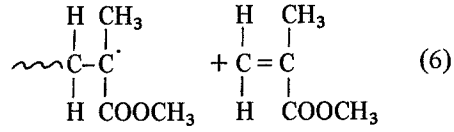
and





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In this case the steric hinderance associated with the CH_3 and $COOCH_3$ groups prevents free radical transfer. The activation energy is variable, depending on the stage of the process, being 32 kcal mol^{-1} at the beginning, rising to around 40 kcal mol^{-1} as the reaction proceeds [10].

Radiative degradation of synthetic polymers largely involves either ultra-violet (u.v.) or high-energy radiation, the latter being defined for these purposes as radiation composed of photons or particles of higher energy than that encountered in binding electron orbitals. As discussed by Shalaby [11], the radiative degradation caused by u.v. light is called photolysis and that caused by high-energy radiation is called radiolysis. Radiolysis is far more significant than photolysis in pure synthetic polymers. The ability to degrade increases as the wavelength decreases or the energy increases. Thus, 300 to 400 nm, corresponding to an energy of 90 to 70 kcal mol^{-1}, represents the limit above which photolysis will not occur. Since radiation from sunlight involves wavelengths greater than 290 nm, and since most pure synthetic polymers will not absorb radiation of this wavelength range, u.v. radiation from sunlight is not very effective for radiative degradation. However, the presence of some impurities (such as ketones) may significantly alter the ability to absorb u.v. radiation, giving greater degradation of the polymer.

Degradation by u.v. radiation usually proceeds via the formation of free radical intermediates while degradation by high-energy radiation proceeds via the formation of both radical and ionic intermediates. The presence of oxygen in the polymer molecule has a significant influence, largely by favouring hydroperoxide formation.

Polyethylene undergoes both chain scission

and cross-linking with the formation of a $-\dot{C}H-$ radical. When irradiated in air, oxidative degradation is predominant [12]:

$$\sim CH_2-\dot{C}H\sim + O_2 \rightarrow \sim CH_2-\underset{\underset{OO^{\cdot}}{|}}{CH}\sim \rightarrow$$

$$\sim CH_2-\underset{\underset{COOH}{|}}{CH}\sim \rightarrow H_2O + \sim CH_2-CO\sim \quad . \quad (7)$$

Polypropylene may degrade via the formation of any of the free radicals

$$\sim CH_2-\dot{\underset{\underset{CH_3}{|}}{C}}-CH_2\sim, \qquad \sim CH_2-\underset{\underset{\dot{C}H_2}{|}}{\overset{\overset{H}{|}}{C}}-CH_2\sim$$

or

$$\sim \overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C}}-\underset{\underset{CH_3}{|}}{\overset{\overset{H}{|}}{\dot{C}}}-C=CH\sim \quad .$$

Polyvinylchloride undergoes dehydrohalogenation when either heated or irradiated:

$$\sim CHCl-CH_2-CHCl-CH_2\sim \rightarrow$$

$$\sim CH-CH_2-CH=CH\sim \rightarrow \qquad (8)$$

$$\sim CH=CH-CH=CH-CH-\dot{C}H-CH_2\sim.$$

The effects of these degradation processes will naturally vary, but generally there will be a change in average molecular weight, molecular-weight distribution, crystallinity and mechanical properties.

Chain scission will generally result in reduced strength and creep resistance, while cross-linking will be associated with an increased modulus of eleasticity.

The purpose of this brief review is to show how and when degradation can occur in these polymers. Activation energies for the degradation of the high molecular-weight polymers used in surgery vary from 30 kcal mol^{-1} to 80 or 90 kcal mol^{-1} and such reactions generally require either heat, u.v. light or high energy radiation, preferably in the presence of oxygen, to proceed. It seems certain from these conditions that no such degradation should occur within the confines of the human body.

While this prediction is largely borne out in practice, there is some evidence that other factors are involved and that unexpected degradation mechanisms operate within the body. One of the first hints of this arose from the work of Oppenheimer *et al.* [13] on the carcinogenic properties of plastics. In attempting to elucidate the mechanisms by which plastic films induced tumours after subcutaneous implantation, some radiolabelled polymers were studied in experimental animals. C^{14}-labelled polystyrene ($-C_6H_5CH-C^{14}H_2-$), polyethylene ($-CH_2-C^{14}H_2-$) and polymethylmethacrylate ($-CH_2-C(CH_3)COOC^{14}H_3-$) were used and urine, faeces and respiratory CO_2 were monitored for periods of over a year. With the polystyrene, nothing radioactive was excreted in the urine until 21 weeks, but some radioactivity was detected after this time. With polyethylene, radioactive species were excreted after 26 weeks; with polymethylmethacrylate, radioactive species were excreted after 54 weeks. Removal of the films caused the urinary radioactivity to decrease. Nothing was found in the expired air, nor in tissues surrounding the implants that were removed at sacrifice. Although the results, which showed that small amounts of degradation products were produced but that these were rapidly removed and excreted, did not help Oppenheimer *et al.* to establish mechanisms for carcinogenicity, they are very interesting from the point of view of the polymer degradation itself.

Perhaps the most significant work in this respect is that of Leibert *et al.* [14] who studied the *in vivo* degradation of polypropylene with a view to determining the degradation rate, the nature of the degradation products and the influence of antioxidant. Samples were implanted subcutaneously in hamsters. Hydroxyl concentration and carboxyl absorbance were determined as a function of implantation time. While neither the hydroxyl concentration nor the carboxyl absorbance were altered by the tissue fluids in the antioxidant-containing material, changes were seen in pure antioxidant-free polypropylene. Here the hydroxyl concentration increased linearly with time up to 100 days, after which it increased at a faster rate. Some 90 days passed before any measurable carboxyl was formed. Gas-phase chromatography (GPC) analysis showed a slight shift in molecular-weight distribution, with a decrease in the proportion of very large molecules and an increase in the number of medium-sized molecules. Dynamic mechanical testing showed a slight decrease in tan δ during the first 40 days for the pure specimens, where δ is the phase angle between the applied strain and the resultant stress.

The authors attempted to compare this degradation with oxidative degradation at high temperatures. It has been suggested that the activation energy for the initiation step in this oxidation is 31 kcal mol^{-1} and there is an induction time which is a function of temperature and oxygen concentration. Hydroperoxides are formed:

$$RH + O_2 \rightarrow ROOH \quad (9)$$

and when these decompose, chain scission occurs, causing carboxyl groups to form:

$$ROOH \rightarrow RO^{\cdot} + HO^{\cdot} \quad (10)$$

$$RH + O_2 \rightarrow R^{\cdot} + HO_2^{\cdot} \quad (11)$$

and

$$R^{\cdot} + O_2 \rightarrow ROO^{\cdot}. \quad (12)$$

Rapid oxidation then follows, causing an increase in carboxyl content and loss of tensile properties. During propagation, both hydroxyl and hydroperoxide content increase:

$$ROO^{\cdot} + RH \rightarrow ROOH + R^{\cdot} \quad (13)$$

and

$$RO^{\cdot} + RH \rightarrow ROH + R^{\cdot}. \quad (14)$$

At 75° C and in 100% oxygen, polypropylene degrades by the above mechanism [15] and extrapolation of data to 37° C under a physiological oxygen partial pressure, pO_2, of 15 mm Hg predicts an hydroxyl production rate of 2.9×10^{-4} (mg OH) (g polymer)$^{-1}$ day^{-1} and an induction period of 20 years. Clearly, in the work of Liebert *et al.*, degradation under these conditions occurred at a much faster rate, with an induction period of about 100 days. They speculated that trace amounts of metallic ions, enzymes or other species could be responsible for this increased oxidation rate.

The suggestion is made, therefore, that enzymes may be influential in degrading polymers. Several authors, in fact, have made this suggestion, but always without proof. Leininger [16], for example, speculated that degradation of polyethylene was caused by enzymatic oxidative chain scission and quoted some unpublished work where changes in polyethylene film were found in a matter of weeks by exposing them to bacterial cultures which produce relatively large amounts of oxidative enzymes.

There is a certain attractiveness in the hypothesis of enzyme-accelerated *in vivo* polymer degradation, since enzymes have the characteristic ability to catalyse certain chemical reactions; it would certainly be very useful to invoke this hypothesis in the case, above, of polypropylene to explain why the degradation, which involves a high activation energy, occurs at room temperature. There are some difficulties involved in confirming the hypothesis, however, since enzymes are normally so substrate specific and one does not normally associate their catalytic effect with synthetic high molecular-weight polymers. Nevertheless, it remains an attractive possibility, worthy of further investigation.

The possible role of enzymes is discussed at greater length in the following section on hydrolyzable polymers.

3. Hydrolyzable polymers

Hetero-chain polymers, particularly those containing oxygen and/or nitrogen atoms in the main chain, are generally susceptible to hydrolysis. Depending on the structure, this hydrolysis may be favoured by either acid or alkaline conditions and naturally is much faster at elevated temperatures. Although hydrolysis of many of these polymers will therefore be most marked under, for example, hot alkaline conditions, the aqueous environment of the body at 37° C is sufficiently hostile to degrade a number of polymers by hydrolysis. It is in this context that enzymes, and especially hydrolytic enzymes, are most likely to have an effect. Amongst the polymers which have been shown to degrade by hydrolysis *in vivo* are certain polyamides, including nylons and polyamino acids, some polyurethanes, cyanoacrylates and some polyesters, both aromatic and aliphatic.

3.1. Nylon

Some 25 years ago, Harrison [17, 18] showed that nylon fabrics lost about 80% of their tensile strength during a three-year implantation. Leininger *et al.* also found considerable degradation of nylon [19]. Some nylons are hydrophilic and hydrolyzable, although the extent of water absorption is variable. Nylon 6, for example, has a water content at saturation of 11%, while nylon 11 has a water content of only 1.5%. The hydrolysis mechanism is quite simple [7], the primary attack being that of the hydrogen ion on the oxygen atom of the carboxyl group

$$R\text{–}\underset{\underset{O}{\|}}{C}\text{–}NHR_1 + H^+ \rightarrow R\text{–}\underset{\underset{OH}{|}}{C} = N^+HR_1 \quad (15)$$

and

$$R\text{–}\underset{\underset{\text{OH}}{|}}{\text{C}}=\text{N}^{+}\text{H}R_1 + \text{OH}^{-} \rightarrow R\text{–}\underset{\underset{\text{OH}}{|}}{\text{C}}=\text{O} + \text{H}_2\text{N}R_1. \quad (16)$$

Thus, acid and amine end groups are formed. Very few studies have been performed on the actual *in vivo* degradation of nylons, although Williams has found that nylon 6-6 degrades faster in the tissues of an acute inflammatory response than in the more quiescent chronic phase of a tissue response [20].

Several reports have also recently been published concerning the unexpected and undesirable degradation of nylon sutures used to secure ophthalmological prostheses in place [21, 22].

3.2. Polyamino acids

Synthetic polyamino acids and polypeptides of more complex main-chain and pendant group structure are often susceptible to hydrolysis. It is now well-known that these materials may be degraded by enzymes *in vitro,* where the enzyme substrate specificity in relation to the bonds broken is unchanged. Much data is available showing the solubility and digestibility of polyamino acids by proteolytic enzymes [23]. For example, synthetic polylysine has been studied on numerous occasions. Trypsin catalyses the degradation of this polymer [24], the chief products being dilysine and trilysine. Interestingly, no lysine is produced, indicating that the terminal peptide bonds are not attacked. This is in contrast to the acid hydrolysis of polylysine where random scission degradation occurs, giving lysine amongst the products.

Further evidence of the role of enzymes on the degradation of polyamino acids *in vivo* and *in vitro* has recently been supplied by Dickinson and coworkers [25, 26]. Several proteolytic enzymes were employed *in vitro* to asses the degradability of cross-linked poly(2–hydroxyethyl–C–glutamine). Trypsin and collagenase had no effect but pronase and papain dissolved the hydrogel. Analysis of the papain digestion products showed that mainly oligomers of degree of polymerization 4 to 9 were produced. It was suggested that trypsin and collagenase were too substrate specific. Degradation of this material was also observed *in vivo,* although this was confined to the first two weeks, as judged by changes in the swelling characteristics. It was suggested that, since this two weeks corresponded with the maximum cellular activity, it was enzymes released from the cells of the wound-healing response that were responsible. The cellular layer at the tissue–implant interface in the chronic response was associated with little or no degradation activity. These conclusions are very interesting in the light of the work of the author discussed later in this paper.

An interesting and complicating factor here is the inhibition of enzyme activity when low molecular-weight peptides are released into enzyme solutions at low concentrations. Thus, while degradation occurs with polyamino acids of molecular weight greater than 40 000, with low molecular weights in the region of 2 500, the enzyme and polymer may form an insoluble complex. This is an important point in the interpretation of *in vitro* work on polyamino acid degradation.

Subtilsin, α-chymotrypsin, ficin, papain and elastase also degrade polylysine, in that order of reactivity [27]. Other polymers of α-amino acids that are degraded by hydrolytic enzymes include poly–DL–alanine, poly–L–aspartic acid and poly–L–proline.

The hydrolytic instability of the amide bond in synthetic amino acid polymers has been used in the formation of intentionally biodegradable polymers. As reviewed by Kopecek [28], these polymers may be designed to give controlled biodegradation via the introduction of segments susceptible to affects by specific enzymes. For example, polymers of *N*–(2–hydroxypropyl) methacrylamide and p–nitrophenyl esters of *N*–methacryloylated amino acids are reacted with compounds containing an aliphatic amino group, with formation of the amide bond. If this bond originates in an amino acid specific for a certain enzyme, an enzymatically cleavable bond is formed. Specific acids for chymotrypsin, for example, and L–phenylalanine, L–tyrosine and L–leucine. A wide variety of degradable polymers has been prepared in this way.

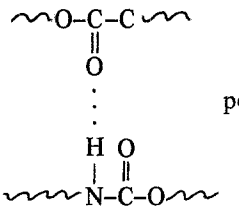
3.3. Polyurethanes

Polyurethane is the name given to a group of polymers containing the urethane group,

$$\text{NH–}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{–O}.$$

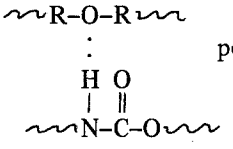
A wide variety of polyurethanes exist in which different groups are present in adjacent molecular chains, most commonly involving urethane, urea,

ester or ether groupings, which are combined through hydrogen bonding. They are generally classified according to whether they are primarily polyester or polyether in nature:



polyester urethane,

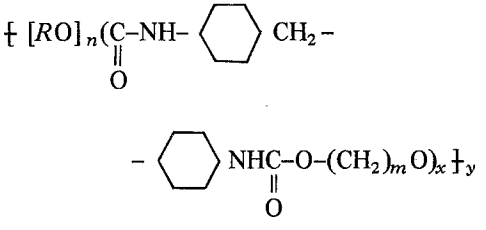
or



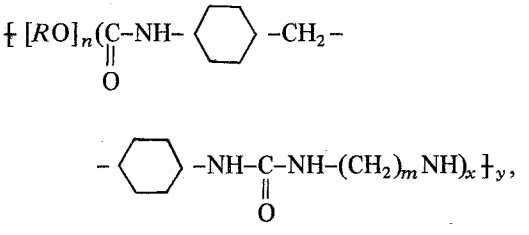
polyether urethane.

The polyester urethanes tend to be hydrolytically unstable due to their highly strained molecular configurations. Unfortunately, the early surgical uses of polyurethanes involved these varieties and *in vivo* degradation and disintegration was common [29–31]. Mirkovitch *et al.* [32] studied polyester urethane used as an aortic graft in dogs and found that the molecular structure changed considerably during a six-month implantation period.

On the other hand, the polyether urethanes are far more stable. Of particular interest here are the segmented polyether urethanes,



and the segmented polyether urethane ureas,



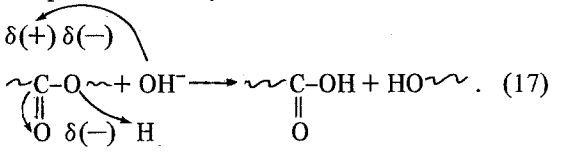
which are flexible stable materials that appear to withstand long implantation times without any noticeable sign of degradation.

3.4. Cyanoacrylates

The degradation of these surgical adhesives and hemostasis agents was thoroughly investigated by Leonard [33, 34]. Using radioactive polymethyl-2-cyanoacrylate, contained in a polyvinyl alcohol sponge, they showed that, after seven days, 0.2% of the radioactivity had been excreted in the faeces and 8.5% had been excreted in the urine, with 85.4% remaining in the sponge and 5.9% unaccounted for. After 159 days only 6.6% remained in the sponge, 45.1% having been removed in the urine and 4.3% in the faeces, the remaining 44% presumably being expired as CO_2. *In vitro,* the degradation appeared to be initiated by OH^- ions and produced formaldehyde and an alkylcyanoacetate after a random hydrolytic chain scission mechanism of propagation. Vezin and Florence [35] have recently studied further the *in vitro* heterogeneous degradation of poly(*n*-alkyl α-cyanoacrylates) and found that the degradation mechanisms proposed by Leonard *et al.* [33] may not always apply but may, depending on molecular weight and molecular-weight distribution, involve initiation at chain ends. Enzyme activity does not appear to have been invoked with these polymers.

3.5. Polyesters

The ester bond is readily hydrolyzed, resulting from the primary attack of the hydroxyl ion on the positive carbonyl C-atom:



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The susceptibility of individual polyesters depends on specific molecular structures and hydrophilicites. In general, the aromatic polyesters are less sensitive to moisture than the aliphatic polyesters because of the greater hydrophobicity of the aromatic parts.

3.6. Aromatic polyesters

Polyethylene terephthalate (PET) is the most relevant polyester to mention here, being widely used for prosthetic devices. Although Harrison and co-workers showed some degradation of a woven PET (Dacron) after a three-year implantation [17, 18] it is generally considered sufficiently hydrophobic to render bulk degradation unlikely. Surface degradation may occur slowly,

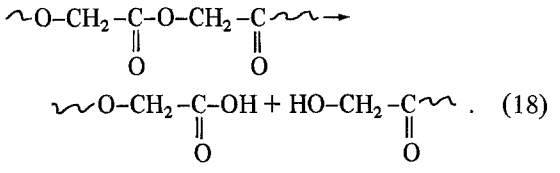
but usually there is little change in mechanical properties over a long period of time [36].

The kinetics of PET degradation have been recently discussed by Rudakova *et al.* [37]. They implanted samples subcutaneously in rabbits and dogs and found the time for complete degradation was 30 ± 7 years. Fifty per cent of the initial strength of PET filaments was lost in 10 ± 2 years.

3.7. Aliphatic polyesters

Aliphatic polyesters, typified by polyglycolic acid and polylactic acid, have been studied extensively, since they provide model systems for investigating biocompatibility and also provide useful materials for applications requiring controlled degradation, such as synthetic absorbable sutures.

Polyglycolic acid is the most hydrophilic of all polyesters [38], hydrolysis readily occurring via the ester bond, yielding alcohol and carboxylic acid groups:



(18)

Reed and Gilding [39] have shown that the loss of tensile strength of polyglycotic acid sutures (Dexon®) is quite rapid when tested *in vitro* at pH 7 and 37° C, with total loss of strength occurring after 4 to 6 weeks. This has been confirmed by Chu [40] and Williams [41]. Reed and Gilding [39] also found that the *in vivo* degradation was similar to *in vitro* degradation, and could, in fact, be modelled *in vitro* by using a 0.2 M phosphate buffer at pH 7 and 37° C. Although the tensile strength is reduced to zero after 32 days, the mass-loss does not begin until 21 days, the oligomeric fraction formed by degradation becoming the main component. The conclusion that the *in vivo* degradation of polyglycolic acid is a result of simple hydrolysis is not totally substantiated by the work of the author, as discussed below. Gilding [38] has stated that the hydrolysis takes place preferentially in the amorphous phase of this semi-crystalline material, and this is supported by the work of Chu [40] who has argued that water is able to penetrate amorphous areas more rapidly than crystalline areas and tie-chain segments in these regions begin to degrade. When the amorphous regions have been removed by hydrolysis, the second stage of degradation starts, thus involving the crystalline areas. The degree of crystallization was observed to increase during the first stage of degradation and then to decrease during the second state.

Other aliphatic polyesters of the same series, and their co-polymers, have been shown to become degraded by hydrolysis, although at substantially slower rates [39]. Further comments on the role of enzymes and bacteria in the degradation of these polymers are given below.

4. Experimental observations on the role of the physiological environment in polymer degradation

In view of the conjecture and discussion concerning the precise mechanisms by which polymers degrade *in vivo*, a series of experiments have been carried out in which certain aspects of the role of the physiological environment in polymer degradation have been studied.

4.1. The effect of enzymes on polyglycolic acid [41, 42]

It was considered important to identify whether enzymes, under any conditions, were able to degrade synthetic high molecular-weight polymers, this hitherto only having been demonstrated in the case of some polyamino acids. Polyglycolic acid was chosen for the initial studies, in which Dexon sutures were incubated in various solutions, since this polymer is hydrolyzed in aqueous media, so that the rates of hydrolysis could be compared in the presence or absence of enzymes. The enzymes studied were acid phosphatase, bromelain, carboxypeptidase-A, chymotrypsin, clostridiopeptidase-A, esterase, ficin, leucine aminopeptidase, papain, peptidase, pepsin, pronase, proteinase-K and trypsin. The sutures were immersed in soluctions of these enzymes in appropriate buffers for varying periods of time at 37° C and the degradation, monitored mechanically, was compared to that produced in buffers alone.

Acid phosphatase, papain, pepsin, peptidase, pronase, proteinase-K and trypsin had no apparent effect on the polymer. Ficin, carboxypeptidase-A, chymotrypsin and clostridiopeptidase-A all produced significantly greater amounts of degradation, often increasing the rate of hydrolysis by a factor of two. Bromelain, esterase and leucine amino-

peptidase all had very significant effects, although it was difficult to take into account quantiatively the amount of degradation due to the ammonium sulphate, present in the solution to stabilize the enzymes.

While the varying activities of these enzymes and the different amounts by which they lose activity during the experimental period preclude a comparative and quantitative analysis of the effect of these enzymes, it was clear that enzymes, under some conditions, are able to influence polymer degradation. It is interesting to note that the enzymes that did influence the hydrolysis were mainly (although not exclusively) of the type that might be expected to attack an aliphatic polyester on the basis of its molecular structure, i.e., esterases.

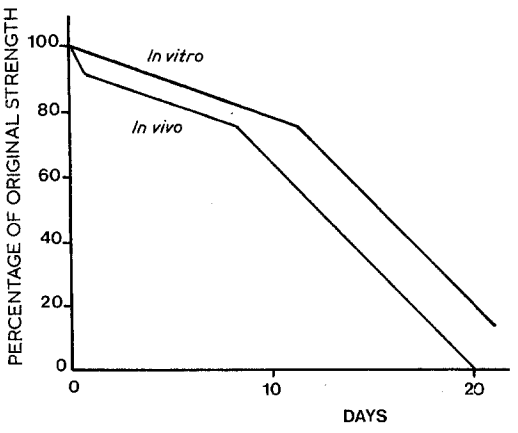
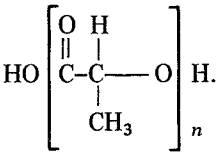


Figure 1 In vivo and *in vitro* profiles for the degradation of polyglycolic acid sutures [41].

4.2. The effect of enzymes on polylactic acid [43]

Similar studies have been carried out on poly-l-lactic acid, of structure



although in this case powdered polymer was used instead of multi-filament sutures and the degradation was monitored analytically, rather than mechanically. Of the enzymes studied, lactate dehydrogenase gave entirely negative results. No lactic acid was detected in solution after exposure of polylactic acid to esterase, but there was a slight weight-loss and fall in pH; it is possible that there was a slight attack on the polymer without yielding any low molecular-weight fractions. Ficin also gave equivocal results with the suggestion of a slow action yielding relatively high molecular-weight degradation products. A slight effect, judged by a small weight-loss and traces of lactic acid was noted with trypsin.

On the other hand, under the conditions employed, pronase, proteinase-K and bromelain all had a significant effect on this polymer. In all three cases, the polymer showed a reduction in weight with the detection of lactic acid in the solution, by both thin-layer chromatography and a qualitative test with p-hydroxydiphenyl, and also a concomitant reduction in pH. The mode of action may not have been the same in these three cases, however, since both pronase and bromelain caused a physical break-down in the polymer, giving a much finer dispersion, while proteinase-K did not substantially alter the physical form of the powder, although there was a similar weight-loss and production of lactic acid. It is conceivable that these enzymes are displaying a different activity in these cases: perhaps the pronase and bromelain exhibiting exokinase behaviour and the proteinase-K exhibiting endokinase behaviour.

4.3. *In vivo* degradation of polyglycolic acid [41]

The degradation of the polyglycolic acid sutures (Dexon®) was studied *in vivo* by the subcutaneous implantation of specimens in rats, monitoring the degradation mechanically. *In vitro* tests were performed in parallel with the *in vivo* tests using Tris buffer at pH 7.4. The degradation profiles are given in Fig. 1, from which it is clear that the material does not display similar behaviour *in vivo* and *in vitro*, as claimed by Reed and Gilding [39]. A considerably greater number of time intervals were chosen for study in the present case, giving an insight into the difference between the two conditions. *In vitro* it is apparent that the rate of loss of strength is linear for about 12 days, by which time a 25% loss has been recorded. At this point the slope changes, the rate of loss becoming more rapid, although still linear, until disintegration between 25 and 30 days. *In vivo* at every time interval studied the strength was less than that recorded *in vitro*. However, this was due to a rapid initial loss of strength, occurring within the first two days. This observation was checked very carefully by subsidiary experiments in which specimens were implanted for short

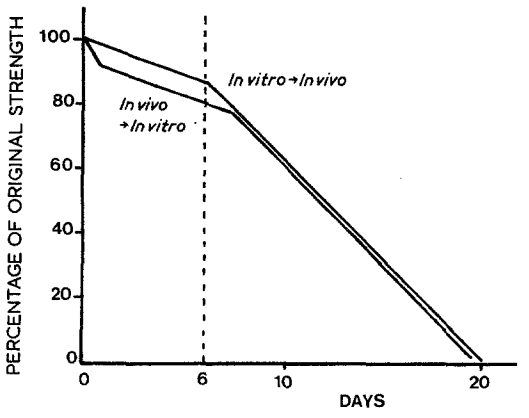


Figure 2 Degradation profiles for polyglycolic acid sutures, with transfer between *in vivo* and *in vitro* conditions at 6 days [41].

period of time, the rapid drop being confirmed. After two days, the suture loses strength at the same rate as those in the first stage of *in vitro* degradation, until the same 25% loss of strength has been reached, in this case, at about 8 days. At this point the rate increased, again to an identical value as the *in vitro* specimens.

These observations would suggest that either the initiation of degradation occurs far more readily in the *in vivo* environment than in a buffer solution but that, once initiated, the degradation proceeds by the same hydrolytic mechanism whatever the environment, or that there is something very specific about the first few days *in vivo* that accelerates the degradation process. This was checked by experiments in which some specimens were kept in buffer for 6 days and then implanted, while other specimens were implanted for 6 days and then removed and kept in buffer. Those which were transferred from *in vivo* to *in vitro* conditions followed the same degradation profile throughout as the previous *in vivo* specimens (see Fig. 2), but those which were transferred from *in vitro* to *in vivo* conditions followed the *in vitro* profile at the beginning, but then suffered a rapid loss of strength on implantation, thereafter following the *in vivo* profile. This would indicate that there is something specific about the immediate environment on implantation that influences the hydrolysis mechanism, at any stage in the degradation process. The fact that the profiles are so similar, apart from the period around the implantation time, however, would suggest that at other times *in vivo*, the degradation process is similar under the two conditions, and the results are quite in keeping with the hypothesis of Chu, discussed earlier [40]. These results are also consistent with those of Dickinson and co-workers [25, 26] discussed earlier, where the *in vivo* degradation of polyamino acids was largely confined to the acute phase of the tissue response.

What it is in the immediate post-implantation physiological environment that has this effect is a matter of speculation. It is tempting to assume that it is enzymes released from cells in response to the trauma of implantation that are responsible, but it is very difficult to prove or deny this. An attempt has been made to investigate this by using a novel technique in which specimens are maintained in varying types of inflammatory tissue. This is based on the hypothesis that, if enzymes are able to influence polymer degradation, then, since different enzymes are being synthesized and released at different rates during the various phases of the tissue response to an implant, the polymer will degrade non-linearly as a function of time. It may be, for example, that the enzymes released by cells, such as polymorpho-nuclear leucocytes, that dominate in the first few days, are the most active in this respect, in which case there will be a rapid initial degradation, followed by a slower rate (ignoring for the moment any variation in degradation rates associated with structural factors). On the other hand, should the polymer be more susceptible to the enzymes released by the macrophages of the chronic response, then the rate would increase with time.

In this particular technique, specimens were implanted in rats, the samples being divided into two groups. Those of the first group were left for the duration of the experiment and checked for degradation on removal. Those of the second group were removed from the animals after a short period of time and re-implanted into fresh animals. This process was repeated at appropriate times during the experiment. In the first group, the specimens experienced an acute response followed by a chronic response, while those in the second group experienced a series of acute responses but were never subjected to the chronic phase. Although, as discussed below, this technique has given very interesting results with other polymers, in the case of polyglycolic acid, in which the second group were re-implanted four times in an eleven-day period, very little change was noted.

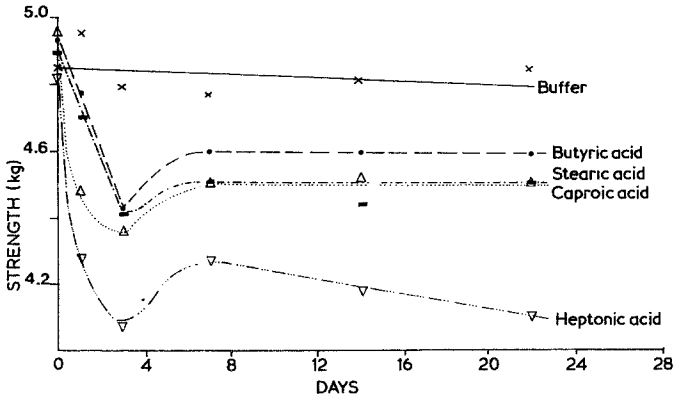


Figure 3 Loss of strength of polyglycolic acid after incubation in lipid solutions [48].

The re-implanted specimens has suffered slightly more degradation (55.8% strength remaining compared to 59.9%) which was statistically significant at $p < 0.005$, but which was hardly a conclusive difference. This was probably due to the fact that the time period is too short for there to be a significant change in the nature of the inflammatory tissue and tends to confirm the observation that the propagation phase of this hydrolysis is largely independent of the nature of the environment. The attention of the author has now been turned to other polymers of a more prolonged degradation profile which hopefully will give better results with the technique.

Enzymes, of course, are only one of several species of the physiological environment which could affect polymers, and it is necessary to consider the alternatives. One group of such alternatives are the lipids present in extra-cellular fluids. It is well-known that lipids are able to influence the structural integrity of some polymeric materials, most notably including silicone rubber [44–47]. Heart valves in which the ball was made of this material have malfunctioned because of structural changes in the rubber and a number of silicone rubber joint prostheses have fractured, apparently because of environmental–mechanical interactions. Although the exact reasons for this degradation are not entirely clear, it does seem certain that lipids and other highly polar substances are involved.

Some *in vitro* experiments were therefore performed in which polyglycolic acid sutures were exposed to varying concentrations of the series of lipids: butyric acid, caproic acid, heptonic acid and stearic acid [48]. Fig. 3 shows the very significant loss of strength of samples during the first few days. Interestingly, samples recover some of the strength and suffer little further degradation over a period of time in these particular solutions (in a phosphate buffer at pH 7.0). This subsequent rise in strength may be associated with an absorption of lipids into the polymer or associated swelling. Fig. 4 shows the relationship between the time taken for a suture to break at a nominal load of 2.55 kg in stearic acid and caproic acid, as a function of concentration. Similar experiments with the polyglycolic acid immersed in distilled water produced no fracture after 24 h. These results confirm that these lipids have a very rapid effect on the polyglycolic acid, which could explain the loss of strength upon implantation.

4.4. *In vivo* degradation of "non-absorbable" sutures [41, 49]

Sutures are conveniently classified into those which are absorbable, i.e., dissolving in body tissues within a few months, and those which are non-absorbable. The difference is only a matter of degree, however, and many non-absorbable sutures

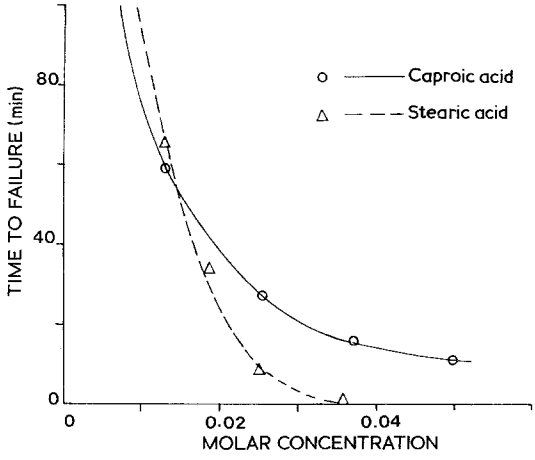


Figure 4 Time to failure of polyglycolic acid sutures immersed in caproic acid and stearic acids at an inital load of 2.55 kg, as a function of lipid concentration [48].

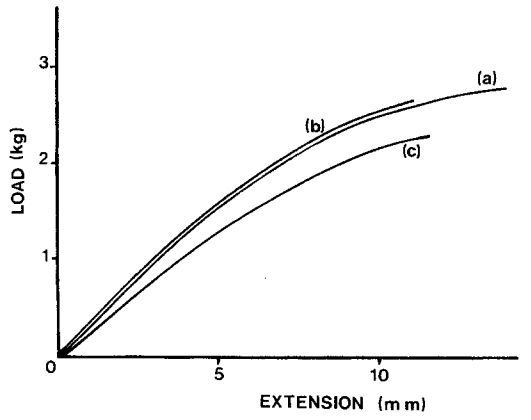


Figure 5 Load–extension curves for nylon: (a) control; (b) after 10 weeks implanted in one rat; and (c) after 10 weeks implanted 1 week in each of 10 rats [41].

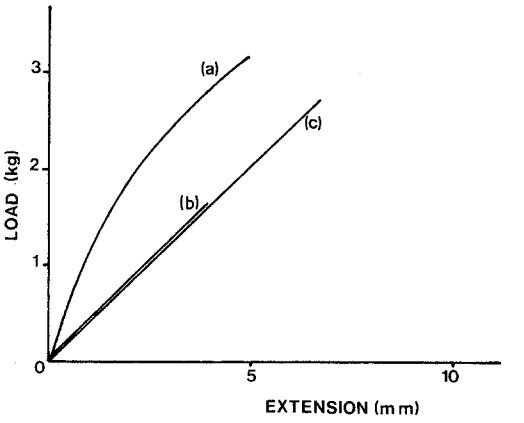


Figure 6 Load–extension curves for silk: (a) control; (b) after 10 weeks implanted in one rat; and (c) after 10 weeks implanted 1 week in each of 10 rats.

do degrade slowly. These materials are, therefore, suitable for study by the re-implantation technique described above. Tests were performed with nylon (Ethilon®, supplied by Ethicon Ltd.) and silk (Mersilk®). With the nylon, differences between specimens are obvious, as shown by the load–elongation curves given in Fig. 5. The specimens implanted in one rat for a total of ten weeks exhibited the same slope as the control, but fractured at a lower load and smaller elongation. Specimens continuously re-implanted every week for the same total of ten weeks, showed a smaller slope and a significantly lower breaking strength.

The curves for the silk sutures, given in Fig. 6, showed that the re-implanted samples gave much higher strengths than those maintained in single animals.

These results indicate that the continued presence of cells of the acute response are more important than cells of the chronic response in producing degradation of the nylon; while, with the silk, the situation is reversed.

Further tests have been carried out with the nylon in which the total period of implantation was 30 weeks with a re-implantation time of 3 weeks [49]. The results of the breaking strength showed the same trend as before, with a mean loss of strength of 11.3% in the re-implanted material and 5.7% in the single-animal experiments. The really interesting observation, however, is that the amount of degradation here is only marginally greater than that observed at 10 weeks, which amounted to just less than 10% in the re-implantation case and 2 to 3% in the single-animal case. This would confirm the hypothesis that much of the degradation is taking place very soon after implantation and that little further degradation occurs thereafter. The significant degradation takes place during one week of implantation, but extending this period to 3 weeks produces little additional effect.

4.5. The effect of bacteria on absorbable sutures [50]

As a final commentary on the role of the physiological environment on polymer degradation, some experiments concerning the effects of bacteria on absorbable suture materials are worth reviewing. It is known that some bacteria are capable of degrading certain non-proteinaceous macromolecular structures, principally through the action of intracellular enzymes [51]. This would suggest that, if polyglycolic acid sutures were degraded by enzymes, then sutures in infected wounds might be more susceptible to degradation than those in clean wounds. Experiments were, therefore, performed to test this hypothesis, using cat-gut sutures for comparison.

Tests were carried out both *in vitro* and *in vivo*. In the former case, cat-gut and Dexon sutures were placed in broths at 37° C containing *Streptococcus mites, Escherichia coli* or *Staphylococcus albus*. Table I shows the results of the breaking strength of sutures after 3 weeks, comparing the effects of incubation in both broths and bacterial cultures. It can be seen here that, while the cat-gut showed no difference, the polyglycolic acid sutures degraded more in the presence of the broth alone than when bacteria were present.

TABLE I Breaking loads of sutures after incubation in broths and bacterial cultures [50]

Suture	Bacteria	Broth	Breaking strength (kg)		
			Control	In broth	In culture
Cat-gut	*Streptococcus mites*	Tryptone soya	3.41	2.34	2.25
	Escherichia coli	Peptone–glucose	2.19	1.70	1.81
	Escherichia coli	Brain–heart	3.38	2.67	2.37
	Staphylococcus albus	Brain–heart	2.85	1.65	2.09
PGA	*Streptococcus mites*	Tryptone soya	4.77	1.31	2.79
	Escherichia coli	Peptone–glucose	4.20	2.06	3.01
	Escherichia coli	Brain–heart	4.55	2.74	3.27
	Staphylococcus albus	Brain–heart	4.63	0.59	0.96

These results were confirmed in additional tests when the broths were artifically acidified to take into account the lowering of the pH by bacteria.

In the *in vivo* experiments, sutures were implanted subcutaneously in rats, half of the sites being inoculated with *Staphylococcus albus.* Several experiments were performed in which the bacterial count and the period of implantation were varied. The conclusion, again, was that bacteria in sufficient numbers inhibited the degradation of polyglycolic acid. It was clear that polyglycolic acid and cat-gut sutures displayed different behaviour in this respect. While the former degraded faster in the absence of bacteria, cat-gut degraded faster in infected tissue, provided the bacterial count was sufficiently high. This indicates a clear superiority for the synthetic absorbable suture in infected tissues, in contrast to the earlier observation by Sebeseri *et al.* [52]. The reason for the observed effects with polyglycolic acid are not clear at this stage, although obviously the expected role of bacterial-produced enzymes has not materialized.

5. Conclusions

This review of the literature and recent experimental work has shown that the degradation of polymers in the physiological environment may show some differences to degradation in other environments. Some polymers which would be expected to be quite stable do degrade slowly under these conditions, whilst hydrolytically unstable polymers show variations in their degradation profile. It is clear now that enzymes are able to influence the degradation of synthetic polymers and there is some circumstantial evidence to implicate lysosomal enzymes in *in vivo* degradation. Other factors, such as the presence of lipids or other organic species, have to be taken into account, however, and more work needs to be carrried out in order to clarify this phenomenon.

Acknowledgements

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